Effectiveness and tolerability of extended biologic treatment for psoriasis in daily practice

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Effectiveness and tolerability of extended biologic treatment for psoriasis in daily practice

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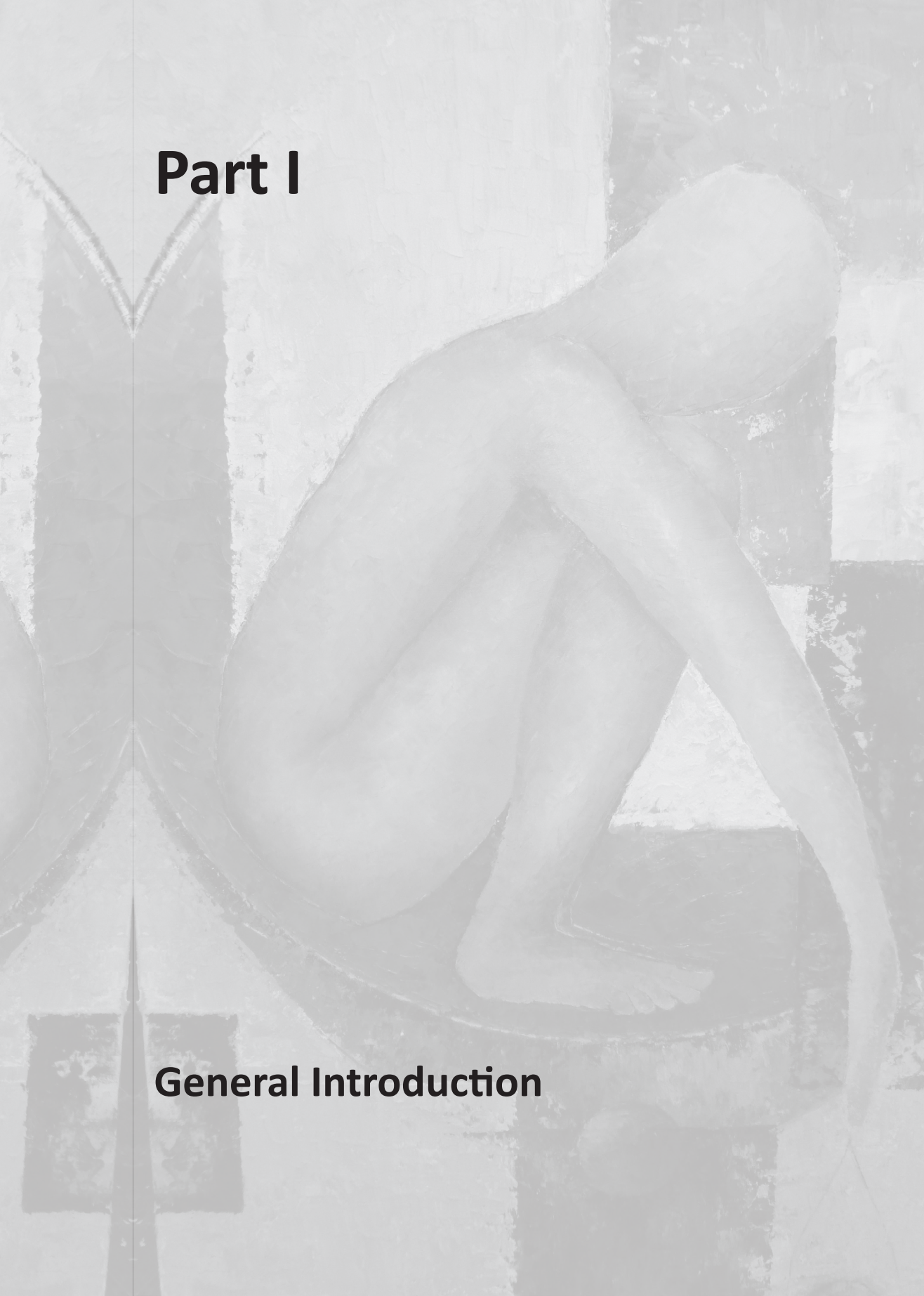
Abbreviations

AAA	Anti-adalimumab antibody
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
BCC	Basal cell carcinoma
BMI	Body mass index
CAPTURE	Continuous Assessment of Psoriasis Treatment Use Registry
CD	Cluster of differentiation
CDR	Complementary determining region
CRP	C-reactive protein
CsA	Ciclosporin A
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
DMF	Dimethyl fumarate
DREAM	Dutch Rheumatoid Arthritis Monitoring
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FDA	Food and Drug Administration
GGT	y-Glutamyl transferase
HLA	Human leukocyte antigen
ICAM	Intercellular adhesion molecule
IL	Interleukin
ITT	Intention-to-treat
JAK	Janus kinase
LCE	Late cornified envelope
LFA	Lymphocyte function-associated antigen
LOCF	Last observation carried forward
MACE	Major adverse cardiovascular event
MTX	Methotrexate
NMSC	Nonmelanoma skin cancer
NRI	Nonresponder imputation
NVDV	Nederlandse Vereniging voor Dermatologie en Venereologie
PASI	Psoriasis Area and Severity Index
PDE	Phosphodiesterase
PGA	Physician's Global Assessment
PML	Progressive multifocal leukoencephalopathy

PSORS	Psoriasis susceptibility
PUVA	Psoralen-ultraviolet A
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SD	Standard deviation
SEM	Standard error of the mean
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TE	Treatment episode
Th1 cells	Type 1 helper T cells
Th17 cells	Type 17 helper T cells
TNF	Tumor necrosis factor
UVA	Ultraviolet A
UVB	Ultraviolet B
WHO	World Health Organization



Part I

General Introduction

1.1 Psoriasis

Introduction

Psoriasis is a common chronic inflammatory skin disease. Psoriasis often impairs physical, psychological and social functioning. The impact of psoriasis on health-related quality of life was shown to be similar to that of other major medical diseases.[1] Due to the negative impact of psoriasis on employment and income and the costs of treatment, psoriasis is also an important health problem from a societal perspective.[2] In recent years, important advances have been made in elucidating the pathogenesis of psoriasis.
This chapter describes the history, epidemiology, clinical and histological features, pathogenesis and comorbidities in psoriasis.

History

Psoriasis is an ancient skin disease, described for the first time in the Corpus Hippocraticum by Hippocrates. The word psoriasis is derived from the Greek word 'psora', meaning 'to itch'.[3] Psoriasis was confused with leprosy for many centuries. Only in the 19th century, psoriasis was recognized as a separate entity.[3, 4]

Epidemiology

A recent systematic review showed that the prevalence of psoriasis in Europe in individuals of all ages varies between 0.7% and 2.9%.[5] The prevalence of psoriasis in studies in populations with different ethnic backgrounds ranged from 0.6% to 4.8%.[6] Psoriasis tends to occur more frequently in Caucasians than in other races and more frequently at higher latitudes than lower latitudes.[7]
In a recent study performed in the United States, the prevalence of psoriasis was 3.2%. From these patients, 17% had moderate to severe disease, in this study defined as an affected body surface area of at least 3%.[6] In another study, 21% of patients had extensive disease, defined as an affected body surface area of at least 10%.[8]
Psoriasis can appear at any age. Nevitt et al. found the mean age at onset to be 33 years, with 75% of cases appearing before the age of 46.[9] However, there also appears to be a bimodal distribution, with a peak at the age of 16-22 years and a peak at the age of 57-60 years.[10] There is no gender predilection, although women do appear to have an earlier age of onset.[6, 11] The higher proportion of men with psoriasis treated with biologics may be explained by more severe disease in men.[12]

Clinical and histological features

Psoriasis is a heterogeneous disease, with several clinical phenotypes. Different forms of psoriasis can coexist. The most common form of psoriasis, which is found in 90% of psoriasis patients, is chronic plaque psoriasis (also known as psoriasis vulgaris). Chronic plaque psoriasis is characterized by well-demarcated erythematous plaques of variable size with white or silvery scale, typically in a symmetrical distribution. Predilection sites are the extensor surfaces of the elbows and knees, the scalp, the lumbosacral region and the umbilicus. The face is infrequently affected. Site-specific variants of plaque psoriasis are inverse psoriasis (also known as flexural psoriasis), scalp psoriasis, seborrhoeic psoriasis (sebopsoriasis) and palmoplantar psoriasis (nonpustular).
Other forms of psoriasis include guttate psoriasis, erythroderma and pustular psoriasis. Pustular psoriasis can be subdivided into localized forms of pustular psoriasis (palmoplantar pustulosis and acrodermatitis continua of Hallopeau) and generalized pustular psoriasis (von Zumbusch). Palmoplantar pustulosis may be a distinct entity rather than a form of psoriasis.[4, 13-15] Furthermore, about 50% of patients have nail psoriasis, most commonly seen in patients with psoriatic arthritis.[14, 16]

Histologically, the psoriatic plaque is characterized by epidermal hyperproliferation, increased vascularity and a predominantly dermal inflammatory infiltrate. The epidermis is characterized by acanthosis with regular elongation of rete ridges, thinning of the suprapapillary plate, parakeratosis and loss of the granular layer. Highly characteristic for psoriasis but infrequently seen, are micropustels of Kogoj and microabcesses of Munro.[4, 14, 17] The papillary dermis contains dilated and tortuous capillaries. The inflammatory infiltrate mainly contains T-cells, dendritic cells, macrophages and neutrophils.[17, 18]

Pathogenesis

Psoriasis is a multifactorial disease, resulting from a combination of genetic and environmental factors. Evidence for a genetic component comes from population studies, showing that the incidence of psoriasis is greater in first and second degree relatives of patients in the general population. In addition, the risk of psoriasis is two to three times higher in monozygotic twins compared with dizygotic twins.[14, 17, 19]
At present, at least nine chromosomal psoriasis susceptibility loci have been identified through linkage analysis, called psoriasis susceptibility 1 through 9 (PSORS1 through PSORS9). By far the major genetic determinant of psoriasis is PSORS1, which probably accounts for 35-50% of the heritability of the disease.[14, 17, 20] The PSORS1 region contains HLA-Cw6, which is involved in antigen presentation. Current data suggest that HLA-Cw6 is the susceptibility locus within the PSORS1 region.[21] This indicates a role for the adaptive

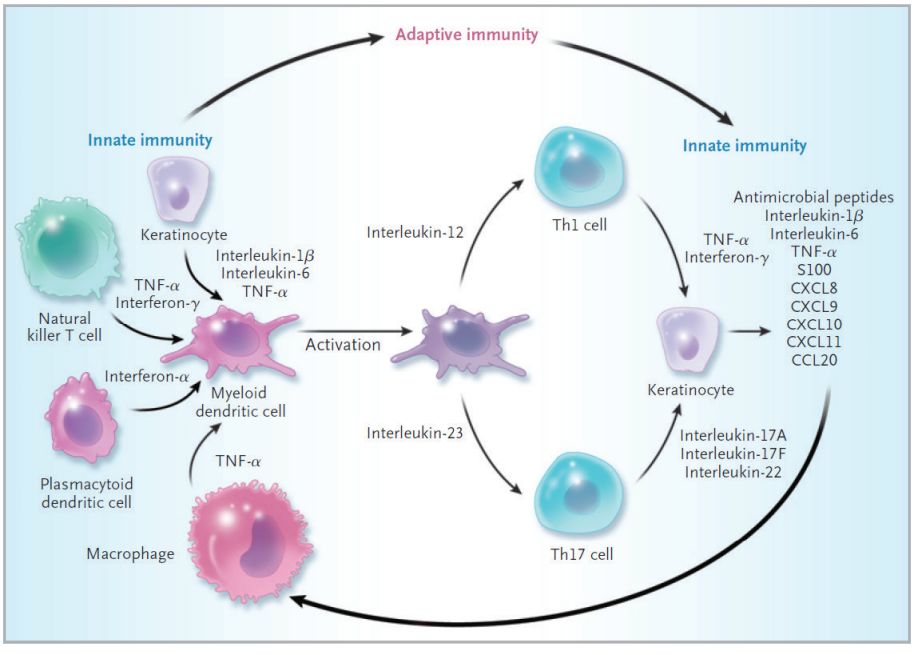


Figure 1. Pathogenesis of psoriasis.[17]

immune system in psoriasis. HLA-Cw6 also is a strong marker for early-onset psoriasis.[14] In addition, several other genes related to adaptive immunity, innate immunity and skin barrier function have been identified by genome wide association studies. As an example, variants in the interleukin-23 receptor (IL23R) gene and the interleukin-12B (IL12B) gene, both involved in adaptive immunity, have been identified. Tumour necrosis factor α-induced protein 3 (TNFAIP3) is an example of a susceptibility gene related to innate immunity.

Most genetic data available support an immune-based pathogenesis. However, copy-number variation in the β-defensin cluster and deletions in the late cornified envelope (LCE) genes have also been associated with psoriasis and support a role for the epidermis.[17, 22, 23]

In paediatric-onset psoriasis, an association was demonstrated with established and recently discovered genetic risk factors, including genes involved in epidermal barrier function and adaptive immunity (ERAP1 and IL23R loci, LCE3C_LCE3B deletion and HLA-Cw6). Data from this study suggest that heritable factors may play a more important role in paediatric-onset psoriasis than in adult-onset psoriasis.[24] It had already been shown that guttate psoriasis (an acute onset form, usually occurring in adolescents), is strongly associated with PSORS1, whereas late onset psoriasis vulgaris (age > 50 years) is not.[17, 25] Environmental triggering factors for psoriasis are infections (especially streptococcal

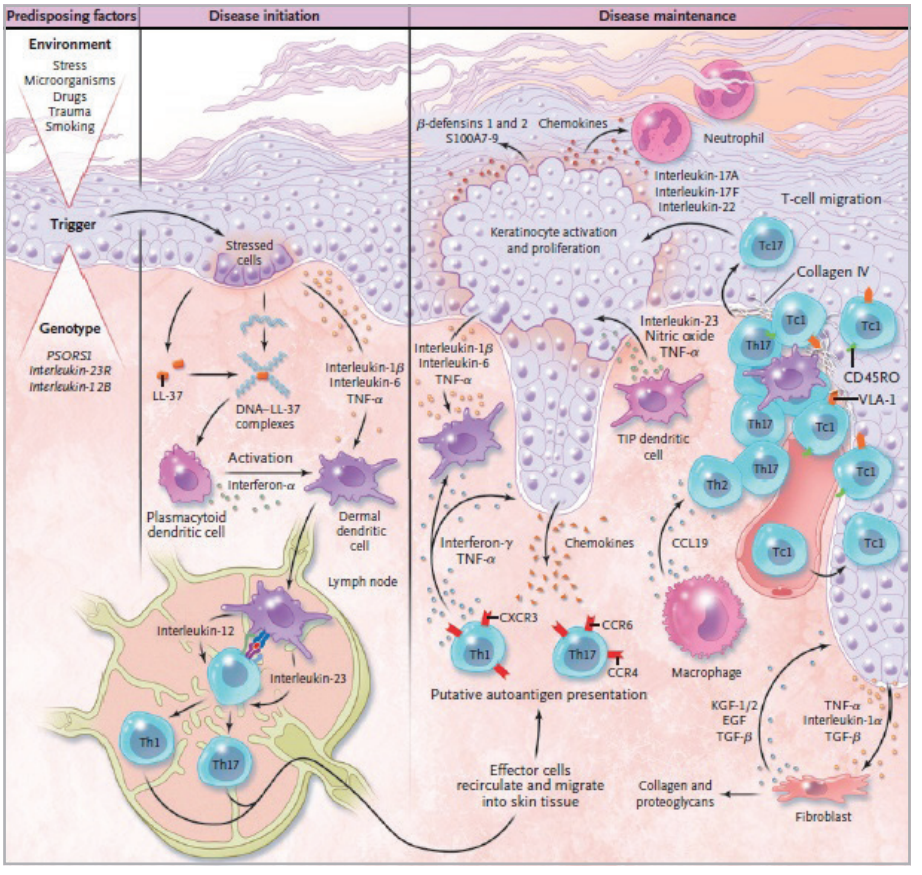


Figure 2. Pathogenesis of psoriasis.[17]

pharyngitis), certain medications, stress, smoking, obesity and trauma to the skin (Koebner phenomenon).[26]

Figure 1 and Figure 2 show a proposed scheme of the evolution of a psoriatic lesion. Triggers such as physical trauma or bacterial products and the production of cytokines by innate immune cells (including tumour necrosis factor α (TNF-α)), lead to the activation of myeloid dendritic cells that migrate into draining lymph nodes. The dendritic cells present antigens to naïve T-cells and induce the differentiation of naïve T cells into effector cells such as type 1 helper T cells (Th1) and type 17 helper T cells (Th17) by the release of interleukin-12 (IL-12) and interleukin-23 (IL-23). T-cells in turn, secrete mediators (TNF-α, interleukin-17A (IL-17A), interleukin-17F (IL-17F) and interleukin-22 (IL-22)), that lead to activation and proliferation of keratinocytes. Activated keratinocytes produce antimicrobial peptides, proinflammatory cytokines (including TNF-α), chemokines and S100 proteins, thereby creating a feedback loop.

The high efficacy of the former biological therapies directed against T-cells (alefacept and efalizumab) and the current biologics directed against cytokines involved in the IL-23/Th17 pathway, demonstrates the importance of these cells and cytokines in the pathogenesis of psoriasis.

Comorbidities

Psoriasis is associated with comorbidities like psoriatic arthritis, the metabolic syndrome, Crohn's disease, diabetes mellitus, depression and cancer.[14] About 25% of patients with psoriasis have psoriatic arthritis.[14, 27] Psoriatic arthritis is nowadays seen as a comorbidity rather than a different manifestation of the same disease, which is supported by genetic and immunological differences and differences in responses to various therapies.[14]

Many observational studies have shown an association between psoriasis and comorbidities, especially the metabolic syndrome and cardiovascular disease.[28, 29] The cardiovascular risk seems to increase with the severity of the disease.[29] However, the association between psoriasis and comorbidities is complex.[28] The question is whether there is a direct link between psoriasis and many of the associated diseases through chronic systemic inflammation (the inflammatory hypothesis). Another possibility is that the associated diseases are in fact comorbidities, indirectly linked to psoriasis through unhealthy lifestyle factors leading to the metabolic syndrome or shared genes increasing the risk for psoriasis as well as for comorbidities.[28, 30] Conversely, smoking and obesity may increase the risk of developing psoriasis.[28, 31, 32]

Many studies that corrected for available confounders have shown an independent association between psoriasis and cardiovascular disease, which has led to the promotion of early aggressive treatment of psoriasis to reduce the risk of cardiovascular disease by some. In contrast, other studies have not shown an independent association.[28, 33] In addition, the coexistence of psoriatic arthritis with psoriasis is an important confounder, which is not corrected for in almost all studies.[34] Large prospective studies specifically designed to investigate a possible causal link between psoriasis and cardiovascular disease are needed.

Recently, a numerical excess of major adverse cardiovascular events (MACE) in phase II/III studies of briakinumab prompted concerns about a possible increased risk of MACE in patients with psoriasis receiving anti-IL-12/IL-23 agents.[35] MACE is a composite endpoint of myocardial infarction, cerebrovascular accident, or cardiovascular death. The clinical development program of briakinumab for psoriasis was discontinued in 2011 because of this finding. A meta-analysis of RCTs of anti-IL-12/IL-23 antibodies and analyses of

pooled data from phase II/III studies for ustekinumab did not show an increased risk for MACE.[36, 37]

Some studies have suggested an increased risk for cancer, especially lymphoma and NMSC in patients with psoriasis.[38-43] However, it is unclear whether these conditions are related to the disease itself or to previous immunosuppressive treatments or phototherapy.[14, 17]

1.2 Treatment of psoriasis

Introduction

Psoriasis is a chronic inflammatory skin disease that presently is not curable, implying lifelong treatment in the majority of patients. Although a number of well-established therapies are available for psoriasis, unmet clinical needs remain, including insufficient efficacy, tolerability and practicability.
The therapeutic modalities available for the treatment of psoriasis can be placed on a so called 'treatment ladder'.[44, 45] This concept reflects the preferential use of therapies with the least potential for side effects. In case of insufficient efficacy, therapies with greater potential toxicity can be used. At the bottom of the ladder, topical therapies are situated. Ascending the ladder, phototherapy followed by conventional systemic treatments and subsequently biological therapies are encountered.
Mild psoriasis can usually be controlled with topical therapies. In patients with refractory mild psoriasis, phototherapy can be applied. In patients with moderate to severe psoriasis, topical therapies often do not suffice. This patient category often needs phototherapy or systemic treatments.[46]

In recent years, new insights into the pathogenesis of inflammatory diseases including psoriasis, have led to the development of biological therapies, also called 'biologics'. These are large molecules produced by living organisms. At this moment, biological therapies are placed at the top of the treatment ladder for psoriasis and can only be prescribed to patients with moderate to severe psoriasis who have not responded to phototherapy and methotrexate ór ciclosporin, or who have contraindications to, or do not tolerate these therapies.

Topical therapies

Topical therapies commonly applied for the treatment of psoriasis include topical corticosteroids, vitamin D3 analogues, calcineurin inhibitors, dithranol and coal tar.[47]

Since their introduction in 1952, topical corticosteroids have become a mainstay in the treatment of psoriasis.[26, 47] Many different topical corticosteroids with different potencies and vehicles exist. Depending on the severity and the location of psoriasis, corticosteroids with different potencies are used. The mechanism of action of corticosteroids is based on influencing the synthesis of different proteins resulting in anti-inflammatory, vasoconstrictive and anti-mitotic effects.[48] Topical corticosteroids can be

used as monotherapy or in combination with vitamin D3 analogues, dithranol or tar.[26] Topical corticosteroids are associated with tachyphylaxis and with well-described local side effects, such as the development of cutaneous atrophy, telangiectasias, striae, and perioral dermatitis. As tachyphylaxis can occur quite rapidly with topical corticosteroid therapy, intermittent treatment is advised for prolonged treatment.[26, 48]

Commercially available vitamin D3 analogues in the Netherlands were calcipotriol (Daivonex®), and calcitriol (Silkis®). Calcipotriol is not available anymore in the Netherlands. The antipsoriatic effect of vitamin D3 analogues can mainly be ascribed to inhibition of keratinocyte proliferation and induction of normal keratinocyte differentiation.[26, 47] Irritation of the skin is the most frequently observed adverse event, especially when used for flexural psoriasis and facial psoriasis.[47] Vitamin D3 analogues can be applied as monotherapy, as a combination therapy (calcipotriol/betamethasone dipropionate ointment and calcipotriol/betamethasone dipropionate gel) or intermittently and alternating with topical corticosteroids.[26, 47, 49, 50] Practical use in psoriasis patients usually involves combination therapy with topical corticosteroids.

Topical calcineurin inhibitors (tacrolimus ointment (Protopic®) and pimecrolimus cream (Elidel®)) are only approved for the treatment of atopic dermatitis, but are sometimes also prescribed for flexural psoriasis and psoriasis affecting the face.[47] Calcineurin inhibitors act by inhibiting the calcium-dependent signal transduction in T-cells. As a consequence, they inhibit the transcription and synthesis of inflammatory cytokines resulting in an anti-inflammatory effect.[48] The most frequent side effect is irritation of the skin.[47]

Dithranol (synonyms anthralin and cignolin) has been available since 1916.[26] The exact mechanism of action is unknown. Dithranol induces a cascade of free radicals in the skin, resulting in antiproliferative effects and a modulation of inflammation in psoriasis.[49] After the introduction of other topical therapies like corticosteroids and vitamin D3 analogues, dithranol was increasingly replaced by these agents because of dithranol's irritating and staining effects. Nevertheless, dithranol still is an important second-line therapy for psoriasis. Dithranol is mainly applied in the context of daycare or inpatient treatment.

Coal tar has been used in the treatment of dermatologic diseases for many decades. Its exact mechanism of action is unclear. A recent study in atopic dermatitis showed that coal tar activates the aryl hydrocarbon receptor (AHR), resulting in induction of epidermal differentiation.[26, 51, 52] Coal tar has antiproliferative effects and, like dithranol, modulates inflammatory events in psoriasis.[49] Coal tar is not a first choice therapy for psoriasis due to its odour and staining properties. However, it can be valuable in patients with pruritic psoriasis.[47]

Phototherapy

Phototherapy modalities applied for the treatment of psoriasis are broadband UVB (280-320 nm), narrowband UVB (emission peak at 311 nm) and UVA (320-400 nm) plus psoralens (PUVA). Photochemotherapy (PUVA) is the combined use of photosensitizing psoralens and UVA radiation. Different types of photochemotherapy exist, namely systemic (oral) PUVA and topical bath and cream PUVA.[53] Phototherapy induces several biological effects that probably contribute to its therapeutic effect in psoriasis. UV induced immunosuppression may account for the major part of the antipsoriatic effect.

Long-term UVB and PUVA phototherapy result in actinic damage and premature aging of the skin.[47, 53] The carcinogenic effect of long-term oral PUVA therapy with respect to the induction of squamous cell carcinoma of the skin and to a lesser extent basal cell carcinoma, is well established.[54, 55] However, the potential carcinogenic effect of UVB phototherapy and topical PUVA is controversial.[47, 53, 56-58] For adults with high UVB exposure levels, UVB may confer a modest increase in nonmelanoma skin cancer risk, but much less than that observed with PUVA.[47, 56] The risk of developing squamous cell carcinoma with PUVA therapy is further increased by the subsequent use of ciclosporin.[59] The risk of melanoma with long-term PUVA therapy might be increased as well.[26, 47, 60-62]

Narrow-band UVB proved more effective than broad-band UVB and is currently recommended as a first choice phototherapy for psoriasis.[47, 53, 63] PUVA is recommended in case UVB is not sufficiently effective.[47, 53] The use of long-term phototherapy, especially PUVA, has diminished in the last decades due to its cumulative carcinogenic potential. The practicability of phototherapy is sometimes limited by time and travel constraints on the part of the patient. Currently, it is not recommended to combine phototherapy with biologics, because of the risk of photocarcinogenesis.[53, 64-66]

Conventional systemic treatments

The conventional or classical systemic treatments most widely used for the treatment of plaque psoriasis are methotrexate, ciclosporin, acitretin and fumarates.

Methotrexate

Methotrexate (MTX) is the oldest drug used today for the systemic treatment of psoriasis and is widely used because of its high efficacy in all clinical variants of psoriasis. MTX is a folic acid analogue and competitively inhibits the enzyme dihydrofolate reductase (DHFR) and several other folate-dependent enzymes.[26, 47, 53] MTX inhibits the synthesis of thymidylate and purine nucleotides, which are required for DNA and RNA synthesis.

Inhibition of nucleic acid synthesis in activated T cells and in keratinocytes probably accounts for the antiproliferative and immunomodulatory effects of MTX. MTX is a slow-acting drug and it may take several weeks to achieve a complete clinical response. MTX is also effective for psoriatic arthritis.

There is some evidence that the concomitant administration of folic acid with MTX therapy may reduce side effects without affecting efficacy,[53, 67-69] and suppletion of folic acid is therefore advised.[47] The two most important side effects associated with MTX therapy are myelosuppression in the early phase of treatment and hepatotoxicity with high cumulative dosages of MTX. The most common side effects are subjective side effects like gastrointestinal complaints.

The combination of methotrexate and biologic agents used for psoriasis (etanercept, infliximab and adalimumab) is common in rheumatology. In psoriasis, this has not been systematically investigated, although some studies have shown greater efficacy with a similar safety profile with combination therapy.[70-81] There is increasing evidence that the combination of infliximab and low-dose methotrexate reduces antibody formation and related infusion reactions. This combination is therefore increasingly advised in patients with psoriasis.[47, 53, 64, 70] Whether this holds true for adalimumab as well is still under investigation.[47, 82]

Ciclosporin

The efficacy of ciclosporin was investigated in immune-mediated diseases like psoriasis after experiences obtained with ciclosporin in transplantation medicine. The efficacy of ciclosporin in the treatment of psoriasis supported the view that T-cell-mediated immunomodulation was important in the pathogenesis of psoriasis.[4] Ciclosporin binds to cyclophilin, a member of the family of intracytoplasmic proteins called immunophilins. This complex blocks the dephosphorylation of nuclear factor of activated T cells (NFAT) and the subsequent upregulation of IL-2 and IL-2 receptors, resulting in a decrease in the number of $CD4^+$ and $CD8^+$ T cells in the skin.[26]

Ciclosporin is indicated in patients with the most severe or therapy-resistant forms of psoriasis. Ciclosporin treatment can result in dramatic rapid improvement of psoriasis, but long-term use is limited by its cumulative toxicity.[26] Ciclosporin is most often used as a short-term therapy lasting 2-4 months to control flares of psoriasis. Treatment courses can be repeated at intervals. Ciclosporin therapy should not be given for more than 1-2 years.[4, 26, 47, 53] Discontinuation of ciclosporin treatment often leads to a relapse of psoriasis, especially with abrupt discontinuation.[4, 47, 53] Important side effects are nephrotoxicity, hypertension and malignancies (especially squamous cell carcinomas of the skin and lymphomas).[47, 83] Hyperlipidaemia is a frequently observed but unwanted side effect of ciclosporin as the cardiovascular risk in patients with psoriasis is already increased.

There are very limited data on the use of ciclosporin in combination with biologics.[76, 78, 84, 85] A small 24-week study showed that the addition of ciclosporin to etanercept seemed to be a safe and effective treatment for patients with psoriatic arthritis with uncontrolled cutaneous psoriasis.[84] Other etanercept/ciclosporin combination studies focused on the transition from ciclosporin to etanercept and showed that a short overlapping period may be useful to maintain disease control previously established by ciclosporin.[72, 86-88] Combination therapy with adalimumab has only been described in two reports.[81, 89] Because of the lack of data and possible shared toxicities of ciclosporin and biologics, specifically with regard to infections and malignancies, combination therapy should by applied with caution and preferably during short periods (e.g. as bridge therapy).[66, 90]

Acitretin

Acitretin is synthetic retinoid and a member of the retinoid family. Retinoids are naturally occurring molecules and also synthetic derivatives with structural and functional characteristics closely related to vitamin A. Retinoids exert their effects primarily by regulating gene transcription via intracellular nuclear receptors.[4, 26]

Retinoids have antiproliferative and immunomodulatory properties. However, the exact mechanism of action of acitretin is still not clearly understood. In the skin, acitretin reduces the proliferation and stimulates the differentiation of epidermal keratinocytes.[53] Acitretin has a special position within the group of systemic antipsoriatic therapies, as it is nonimmunosuppressive and can therefore also be applied in immunosuppressed patients with psoriasis.[4, 45]

Plaque-type psoriasis responds variably to acitretin. Therefore in these patients, acitretin is often used in combination with topical treatment or phototherapy to achieve sufficient efficacy. As monotherapy, acitretin is highly effective in erythrodermic and pustular psoriasis.[26,53]

Dose-dependent reversible mucocutaneous toxicity like dryness of mucosa and skin and cheilitis are the most commonly observed side effects of oral retinoids. At the same time, these side effects are also a parameter for the drug's bioavailability due to the fairly narrow therapeutic window of retinoids.[4, 26, 53] Hyperlipidaemia is a frequently observed but unwanted side effect of acitretin in patients with psoriasis. Acitretin is teratogenic and should be avoided in women of childbearing age.

Acitretin is unique to dermatology and data about the combination of acitretin and biologics are sparse. Gisondi et al. showed that a combined therapeutic regimen with etanercept 25 mg once weekly and acitretin 0.4 mg/kg daily was as effective as etanercept 25 mg twice weekly, and more effective than acitretin alone, suggesting that concomitant use of acitretin can lower the required dose of etanercept.[91] The safety profile was similar for the three groups. The effect of adding acitretin to a standard dose of etanercept (25 mg twice a week) was not investigated in this study. Small clinical case series have

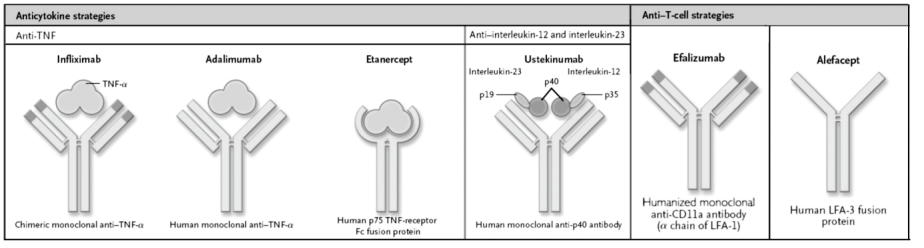


Figure 3. Biological therapies for psoriasis classified according to mechanism of action.[17]

also evaluated the use of etanercept, infliximab or adalimumab in combination with acitretin.[78, 87, 92, 93] In all cases, combination therapy resulted in better disease control.

Fumarates

Fumarates were specifically developed for the treatment of psoriasis.[47] Fumarates are not registered in the Netherlands. Fumarates are available in different preparations. Dimethyl fumarate (DMF) is considered to be the active ingredient.[53]
The mode of action of fumarates can be attributed to a number of effects. DMF inhibits the activity of the transcription factor NF-κB. This leads to an inhibition of the transcription of a variety of NF-κB-dependent intracellular mediators and adhesion molecules. DMF and its metabolite monomethyl fumarate inhibit the maturation of dendritic cells. DMF can induce apoptosis, particularly in activated T cells. Furthermore, there is evidence that monomethyl fumarate stimulates the shift of a Th1-type of immune response towards a Th2-type by stimulating the production of Th2 specific cytokines.[4, 47, 53]

Treatment of psoriasis with fumarates follows an established dosing regimen, with a slow increase in dose to improve tolerance, especially with regard to gastrointestinal complaints. The dose is increased until a clinical response is achieved. Thereafter tapering down to an individual maintenance dose is recommended. The most frequent side effects observed during treatment with fumarates are gastrointestinal complaints (particularly in the first weeks after initiation of therapy) and flushing.[4, 47, 53] Combination therapy of fumarates and biologics for psoriasis has not been systematically investigated.[53, 78]

Biologics

During the last decade a number of biological therapies have become part of the therapeutic arsenal for psoriasis. According to the United States Food and Drug Administration (FDA), biologics, also called biologicals, are components derived from living organisms used for the treatment, prevention or cure of disease in humans.[94, 95] The biologics prescribed for psoriasis are therapeutic proteins produced by recombinant

DNA technology, which selectively interfere in the pathogenesis of psoriasis.

The biologics that are approved and reimbursed for the treatment of psoriasis in Europe at this moment are etanercept (Enbrel®), infliximab (Remicade®), adalimumab (Humira®) and ustekinumab (Stelara®). The market authorization of efalizumab (Raptiva®) was withdrawn in February 2009 due to a risk of serious side effects. In November 2011, alefacept was voluntarily withdrawn from the market.

Table 1. Nomenclature of biological substances.

Stem	Indicating
Suffix	
-cept	Receptor molecules
-mab	Monoclonal antibodies
Infix	
-lefa-	lymphocyte function-associated antigen
-ner-	tumour necrosis factor
-k(i)-	interleukin
-l(i)-	immunomodulating
-u-	human
-xi-	chimeric
-zu-	humanized

The biological therapies for psoriasis can be classified according to their mechanism of action (Figure 3).[17, 26] The two main classes are the T-cell targeted therapies (alefacept and efalizumab) and the cytokine inhibitors (etanercept, infliximab, adalimumab and ustekinumab). The anti-cytokine therapies for psoriasis consist of the tumour necrosis factor-α (TNF-α) antagonists etanercept, infliximab and adalimumab and an inhibitor of interleukin (IL)-12 and IL-23, ustekinumab. The application for a marketing authorization for briakinumab (Ozespa®), another inhibitor of IL-12 and IL-23, was withdrawn in 2011 awaiting additional new data and analyses after a signal of a possible increased risk of major cardiovascular events (MACE).

The World Health Organization (WHO) has developed a nomenclature scheme for naming biologics, so that each substance would be recognized globally by a unique name (Table 1).[96, 97] In names of compounds related by structure and/or function, specific letter groups, called stems, are included to aid recognition by healthcare professionals.
Alefacept and etanercept are receptor molecules. The common stem for receptor molecules is 'cept', placed as a suffix. A preceding infix designates the target, which is lymphocyte function-associated antigen 3 ('-lefa-') in case of alefacept, and tumour necrosis factor ('-ner-') in case of etanercept. Efalizumab, infliximab, adalimumab, ustekinumab and briakinumab are monoclonal antibodies. The common stem for monoclonal antibodies is '-mab', placed as a suffix. The names of monoclonal antibodies are composed of a prefix, a substem A, a substem B and a suffix. Substem A (infix) indicates the target class (molecule, cell or organ). Substem B (infix) indicates the species on which the immunoglobulin sequence of the monoclonal antibody is based.

In the Netherlands, biological treatment was reimbursed for the treatment of patients with moderate to severe plaque psoriasis who had not responded to phototherapy, methotrexate (at a dose of 22.5 mg per week) *and* ciclosporin, or who had contra-indications to, or did not tolerate these therapies since 2005.[98] In September 2010, the reimbursement criteria were changed into moderate to severe plaque psoriasis with nonresponse, contraindications or intolerance to phototherapy and methotrexate (at a dose of 22.5 mg per week) *or* ciclosporin. Furthermore, a Psoriasis Area and Severity Index (PASI)[99] of at least 10 or a PASI ≥ 8 and a Skindex-29 score ≥ 35 (quality of life index)[100] is required since 2005.

T-cell inhibitors

Alefacept

Alefacept is a human fusion protein consisting of the extracellular CD2-binding portion of the human lymphocyte function-associated antigen-3 (LFA-3) linked to the Fc portion of human immunoglobulin G1 (IgG1). Alefacept interferes with T-cell activation by binding to the T-cell antigen CD2, thereby inhibiting the interaction between CD2 on T-cells and its ligand LFA-3 on antigen-presenting cells.[17, 101]

The recommended dose of alefacept was 7.5 mg given once weekly as an intravenous (iv) bolus or 15 mg given once weekly as an intramuscular injection in 12-week courses. The half-life of intravenously administered alefacept is approximately 270 hours. Antibodies to alefacept have been detected in some patients treated with alefacept. However, no correlation between antibody development and clinical response or adverse events was observed.

Common adverse events reported in randomized controlled trials (RCTs) were pharyngitis, chills, headache, pruritis and infection. The most common serious adverse events in RCTs were coronary artery disorder, cellulitis and myocardial infarction.[102] Treatment with alefacept results in a reduction in circulating total CD4+ and CD8+ T lymphocyte counts. Therefore, monitoring lymphocyte counts was an important safety measure.[53, 101]

Alefacept (Amevive®) was approved in only a few countries including the United States of America, Canada, and Switzerland. In November 2011, alefacept was voluntarily withdrawn from the market due to business needs.

Efalizumab

Efalizumab is a humanized monoclonal antibody. It is an IgG1 kappa (IgG1κ) immunoglobulin, containing human constant region sequences and murine light- and heavy-chain complementary determining region (CDR) sequences. Efalizumab binds specifically to the CD11a subunit of lymphocyte function-associated antigen-1 (LFA-1), a T-cell cell surface protein.[17, 26, 103] By this mechanism, efalizumab inhibits the binding of LFA-1 to intercellular adhesion molecule 1 (ICAM-1) on antigen-presenting cells, which

interferes with T-cell activation. Efalizumab also interferes with T-cell trafficking in the skin by blocking the adhesion of LFA-1 on circulating T-cells to ICAM-1 on endothelial cells, which normally allows T-cell migration into the skin.
The recommended dose of efalizumab was an initial single dose of 0.7 mg/kg body weight subcutaneously (sc) followed by weekly injections of 1.0 mg/kg body weight.[103] The half-life of efalizumab is approximately 5.5-10.5 days. Antibodies to efalizumab have been detected in some patients treated with efalizumab. However, antibody formation did not lead to clinically noteworthy adverse events or diminished clinical efficacy.

The most frequent adverse events observed during efalizumab therapy were mild to moderate dose-related acute flu-like symptoms including headache, fever, chills, nausea and myalgia.[103] Serious adverse events like serious infections, malignancies, thrombocytopenia, arthritis and flare of psoriasis have been observed with efalizumab therapy.[53, 64, 102, 103] Efalizumab was approved for psoriasis by the European Medicines Agency (EMA) in September 2004. The EMA withdraw its marketing authorization in February 2009 because of concerns about the development of progressive multifocal leukoencephalopathy (PML).

Cytokine inhibitors

Etanercept

Etanercept is a human fusion protein consisting of the extracellular ligand binding domain of the human 75-kilodalton (p75) tumour necrosis factor receptor linked to the Fc domain of human IgG1. Etanercept is a competitive inhibitor of TNF-α binding to its cell surface receptors, and thereby inhibits the biological activity of TNF-α.[53, 104] Etanercept also binds to members of the lymphotoxin family (LTα3 (also known as TNF-β) and LTα2β1).[64] TNF-α and lymphotoxin are pro-inflammatory cytokines that bind to two distinct cell surface receptors: the 55-kilodalton (p55) and 75-kilodalton (p75) tumour necrosis factor receptors.[104] The biological significance of lymphotoxin binding is unclear.[64, 105]

Etanercept was approved for plaque psoriasis by the EMA in September 2004. Other therapeutic indications of etanercept are rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis and paediatric plaque psoriasis. Etanercept, in contrast with adalimumab and infliximab, lacks efficacy in granulomatous diseases, such as Crohn's disease.[105, 106]
The recommended dose of etanercept for psoriasis is 25 mg sc administered twice weekly or 50 mg sc administered once weekly. Alternatively, 50 mg given twice weekly may be used for up to 12 weeks followed, if necessary, by a dose of 25 mg twice weekly or 50 mg once weekly. The half-life of etanercept is approximately 70 hours. Antibodies to etanercept have been detected in some patients. However, these antibodies have all been non-neutralizing and there appears to be no correlation between antibody development and clinical response or adverse events.

The most common adverse events reported in RCTs were injection-site reactions, headache and upper respiratory tract infections.[102] Serious adverse events like serious infections, malignancies, hepatitis B virus reactivation, congestive heart failure, demyelinating diseases, systemic lupus erythematosus/lupus-like syndrome and serious haematological reactions have also been reported with etanercept use and TNF-α blockers as a class.[53, 64, 104]

Infliximab

Infliximab is a chimeric human-murine IgG1 monoclonal antibody. Infliximab contains approximately 30% murine variable region amino acid sequence, which confers antigen-binding specificity to human TNF-α. The remaining 70% correspond to a human IgG1 heavy chain constant region and a human kappa light chain constant region.[64, 107]

Infliximab binds with high affinity to TNF-α, thereby inhibiting the functional activity of TNF-α. It was approved for plaque psoriasis by the EMA in September 2005. Infliximab is also approved for the treatment of rheumatoid arthritis, adult Crohn's disease, paediatric Crohn's disease, adult ulcerative colitis, paediatric ulcerative colitis, ankylosing spondylitis and psoriatic arthritis.[107]

The recommended dose of infliximab for psoriasis is 5 mg/kg iv at day 0 followed by additional 5 mg/kg infusions at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. The half-life of infliximab ranges from 8 to 9.5 days. Antibodies to infliximab may develop and have been associated with an increased frequency of infusion reactions. An association between development of antibodies to infliximab and reduced duration of response has also been observed.

The most common adverse events in RCTs were upper respiratory tract infections, headache, increased hepatic enzymes and infection.[102] Serious adverse events reported with infliximab use are mentioned above. In addition, serious infusion reactions and hepatobiliary events have occurred with infliximab use.[53, 64, 107]

Adalimumab

Adalimumab is a human IgG1 monoclonal antibody that binds to human TNF-α and neutralizes the biological function of TNF-α by blocking its interaction with the p55 and p75 cell surface TNF receptors.[53, 108]

Adalimumab was approved for plaque psoriasis by the EMA in December 2007. Other therapeutic indications of adalimumab are rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, adult Crohn's disease, paediatric Crohn's disease and ulcerative colitis.[108]

The recommended dose of Humira for psoriasis is an initial dose of 80 mg sc, followed by 40 mg sc given every other week starting one week after the initial dose. The half-life is of adalimumab is approximately 2 weeks. Formation of anti-adalimumab antibodies is associated with increased clearance and reduced efficacy of adalimumab.[82, 108]

The most commonly reported adverse events are infections (such as nasopharyngitis, upper respiratory tract infection and sinusitis), injection site reactions, headache and musculoskeletal pain.[108] Serious adverse events reported with adalimumab use are mentioned above.

Ustekinumab

Ustekinumab is a human IgG1κ monoclonal antibody to the shared p40 protein subunit of interleukin (IL)-12 and IL-23.[109] Ustekinumab was approved for psoriasis by the EMA in January 2009. Recently, ustekinumab was also approved for the treatment of psoriatic arthritis.[110] Ustekinumab inhibits the activity of IL-12 and IL-23 by preventing these cytokines from binding to their IL-12Rβ1 receptor expressed on the surface of immune cells.

The recommended dose of ustekinumab for psoriasis is an initial dose of 45 mg sc, followed by a 45 mg sc dose 4 weeks later, and then every 12 weeks thereafter. For patients with a body weight over 100 kg the initial dose is 90 mg, followed by a 90 mg dose 4 weeks later, and then every 12 weeks thereafter. The half-life of ustekinumab is approximately 3 weeks, ranging from 15 to 32 days. Antibodies to ustekinumab may develop. No apparent correlation of antibody development to injection site reactions was seen. Efficacy tended to be lower in patients positive for antibodies to ustekinumab.[109, 111, 112]

Common adverse events observed with ustekinumab use in RCTs included upper respiratory tract infection, nasopharyngitis, arthralgia, cough and headache.[64, 109, 111, 112] Serious infections and malignancies have been observed in the RCTs, but rates were low.[109, 111, 112]

Future therapies

Anti-cytokine therapies currently being tested in clinical trials are targeted at specific components of the IL-23/Th17 pathway, such as the p19 protein subunit of IL-23, the Th17 cytokine IL-17, the IL-17 receptor and the Th22 cytokine IL-22.[113] Secukinumab and ixekizumab, new monoclonal anti-IL-17A antibodies have already shown positive results in phase II trials.[114, 115] Moreover, brodalumab, an anti-interleukin-17-receptor monoclonal antibody, significantly improved plaque psoriasis in a phase II study.[116]

In addition, small molecules (i.e. low molecular-weight organic compounds) administered orally and targeting intracellular signaling pathways, like apremilast (phosphodiesterase-4 (PDE4) inhibitor)) and tofacitinib (Janus kinase (JAK) inhibitor), are currently being tested in clinical trials.[117-119] Topical preparations may also be produced from these molecules.[120]

Patent expirations of the currently available biologics in the coming years could lead to the development of less expensive generic agents, also called 'biosimilars'. Biosimilars could offer cost savings. However, it is difficult to prove that biosimilars are equal to the original biologics, due to the complexity of the molecule structures and the manufacturing process. Slight differences in the production process may have an important impact on the biologic functions of biosimilars. In particular the question about long-term efficacy and safety has to be answered. Therefore, the introduction of biosimilars might require studies investigating efficacy and safety.[121]

Psoriasis Area and Severity Index

The Psoriasis Area and Severity Index (PASI) was first described by Frederiksson in 1978.[99] The PASI is a clinical measure of psoriasis severity and is the most commonly used clinical measure in psoriasis research.[122]

For calculation of the PASI, four body areas are assessed: the head (h), the upper extremities (u), the trunk (t) and the lower extremities (l), corresponding to 10%, 20%, 30% and 40% of the total body surface area, respectively. The skin area affected by psoriasis within each body area (A_h, A_u, A_t, and A_l) is given a numerical value: 0 = no involvement; 1 = 0-<10%; 2 = 10-<30%; 3 = 30-<50%; 4 = 50-<70%; 5 = 70-<90% and 6 = 90-100%. Within each body area, the severity of three target signs, erythema (E), induration (I) and desquamation (D), is assessed on a five-point scale: 0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe. The PASI is then calculated using the formula $0.1(E_h + I_h + D_h)A_h + 0.2(E_u + I_u + D_u)A_u + 0.3(E_t + I_t + D_t)A_t + 0.4(E_l + I_l + D_l)A_l$.

The PASI ranges from 0 (no disease) to 72 (maximum score), with a higher score representing greater disease severity. However, in practice only half of the scale is used.

There is no generally accepted definition of mild versus moderate to severe psoriasis.[46] According to the 'rule of tens', severe psoriasis is defined as body surface area (BSA) involved of at least 10 per cent, PASI of at least 10, or Dermatology Life Quality Index (DLQI) of at least 10.[99, 123] This cut-off point of 10 has been widely adopted in research and by healthcare organizations and regulatory authorities from different countries. A PASI of at least 10 is often one of the requisites for inclusion in RCTs with biologics.

In the Netherlands, biological therapies are reimbursed for patients with moderate to severe plaque psoriasis, defined as a PASI of at least 10 or a PASI ≥ 8 and a Skindex-29 score ≥ 35 (quality of life index).

The PASI 75 response, which means at least 75 percent improvement in PASI from baseline, is the most commonly used primary efficacy outcome measure in psoriasis research at the moment and is accepted as a clinically meaningful improvement of psoriasis.[53]

1.3 Registries

Introduction

The efficacy and safety of biological treatments for psoriasis has been established in randomized placebo-controlled trials (RCTs) and open-label extension studies.
RCTs are the gold standard for evaluating the efficacy of new drugs.[124] However, randomized controlled trials cannot answer all questions about a certain therapy. Increasingly, questions in medical research are investigated in observational studies. One form of observational studies are cohort studies, with data being recorded in registries.[125]
Registries provide complementary information to RCTs about the effectiveness and safety of biologics for psoriasis in daily practice.[126, 127]
Data from RCTs may not reflect the daily practice situation due to strict inclusion and exclusion criteria, eligibility criteria that differ from reimbursement criteria, treatment according to a predefined protocol and washout periods.[89, 128, 129] This limits the generalizability of the results, whereas enrolment in registries does reflect daily clinical practice.
RCTs are often underpowered and of too short duration to detect rare or long-term adverse events.[124] Open-label extension studies have provided some long-term information, but lack a control group. In addition, open-label extension studies are still performed in a selected patient group initially included in RCTs, with mostly only responders being allowed to enter the open-label extension phase. Observational studies offer the advantage of the ability to include larger numbers of patients and are suitable for long-term follow-up.

Besides monitoring long-term safety, registries can provide information on many aspects of clinical effectiveness of biological therapies in daily practice, including the effectiveness in the short term and the long term, consecutive biological treatment, nonstandard dosing regimens, combination therapy with conventional systemic therapies, transitioning from conventional systemic therapies to biologics and the influence of prior exposure to biologics. Furthermore, registries offer the possibility of studying many other aspects of biological treatment, including cost-effectiveness and impact on the quality of life, which is important from a societal perspective and for the optimum choice of treatment.

Psoriasis registries

After the registration of biologics for various indications including psoriasis, rheumatologic diseases and inflammatory bowel disease, registries were set up in several countries to collect long-term safety and effectiveness information on this new generation of drugs.
In rheumatology, there is a large number of registries covering different indications.[130]

In the Netherlands, the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry was founded in 2003 to prospectively evaluate the use of biologics in patients with rheumatoid arthritis.[131] Patients with psoriasis, however, differ in several aspects from patients with rheumatologic diseases or inflammatory bowel disease, such as in the treatments received prior to the initiation of biological treatment, types and doses of biologics prescribed, body weight and in the nature of the disease itself. Therefore, psoriasis-specific registries were established.[132]
Some psoriasis registries solely collect information on biological therapies, whereas others also include patients on classical systemic therapies. The comparator group of patients treated with classical systemic therapies aids in attributing causality in adverse events detected and in studying the relative effectiveness of biological and conventional systemic treatments. In addition, such registries provide long-term information on the safety and effectiveness of classical systemic therapies for psoriasis, which have only been sparsely investigated until now.[132]

In Europe, there are several local and national registries that collect data on systemic treatments for psoriasis. These registries differ in certain aspects of study design and methodology, funding and voluntarily or compulsory participation.[133]
National and international collaboration is present in this field of research. Recently, ZonMW has awarded a grant for the establishment of a Dutch national registry to collect data on the use of biologics and other systemic treatments for psoriasis. This project is a collaboration between the Dutch Society of Dermatology and Venereology (NVDV), the Radboudumc and the Academic Medical Center (University of Amsterdam).
In Europe, an international collaborative network of independent registries of patients with psoriasis treated with systemic agents, named Psonet, was established.[133] Systemic therapies can involve both conventional and biological agents or are restricted to biological agents. Currently, registries from 13 countries are participating in Psonet. By combining data from multiple registries, analyses with greater power can be performed.

As the role of registries in studying the benefits and harms of medical interventions is increasingly being recognized, quality standards regarding various aspects of registries have been formulated.[134] Furthermore, criteria for reporting observational studies have been formulated, named the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria.[125]

Continuous Assessment of Psoriasis Treatment Use Registry (CAPTURE)

Right after the registration and reimbursement of etanercept and efalizumab in the Netherlands, a registry was set up at the department of Dermatology of the Radboudumc,

with the aim to collect effectiveness, safety, quality of life and cost-effectiveness information on all patients with psoriasis treated with biologics in daily practice.[135] The first patient was enrolled in February 2005. In 2008, a registry collecting data on various aspects of childhood psoriasis was founded. At that time, the registry was named 'CAPTURE', an acronym for Continuous Assessment of Psoriasis Treatment Use Registry. The registry concerning biological treatment was named 'Bio-CAPTURE' and the registry concerning childhood psoriasis was named 'Child-CAPTURE'.[136, 137]
Moreover, in 2010 a registry with a similar design and methodology was set up, collecting information on patients with psoriasis treated with methotrexate (MTX-CAPTURE). This registry can serve as a comparator for the Bio-CAPTURE registry and will be an important source of information on the effectiveness and safety of methotrexate.

Data collected in the Bio-CAPTURE registry include demographics, medical history, comorbidities, previous treatments for psoriasis, type of biologic used, doses of biologics used including dose adjustments, concomitant therapies, adverse events and parameters for effectiveness, quality of life, treatment satisfaction and costs.
Since 2010, a network consisting of the department of Dermatology of the Radboudumc and 8 nonacademic dermatology departments has been established. All participating centres contribute to the Bio-CAPTURE registry. Additional centres will be recruited in the future. By combining data, analyses can be performed in larger numbers of patients and comparisons can be made between academic and nonacademic patients.

Questions to be answered at the start of the studies included in the present thesis were the following: what is the long-term efficacy and safety of biological therapies for psoriasis in daily practice? What is the efficacy and safety of consecutive biological treatment regimens? What is the efficacy and safety of dose escalation or combination therapy in patients with insufficient efficacy? Is there a difference in efficacy between biologic-naïve and non-naïve patients? What is the clinical relevance of repeated laboratory investigations?
At present, the registries are still running and the inclusion of patients is still ongoing. In the current thesis, the outcomes from the Bio-CAPTURE registry are described.

1.4 Outline of the thesis

There are many unanswered questions about the long-term efficacy and safety of biological therapies for psoriasis. Observational studies are an important source of information for evaluating these questions. This thesis concerns the outcomes of a prospective observational study investigating the efficacy and safety of biological treatments for psoriasis in daily clinical practice. Data are extracted from the Bio-CAPTURE registry (Continuous Assessment of Psoriasis Treatment Use Registry concerning biologics), that was founded in 2005.

Main study objective

To prospectively investigate the long-term efficacy and safety of biologics in the treatment of patients with moderate to severe psoriasis in daily clinical practice.

Research questions

Part II Long-term efficacy and safety of biologic treatment for psoriasis in daily practice

1. What is the long-term efficacy of biologics for psoriasis in daily practice?
2. Is consecutive treatment with a second biologic therapy effective and safe? Is there an influence of biologic-naïvety versus non-naïvety on the efficacy results?
3. What is the efficacy and safety of adalimumab dose escalation or combination therapy with methotrexate?
4. What is the influence of different analytical methods on the efficacy results?
5. What is the safety profile of biologic treatment for psoriasis with extended exposure?

Part III Monitoring of biologic treatment

6. Is there a difference in time to first NMSC and the incidence of NMSC between patients with psoriasis and patients with rheumatoid arthritis treated with TNF-inhibitors?
7. Is monitoring with regard to laboratory investigations needed in patients with psoriasis with extended exposure to etanercept or adalimumab?

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Part II

Long-term efficacy and safety of biologic treatment for psoriasis in daily practice

Chapter 2

Long-term efficacy of etanercept for psoriasis in daily practice

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Long-term efficacy of etanercept for psoriasis in daily practice

Since the approval and reimbursement of etanercept treatment for psoriasis in Europe, this agent has been prescribed in daily practice for the treatment of patients with psoriasis. However, daily practice efficacy data on etanercept for psoriasis are limited to 3 years of treatment.[1-3] Although most patients benefit from this therapy, some patients discontinue etanercept treatment due to lack of efficacy, loss of efficacy, adverse events or other reasons.

The purpose of our study was to describe the long-term efficacy of etanercept for psoriasis in real-world practice, as opposed to the selected patient population and short duration of randomized controlled trials (RCTs). Therefore, a prospective patient registry was started in 2005, enrolling all patients starting biological treatment for psoriasis in the dermatology outpatient department of the Radboud University Nijmegen Medical Centre. This analysis involved all consecutive patients who were enrolled in the registry at the time of initiation of a (new) biologic therapy between February 2005 and February 2011.

Efficacy was expressed as the percentage of patients achieving PASI 50, PASI 75 or PASI 90, i.e. reductions of at least 50%, 75% and 90%, respectively, in Psoriasis Area and Severity Index (PASI) compared with baseline. Where patients received more than one treatment episode of etanercept, efficacy was analysed per treatment episode. Restarting etanercept treatment after an interruption lasting 6 months or longer constituted a new treatment episode. An observed values (as-treated) analysis was performed, which means that all available PASI data at predefined time points according to the length of follow-up were analysed.[4]

In this cohort, 152 patients were treated with etanercept during 158 treatment episodes (Figure 1). Ninety-five patients were male (62%). The mean ± SD age at the start of etanercept treatment was 47.8 ± 11.5 years. From this cohort, 114 patients completed 1 year of treatment, 76 completed 2 years, 52 completed 3 years, 34 completed 4 years, and 16 completed 5 years of therapy.
In daily practice, two etanercept dosing regimens were used for the first 12 weeks: 25 mg twice weekly (25 treatment episodes (16%)) or 50 mg twice weekly (133 treatment episodes (84%)). In the treatment period thereafter, (temporary) dosage adjustments could be made according to the opinion of the treating physician. Patients were allowed to use concomitant topical or systemic therapies when indicated. The mean ± SD weekly dose of etanercept was 68.3 ± 19.8 mg.

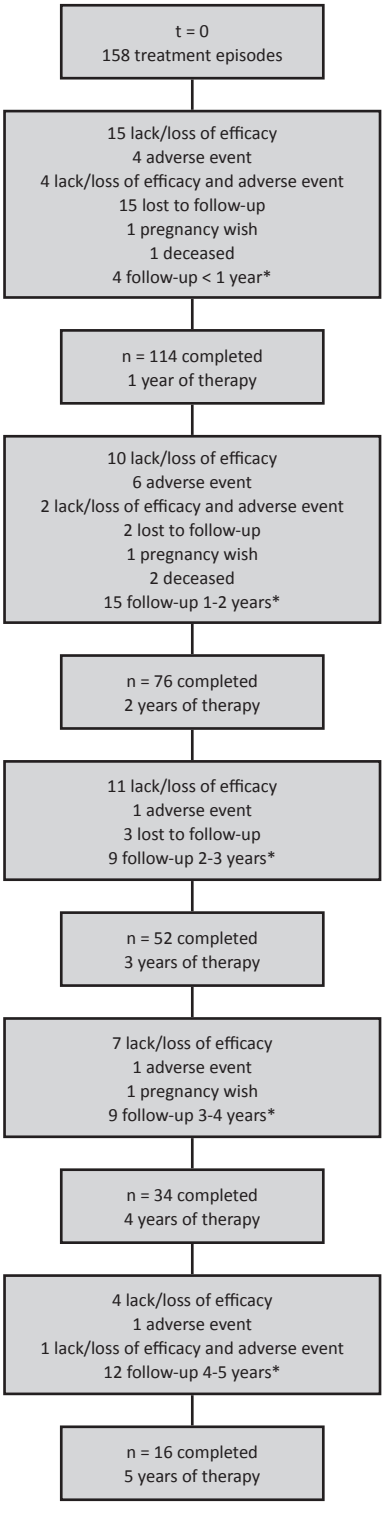

Figure 1. Patient disposition.
*These patients were actively being treated with etanercept, but their follow-up did not reach the subsequent evaluation time point.

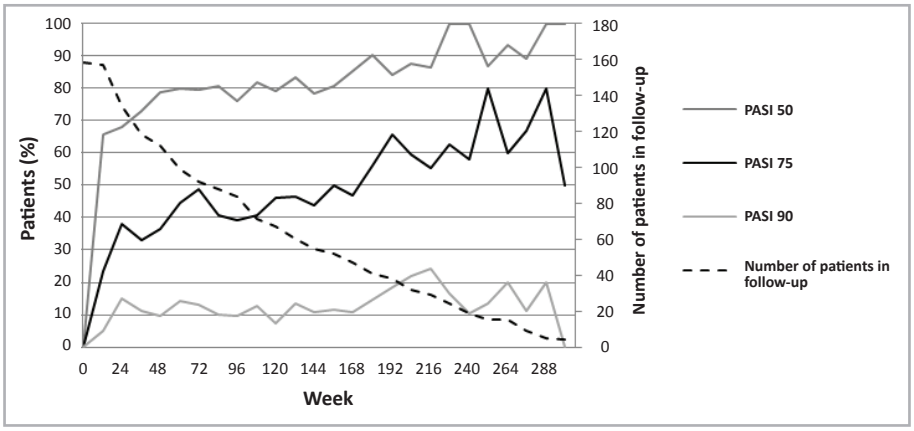

Figure 2. PASI 50, PASI 75 and PASI 90 response in patients with psoriasis treated with etanercept in daily practice, observed values analysis.

Fifty-one etanercept treatment episodes (32%) were combined with at least one concomitant systemic antipsoriatic therapy to prevent a flare of psoriasis when transitioning from the systemic treatment to biologic treatment, as add-on therapy during biologic treatment because of inadequate response or worsening of psoriasis, or as a continuous concomitant therapy. Five etanercept treatment episodes were consecutively combined with two different systemic antipsoriatic therapies. Concomitant systemic treatments consisted of methotrexate (n = 29), acitretin (n = 14), ciclosporin (n = 10), fumarates (n = 2) and mycophenolate mofetil (n = 1).

Figure 1 shows the disposition of the patients at 1-yearly evaluation time points. Forty-seven treatment episodes (30%) were discontinued due to loss of efficacy, 13 (8%) due to adverse events, 7 (4%) due to a combination of loss of efficacy and adverse events, 3 patients (2%) died and 3 patients (2%) discontinued etanercept treatment because of a desire for pregnancy. In addition, 20 patients (13%) were lost to follow-up.

Efficacy results are presented in Figure 2. For one patient, the efficacy of etanercept could not be analysed, as this patient died of myocardial infarction 4 days after the start of etanercept. At week 12, 103 (65.6%), 37 (23.6%) and eight (5.1%) treatment episodes resulted in PASI 50, PASI 75 and PASI 90, respectively. At week 24, these figures were 91 (67.9%), 51 (38.1%) and 20 (14.9%), respectively. A PASI 75 response was achieved in 41 (36.6%) treatment episodes at week 48, 29 (40.8%) at week 108, 26 (50.0%) at week 156, 19 (59.4%) at week 204 and nine (60.0%) at week 264. The PASI 50 and PASI 90 responses are presented in Figure 2.

The response rates in this study in patients treated with etanercept in clinical practice are lower than in RCTs, a finding which has been described previously.[5-9] The eligibility criteria in the Netherlands requiring ineffectiveness, intolerance or contraindications to classic systemic therapies and ultraviolet (UV) B or psoralen plus UVA (PUVA) therapy might account for a more therapy-resistant group of patients treated with biologics in daily practice compared with RCTs. Patients in daily practice also have comorbidities and comedication, which can negatively influence the efficacy of etanercept. On the other hand, the analysis performed in this study is less conservative than the intention-to-treat analysis used in RCTs and introduces a bias towards too favourable efficacy outcomes.[3]

In conclusion, observational research provides data that reflect clinical reality and generates additional evidence to RCTs that can be of added value for guidelines. Long-term efficacy of etanercept for psoriasis in daily practice is substantial, but lower than in long-term extension studies of RCTs.[10]

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Chapter 3

Switching from etanercept to adalimumab is effective and safe: results in 30 patients with psoriasis with primary failure, secondary failure or intolerance to etanercept

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Abstract

Background

Knowledge on the sequential treatment of psoriasis with biologics with regard to efficacy and safety is sparse. This also applies to the efficacy and safety of adalimumab in patients previously treated with etanercept. The relationship between the reasons for discontinuation of etanercept and the response to adalimumab is not clear in psoriasis.

Objectives

To evaluate the efficacy and safety of adalimumab in patients with psoriasis with primary failure, secondary failure or intolerance to etanercept in daily practice.

Methods

Data were extracted from two prospective registries from all patients with psoriasis with failure on etanercept, who switched to adalimumab therapy. Thirty patients fulfilled these criteria. All patients were naïve to biologics when etanercept was initiated. Primary endpoints were the percentage of patients achieving a 50% or 75% improvement of the baseline Psoriasis Area and Severity Index (PASI 50 and PASI 75, respectively) at week 12, 24 and 48. Secondary endpoints were the percentage of patients achieving PASI 90, the mean percentage improvement in PASI from baseline and the adverse event rate.

Results

Compared with the baseline PASI before the start of etanercept, the mean percentage improvement in PASI and the PASI 50/75/90 response rates to adalimumab until week 48 were comparable to those achieved with etanercept. In the patients failing on etanercept, PASI 75 was achieved by 27%, 36% and 54% at week 12, 24 and 48 of adalimumab treatment, respectively. The majority of patients showed a beneficial response to adalimumab, irrespective of the reason for discontinuation of etanercept. Previous treatment with etanercept did not increase the adverse event rate nor change the nature of the side effects.

Conclusions

Adalimumab seems to be an effective and safe treatment option for patients with psoriasis who failed on etanercept treatment irrespective of the reason for discontinuation.

Introduction

The introduction of antitumour necrosis factor-α (anti-TNFα) agents has made an important contribution to the therapeutic arsenal for patients with moderate to severe psoriasis. However, a proportion of patients do not benefit from anti-TNFα treatment. Some patients fail to achieve an initial response to an anti-TNFα agent (primary failure), others lose efficacy during the course of therapy (secondary failure) or experience adverse events (intolerance).[1-4]

As the biologics are often prescribed as last treatment options, knowledge about consecutive biologic treatments for psoriasis concerning efficacy and safety is very important. However, this information and especially long-term information is sparse. In some short-term or small studies adalimumab in different dosing regimens has been shown to be effective and well tolerated in patients with psoriasis refractory to various other biologic treatments and/or other systemic therapies.[3, 5-8] Reports on small cohorts of patients who successfully switched from etanercept to adalimumab have been published.[5, 6] The relationship between the reasons for failure on etanercept and the response to adalimumab has not been investigated previously.

In the present prospective study we describe the efficacy and safety of 48 weeks of adalimumab treatment in 30 patients who failed etanercept treatment in daily practice.

Patients and methods

Patients

All patients who receive treatment with biologics for psoriasis in the departments of Dermatology of the Radboud University Nijmegen Medical Centre and the Academic Medical Center (University of Amsterdam) are enrolled in a prospective patient registry, in which daily practice efficacy and pharmacovigilance data of these therapies are collected.[5, 9-11] Data were extracted on all patients treated with etanercept for an indefinite period of time, who subsequently switched to adalimumab because of primary failure or secondary failure of etanercept, intolerance to etanercept or other reasons. All patients were naïve to biologics when etanercept was initiated.

All patients fulfilled the reimbursement criteria for treatment with a biologic at the time of the start of etanercept therapy, e.g. they had failed to respond to phototherapy, methotrexate and ciclosporin in the past, or they had a contraindication to, or were intolerant of these treatments. In addition, a Psoriasis Area and Severity Index (PASI)[12] of at least 10 was required at the time of screening.

Protocol

Before treatment, a chest X-ray and a purified protein derivative skin test were performed

to exclude tuberculosis. A general urine and blood screening was performed in each patient. There were no known contraindications as per label.
After 12 weeks of biologic treatment, the guideline of the Dutch Society of Dermatology and Venereology and the Dutch reimbursement guideline require the achievement of a 50% improvement of the baseline PASI (PASI 50). Patients who did not achieve PASI 50 had to discontinue biologic treatment.

For etanercept, two dosing regimens were used. Twenty-three (77%) patients were treated with etanercept 50 mg subcutaneously twice weekly for at least 12 weeks. Seven (23%) patients were treated with etanercept 25 mg subcutaneously twice weekly for at least 12 weeks. Adalimumab was administered according to the label for at least 12 weeks. After these 12 weeks, patients were treated according to the opinion of the treating dermatologist, including dosage increments or dosage reductions in the case of etanercept (dose ranging from 50 mg per week to 100 mg per week) and shortening of the treatment interval in the case of adalimumab (40 mg every 10 days or 40 mg per week). No adjustments according to body weight were made.
Patients were seen every 12 weeks. Demographic data were documented at the time of screening and PASI scores and adverse events were prospectively collected at each hospital visit. Interpolated PASI data derived from the two closest visits and extrapolated PASI data up to maximal 7 days of extrapolation were used when visits did not occur at the indicated time points.
Patients started adalimumab treatment at different time points before the moment of analysis. Therefore the amount of available PASI data from patients treated with adalimumab decreases over time according to the length of treatment or the cessation of treatment.

Analysis
All patients who were treated with etanercept followed by adalimumab between September 2002 and January 2010 were included for analysis.

Demographics
Demographic data and patients characteristics were recorded and expressed as numbers (percentages) and means (± SD).

Primary failure, secondary failure and intolerance
Failure on etanercept was categorized into primary failure, secondary failure and intolerance. Primary failure on etanercept was defined as an insufficient response (patients not achieving PASI 50) at week 12.[3, 6] Secondary failure on etanercept was defined as the loss of response in a patient who achieved a PASI 50 response at week 12. Intolerance was defined as cessation of treatment caused by side effects.

Primary failure on adalimumab was defined as an insufficient response (patients not achieving PASI 50) at week 12, relative to the original baseline.
The response to consecutive treatment with adalimumab was investigated in the total group and in the subgroups with primary failure, secondary failure or intolerance to etanercept.

Efficacy

Treatment efficacy was analysed at indicated time points, i.e. week 12, 24 and 48 of each treatment. Primary endpoints were the percentage of patients achieving at least PASI 50 and PASI 75. Secondary endpoints were the percentage of patients achieving PASI 90 and the mean percentage improvement in PASI from baseline at the indicated time points. The response to adalimumab was compared with the response to etanercept in the same patients, each patient serving as his or her own control.
The response to adalimumab was evaluated in comparison with the baseline PASI for adalimumab (course baseline) and with the baseline PASI for etanercept (original baseline).[4, 13, 14] In addition, the mean best PASI obtained during etanercept and adalimumab therapy and the mean last PASI obtained with etanercept, irrespective of the time point, were calculated.[14]
The correlation between the duration of the transition interval and the subsequent response to adalimumab was investigated, as well as the correlation between the etanercept treatment duration and the response to adalimumab.

Safety

The adverse event rate was a secondary endpoint. Reported adverse events were analysed and categorized in predefined categories. The adverse event rate was expressed per patient-year exposed to etanercept and adalimumab, respectively.

Statistics

McNemar's test was performed to analyse the differences in the PASI 50 and PASI 75 response rates at week 12 during etanercept and adalimumab treatment. The Spearman correlation coefficient was calculated to analyse correlations. $P < 0.05$ was considered statistically significant.

Results

Demographics

Nineteen patients from the Radboud University Nijmegen Medical Centre and 11 patients from the Academic Medical Center were treated with etanercept as the first biologic therapy followed by adalimumab. Nineteen patients (63%) were male and the mean

Table 1. Demographics and patient characteristics (n = 30).

Demographics and patient characteristics	
Male, n (%)	19 (63.3)
Age (years)	
Mean (± SD)	51.5 (12.4)
Range	29-75
Duration of psoriasis (years)	
Mean (± SD)	26.3 (11.5)
Range	10-48
Psoriatic arthritis, n (%)	9 (30.0)
Other comorbidities, n (%)	23 (76.7)
BMI (kg/m^2), mean (± SD)	29.5 (7.1)
Obesity (BMI > 30), n (%)	14 (46.7)
Diabetes, n (%)	8 (26.7)
Hypertension, n (%)	12 (40.0)
Hyperlipidaemia, n (%)	9 (30.0)
Myocardial infarction, n (%)	2 (6.7)
Cerebrovascular disease, n (%)	1 (3.3)
Previous therapies, n (%)	
UVB	29 (96.7)
Psoralen plus UVA	14 (46.7)
Methotrexate	28 (93.3)
Ciclosporin	23 (76.7)
Acitretin	20 (66.7)
Fumarates	13 (43.3)

BMI, body mass index; UV, ultraviolet.

age was 51.5 (± 12.4) years (Table 1). The mean duration of psoriasis was 26.3 (± 11.5) years. Nine patients (30%) had concomitant psoriatic arthritis and 23 patients (77%) had one or more other comorbidities. The mean number of different systemic therapies that patients had used before the start of etanercept was 4.2 (± 1.3).

Treatment characteristics

All patients had moderate to severe psoriasis with a mean baseline PASI of 17.7 (± 8.6) at the start of etanercept (original baseline) (Table 2). The mean treatment duration with etanercept was 2.1 (± 1.3) years. The number of patient-years for etanercept was 64.2.

The time between the cessation of etanercept and the introduction of adalimumab varied in duration from 0 days to 1.8 years (mean 1.9 ± 5.2 months). One patient continued methotrexate therapy throughout the transition period and another patient was treated with dithranol. The other patients did not receive any systemic or dithranol therapy during the transition period.

Table 2. Treatment characteristics.

	Etanercept (n = 30)	**Adalimumab** (n = 30)
Baseline PASI		
Mean (± SD)	17.7 (8.6)	10.7 (4.0)
Range	5.9 – 39.0	3.0 – 19.4
Duration of treatment (years)		
Mean (± SD)	2.1 (1.3)	1.1 (0.4)
Range	0.2 – 5.7	0.6 – 2.2
Follow-up, patient-years	64.2	33.9
Concomitant therapy*, n		
Methotrexate	6 (3 days; 3 weeks; 2 months; 3 months; 8.4 months; 1 year)	2 (6 months; 9.2 months)
Ciclosporin	2 (4.6 months; 3.3 weeks)	0
Acitretin	2 (12 days; 9 months)	0
Fumarates	1 (2 months)	0
UVB	0	1
Dithranol	2 (2.2 months; 5 weeks)	3 (1 month; 7.4 weeks; 4.4 months)
Mean weekly dose (mg)	73.4	23.0

*Duration of concomitant therapy is shown in parentheses. PASI, Psoriasis Area and Severity Index.

The mean baseline PASI before the initiation of adalimumab (course baseline) was 10.7 (± 4.0). At the time of analysis, the mean adalimumab treatment duration was 1.1 (± 0.4) years. The exposure rate for adalimumab was 33.9 patient-years.

Eleven patients (37%) used concomitant systemic and/or dithranol therapy for their psoriasis during etanercept treatment (Table 2). Five patients (17%) received additional systemic and/or dithranol treatment during adalimumab treatment. In most patients the additional systemic therapies were temporarily applied.

Taking into account the dosage increases and the treatment interruptions that occurred, the mean weekly dose was 73.4 mg for etanercept and 23.0 mg for adalimumab. The mean weekly dose of etanercept in the group of 14 obese patients was 71.1 mg and in the 16 nonobese patients 75.8 mg. The mean weekly dose of adalimumab in the obese patients was 24.0 mg and in the nonobese patients 22.1 mg.

Primary failure, secondary failure and intolerance

Eleven patients were primary nonresponders to etanercept and 14 patients were secondary nonresponders (Figure 1). Three patients discontinued etanercept because of intolerance to this agent. The two remaining patients did not fail etanercept treatment according to the predefined terms, but they were dissatisfied with the effect of etanercept in the long term.

Of the eleven primary nonresponders to etanercept, six were primary responders to

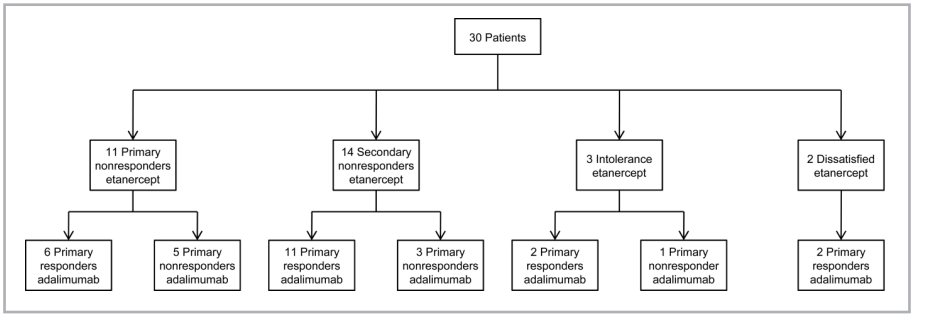

Figure 1. Results of etanercept and adalimumab treatment in the 30 patients with psoriasis.

adalimumab and five were primary nonresponders to adalimumab as well (Figure 1).
Eleven out of 14 secondary nonresponders to etanercept were primary responders to adalimumab and three patients were primary nonresponders to adalimumab. Of the three patients who discontinued etanercept because of intolerance, two were primary responders and one patient was a primary nonresponder to adalimumab. The remaining two patients who were dissatisfied with the effect of etanercept achieved PASI 50 at week 12 of adalimumab treatment.
Four out of 18 patients who were primary responders to etanercept experienced primary therapeutic failure on adalimumab (not shown in Figure 1). Fourteen patients achieved PASI 50 at week 12 on etanercept as well as adalimumab.
Relative to the original baseline, nine patients failed to achieve PASI 50 at week 12 with adalimumab and were hence defined as primary nonresponders to adalimumab.
Twenty-eight patients (93%) were still being treated with adalimumab at the moment of evaluation. Of the two patients who discontinued adalimumab treatment, one patient was a primary nonresponder and the other patient was a secondary nonresponder.
Seven out of 11 (64%) primary nonresponders to etanercept and five out of nine (56%) primary nonresponders to adalimumab were obese. Three out of 5 (60%) primary nonresponders to both drugs were obese.

Efficacy

The mean best PASI obtained during etanercept therapy was 5.0 (± 3.6) at a mean treatment duration of 1.2 (± 1.0) years (range 30.0 days – 4.0 years) (Figure 2). The mean last PASI on etanercept was 10.2 (± 4.1) at a mean treatment duration of 2.1 (± 1.3) years (range 2.7 months – 5.5 years). The mean best PASI achieved with adalimumab until the moment of evaluation was 4.2 (± 3.8), at a mean treatment duration of 6.0 (± 3.3) months (range 30.0 days – 1.0 year).
When the response to adalimumab is expressed in relation to the course baseline, the mean percentage improvement in PASI achieved at week 12, 24, 36 and 48 is less than the improvement achieved during etanercept treatment (Figure 3). However, when the

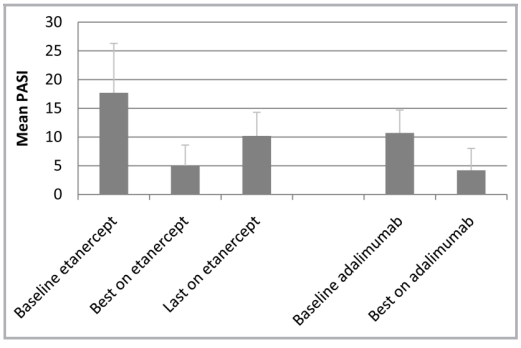

Figure 2. Values shown are the mean (± SD) baseline PASI before the start of etanercept (original baseline), the mean (± SD) best PASI achieved during etanercept therapy, the mean (± SD) last PASI on etanercept, the mean (± SD) baseline PASI before the start of adalimumab (course baseline) after a transition period and the mean (± SD) best PASI achieved with adalimumab until the moment of evaluation, irrespective of the time point.

response to adalimumab is represented in relation to the original baseline, there is more improvement in PASI during adalimumab therapy than during etanercept therapy.
During etanercept treatment, 18 patients (60%) achieved PASI 50 at week 12 (Figure 4). The percentage of patients having a PASI 50 response to adalimumab at week 12 in comparison to course baseline and original baseline was 30% (n = 9) and 70% (n = 21), respectively. PASI 75 was achieved at week 12 in 13% (n = 4), 13% (n = 4) and 27% (n = 8) of patients in the three different categories.

At week 24, 58% (n = 15), 50% (n = 14) and 61% (n = 17) of patients obtained a PASI 50 response in the etanercept, adalimumab vs. course baseline and adalimumab vs. original baseline categories, respectively (Figure 5). Nineteen percent (n = 5), 7% (n = 2) and 36% (n = 10) of patients in the three different categories, respectively, achieved PASI 75.
At week 48, 79% (n = 19), 54% (n = 7) and 77% (n = 10) of patients in the three different categories achieved PASI 50 (Figure 6). Twenty-five percent (n = 6), 23% (n = 3) and 54% (n = 7) of patients achieved PASI 75.
During etanercept therapy, one patient achieved PASI 90 at week 12 and one patient achieved PASI 90 at week 24. In comparison to the course baseline, a PASI 90 response to adalimumab was obtained by four (13%) and two patients (15%) at week 12 and 48, respectively. In comparison to the original baseline, a PASI 90 response to adalimumab was achieved by three (10%), two (7%) and two (15%) patients at week 12, 24 and 48, respectively.

The differences in the percentages of patients achieving PASI 50 and PASI 75 at week 12 of etanercept and adalimumab treatment were not statistically significant. There was no correlation between the duration of the transition interval and the subsequent response to adalimumab, or between the etanercept treatment duration and the response to adalimumab (reduction (%) in PASI at week 12 and 24).

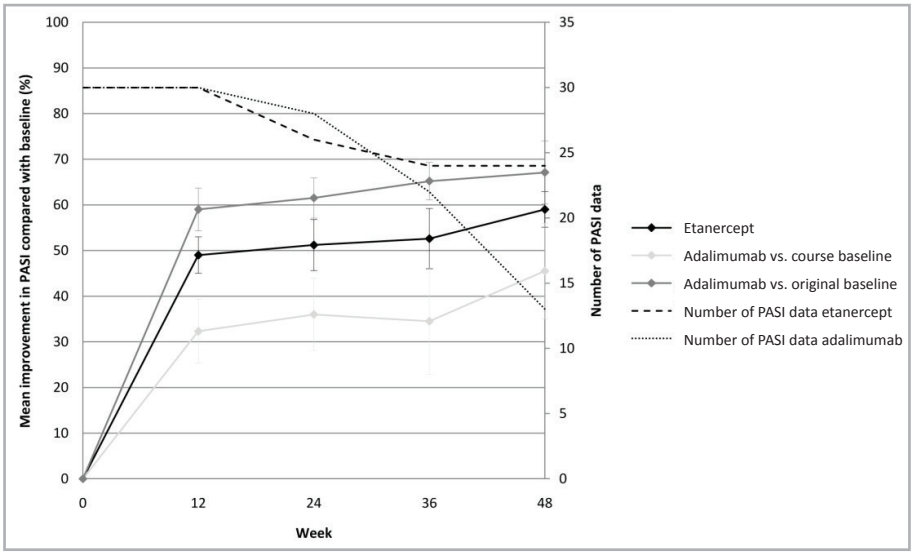

Figure 3. Mean (± SEM) improvement in PASI during etanercept therapy and adalimumab therapy at week 12, 24, 36 and 48. The response to adalimumab was compared with the baseline PASI before the start of adalimumab (course baseline) and the baseline PASI before the start of etanercept (original baseline). Note: the number of PASI data for adalimumab does not correspond with the number of patients in follow-up, as only the 12-week adalimumab follow-up time point was completed by all patients. SEM; standard error of the mean.

Safety

Etanercept and adalimumab were generally well tolerated. The total rate of adverse events reported during etanercept therapy was 3.41 per patient-year compared with 3.18 adverse events per patient-year during adalimumab treatment (Table 3).
Rates of infections per patient-year were 1.03 for etanercept and 0.91 for adalimumab. Upper respiratory tract infections were the adverse events most frequently encountered, followed by dermatological conditions, muscle and joint complaints and flu-like symptoms.

The rate of serious infections seen during etanercept treatment was 0.03 per patient-year. One patient was admitted with erysipelas and another patient was admitted with pneumonia. There have not been any reports of serious infections in the course of adalimumab therapy up until the moment of evaluation (Table 4).

One patient with a medical history of nonmelanoma skin cancer was diagnosed with two squamous cell carcinomas during etanercept therapy and three squamous cell carcinomas during adalimumab therapy. The first squamous cell carcinoma was diagnosed within a few weeks after the start of etanercept. Another patient was diagnosed with two basal cell carcinomas during adalimumab therapy, 3 months after the start of this treatment.

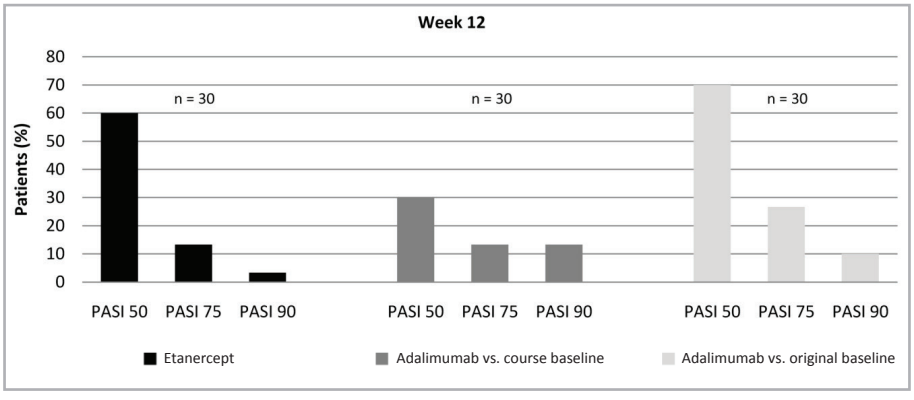

Figure 4. The percentage of patients achieving PASI 50, PASI 75 and PASI 90 at week 12 in the etanercept, adalimumab vs. course baseline and adalimumab vs. original baseline categories. The number of available PASI data at week 12 is represented above the bars.

Discussion

Most patients in our department were treated with etanercept as the first biologic therapy, as etanercept was one of the first registered biologics for psoriasis in Europe. When etanercept was discontinued because of inefficacy or intolerance, patients were mainly treated with adalimumab. Infliximab is reserved for patients with very severe psoriasis that warrants a rapid improvement, because of practical reasons and the infusion reactions observed with infliximab treatment. The recent registration of ustekinumab for the treatment of psoriasis has brought us an alternative treatment option besides the TNF-inhibitors, but experience with this new drug is limited at this moment.

In this study we focused on consecutive treatment with etanercept and adalimumab in biologic-naïve patients in daily practice and the relationship between reasons for discontinuation of etanercept and the response to adalimumab. The identification of groups of patients, who may benefit most from a switch to adalimumab when classified by reason of discontinuation of etanercept, would be useful to optimize treatment for each individual patient.

The majority of patients showed a beneficial response to adalimumab, irrespective of the reason for discontinuation of etanercept. In our patient group, previous treatment with etanercept did not increase the adverse event rate nor change the nature of the side effects. During the 24-week double-blind, randomized controlled ADEPT trial[15] in which biologic-naïve patients with psoriatic arthritis were treated with adalimumab 40 mg every other week, the infection rate was 1.53 per patient-year compared with 0.91 per patient-year in our patients. Thus, pretreatment with etanercept did not increase the infection rate during adalimumab treatment during the studied treatment period. Other

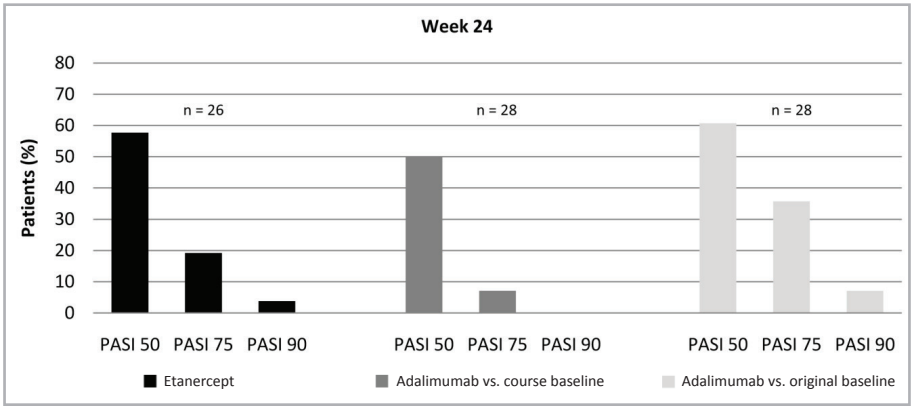

Figure 5. The percentage of patients achieving PASI 50, PASI 75 and PASI 90 at week 24 in the etanercept, adalimumab vs. course baseline and adalimumab vs. original baseline categories. The number of available PASI data at week 24 is represented above the bars.

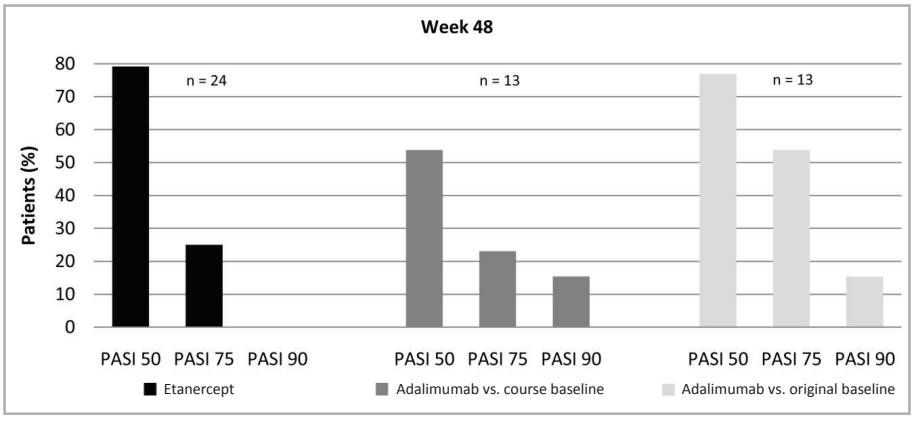

Figure 6. The percentage of patients achieving PASI 50, PASI 75 and PASI 90 at week 48 in the etanercept, adalimumab vs. course baseline and adalimumab vs. original baseline categories. The number of available PASI data at week 48 is represented above the bars.

studies support our findings regarding the safety of adalimumab in patients previously treated with other biologics.[3, 7, 16] A possible disadvantage of switching to adalimumab can be the formation of antibodies against adalimumab and an associated decline in efficacy in a proportion of patients.[17]

The response to adalimumab was calculated in two different ways. Compared with the original baseline PASI, the response rates to adalimumab were generally better than those achieved with etanercept. On the other hand, when the response to adalimumab was compared with the course baseline PASI, the response rates were generally lower. This can be explained by the carry-over effect of etanercept, i.e. patients are starting

Table 3. Incidence of adverse events in patients treated with etanercept followed by adalimumab per patient-year. Multiple occurrences of the same adverse event in the same individual were counted multiple times.

Adverse events	Etanercept	Adalimumab
Infections	1.03	0.91
Flu-like symptoms	0.23	0.09
Upper respiratory tract infections	0.56	0.56
Skin infections	0.11	0.06
Urinary tract infections	0.04	0
Gastrointestinal infections	0.02	0.03
Lower respiratory tract infections	0.03	0.12
Eye infections	0.03	0.06
(Pre)malignancies	0.03	0.18
Actinic keratosis	0	0.03
Basal cell carcinoma	0	0.06[b]
Squamous cell carcinoma	0.03[a]	0.09[a]
Muscle and joint complaints	0.34	0.35
Dermatological conditions	0.47	0.44
Gastrointestinal complaints	0.14	0.09
Cardiovascular events	0.06	0.03
Ear complaints	0.06	0
Eye complaints	0.06	0
Endocrine diseases	0.03	0.03
Miscellaneous	1.18	1.15
Total	3.41	3.18

[a]One patient was diagnosed with five squamous cell carcinomas, two during etanercept therapy and three during adalimumab therapy. [b]One patient was diagnosed with two basal cell carcinomas. Note: the follow-up for adalimumab was shorter than the follow-up for etanercept.

adalimumab treatment from a point of partial response with a lower course baseline PASI than the original baseline PASI.[14]

The results are also influenced by a phenomenon called 'regression to the mean'.[5, 18-20] There was less regression to the mean during adalimumab treatment because of the lower baseline PASI. To overcome these influences on the PASI response, we prefer the fairer comparison with the original baseline.

In addition, the reasons for discontinuation in daily practice are not always straightforward. Besides lack or loss of efficacy and adverse events, general dissatisfaction and the availability of other biologics may play a role as well.[21]

With this study we also showed that adalimumab is an effective and well tolerated therapy in patients who failed on etanercept. However, the relationship between the reasons for failure of etanercept and the response to adalimumab in patients with psoriasis had not been investigated in previous studies.

Table 4. Incidence of serious adverse events in patients treated with etanercept followed by adalimumab per patient-year. Multiple occurrences of the same serious adverse event in the same individual were counted multiple times.

Serious adverse events	Etanercept	Adalimumab
Basal cell carcinoma	0	0.06[c]
Squamous cell carcinoma	0.03[a]	0.09[a]
Erysipelas	0.02	0
Pneumonia	0.02	0
Myocardial infarction	0.03	0
Atrial fibrillation	0.02	0.03
Psoriasis exacerbation	0.06[b]	0
Cicatricial hernia surgery	0.02	0
Tendon rupture shoulder	0.02	0
Shoulder fracture	0.02	0
Joint complaints, weight loss, malaise	0	0.03
Total	0.22	0.21

[a]One patient was diagnosed with five squamous cell carcinomas, two during etanercept therapy and three during adalimumab therapy. [b]One patient experienced two exacerbations of psoriasis. [c]One patient was diagnosed with two basal cell carcinomas. Note: the follow-up for adalimumab was shorter than the follow-up for etanercept.

In our study, primary failure on etanercept did not preclude the efficacy of adalimumab, which is also a TNF-inhibitor. On the contrary, the chance of achieving a primary response on adalimumab at week 12 was even greater than the chance of primary failure. The same applies to the patients with secondary failure on etanercept, intolerance to etanercept or dissatisfaction with the effect of etanercept.
A limitation of this study is the shorter follow-up for adalimumab than for etanercept. As a result, we could only identify the primary nonresponders and one secondary nonresponder to adalimumab up until the moment of evaluation. In addition, the safety of adalimumab after etanercept treatment could be different in the long term.
The lower mean weekly dose of etanercept and the small increase in mean weekly dose of adalimumab in the obese patients compared with the nonobese patients could possibly explain the relatively high proportion of obese patients among the primary nonresponders to each drug and the primary nonresponders to both drugs. However, studies with larger numbers of patients are needed to perform subgroup analysis.

Large rheumatoid arthritis studies have shown that the efficacy of a second TNF-inhibitor is less than the efficacy of a first TNF-inhibitor.[18] This was not found in our study in patients with psoriasis. Studies in patients with rheumatoid arthritis also showed that the response to a second TNF-inhibitor depends on the reason for discontinuation of the first TNF-inhibitor. In general, a second TNF-inhibitor appeared to be more effective in

patients with secondary failure rather than primary failure of the first TNF-inhibitor. In our study, the percentage of patients with psoriasis achieving PASI 50 at week 12 with adalimumab was also higher among the secondary nonresponders than among the primary nonresponders.
Studies with larger numbers of patients are needed to investigate the correlation between the duration of the transition interval and the subsequent response to adalimumab, as well as the correlation between the etanercept treatment duration and the response to adalimumab.

The efficacy of adalimumab in etanercept nonresponders is not clear. Differences in molecule structure, pharmacological properties or genetic predisposition of patients could be possible explanations. Etanercept failure could possibly be explained by decreased bioavailability of the drug or biological adaptation to chronic TNF-α blockade.[2] Differences in the mechanisms of action could explain the efficacy of adalimumab after etanercept failure due to biological adaptation. Further research is needed to answer these questions.
The PASI 50/75/90 response rates of adalimumab in comparison to the original baseline at the different time points until week 48 were higher than the response rates achieved with etanercept, but lower than the response rates found in other daily practice studies and randomized clinical trials with adalimumab.[3, 6, 7, 16, 22-25] The efficacy results found in other daily practice studies are quite similar to those found in randomized controlled clinical trials.[3, 6, 7, 16] However, these daily practice studies are often limited by small numbers of patients and an adalimumab treatment regimen starting with 40 mg weekly instead of the registered 40 mg fortnightly dosage.

Other consecutive treatment regimens have been studied as well. Mazzotta et al. demonstrated that etanercept treatment after infliximab and/or efalizumab failure was more effective in those patients who had not previously received other biologic therapies than in those who had.[26] Nevertheless, etanercept was considered to be a good treatment option even after failure to respond to other biologic therapies.
Haitz et al. and Pitarch et al. showed that switching from infliximab to etanercept and vice versa is useful, although in the latter case shortening of the treatment interval was required to maintain the treatment response.[2, 4] No relevant adverse events were observed after switching from infliximab to etanercept. Infliximab treatment after etanercept treatment was associated with a possible increased incidence of adverse events.

In conclusion, switching from etanercept to adalimumab in patients with primary failure, secondary failure or intolerance to etanercept seems to be an effective and safe treatment option in psoriasis. Continuous prospective cohort monitoring is important to gain more and long-term efficacy and safety data from these patients in daily practice.

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Chapter 4

Adalimumab therapy for psoriasis in real-world practice: efficacy, safety and results in biologic-naïve vs. non-naïve patients

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Abstract

Background

Patients and the course of treatment in daily practice are different from randomized controlled trials (RCTs).

Objectives

Primary objective: to analyse the percentage of patients achieving PASI 75. Secondary objectives: PASI 50, PASI 90, PASI 100 responses, the percentage of patients experiencing at least one serious adverse event (SAE) and the response in biologic-naïve vs. non-naïve patients.

Methods

Prospectively collected efficacy and safety data of a cohort of psoriasis patients treated with adalimumab in daily practice between May 2007 and July 2011 were analysed. Efficacy was determined using an intention-to-treat analysis and an as-treated analysis, in comparison with the course baseline PASI before the start of adalimumab and the original baseline PASI before the start of any biologic therapy.

Results

Eighty-five patients received adalimumab therapy with a mean treatment duration of 1.4 (range 0.02 – 3.1) years. Compared with the original baseline PASI, PASI 75 response rates at week 12 and 24 were 34% and 38% (ITT). PASI 75 responses were well maintained until week 132.

Only the PASI 75 response rate at week 12 differed significantly between biologic-naïve (56%) and non-naïve patients (29%). Sixteen patients (19%) experienced 28 SAEs. Seven patients (8%) experienced SAEs considered possibly or probably related to adalimumab.

Conclusions

In this cohort, PASI 75 responses were substantial but lower than in RCTs and other daily practice studies. Efficacy was well maintained during more than 2 years of follow-up and differed only between biologic-naïve and non-naïve patients at week 12. The incidence of SAEs was low but seems higher than observed in RCTs.

Introduction

The efficacy and safety of adalimumab for psoriasis has been studied in randomized controlled trials (RCTs), one with an extension study up to 3 years of therapy.[1-4] These studies showed that adalimumab was efficacious and well tolerated in the short-term,[2-4] but also that efficacy was well maintained over more than 3 years of treatment and that the long-term benefit-risk profile was favourable with adverse event (AE) rates being generally stable over time.[1]

However, RCTs were conducted in selected patients fulfilling strict inclusion and exclusion criteria. In addition, the course of therapy in RCTs is predefined with strict continuation and discontinuation criteria. Therefore, the results of RCTs cannot simply be extrapolated to daily practice. Moreover, one of the phase III trials of adalimumab for psoriasis excluded patients who previously failed a TNF-antagonist and therefore did not provide information about the efficacy and safety of adalimumab in these patients.[4] Prospective observational cohort studies provide complementary information about the efficacy and safety of biologics for psoriasis in daily practice and in the long term. However, there are few reports on the management of unselected patients in day-to-day practice.

Published daily practice studies are limited to a maximum of 46 patients and a maximum mean treatment duration of 61.5 weeks.[5, 6] Moreover, most daily practice studies performed an 'as-treated analysis',[5-8] which makes comparisons with RCTs difficult, as those performed an intention-to-treat analysis.[2-4]

The purpose of this study was to analyse the efficacy and safety of adalimumab for psoriasis in daily practice in a larger number of patients with a longer follow-up and to compare response rates in biologic-naïve patients with patients who had previously been exposed to biologic agents and therefore possibly comprise a more therapy-resistant group.

Patients and methods

Patients

In February 2005, the department of Dermatology of the Radboud University Nijmegen Medical Centre started a prospective registry, containing efficacy and safety data of all consecutive patients treated with biologics for psoriasis in daily practice.[9] For the current analysis, data were extracted from all patients treated with adalimumab.

In the Netherlands, biologics were approved and reimbursed for patients with moderate to severe plaque psoriasis who had not responded to phototherapy, methotrexate and ciclosporin, or who had contraindications to, or did not tolerate these therapies. In 2010, the reimbursement criteria were changed into moderate to severe plaque psoriasis with

nonresponse, contraindications or intolerance to phototherapy and methotrexate ór ciclosporin. Furthermore, a Psoriasis Area and Severity Index (PASI)[10] of at least 10 or a PASI ≥ 8 and a Skindex-29 score ≥ 35 (quality of life index)[11] was required.

Methods

Patients were seen at screening, week 6 and 12 of adalimumab therapy and subsequently every 12 weeks. At screening, demographic data and information about the medical history, previous medication use for psoriasis and current medication use for psoriasis and other indications were recorded.

PASI scores were calculated at each visit. Patients were asked to report all AEs since the last visit and to report changes in comorbidity and concomitant medication. When visits did not occur at the exact time points, PASI scores were interpolated to the most nearby time point, allowing 7 days of extrapolation.

The primary objective was to analyse the percentage of patients achieving PASI 75. Secondary objectives were the percentage of patients achieving PASI 50, PASI 90 and PASI 100, the percentage of patients experiencing at least one serious adverse event (SAE) and the response in biologic-naïve patients compared with biologic-exposed patients.

Patients started adalimumab with a loading dose of 80 mg subcutaneously, followed by 40 mg every other week starting 1 week after the initial dose. In case of insufficient efficacy, the dose could be increased to 40 mg weekly or a topical or conventional systemic antipsoriatic therapy could be added. The decision to change the therapeutic regimen was based on clinical judgment of the treating dermatologist. The mean weekly dose of adalimumab was calculated.

As it is known that the method of analysis applied is of great importance for the efficacy results,[12] efficacy was analysed using two methods: (i) observed values of continuing patients only (as-treated analysis), and (ii) intention-to-treat (ITT) analysis with the last available PASI carried forward (LOCF) in case of missing data due to discontinuation of adalimumab or insufficient follow-up.

The response to adalimumab was evaluated in comparison with the baseline PASI before the start of adalimumab (course baseline) and with the first available baseline PASI before the start of any biologic therapy and enrolment in the registry (original baseline). This was done because patients switching to adalimumab after a previous biologic sometimes can be partial responders to the previous treatment, and therefore start with a lower course baseline PASI than the original baseline PASI.[13, 14]

The total group of patients was subdivided in patients who were biologic-naïve (defined as patients who had not previously been treated with a biologic agent (TNF-inhibitor or a biologic agent with another mechanism of action (efalizumab, alefacept and/or ustekinumab, partly in the context of clinical trials))) at the time of adalimumab initiation

and patients who had previously been treated with at least one biologic agent. PASI 50/75/90 response rates in comparison with the original baseline until week 48 were calculated and compared between the groups.

Serious adverse events were defined as life-threatening events, events requiring (prolongation of) hospitalization, congenital anomalies/birth defects, events resulting in persistent or significant disability/incapacity or death and important medical events according to medical and scientific judgment, consistent with the EMEA definition.[15]

Statistics

Descriptive statistics were used to represent study results as percentages, means (± standard deviation (SD)) and medians (range). The chi-square test or Fisher's exact test were used to compare responses in biologic-naïve and biologic-exposed patients. An independent samples t-test was performed to compare means. $P < 0.05$ was considered statistically significant.

Results

Patients

Between May 2007 and July 2011, 85 patients were treated with adalimumab during 120 patient-years of follow-up. The mean treatment duration was 1.4 (± 0.8) years and the median treatment duration was 1.4 (range 0.02 – 3.1) years. Forty-eight patients were male (56%) and the mean age at the start of adalimumab treatment was 48.8 (± 12.4) years. The mean duration of psoriasis was 23.0 (± 11.3) years (Table 1). Twenty-five patients (29%) had psoriatic arthritis. The mean weekly dose of adalimumab was 24.0 mg.

Sixteen patients (19%) were biologic-naïve at the start of adalimumab therapy. Sixty-nine patients (81%) had previously been treated with biologics in daily practice or a clinical trial. Sixty-six patients out of these 69 patients (96%) had previously been treated with at least one TNF-α blocking agent. Previous biologic therapies are presented in Table 1.
The number of different previous biologics that patients had used varied between 0 and 4. Thirty-eight patients out of 85 (45%) had only received etanercept therapy and fifteen patients (18%) had been treated with etanercept and efalizumab, as these were the first registered biologics for psoriasis in Europe. The other 16 patients (19%) had been treated with varying consecutive biologics.
At least one concomitant systemic antipsoriatic therapy was used in 25 patients (29%), as bridging therapy or added therapy to improve efficacy. These comprised methotrexate (n = 17), acitretin (n = 3), ciclosporin (n = 6) and fumarates (n = 1).

Table 1. Patient characteristics.

Patient characteristics	n = 85
Male gender, n (%)	48 (56)
Age (years), mean ± SD	48.8 (12.4)
Duration of psoriasis (years), mean ± SD	23.0 (11.3)
Psoriatic arthritis, n (%)	25 (29)
Original baseline PASI, mean ± SD[a]	15.1 (7.9)
Course baseline PASI, mean ± SD[b]	10.9 (5.6)
Previous biologic therapies, n (%)	
Etanercept	62 (73)
Efalizumab	21 (25)
Alefacept	8 (9)
Infliximab	6 (7)
Ustekinumab	1 (1)

[a]Original baseline PASI, first available baseline PASI before the start of biologic treatment and enrolment in the registry. [b]Course baseline PASI, baseline PASI before the start of adalimumab.

Treatment status

Fifty-four patients (64%) completed one year of adalimumab therapy, 25 patients (29%) completed two years and one patient (1%) completed three years (Figure 1). Sixteen treatment episodes (19%) were discontinued due to insufficient efficacy, two (2%) due to AEs, four (5%) due to a combination of insufficient efficacy and AEs, one patient (1%) died (unrelated to adalimumab therapy) and seven patients (8%) were lost to follow-up.

Efficacy

Figure 2 and 3 present the ITT analysis with the PASI response compared with the original baseline PASI and the course baseline PASI, respectively. Figure 4 and 5 present the as-treated analysis with the PASI response in relation to the original baseline PASI and the course baseline, respectively.

Intention-to-treat analysis

When the response to adalimumab was expressed in relation to the original baseline, PASI 75 was obtained by 34% (n = 29) and 38% (n = 32) of patients at week 12 and 24 (Figure 2). At week 48, 96 and 132, PASI 75 response rates were 40% (n = 34), 38% (n = 32) and 36% (n = 31), respectively.

At both week 12 and 24, PASI 50 was achieved in 65% of patients (n = 55). Eleven per cent (n = 9) and 14% (n = 12) of patients attained PASI 90 at these time points. From week 36 until 132, PASI 50 response rates varied between 66% and 68% and PASI 90 response

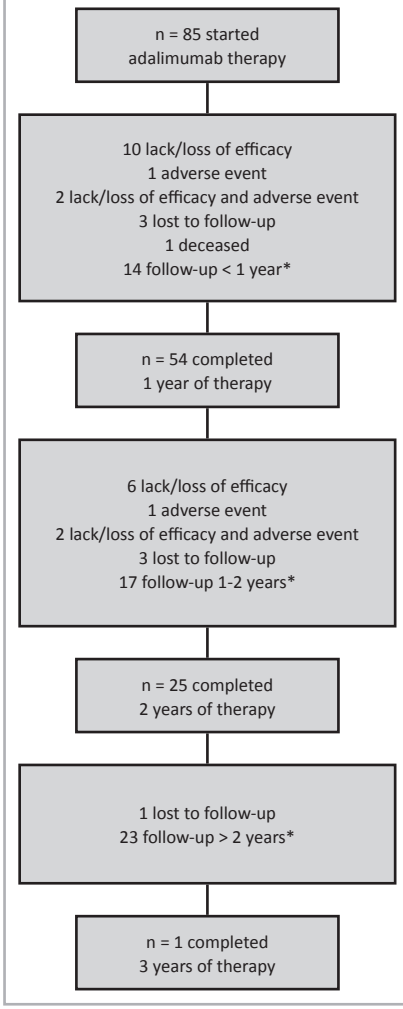

Figure 1. Patient disposition.
*These patients were actively being treated with adalimumab and included in the efficacy analysis until the last available visit.

rates were 13% to 19%. None of the patients achieved PASI 100 at week 12. At week 24, four patients (5%) achieved PASI 100 and from week 36 until 132, this applied to three patients (4%).

In relation to the course baseline, 27% (n = 23) and 26% (n = 22) of patients achieved PASI 75 at week 12 and 24 (Figure 3). At week 48, 96 and 132, these figures were 26% (n = 22), 26% (n = 22) and 25% (n = 21), respectively. PASI 50 response rates at week 12 and 24 were 46% (n = 39) and 49% (n = 42). PASI 90 response rates at these time points were 8% (n = 7) and 9% (n = 8). From week 36 until week 132, PASI 50 response rates varied between 52% and 55% and PASI 90 response rates varied between 8% and 13%. PASI 100 response rates are described above.

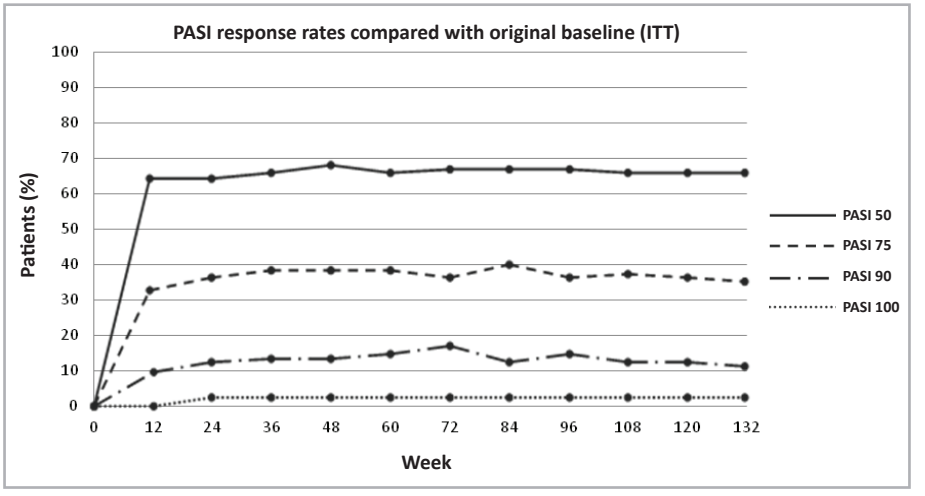

Figure 2. PASI 50/75/90/100 response rates in patients with psoriasis treated with adalimumab in comparison with the original baseline, ITT analysis with LOCF.

As shown in Figures 2-3, the long-term efficacy of adalimumab was relatively stable over time with the ITT analysis.

As-treated analysis

In relation to the original baseline, PASI 75 response rates at week 12 and 24 were 35% (n = 29) and 45% (n = 32) (Figure 4). At week 48, 96 and 132, PASI 75 response rates were 57% (n = 30), 44% (n = 8) and 50% (n = 3), respectively.

At week 12 and 24, PASI 50 was achieved in 65% (n = 55) and 69% of patients (n = 49). PASI 50 response rates at week 48, 96 and 132 were 83% (n = 44), 94% (n = 17) and 83% (n = 5), respectively.

PASI 90 response rates at week 12 and 24 were 11% (n = 9) and 17% (n = 12). At week 48, 96 and 132, a PASI 90 response was obtained by 21% (n = 11), 22% (n = 4) and 0% of patients, respectively.

None of the patients achieved PASI 100 at week 12. At week 24 and 48, complete clearance of psoriasis was seen in 6% (n = 4) and 4% (n = 2) of the patients. From week 96 until week 132, none of the patients obtained PASI 100.

In relation to the course baseline, 27% of patients (n = 23) achieved PASI 75 at week 12, 31% (n = 22) at week 24, 38% (n = 20) at week 48, 44% (n = 8) at week 96 and 50% (n = 3) at week 132 (Figure 5).

PASI 50 response rates at week 12 and 24 were 46% (n = 39) and 56% (n = 40). PASI 50 response rates at week 48, week 96 and week 132 were 72% (n = 38), 72% (n = 13) and 50% (n = 3), respectively. At week 12 and 24, PASI 90 was achieved by 8% (n = 7) and 11%

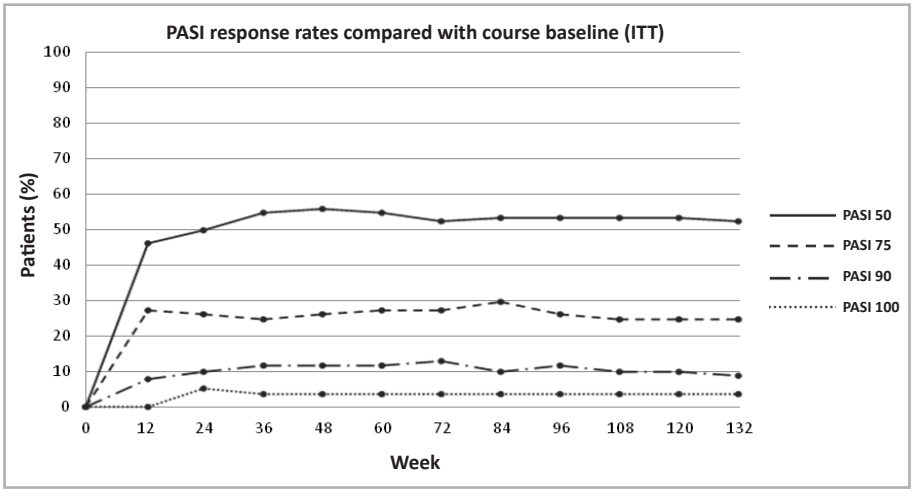

Figure 3. PASI 50/75/90/100 response rates in patients with psoriasis treated with adalimumab in comparison with the course baseline, ITT analysis with LOCF.

(n = 8) of patients. PASI 90 response rates at week 48, week 96 and week 132 were 15% (n = 8), 22% (n = 4) and 0%, respectively. PASI 100 response rates are described above.
As shown in Figures 4-5, efficacy continued to improve through weeks 60-96, with fluctuating efficacy afterwards, using an as-treated analysis.

Response rates in biologic-naïve and non-naïve patients

The mean original baseline PASI in the biologic-naïve patients (n = 16) was 13.0 (± 7.5). In the non-naïve patients (n = 69), the original baseline PASI was 15.6 (± 7.9). This difference was not statistically significant.
Compared with the original baseline PASI, 56% of biologic-naïve patients achieved PASI 75 at week 12 (ITT analysis with LOCF) (Figure 6). In the non-naïve patients, this was 29%. This difference was statistically significant (p = 0.04). PASI 75 response rates were not significantly different at week 24-48. PASI 50 and PASI 90 responses were not significantly different between the groups at any time point.
The mean course baseline PASI in the biologic-naïve patients corresponds with the mean original baseline PASI (13.0 (± 7.5)). In the biologic-exposed patients (n = 69), this was 10.4 (± 5.1). This difference was also not statistically significant.

Serious adverse events

Sixteen patients (19%) experienced 28 SAEs (0.23 events per patient-year) (Table 2). Eight out of 28 SAEs (29%) were considered possibly or probably related, which concerned 7 out of 85 patients (8%).
One patient was diagnosed with two basal cell carcinomas after 3 months of adalimumab

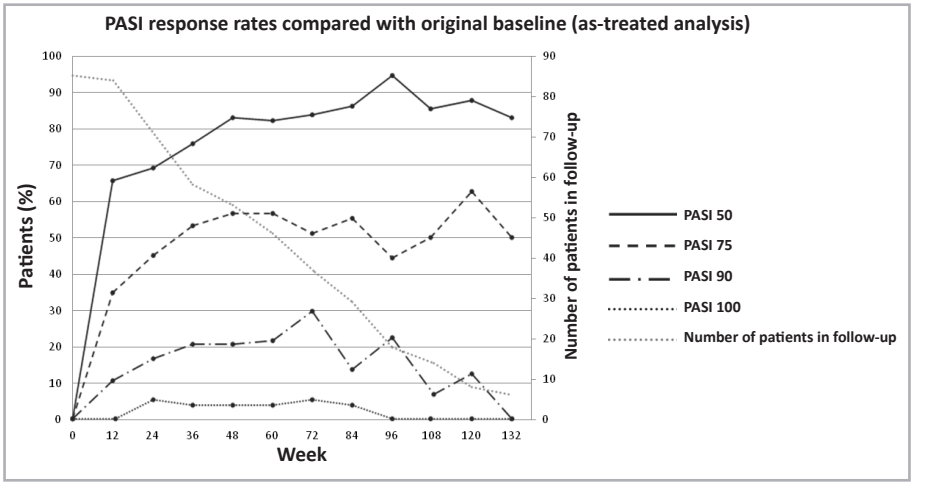

Figure 4. PASI 50/75/90/100 response rates in patients with psoriasis treated with adalimumab in comparison with the original baseline, as-treated analysis.

therapy, which were considered unlikely related to adalimumab therapy due to the rapid occurrence and the extensive history of previous immunosuppressive therapies.
Two patients developed a serious infection, comprising a Legionella pneumonia and hospital-acquired pneumonia (possibly related).
One patient experienced a gastric perforation occurring after 4 months, which was considered possibly related. Another patient died from internal bleeding after 9 months, which was considered unrelated because of a history of alcoholic liver cirrhosis and oesophageal variceal bleeding.

A patient with psoriatic arthritis developed joint complaints, malaise and weight loss after 2.5 months. We considered these complaints to be probably related to immune complex formation of anti-adalimumab antibodies (AAAs) (53.000 AE/mL) and adalimumab (trough level < 0.002 µg/mL). Adalimumab antibodies were measured using a radioimmunoassay and adalimumab trough concentrations were measured by enzyme-linked immunosorbent assay (ELISA), as described previously.[16, 17]

Another patient with plaque psoriasis developed palmoplantar pustulosis and generalized pustular psoriasis after 4.5 months. Histology showed pustular psoriasis or a combination with toxicodermia. Adalimumab was discontinued and acitretin was started. Three weeks later the patients developed suberythrodermia. This patient responded very well to successive treatment with etanercept. We considered this to be probably related.

Four patients experienced 9 hospitalizations for exacerbations of psoriasis. Two of these patients tested positive for AAAs, which might have contributed to the exacerbation.

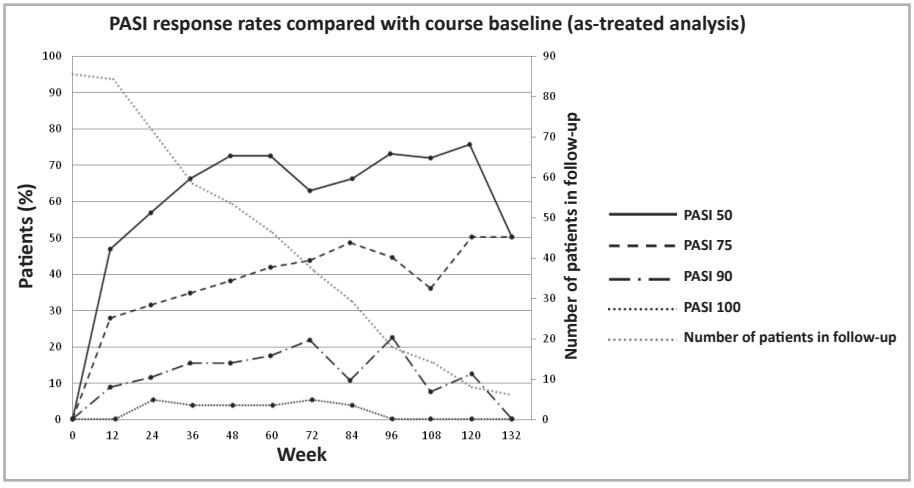

Figure 5. PASI 50/75/90/100 response rates in patients with psoriasis treated with adalimumab in comparison with the course baseline, as-treated analysis.

Possible explanations for the exacerbations in the other patients were psychological distress, discontinuation of concomitant ciclosporin therapy, interruption of therapy because of influenza and a compliance problem.
Other SAEs, which were considered probably unrelated, are presented in Table 2.

Discussion

The efficacy and safety of adalimumab for psoriasis has been investigated in RCTs, one with an extension study up to 3 years of treatment.[1-4] Prospective observational cohort studies provide complementary information about the efficacy and safety in daily practice and in the long term.

In this daily practice study, PASI 75 response rates on adalimumab compared with the original baseline PASI until week 132 were lower than in RCTs and other daily practice studies. PASI 75 at week 12 was achieved by 68% of patients in the REVEAL study, compared with 34% in this study (both ITT analysis).[3] At week 24, these results were 70% and 38%, respectively. In the daily practice study of Warren et al., PASI 75 at week 16 was achieved by 64% of patients, compared with 35% at week 12 in this study (both as-treated analysis). At week 24, these results were 65% and 45%, respectively.
A few explanations can be given for this observation. Firstly, this study concerned patients treated in a university hospital fulfilling strict reimbursement criteria, with treatment failure on conventional systemic therapies and in the majority of patients (81%) also on biologics. Therefore, the patients in this study could be more therapy-resistant.

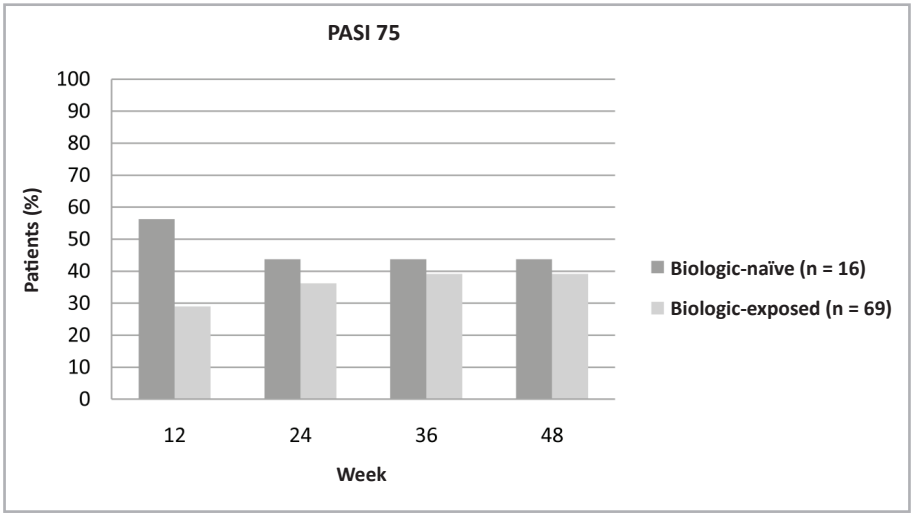

Figure 6. PASI 75 response in biologic-naïve and non-naïve patients in comparison with the original baseline PASI*, ITT analysis with LOCF. *Original baseline PASI corresponds with course baseline PASI in biologic-naïve patients.

Secondly, the course baseline PASI in this study was considerably lower than in RCTs and other daily practice studies.[2-8, 18] This can be explained by lengthy washout periods applied in RCTs and also in the study of Papoutsaki et al.,[18] whereas in our department, most patients started adalimumab treatment from a point of partial response due to the effect of previous (biologic) therapies or switched to adalimumab due to AEs during the previous biologic therapy but with low disease activity.[14] However, this situation reflects daily clinical practice, as most dermatologists apply short intervals between discontinuation of the previous biologic and the start of a new biologic, sometimes accompanied by the use of overlapping traditional systemic therapies.

A result of the lower course baseline PASI is that there is less regression to the mean and that a smaller absolute reduction in PASI is needed to achieve PASI 75.[19] However, a residual PASI of between 5 and 6 at week 36-84 was observed in this study and has also been described in studies on etanercept for psoriasis.[9, 20] Due to this remaining PASI and limitations of the PASI itself in limited psoriasis,[21] PASI 75 is difficult to attain starting from a low baseline PASI. We prefer the fairer comparison with the original baseline PASI, which has also been applied in other studies.[13, 14, 22, 23]

Other explanations for the lower efficacy of adalimumab in daily practice compared with RCTs could be comorbidity and concomitant medication, intercurrent infections or interruptions of therapy due to infections or elective surgery in daily practice. Higher efficacy in other daily practice studies could also be explained by adalimumab administration at a dosage of 40 mg weekly, instead of the registered 40 mg fortnightly dosage.[7, 18]

Table 2. Serious adverse events (SAEs) in patients with psoriasis treated with adalimumab.

Serious adverse event	Number of events	Number of patients (%)
Basal cell carcinoma	1*	1 (1)
Legionella pneumonia	1	1 (1)
Hospital-acquired pneumonia	1	1 (1)
Exacerbation of psoriasis with hospitalization	9	4 (5)
Palmoplantar pustulosis and pustular psoriasis	1	1 (1)
Suberythrodermia	1	1 (1)
Lymphoedema	1	1 (1)
Pulmonary embolism	1	1 (1)
Nefrolithiasis	1	1 (1)
Ablation therapy for atrial fibrillation	1	1 (1)
Hysterectomy for menorrhagia	1	1 (1)
Abdominal aortic aneurysm surgery	1	1 (1)
Traumatic wrist fracture	1	1 (1)
Malaise, joint complaints, weight loss	1	1 (1)
Knee surgery for osteoarthritis	2	1 (1)
Gastric perforation	1	1 (1)
Liver cirrhosis	1	1 (1)
Oesophageal variceal haemorrhage	1	1 (1)
Death	1	1 (1)

*One patient was diagnosed with 2 basal cell carcinomas at the same time.

In this study, two methods of analysis were used. The as-treated analysis introduces a positive bias, as patients who continue treatment for a long time are usually good responders.[1] The more conservative results of the ITT analysis may approximate the true efficacy of adalimumab, although efficacy may be a little overestimated, as it is known that efficacy does not remain constant in all patients. Both methods are important to be able to compare results from different studies.

Serum adalimumab concentrations and AAAs were not determined on a regular basis in patients with insufficient efficacy. AAA formation could have been the cause of exacerbations of psoriasis in two patients who tested positive for AAAs. The effect of AAA formation on the efficacy of adalimumab for psoriasis needs further investigation.[16]

At week 12, the percentage of biologic-naïve patients achieving PASI 75 was significantly higher than the percentage of non-naïve patients. However, PASI 75 response rates at week 24-48 and PASI 50/90 responses did not differ.

Gniadecki et al. showed that the drug survival of infliximab, etanercept and adalimumab for psoriasis, which is an indicator of treatment success, was higher in anti-TNFα-naïve

patients compared with patients who previously failed anti-TNFα therapy.[24] However, Ortonne et al. found only modestly reduced efficacy responses to adalimumab in patients with prior anti-TNFα exposure compared with anti-TNFα-naïve patients.[25] Clemmensen et al. found no difference in the efficacy of ustekinumab in anti-TNFα-naïve patients compared with anti-TNFα unresponsive patients.[26] Additional studies with larger numbers of patients are needed to address the question whether biologic-naïve patients are better responders than non-naïve patients.

Sixteen patients (19%) experienced 28 SAEs. Only 8 out of 28 SAEs (29%) were considered possibly or probably related and this concerned only 7 out of 85 patients (8%). The incidence of SAEs observed in this daily practice study (0.23 events per patient-year) is higher than reported in the REVEAL randomized controlled trial (0.06 events per patient-year).[3] However, the treatment duration with adalimumab in the REVEAL study (52 weeks) was shorter than in this study, which can be important in a setting where an adverse event requires prolonged exposure to adalimumab to become clinically detectable, for instance in case of malignancies.[27] In addition, the mean weekly dose of adalimumab in this study was higher than in the REVEAL study, as in the latter study the dose of adalimumab could not be escalated.
The number of patients and events in this study is too small to draw firm conclusions about safety, but the results point to future directions. Studies with larger numbers of patients have shown that SAE rates are stable over time.[1, 28]

In conclusion, in this cohort PASI 75 response rates were substantial but lower than in RCTs and other daily practice studies. Efficacy was well maintained over more than 2 years of follow-up and did only differ between biologic-naïve and non-naïve patients at 12 weeks of treatment, but not during prolonged treatment. The incidence of therapy-related SAEs was low.

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Chapter 5

Effectiveness of adalimumab dose escalation, combination therapy of adalimumab with methotrexate, or both in patients with psoriasis in daily practice

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Abstract

Background

To increase effectiveness of standard adalimumab treatment 40 mg every other week (EOW) for patients with psoriasis, dose escalation to 40 mg every week or addition of methotrexate (MTX) are possible strategies.

Methods

Daily practice data on adalimumab treatment were extracted from a prospective observational cohort. We analysed all patients with insufficient efficacy of adalimumab EOW who received 1) adalimumab dose escalation, 2) addition of MTX to adalimumab EOW, or 3) both. Effectiveness was analysed after 12 and 24 weeks using PASI 50, PASI 75, and differences in mean PASI.

Results

Forty-seven treatment episodes (TE) of adalimumab dose escalation, 11 of MTX addition and six combinations were analysed. After a first episode of adalimumab dose escalation, 25% and 34% resulted in PASI 50 after 12 and 24 weeks, respectively. Addition of MTX to adalimumab EOW, resulted in PASI 50 in 9% of TE after 12 weeks and 18% of TE after 24 weeks. No therapy-related serious adverse events were reported.

Conclusions

Twenty-five percent of first TE with adalimumab dose escalation induced a PASI 50 response after 12 weeks and 34% after 24 weeks. Addition of MTX to adalimumab EOW resulted in PASI 50 in 9% after 12 weeks and 18% after 24 weeks. Defining patient groups that will benefit from these interventions is important.

Introduction

Treating patients with moderate to severe psoriasis with biologics is a major step forward for patients with recalcitrant disease. In a subgroup of these patients, the normal dosage schedule (40 mg every other week) does not induce a sufficient response.[1] Modification strategies include dose escalation (reducing dose interval or increasing dose) or adding another systemic therapy.[2,3] Before switching to another systemic agent, it is recommended to first use these strategies mentioned.[2] In case a patient uses the TNF-antagonist adalimumab (Humira®), dose escalation (a decrease of dose interval from 2 weeks to 1 week) is frequently applied for suboptimal responders in clinical practice. In an open-label study, Leonardi et al. found a substantial improvement in clinical outcome in a quarter of psoriasis patients undergoing dose escalation.[4] In rheumatoid arthritis, there was no significant improvement in clinical outcome after dose escalation of adalimumab.[5]

Another option is to add methotrexate (MTX), which has been combined in previous studies with TNF-antagonists in patients with rheumatoid arthritis and psoriatic arthritis.[6-9] Combination with MTX is known to improve the clinical response and decrease the formation of antibodies against adalimumab in patients with rheumatoid arthritis.[10-12] However, for psoriatic arthritis, the addition of MTX to adalimumab has not been shown to enhance improvement of joint symptoms.[7,9] The combination of MTX and the TNF-antagonist etanercept has been proven to be successful in the treatment of moderate-to-severe psoriasis.[13,14] However, data on the effects of addition of MTX in patients who do not respond to adalimumab monotherapy in daily practice are scarce. In a recent case study, including 32 patients treated with MTX concomitant with adalimumab (early or late in the course of treatment), the majority of patients had a good or very good response.[15] In that case series, varying adalimumab dose schedules were described and the response was not analysed at fixed time points.

In the present study, we analysed all patients who started with adalimumab monotherapy per label (40 mg every other week) and needed treatment adjustment. All analyses commenced at the starting point of intervention. We included all patients with 1) adalimumab dose escalation (40 mg every week), 2) addition of (low-dose) MTX to adalimumab 40 mg every other week (EOW), or 3) the combination of adalimumab dose escalation and addition of MTX. All data were collected in an academic hospital in the Netherlands in a daily practice setting.

The objective of this study was to establish the effectiveness of these treatment strategies using the change in PASI after 12 and 24 weeks expressed as PASI 50, PASI 75, and the difference in mean PASI between time points (ΔPASI). In addition, the safety of these interventions in daily practice was described.

Methods

Since 2005, daily practice data of all patients starting a biologic agent are collected prospectively at the department of Dermatology of the Radboud University Nijmegen Medical Centre. In general, patients were eligible for adalimumab treatment if they had failed to respond to phototherapy, MTX and/or ciclosporin in the past, or if they had a contraindication to or were intolerant for these treatment modalities. Patients needed to have a Psoriasis Area and Severity Index (PASI) of at least 10. Patients visited the clinic 6 and 12 weeks after starting a biologic agent, and every 3 months thereafter.

For this study, we selected all patients with an insufficient response to 40 mg adalimumab every other week and requiring adalimumab dose escalation to 40 mg per week and/or addition of MTX. The decision whether a response to standard adalimumab dosing was considered 'insufficient' was made by the treating physician to his/her own discretion. The choice between pharmacological interventions (adalimumab dose escalation and/or MTX addition) was also made by the treating physician. Data were analysed from the start of adalimumab treatment until discontinuation or the last date of data inclusion (July 13, 2012).
Effectiveness of the interventions was analysed in treatment episodes (TE). A treatment episode was defined as a continuous episode of a single intervention (adalimumab dose escalation or MTX addition). If a patient received more than one episode of the same intervention, the interventions were regarded as different TEs when interrupted for at least 6 weeks. In case a patient underwent two different interventions (adalimumab dose escalation and MTX addition), these interventions were considered as one combined TE when there was overlap in time, or as different TEs if there was no overlap in time. These combined episodes were analysed separately from the other treatment episodes described above. The PASI measurements were related to the interventions in a graph, to visualize the effects of the intervention.
Patients undergoing two TEs of adalimumab dose escalation were described separately as well. This separation was made because patients undergoing a second TE were probably good initial responders to adalimumab dose escalation. Hypothetically, they could respond differently compared with patients naïve for this intervention and/or the baseline PASI could be lower due to the ongoing effects of the first episode.

Descriptive statistics were summarized for the total cohort. Clinical characteristics were summarized for the TE with first and second adalimumab dose escalation separately, MTX addition, or the combination of both. The analysis of third and fourth time adalimumab dose escalation was not described separately due to the low number of episodes. Effectiveness was expressed as PASI 50 (reduction of PASI of 50%) and PASI 75 (reduction of PASI of 75%). Mean PASI scores with standard error of the mean (SEM)

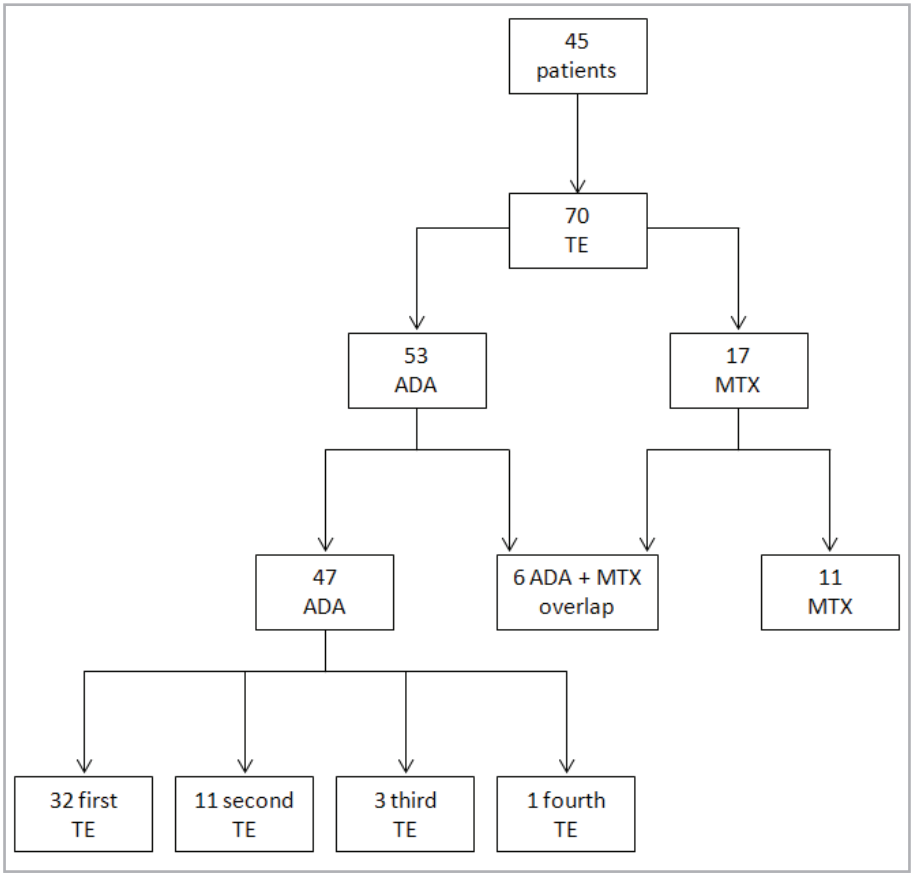

Figure 1. Diagram of included patients and treatment episodes.

from baseline of treatment intervention until week 6, 12 and 24 were calculated (data are presented as mean PASI ± SEM). Differences in mean PASI (mean PASI at start of TE minus mean PASI at end of TE) at fixed time points were represented as ΔPASI. The PASI at different time points compared with the moment of intervention was analysed with a paired t-test.

PASI courses were analysed using both an 'as-treated' analysis and an 'intention-to-treat' analysis with 'last observation carried forward' (ITT with LOCF). Analyses were performed on all available data per TE, but TEs were not allowed to overlap. In an 'as-treated' analysis, the focus is on the actual results for the remaining patients in the study at the time of analysis. To include ongoing effects after discontinuation of the intervention and to prevent for selection bias, ITT with LOCF is a good method.[16] When PASI measurements were not available at the date of initiation of the treatment intervention, the PASI before or shortly (max. 2 weeks) after introduction of the treatment intervention, which represented the moment of initiation of the intervention best, was used.

Table 1. Demographic and clinical characteristics of the patients treated with adalimumab EW, addition of methotrexate to adalimumab EOW, or the combination of MTX and adalimumab EW.

	All patients (n = 45)
Male gender, n (%)	25 (55.6)
Age at inclusion (years), mean ± SD	49.1 ± 13.6
Duration of psoriasis (years), median [range][a]	20.9 [4.3 - 53.6]
Total patient-years in follow-up (years on adalimumab)	66.9
Episodes of ADA dose escalation, n	53
Episodes of MTX addition, n	17
Known diagnosis of psoriatic arthritis, n (%)	12 (26.7)[b]
Smoking (yes), n (%)	37 (82.2)[c]
Alcohol (yes), n (%)	30 (66.7)[c]
BMI (kg/m^2), mean ± SD	29.9 ± 6.3

[a]Of 44 valid data. [b]Four cases unknown. [c]One case unknown. ADA, adalimumab; EOW, every other week; EW, every week; MTX, methotrexate.

Serious adverse events (SAEs) were recorded and the relation of the pharmacological intervention with the SAE was determined. Statistical analyses were done with PASW 18.0 (Chicago).

Results

From the prospective database, 112 patients were identified who used adalimumab in the past or were still actively treated. Forty-five patients (40.2%) underwent one or more treatment adjustments of interest, consisting of 47 TE of adalimumab dose escalation, 11 TE of addition of MTX to adalimumab 40 mg EOW, and 6 TE of adalimumab dose escalation combined with addition of MTX (Figure 1).

Patient characteristics

As show in Table 1, the mean age at the moment of inclusion (± SD) of all 45 patients was 49.1 ± 13.6 years. Twenty-five patients were male (55.6%). Twelve patients (26.7%) were diagnosed with psoriatic arthritis. The mean body mass index (BMI) was 29.9 ± 6.3 kg/m^2. Thirty-seven patients were (previous) smokers (82.2%) and 30 patients (66.7%) were alcohol users.

The median psoriasis duration was 20.9 [4.3-53.6] years at the time of starting adalimumab treatment in our hospital. A total of 66.9 patient-years (years actively treated with adalimumab) were analysed.

Table 2. Clinical characteristics per pharmacological intervention.

	All TE	First episode of ADA dose escalation[b]	Second episode of ADA dose escalation[b]	Addition of MTX	Combined episodes (ADA dose escalation and addition of MTX)
Number of TE	70	32	11	11	6
Duration of adalimumab dose escalation per TE (months)[a]	2.7 [0.4-27.4]	2.7 [0.5-24.3]	1.6 [0.4-27.4]	NA	4.6 ± 4.1
Total patient-years of adalimumab use[a]	66.9	NA	NA	NA	NA
Total patient-years of adalimumab dose escalation[a]	21.1	12.5	4.9	NA	2.3
Adalimumab cumulative escalation dose per TE (mg)	474.3 [74.3-4771.4]	477.1 [80.0-4228.6]	285.7 [74.3-4771.4]	NA	795.3 ± 710.9
Duration of MTX use per TE (months)[a]	3.0 [0.5-16.9]	NA	NA	3.0 [1.0-15.1]	5.2 ± 6.3
Total patient-years of MTX use[a]	6.15	NA	NA	3.55	2.61
MTX cumulative dose per TE (mg)	94.7 [11.0-748.2]	NA	NA	105.7 [11.0-748.2]	92.2 [19.9-625.0]
Weekly dose of MTX per TE (mg)	10.0 [2.5-14.1]	NA	NA	9.5 ± 3.2	9.8 [5.6-10.0]

[a]Median duration of intervention until discontinuation of adalimumab or July 13 2012 (last date of data inclusion). [b]A separate analysis of the third and fourth episodes was omitted due to an insufficient number of TE. Mean ± SD or median [range]. ADA, adalimumab; MTX, methotrexate; NA, not applicable.

Adalimumab dose escalation: all TE

A total of 47 TE of adalimumab dose escalation were identified and analysed, excluding combinations with MTX, which were analysed separately. Thirty-two, eleven, three and one dose escalations were given as a first, second, third and fourth TE, respectively (Figure 1).

Of all dose escalations (47 TE), the median treatment duration was 2.7 [0.4-27.4] months (Table 2). The mean PASI (± SEM) before dose escalation was 10.0 ± 0.9. Using an 'as-treated' approach, the course of the mean PASI was 9.3 ± 0.9, 7.7 ± 1.1 and 5.1 ± 1.0 after 6, 12 and 24 weeks, respectively (Table 3). After 12 weeks, 32% of TE resulted in PASI 50 and 3% in PASI 75. After 24 weeks, 47% of TE resulted in PASI 50 and 18% in PASI 75 (Figure 2).

Figure 3 shows the PASI course using an ITT with LOCF approach. PASI 50 was achieved for 26% and PASI 75 for 2% of TE after 12 weeks. After 24 weeks, PASI 50 was achieved for 36% and PASI 75 for 11% of TE.

Separate analysis of first and second TE of adalimumab dose escalation

Thirty-two dose escalation TE were administered as a first course of dose escalation and 11 dose escalation TE were administered as a second course of dose escalation. Three

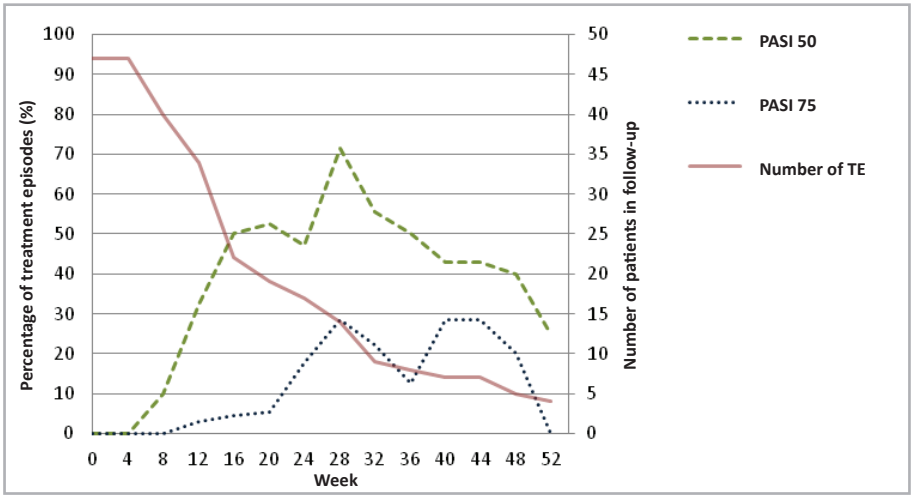

Figure 2. Efficacy of adalimumab dose escalation, all treatment episodes (as-treated analysis).

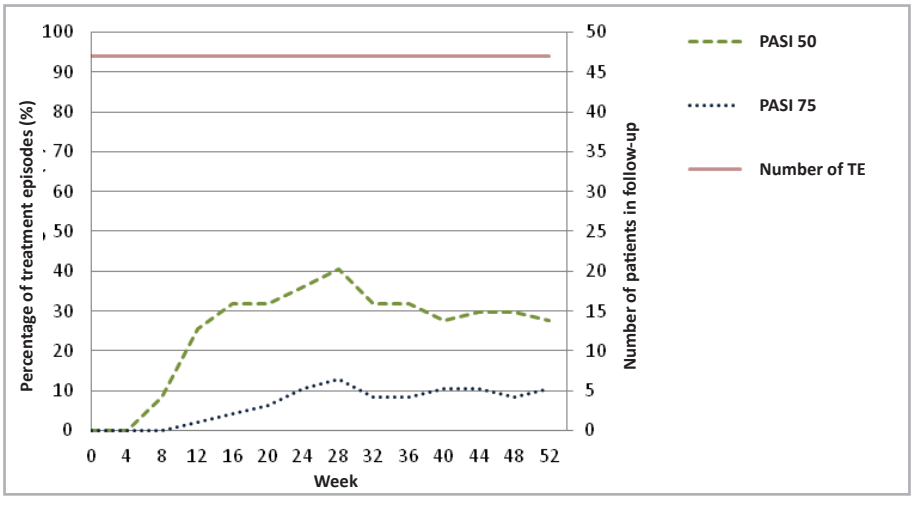

Figure 3. Efficacy of adalimumab dose escalation, all treatment episodes (ITT with LOCF).

and one patients received a third or fourth course of adalimumab dose escalation, respectively (Figure 1).

The 32 first time dose escalations had a median duration of 2.7 [0.5-24.3] months (Table 2). As shown in Table 3, the last mean (± SEM) PASI before intervention was 10.6 ± 1.2. The mean PASI was 9.7 ± 1.3, 8.7 ± 1.7 and 5.3 ± 1.6 after 6, 12 and 24 weeks, respectively, using an as-treated analysis. Figure 4 shows the PASI course using an ITT with LOCF approach. After 12 weeks, PASI 50 was achieved in 25% of TE. PASI 75 was not achieved at that time (ΔPASI all first TE: 1.6, ΔPASI of responders: 8.8). After 24 weeks, 34% of TE achieved PASI 50 and 9% PASI 75 (ΔPASI all first TE: 2.5, ΔPASI of

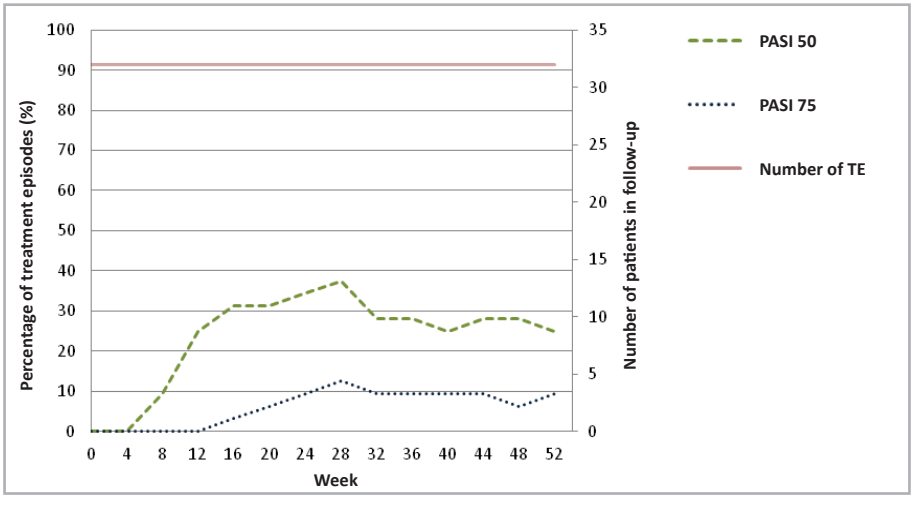

Figure 4. Efficacy of adalimumab dose escalation, first episode (ITT with LOCF).

responders: 8.9). The mean PASI of the whole group had significantly decreased after 24 weeks (p = 0.03), but not after 12 weeks (p = 0.14). The number needed to treat (NNT) to identify one responder (PASI 50) after 12 weeks in patients naïve for dose escalation was 4.

The 11 second time dose escalations lasted 1.6 [0.4-27.4] months (Table 2). The mean PASI was 8.2 ± 1.3 shortly before commencing the second-time dose escalation and 8.1 ± 1.7, 5.5 ± 1.4 and 4.2 ± 0.8 after 6, 12 and 24 weeks, respectively (as-treated analysis) (Table 3).

Figure 5 shows the PASI course of the first and second episode using an ITT with LOCF analysis. The second episodes started with a slightly lower mean PASI (8.2) compared with the first episode (mean PASI 10.6). This could be due to the fact that most patients who received a second episode, had a good response on their first TE with dose escalation. Consequently, these responses could still be positively influencing the baseline PASI of the second episode. Also, the ΔPASI of the first episode was higher compared with the second episode (4.4 vs. 2.5) after 24 weeks. Note that this could be due to the lower baseline PASI of the latter as well. The achieved mean PASI after 24 weeks was comparable for these episodes (mean PASI 5.0 vs. 5.6).

Addition of MTX without adalimumab dose escalation

Eleven TE of MTX addition combined with normal adalimumab dosing were analysed (six combined TE of adalimumab dose escalation and MTX addition were analysed separately). A mean weekly dose of 9.5 ± 3.2 mg MTX per TE was used with a median duration of 3.0 [1.0-15.1] months (Table 2). The last PASI (± SEM) before addition of MTX was 9.8 ± 1.9. The mean PASI was 9.4 ± 2.2, 7.9 ± 3.2 and 11.4 ± 9.1 after 6, 12 and 24

Table 3. Mean PASI after 6, 12 and 24 weeks of intervention (adalimumab dose escalation or MTX addition to adalimumab 40 mg EOW), as-treated analysis.

Pharmacological intervention	Baseline[a]	Week 6	Week 12	Week 24
Adalimumab dose escalation				
Number (n) of patients with increase of adalimumab frequency (1st, 2nd, 3rd and 4th episodes)[b]	47	45	34	17
PASI ± SEM	10.0 ± 0.9	9.3 ± 0.9	7.7 ± 1.1	5.1 ± 1.0
Number (n) of patients with increase of adalimumab frequency, first episode only[b]	32	30	21	10
PASI ± SEM	10.6 ± 1.2	9.7 ± 1.3	8.7 ± 1.7	5.3 ± 1.6
Number (n) of patients with increase of adalimumab frequency, second episode only[b]	11	11	9	5
PASI ± SEM	8.2 ± 1.3	8.1 ± 1.7	5.5 ± 1.4	4.2 ± 0.8
Methotrexate addition (to adalimumab 40 mg EOW)				
Number (n) of patients with MTX addition	11	10	7	3
PASI ± SEM	9.8 ± 1.9	9.4 ± 2.2	7.9 ± 3.2	11.4 ± 9.1

[a]The last PASI measured before or shortly after the pharmacological intervention. [b]A separate analysis of the third and fourth episodes was omitted due to an insufficient number of TE. PASI, Psoriasis Area and Severity Index.

Table 4. PASI response of patients with a first episode of adalimumab dose escalation or MTX addition to adalimumab 40 mg EOW after 12 and 24 weeks, ITT with LOCF analysis.

	Adalimumab dose escalation (first episode) (n = 32)	**MTX addition** (n = 11)
PASI 50[a] at week 12, n (%)	8 (25)	1 (9)
PASI 75[a] at week 12, n (%)	0 (0)	1 (9)
ΔPASI[a] at week 12, all patients	1.6 (p = 0.14)	1.2 (p = 0.3)
ΔPASI[a] at week 12, responders[b]	8.8	5.9
PASI 50[a] at week 24, n (%)	11 (34)	2 (18)
PASI 75[a] at week 24, n (%)	3 (9)	1 (9)
ΔPASI[a] at week 24, all patients	2.5 (p = 0.03)	1.1 (p = 0.05)
ΔPASI[a] at week 24, responders[b]	8.9	7.1

[a]PASI at the moment of initiation of the intervention was used for comparison. [b]Patients with PASI 50 response. PASI, Psoriasis Area and Severity Index.

weeks, respectively, using an 'as-treated' approach (Table 3).

Using an ITT with LOCF approach, PASI 50 and PASI 75 was achieved for 9% of TE after 12 weeks (ΔPASI of all patients: 1.2, ΔPASI of responders: 5.9). After 24 weeks, PASI 50 was achieved for 18% and a PASI 75 for 9% of TE (ΔPASI of all patients: 1.1, ΔPASI of responders: 7.1). There was no significant difference in mean PASI for the whole group after 12, nor after 24 weeks (Figure 6, Table 4).

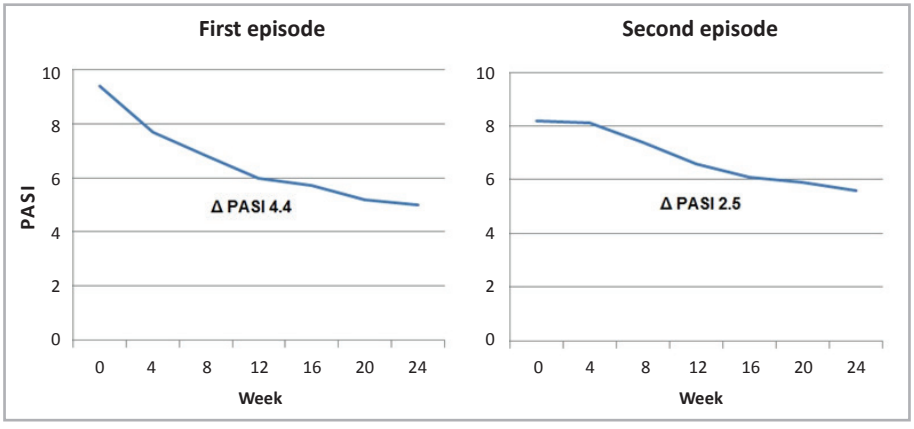

Figure 5. PASI course of 11 patients after introduction of adalimumab dose escalation as a first and second TE (ITT with LOCF).

Adalimumab dose escalation combined with methotrexate

Six patients received adalimumab dose escalation and addition of methotrexate with significant overlap in time. Since all six patients received only one combined TE each, we refer to 'patients' instead of 'TE' in this section. Adalimumab dose escalation was given with a mean cumulative dose of 795.3 ± 710.9 mg per TE for a mean duration of 4.6 ± 4.1 months (Table 2). MTX was given with a median weekly dose of 9.8 [5.6-10.0] mg per TE with a mean duration of 5.2 ± 6.3 months.

Figure 7 shows the PASI course for these six patients. The black arrow represents the introduction of MTX in patient 1. All other patients received adalimumab dose escalation and MTX introduction simultaneously (week 0 in Figure 7). As can be seen in Figure 7, patients 3, 4 and 5 show an initial improvement in PASI. The deterioration of the PASI in patient 2 is stabilized after the introduction of MTX and adalimumab dose escalation. Patients 1 and 6 show a (further) increase in PASI.

Serious adverse events

Two serious adverse events were recorded after adalimumab dose escalation. One patient died due to bleeding of oesophageal varices, which was considered probably unrelated to adalimumab treatment. This patient suffered from liver cirrhosis and oesophageal varices with bleeding as a complication of cirrhosis. Another patient experienced an exacerbation of psoriasis, 13 months after adalimumab dose escalation. He was still using adalimumab in an escalated dose when he was admitted to the hospital. This event was considered to be probably unrelated, since he had been using an escalated dose of adalimumab for months. No SAEs were reported after the addition of MTX.

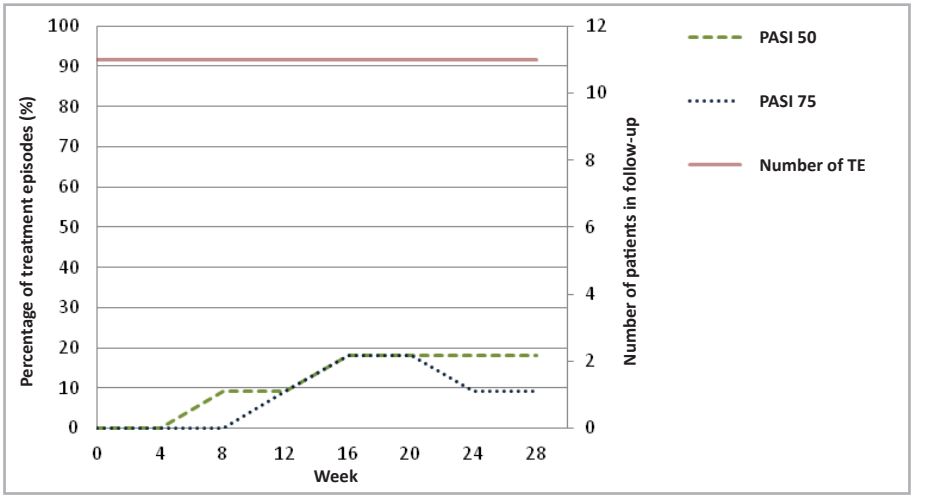

Figure 6. Efficacy of methotrexate addition to adalimumab 40 mg EOW, all treatment episodes (ITT with LOCF).

Discussion

In this prospective observational cohort study, we described the effect of dose escalation of adalimumab and combination therapy of MTX with adalimumab. Twenty-five percent of first TE with adalimumab dose escalation resulted in a PASI 50 response after 12 weeks and 34% after 24 weeks. In TE with adalimumab in a standard dose, addition of methotrexate resulted in a PASI 50 response in 9% after 12 weeks and 18% after 24 weeks. All first adalimumab dose escalations resulted in a ΔPASI of 1.6 after 12 weeks. The ΔPASI of responders to a first TE was 8.8 after 12 weeks. When second, third and fourth adalimumab treatment episodes were taken into account, the percentage of PASI 50 responders increased to 36% after 24 weeks.

The addition of MTX to adalimumab EOW induced a PASI 50 response in 9% of TE after 12 weeks. The ΔPASI of the whole group was 1.2 after 12 weeks; the responders achieved a ΔPASI of 5.9 after 12 weeks. These results indicate that a subgroup of patients benefited from these treatment strategies, but that the ΔPASI was hampered by the influence of nonresponders. The combination of both strategies showed mixed results.

Second episodes of adalimumab dose escalation were analysed separately as well. The mean PASI in the second episode group was slightly lower at start of the second TE compared with the first. This could be due to the fact that most patients who received a second episode had a good response on their first TE with dose escalation. Consequently, these responses could still be positively influencing the baseline PASI of the second episode. The ΔPASI of the first episode was higher compared with the second episode

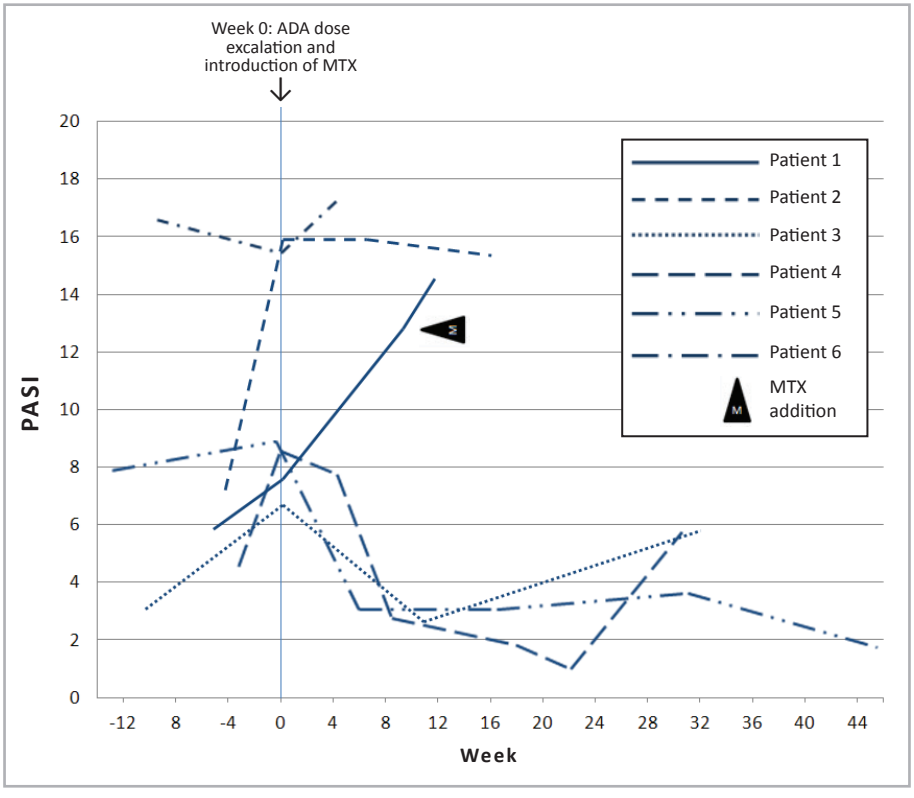

Figure 7. PASI course of 6 patients with a combined TE (adalimumab dose escalation and MTX addition).

(4.4 vs. 2.5) after 24 weeks. Note that this could also be due to the lower baseline PASI of the latter. The achieved mean PASI after 24 weeks was comparable for these episodes (mean PASI 5.0 vs. 5.6). In some patients, the normal dosage schedule (40 mg every other week) does not induce a sufficient response.

Both pharmacological interventions (and the combination of both) were well tolerated in this study. Two SAEs were reported after adalimumab dose escalation and were considered 'probably unrelated'. No SAEs were reported shortly after the introduction of MTX. Although both pharmacological interventions seemed safe in this relatively small group, attention for safety in treatment with these agents is still needed.

The REVEAL study showed that 71% responded, which means that 29% of the patients did not achieve a PASI 75 response after 16 weeks of adalimumab treatment in a standard dose.[1] Compared with a study of Leonardi et al., the present study is in line with the percentage of people benefiting from adalimumab dose escalation for psoriasis in a randomized controlled trial.[4] A difference is that Leonardi et al. showed that 25% achieved

PASI 75 compared with PASI 50 for 25% in this daily practice study.[4] Although PASI 50 is lower than PASI 75, it is considered a clinical meaningful response.

It has been described before that the effects of TNF-antagonists in patients with rheumatoid arthritis in daily practice studies are usually smaller than in RCTs.[17] It is plausible that this phenomenon is seen in psoriasis research as well. Another important issue is that in most RCTs, the PASI change is analysed using the first PASI at the start of biological treatment as a comparator. In this study, the PASI at the start of the intervention is chosen as a comparator, which leads to lower responder percentages. In our opinion, the PASI before intervention is more appropriate since at the moment of intervention, a significant change in PASI (PASI 50 or PASI 75) is desired.
A factor that could influence the response to a biologic is the previous treatment with other biologics. In the literature, the response to a second biologic was lower in some studies in RA. To date, there has been no convincing evidence that treating a patient with a second biologic is less effective than the first in dermatology.

In this study, we showed that four patients had to be treated with adalimumab dose escalation to identify one responder (defined as at least a PASI 50) (NNT = 4). This NNT must be carefully weighed against the costs that dose escalation of adalimumab entail. However, a decision must be made for every individual patient since other issues are important as well for successful treatment, such as long-term maintenance. It is important to use the full potential of a treatment before switching to another, as switching reduces the number of available treatment options.

This study has some limitations that need to be kept in mind. Firstly, analysing more treatment episodes in a single patient gives rise to the problem that effects can be carried forward to the next episode. It must be taken into account that a lower PASI at the start of the next episode hampers the netto effect (ΔPASI). Secondly, interpreting efficacy data is highly dependent on the method of analysis.[16] An as-treated analysis and intention-to-treat with last observation carried forward analysis were therefore both used, with emphasis on the latter. ITT with LOCF carries forward the ongoing effects of ceased interventions and therefore provides a better reflection of the real effects as both success and failure are frequently characterized by ending the intervention. Thirdly, it must also be noted that our patients treated with additional MTX received a relatively low dose of MTX and in some cases only for short episodes. Long-term MTX addition in a higher dose could lead to better results and therefore could be interesting for further studies. In addition, the study is based on a limited number of patients.

Adalimumab dose escalation and/or addition of methotrexate were good strategies for increasing efficacy in a subgroup of patients with an insufficient response to adalimumab

40 mg every other week. For safety and cost issues, it may be important to escalate the dose for a limited period of time. If a patient responds well, the dose can be de-escalated again. As can be seen in this study, these patients can start a dose re-escalation for a second period. In this daily practice study, it was not possible to define characteristics of (non)responders. Previously it was shown that secondary nonresponders, patients with a body weight of ≤102 kg and a disease duration <8.3 years were most likely to benefit from adalimumab dose escalation.[4] Defining subgroups of patients who will respond to the various treatment strategies in daily practice is a challenge for future studies.

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Chapter 6

Results of three analytical approaches on long-term efficacy of etanercept for psoriasis in daily practice

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Abstract

Background

A problem encountered when analysing long-term efficacy is that the number of patients in follow-up decreases with time for different reasons. The method used to account for missing observations for the therapy under analysis has a great influence on the inference of efficacy.

Objectives

To describe the long-term efficacy of etanercept for psoriasis in daily practice using 3 analytical approaches.

Methods

Prospective data from a cohort of patients with psoriasis treated with etanercept for at least 24 weeks were analysed using 3 analytical approaches: as-treated analysis, intention-to-treat analysis (ITT) with last observation carried forward (LOCF) and intention-to-treat analysis with modified nonresponder imputation (modified NRI).

Results

One hundred thirty-one patients were treated with etanercept during 134 treatment episodes with a mean treatment duration of 2.7 years. The maximum follow-up was 6.0 years. The methodological approach chosen had a great influence. Psoriasis Area and Severity Index (PASI) 75 response rates varied from 60% in the as-treated approach to 34% in LOCF and to 29% in modified NRI at week 264.

Limitations

All analytical methods applied have limitations. Other outcome measures could be used to overcome the bias introduced by each method of analysis, such as drug survival.

Conclusions

The methodological approach chosen to analyse long-term efficacy data has a great influence on the inferences that may be drawn regarding the degree of efficacy. Therefore we support the use of different methods to present long-term efficacy data.

Introduction

The efficacy and safety of etanercept for psoriasis have been studied in randomized controlled trials with open-label extension studies for up to 4 years of treatment.[1-3] Open-label extension studies have shown some loss of efficacy of etanercept after week 48-52.[2,3] However, the results from randomized controlled trials (RCTs) may not reflect the daily clinical practice situation, as patients included in RCTs are highly selected and treated according to a predefined treatment schedule. There are few reports on the management of unselected patients in day-to-day practice, especially in the long term. This study provides complementary information to RCTs about the efficacy and safety of etanercept for psoriasis in daily practice up to 300 weeks of treatment.

Observational cohort studies can be analysed according to the intention-to-treat (ITT) principle and the as-treated principle. The intention-to-treat principle was originally designed for the analysis of RCTs. In an intention-to-treat analysis, all patients are analysed according to the initial treatment intent following randomization, irrespective of the treatment actually received. This is different from an as-treated analysis, in which the analysis is based on the treatment that patients actually received.

A problem encountered when analysing long-term efficacy data is that the number of patients with available efficacy data for the therapy under analysis decreases with time. In observational studies, inclusion of patients is continuously ongoing. At the time of analysis a data lock is performed, including patients with a short follow-up for the therapy under analysis. Furthermore, in some patients, biologic therapy is discontinued because of insufficient efficacy or intolerance. In that case, efficacy data for the therapy analysed are not available anymore and can only be measured when patients are on another therapy or no therapy. In addition, in case of loss of follow-up, outcome measures cannot be measured anymore.
In an ITT analysis, none of the patients are excluded from the analysis. This is different from an as-treated analysis, in which patients with insufficient follow-up for the therapy under analysis are excluded from the analysis. In order to include patients with missing efficacy data for the therapy under analysis in the ITT analysis, the last observation available for the therapy analysed can be extrapolated, which is also applied in the RCTs with etanercept for psoriasis. This involves making assumptions about the outcomes, which can be done with the last observation carried forward (LOCF) method or the (modified) nonresponder imputation ((modified) NRI) method.
The method used has a great influence on the inference of efficacy.[4, 5] The ITT analysis with (modified) nonresponder imputation approach may give a too negative view of the efficacy of etanercept. On the other hand, the as-treated analysis introduces a bias towards a too positive outcome. The ITT analysis with LOCF approach produces intermediate results.

The primary objective of this study was to describe the long-term efficacy of etanercept therapy for psoriasis in daily practice and to compare 3 analytical approaches. Efficacy was expressed as the percentage of patients reaching a reduction of the Psoriasis Area and Severity Index (PASI)[6] of 50% (PASI 50), 75% (PASI 75) or 90% (PASI 90). Results are described as follows: as-treated analysis, LOCF, and modified NRI.[4]

Patients and methods

Patients

This prospective cohort study involved all consecutive patients with psoriasis treated with etanercept between February 2005 and February 2011 for at least 24 weeks. Efficacy data were extracted from a prospective patient registry, containing data from all patients starting biological treatment for psoriasis in the Dermatology outpatient department of the Radboud University Nijmegen Medical Centre.[7] In the Netherlands, biological treatment was approved for the treatment of patients with psoriasis who had not responded to phototherapy, methotrexate and ciclosporin, or who had contraindications to, or did not tolerate these therapies. Furthermore, a PASI[6] of at least 10 was required.
The study protocol was presented to the institutional review board (IRB). A formal IRB procedure was considered unnecessary by the board because of the noninterventional character of the study.

Methods

Efficacy and safety evaluations were scheduled at baseline, week 6 of treatment, week 12, and subsequently every 12 weeks. At baseline, demographic information and information about the medical history, previous medication use for psoriasis and concomitant medication was collected. PASI scores were collected at baseline and at each subsequent visit, as well as information on concomitant medication use and adverse events.

The long-term efficacy of etanercept was investigated in patients with a follow-up of at least 24 weeks. The primary objective of this study was to analyse the percentage of patients achieving a 50%, 75% or 90% reduction in PASI (PASI 50/75/90) at multiple time points.
Treatments were analysed as separate treatment episodes. A new treatment episode was started when patients started a new biologic therapy or when the same biologic was restarted after an interruption lasting 6 months or longer.

In this daily practice study, hospital visits did not always take place at the scheduled time points (week 6, week 12, and subsequently every 12 weeks). In that case, PASI scores at the scheduled time points were obtained with interpolation, using the PASI

score at the hospital visit closest before the scheduled time point and the PASI score at the hospital visit closest after the scheduled time point. This was done using the linear function $y = ax + b$, in which a is the slope of the curve representing the course of the PASI score between the two hospital visits closest to the scheduled time point and b is the PASI score measured at the hospital visit closest before the scheduled time point. Extrapolation of PASI scores obtained before a scheduled time point was allowed up to maximal 7 days of extrapolation, using the same linear function.

The long-term efficacy of etanercept was analysed in 3 ways. The following approaches were used: (1) analysis of continuing patients only (as-treated analysis), (2) ITT analysis with imputation of missing PASI data for etanercept therapy over the remainder of the 300 weeks using LOCF and (3) ITT analysis with imputation of missing PASI data for etanercept therapy using the modified nonresponder imputation approach (modified NRI).[2, 4]
The LOCF method carries forward the last available PASI score until the last evaluation time point. With the nonresponder imputation method, patients with missing PASI scores for etanercept therapy at predefined evaluation time points are assumed not to have achieved binary efficacy endpoints (PASI 50/75/90).[2] In this study, a less conservative modification of the nonresponder imputation approach as described by Papoutsaki et al.[4] was used, as the inclusion of patients in this observational cohort study is continuously ongoing; nonresponder imputation for patients who were still taking etanercept at the time of analysis but did not reach subsequent evaluation time points was considered inappropriate.
The modified NRI method consists of analysing patients as nonresponders for the PASI 50/75/90 calculation in case the patient discontinued etanercept due to loss of efficacy or a combination of loss of efficacy and adverse events, whereas the last available PASI was carried forward in case a patient discontinued etanercept treatment due to adverse events only or other reasons. In case the patient was lost to follow-up or in case the patient was still taking etanercept but the length of follow-up did not reach the subsequent evaluation time points, the last available PASI was carried forward as well.[2, 4]

In this ongoing registry, patients started etanercept treatment at different time points before the moment of analysis. Therefore in the 'as-treated analysis' the number of available PASI data of patients treated with etanercept decreases over time according to the length of follow-up or the cessation of treatment. In the intention-to-treat analysis with imputation using the LOCF approach or the modified NRI approach the number of patients in follow-up remains constant, as a result of the methods used to account for missing PASI scores for etanercept therapy.
Patients were treated according to the opinion of the treating physician, including dose and interval changes of etanercept therapy and the addition of topical or systemic therapies.

Statistics

Descriptive statistics were used to represent study results as percentages, means (± standard deviation (SD)) and medians (range).

Results

Patients

The cohort consisted of 131 patients treated with etanercept during 134 treatment episodes lasting for 24 weeks or longer. The number of patient-years of follow-up was 362. Eighty-one patients were male (62%), the mean age at the start of etanercept treatment was 47.5 (± 11.4) years, and the mean duration of psoriasis was 22.4 (± 10.6) years (Table 1). The mean body mass index (BMI) was 28.7 (± 5.6) kg/m^2 and 40 patients (31%) suffered from psoriatic arthritis. The mean duration of an etanercept treatment episode was 2.7 (± 1.6) years. The median duration was 2.4 years (range 0.5 – 6.0 years).
The number of different systemic therapies (including biologics applied in our hospital, other hospitals, and in clinical trials) that patients had used before the start of an etanercept treatment episode in daily practice and enrolment in the registry varied between 2 and 8; the mean number was 4.8 (± 1.4). Forty-three patients (33%) had been treated with at least one biologic before the start of etanercept in daily practice and enrolment in the registry. This mainly concerned biologic treatment in the context of clinical trials.

Forty-two etanercept treatment episodes (31%) were combined with at least one concomitant systemic antipsoriatic therapy as bridge therapy when transitioning to biologic treatment, as rescue therapy during the course of biologic treatment because of unsatisfactory efficacy or as a continuous concomitant therapy. Five etanercept treatment episodes were consecutively combined with 2 different systemic antipsoriatic therapies.
Twenty-four etanercept treatment episodes were combined with methotrexate, 11 with acitretin, 9 with ciclosporin, 2 with fumarates and 1 with mycophenolate mofetil.
The median time between the start of etanercept and the start of a concomitant systemic therapy as add-on therapy was 27 weeks (range 1 – 202 weeks). The mean weekly dose of etanercept was 64.1 (± 14.0) mg.

Treatment status

From this cohort, 114 patients completed one year of treatment, 76 completed two years, 52 patients completed three years, 34 patients completed four years, and 16 patients completed five years of therapy (Figure 1). These patients were actively being treated with etanercept at the time of analysis. Thirty-seven treatment episodes (28%) were discontinued due to loss of efficacy, 12 (9%) due to adverse events, 3 (2%) due to

Table 1. Patient characteristics.

Patient characteristics	n = 131
Male gender, n (%)	81 (62%)
Age (years)	
Mean ± SD	47.5 (11.4)
Median (range)	47.9 (21.7-77.3)
Duration of psoriasis (years)	
Mean ± SD	22.4 (10.6)
Median (range)	20.8 (1.9-46.2)
Body mass index (kg/m^2)	
Mean ± SD	28.7 (5.6)
Median (range)	28.1 (15.9-54.1)
Psoriatic arthritis, n (%)	40 (31)
Previous classical systemic therapies, n (%)	
Ultraviolet (UV) B	116 (89)
Psoralen plus UVA	91 (69)
Methotrexate	127 (97)
Ciclosporin	97 (74)
Acitretin	81 (62)
Fumarates	58 (44)
Azathioprine	2 (2)
Previous biologic therapies, n (%)	
Etanercept	16 (12)
Efalizumab	15 (11)
Alefacept	11 (8)
Onercept	7 (5)
Adalimumab	3 (2)
Infliximab	2 (2)

a combination of loss of efficacy and adverse events, 2 patients (1%) died and 2 female patients (1%) discontinued etanercept therapy because of a pregnancy wish. In addition, 15 patients (11%) were lost to follow-up.

Efficacy

As-treated analysis

Results from the as-treated analysis are presented in Figures 2-4. At week 24, 67.9% (n = 91), 38.1% (n = 51) and 14.9% (n = 20) of treatment episodes resulted in PASI 50, PASI 75 and PASI 90, respectively. Efficacy continued to improve through week 288. A PASI 75 response was obtained in 36.6% of treatment episodes (n = 41) at week 48, 40.8% (n = 29) at week 108, 50.0% (n = 26) at week 156, 59.4% (n = 19) at week 204 and 60% (n = 9) at week 264. The PASI 50 and PASI 90 response rates are presented in Figures 2 and 4.

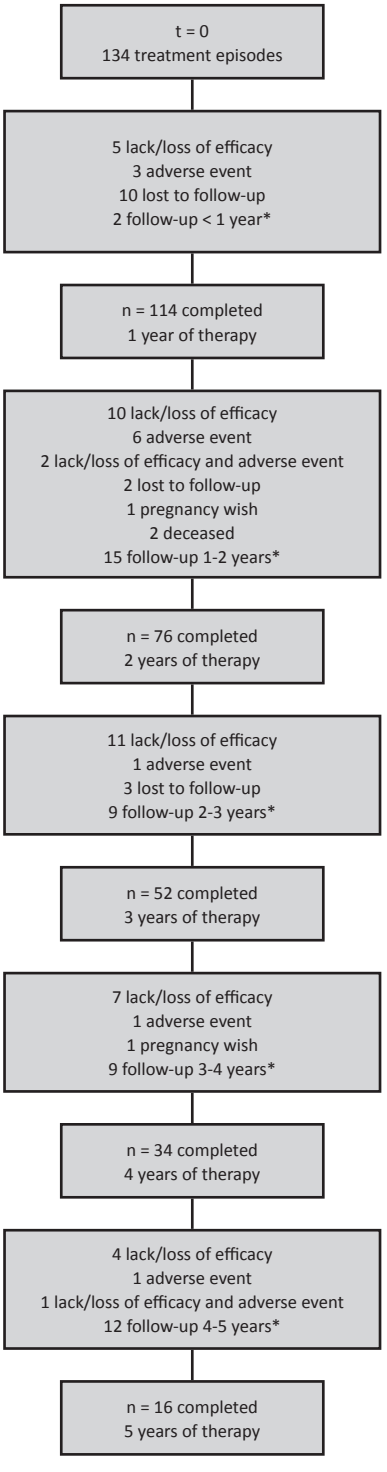

Figure 1. Patient disposition.
*These patients were actively being treated with etanercept at the time of analysis and included in the efficacy analysis until the last available visit.

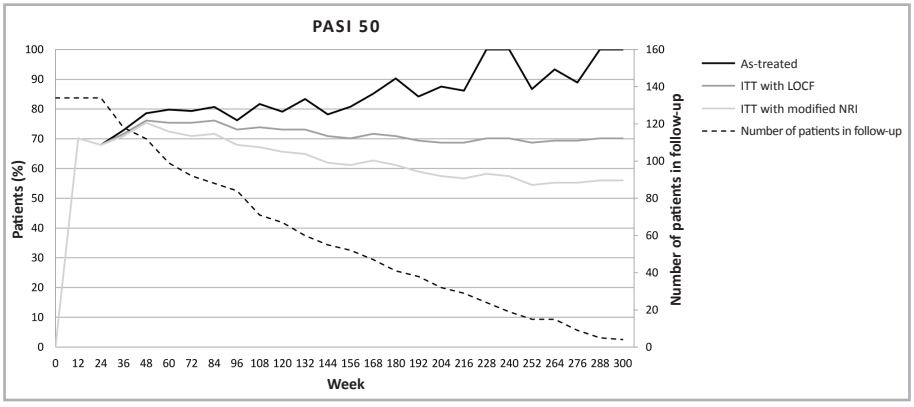

Figure 2. PASI 50 response by analysis method.

Last observation carried forward (LOCF)

Efficacy results at week 24 were the same as in the as-treated analysis. Data from the LOCF analysis show almost constant efficacy over time, although there is some loss of efficacy. A PASI 75 response was obtained in 35.1% of treatment episodes (n = 47) at week 48, 35.1% (n = 47) at week 108, 38.1% (n = 51) at week 156, 37.3% (n = 50) at week 204 and 34.3% (n = 46) at week 264. The PASI 50 and PASI 90 response rates are presented in Figures 2 and 4.

Modified nonresponder imputation (modified NRI)

Efficacy results at week 24 were the same as in the as-treated analysis. This approach shows declining efficacy. A PASI 75 response was obtained in 34.3% of treatment episodes (n = 46) at week 48, 32.8% (n = 44) at week 108, 34.3% (n = 46) at week 156, 32.8% (n = 44) at week 204 and 29.1% (n = 39) at week 264. The PASI 50 and PASI 90 response rates are presented in Figures 2 and 4.

Discussion

As shown in this study, the methodological approach chosen to analyse long-term efficacy has a great influence on the efficacy results. As an example, the PASI 75 response rate varied from 60% in the as-treated approach to 34% in LOCF and 29% in modified NRI at week 264. This means that efficacy doubled when the as-treated approach was used instead of modified NRI. Therefore, when comparing efficacy data from different studies, it is important to consider the analysis method used.

With the as-treated approach, a selection bias is introduced, as patients who are treated for a long time are usually the patients who respond well to a certain therapy.[2] As reflected

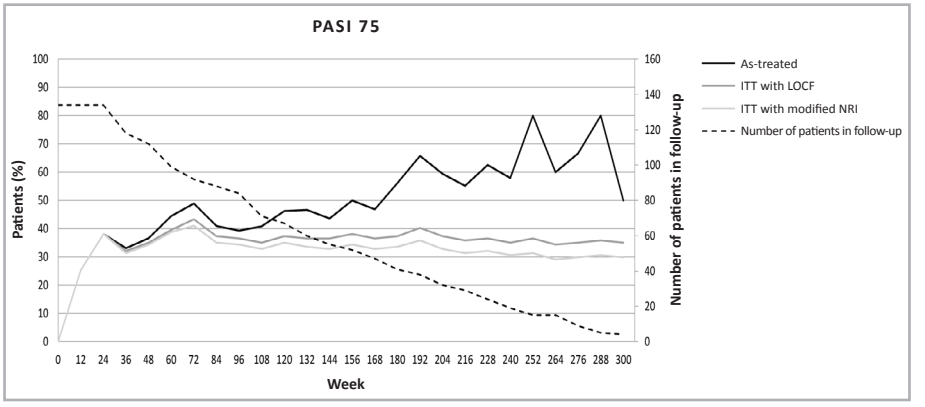

Figure 3. PASI 75 response by analysis method.

in this study, the most frequent reason for discontinuing etanercept treatment was loss of efficacy or a combination of loss of efficacy and adverse events. This information is left out of consideration in the as-treated analysis.[4]

In the short-term RCTs with etanercept for psoriasis, a modified ITT analysis with missing efficacy data imputed using LOCF was used as the primary efficacy analysis.[8-11] The problem with using LOCF for analysing long-term efficacy results is that efficacy data may be carried forward for a very long time and that this analysis method assumes that efficacy will remain constant, consistent with the last known value.[4]
The LOCF method is a single imputation method. Besides single imputation methods, multiple imputation methods exist, which may be more accurate. Instead of filling in a single value for each missing value, multiple imputation replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute.[12]

The most conservative approach is NRI, in which patients with missing efficacy data for a specific therapy at predefined evaluation time points are assumed not to have achieved binary efficacy endpoints (PASI 50/75/90), irrespective of the reason of missing data and the actual PASI improvement.[2]
Applying NRI in an observational cohort study is problematic, as the inclusion of patients in such studies is continuously ongoing. At the time of analysis, a data lock is performed, including patients with a short follow-up period. Applying NRI for patients who were still treated with etanercept at the time of analysis but did not reach subsequent evaluation time points was considered inappropriate. Therefore, in this study, a less conservative modification of the NRI approach, as described by Papoutsaki et al.[4] was used. The advantage of the modified NRI approach is that reasons for missing PASI scores for etanercept therapy are taken into account.
All 3 analysis methods introduce a bias; therefore the true efficacy of etanercept is

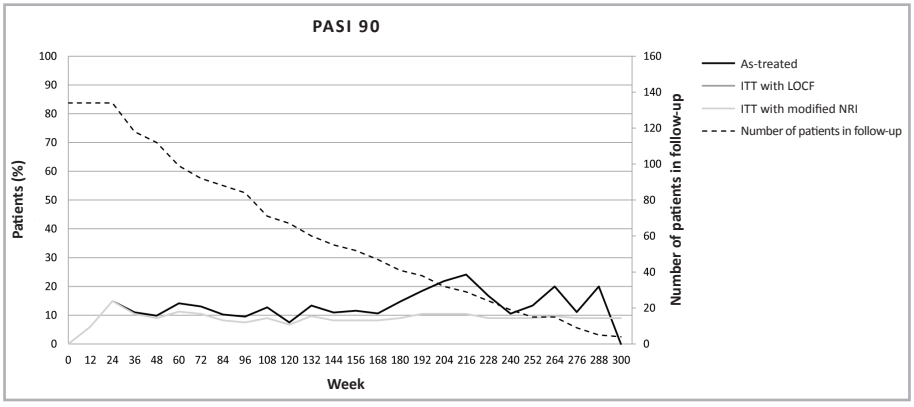

Figure 4. PASI 90 response by analysis method. Efficacy results for the LOCF approach and modified NRI approach are equal.

unknown. A way to overcome this problem is to change the outcome measure. A possible outcome measure could be represented by the amount of time patients remain on a specific treatment, which is also referred to as 'drug survival'. Drug survival is a surrogate measure of treatment success, as it depends on the efficacy of the drug. However, drug survival is also dependent on tolerance, general satisfaction with the treatment, and patients who are lost to follow-up.[13] An alternative outcome measure could be represented by the number of patients with psoriasis in remission at specific time points. However, there are no biomarkers for remission of psoriasis available at this moment.

The PASI 50/75/90 response rates at week 12 and 24 in this study in patients treated with etanercept in daily practice are lower than that reported in the RCTs.[8-11] The difference in efficacy between RCTs and daily practice could be explained by multiple factors. Patients in daily practice are possibly more therapy-resistant or show less efficacy of treatment because of comorbidity, concomitant medication, intercurrent infections, or interruptions of therapy due to infections or elective surgery. On the other hand, patients in daily practice can use concomitant topical or systemic therapies for psoriasis, which may have biased the efficacy results of etanercept towards a more favourable outcome. Because of the variability in concomitant topical and systemic therapies used and the variability in dosages used, this source of bias was not addressed.

In conclusion, the methodological approach chosen to analyse long-term efficacy has a great influence on the efficacy results. Therefore we support the use of all 3 methods to present long-term efficacy and the use and development of other outcome measures.

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Chapter 7

Safety of treatment with biologics for psoriasis in daily practice: 5-year data

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Abstract

Background

The cumulative exposition to biologics is increasing with prolonged treatment with a certain biologic or consecutive biological treatment. However, long-term safety data are limited available.

Objectives

The aim of this study was to prospectively evaluate the 5-year safety of biological treatment for psoriasis in daily practice.

Methods

A cohort of 173 psoriasis patients on biologics was prospectively followed for 5 years. All adverse events reported were documented and analysed. Primary endpoint was the percentage of patients reporting at least one serious adverse event. The rate of malignancies, serious infections and serious cardiovascular events was compared with the general population incidence rate. The nature and rate of dermatological adverse events was compared with a group of prospectively followed rheumatoid arthritis patients on TNF-α blocking therapy.

Results

Between February 2005 and April 2010, 173 patients were enrolled in the registry and went through a total number of 263 treatment episodes. The total number of patient-years of follow-up in the registry was 409. The number of patient-years was the highest for etanercept. Forty-nine patients (28%) reported 88 serious adverse events. Only one serious adverse event was certainly causally related to the biologic and 21 events (24% of SAEs) were considered possibly related. The incidence of malignancies, serious infections and serious cardiovascular events was comparable with the population incidence rate, except for skin malignancies. The incidence of skin malignancies was significantly higher than the general population incidence rate. The nature and rate of dermatological adverse events differed from the rheumatoid arthritis cohort.

Conclusions

In this cohort, the safety of biological therapies for psoriasis was favourable with a low incidence of therapy-related serious adverse events.

Introduction

The safety of biological treatment for psoriasis is an important issue. Concerns exist about a possible increased risk of cancer, including nonmelanoma skin cancer and lymphomas in psoriasis patients treated with TNF-inhibitors.[1] A potential risk for the development of other malignancies cannot be excluded based on the current knowledge either.[2] Other important safety aspects are the development of or worsening of pre-existing heart failure and demyelinating diseases and drug-induced lupus for the TNF-α blockers and infections for the biologics in general.[2, 3]

The cumulative exposition to biologics is increasing with prolonged treatment with a certain biologic or consecutive biological treatment, but long-term safety data are limited available. Moreover, these patients often already have an increased risk of malignancies due to previous UV phototherapy, particularly PUVA and/or the use of immunosuppressive drugs.[1] Dermatological conditions have been shown to be a significant and clinically important problem in rheumatoid arthritis patients receiving TNF-α blocking therapy.[4]

We now present 5-year safety data of biological treatment for psoriasis in daily practice with a focus on serious adverse events (SAEs).

Methods

Patients

All consecutive patients starting biological treatment for psoriasis in the Dermatology outpatient clinic of the Radboud University Nijmegen Medical Centre are enrolled in a registry, in which efficacy and pharmacovigilance data are collected.[5-7] In the Netherlands, biological treatment is approved for the treatment of psoriasis patients who have not responded to phototherapy, methotrexate and ciclosporin, or who have contraindications to, or do not tolerate these therapies. Furthermore, a PASI[8] of at least 10 is required.

Protocol

Screening procedures included a chest X-ray, Mantoux test, urine screening, routine chemistry and haematology, antinuclear antibodies (ANA), hepatitis serology and a serum pregnancy test if applicable. A general blood screening was repeated every 12 weeks during therapy (Table 1).

Patients were treated according to the opinion of the dermatologist, including dose and interval changes and the addition of topical or systemic therapies. Women of childbearing potential were strongly recommended to use adequate contraception to prevent pregnancy.

Table 1. Laboratory investigations.

Chemistry	Haematology	Additional
Creatinine	Haemoglobin	Antinuclear antibodies*
C-reactive protein (CRP)	Haematocrit	Hepatitis B/C serology*
Direct bilirubin	White blood cell count	Serum pregnancy test*
Total bilirubin	White blood cell differentiation	
Alkaline phosphatase (ALP)	Platelet count	
Alanine aminotransferase (ALT)		
y-Glutamyl transferase (GGT)		
Cholesterol*		
Triglycerides*		
Urinalysis*		

*These laboratory tests were only performed at screening. The other tests were performed at screening and every 12 weeks during therapy.

Outpatient clinic visits were planned every 4 to 6 weeks during the first 12 weeks of treatment, every 6 weeks until week 24 and every 12 weeks afterwards. Demographic data, the medical history and previous (antipsoriatic) medication use were recorded at the time of screening. Adverse events were prospectively collected at each hospital visit.

Analysis

Reported adverse events and comorbidities were categorized in line with the ICD-10.[9] Primary endpoint was the percentage of patients reporting at least one SAE. The SAE rate was compared with the general population incidence rate from a Dutch general practice registry (CMR).[10, 11] The CMR collects data concerning all morbidity that patients present to the involved general practitioners, including diagnoses made by specialists after referral.

Adverse events were defined as serious in case of life-threatening events, events requiring (prolongation of) inpatient hospitalization, congenital anomalies and events resulting in persistent or significant disability/incapacity or death.[12]
The nature and rate of dermatological adverse events was compared with an article about a group of prospectively followed rheumatoid arthritis (RA) patients on TNF-α blockers from the same hospital, who were followed in the same way as the present cohort.[4]

Adverse events were analysed per patient as well as per treatment episode. A new treatment episode was started when patients started a new biologic therapy or when the same biologic was restarted after an interruption lasting more than 6 months. The number of patients having at least one adverse event in a predefined category was represented. Patient characteristics were expressed as numbers (percentages) and means (± standard deviation (SD)).

Table 2. Patient characteristics.

Patient characteristics	n = 173
Male gender, n (%)	109 (63.0)
Age (years), mean ± SD	50.6 ± 12.1
Duration of psoriasis (years), mean ± SD	26.0 ± 12.8
Psoriatic arthritis, n (%)	51 (29)
Total duration of exposition to biologics[a]	
Mean ± SD (years)	2.7 ± 1.6
Median (years) (range)	2.7 (4 days – 7.4 years)
Duration of registry follow-up	
Mean ± SD (years)	2.3 ± 1.6
Median (years) (range)	2.3 (4 days – 5.2 years)
Number of different biologics[b], n (%)	
One	88 (50.9)
Two	53 (30.6)
Three	24 (13.9)
Four	7 (4.0)
Five	1 (0.6)

[a]Data on the total duration of exposition to biologics (consisting of pre-enrolment and postenrolment biological treatment) were available for 170 patients (98%). [b]Consisting of pre-enrolment and postenrolment biological treatment.

Statistics

Relative rates, defined as the ratio of the observed to the expected number of serious adverse events, were calculated. The expected number of serious adverse events was calculated by multiplying the gender- and 10-year-age-group incidence rates in the CMR by the patient-year distribution of the psoriasis cohort. We calculated the 95% confidence interval for each relative rate on the assumption of a Poisson distribution of the number of observed cases.

Results

Patients

Between February 2005 and April 2010, 173 patients were enrolled in the registry and went through a total number of 263 treatment episodes. Sixty-three percent of patients were male and the mean age was 50.6 (± 12.1) years (Table 2). The mean psoriasis disease duration was 26.0 ± 12.8 years.

The number of different biologics applied per patient, including pre-enrolment biological treatment (e.g. biological treatment in other hospitals and biologics applied in clinical trials) and postenrolment biological treatment (e.g. biological treatment in our university hospital), varied between one and five (Table 2).

Table 3. Comorbidities in the cohort of 173 psoriasis patients treated with biologics up until the moment of evaluation. Only comorbidities occurring in ≥ 5 patients are represented.

Comorbidities	**n = 173** **n (%)**
Diseases of the blood and blood-forming organs, total*	8 (5)
Diseases of the circulatory system, total	74 (43)
Cardiac arrhythmia	6 (3)
Cerebrovascular disease	10 (6)
Diseases of veins, lymphatic vessels and lymph nodes	18 (10)
Hypertension	55 (32)
Ischaemic heart disease	12 (7)
Diseases of the digestive system, total	58 (34)
Appendectomy	13 (8)
Disorders of gallbladder, biliary tract and pancreas	13 (8)
Fatty liver	8 (5)
Liver fibrosis	8 (5)
Hernia	16 (9)
Diseases of the ear and mastoid process, total	9 (5)
Diseases of the eye and adnexa, total	12 (7)
Diseases of the genitourinary system, total	37 (21)
Urolithiasis	6 (3)
Diseases of the musculoskeletal system, total	57 (33)
Osteoarthritis	7 (4)
Gout	7 (4)
Meniscus derangement	9 (5)
Shoulder lesion	5 (3)
Surgery, NOS	25 (14)
Diseases of the nervous system, total	28 (16)
Epilepsy	10 (6)
Herniated nucleus pulposus	10 (6)
Nerve, nerve root and plexus disorders	9 (5)
Diseases of the respiratory system, total	3 (19)
Chronic lower respiratory diseases	13 (8)
Diseases of the upper respiratory tract	19 (11)
Diseases of the skin and subcutaneous tissue, total	25 (14)
Hidradenitis suppurativa	5 (3)
Endocrine, nutritional and metabolic diseases, total	45 (26)
Diabetes mellitus	22 (13)
Hypercholesterolaemia	25 (14)
Hypothyroidism	6 (3)
Certain infectious and parasitic diseases, total	33 (19)
Viral hepatitis	10 (6)
Mental and behavioural disorders, total	22 (13)
Depressive disorder	7 (4)
Neoplasms, total	20 (12)
Benign neoplasms	9 (5)
Malignant neoplasms	15 (9)
Other	66 (38)

*Including certain disorders involving the immune mechanism. NOS, not otherwise specified.

Table 4. Treatment characteristics.

Biological	No. of treatment episodes	No. of patients	Treatment episode duration (years)		Patient-years	Dose (mg)
			Mean ± SD	Median (range)		
Etanercept	159	150	2.0 ± 1.5	1.7 (0.01 – 5.2)	319.8	67.6[a]
Adalimumab	59	59	0.9 ± 0.5	0.9 (0.02 – 1.9)	55.4	25.5[a]
Efalizumab	28	27	0.9 ± 0.9	0.5 (0.08 – 3.4)	24.8	Per label
Infliximab	9	7	0.6 ± 0.5	0.5 (0.04 – 1.6)	5.3	Per label[b]
Ustekinumab	8	8	0.5 ± 0.4	0.4 (0.14 – 1.1)	4.0	Per label[c]

[a]Mean weekly dose. [b]One patient was initially treated with 3 mg/kg infliximab. [c]Ustekinumab was applied per label in all but two patients. In one patient shortening of the treatment interval to 8 weeks and in another patient shortening of the treatment interval as well as a dosage increment to 90 mg was necessary.

Concomitant systemic antipsoriatic treatment consisted of methotrexate (n = 37), acitretin (n = 12), ciclosporin (n = 13), fumarates (n = 2) and mycophenolate mofetil (n = 1). One hundred and sixty-four patients reported 755 comorbidities (Table 3). Common comorbidities were hypertension (n = 55 (32%)), hypercholesterolaemia (n = 25 (14%)) and diabetes mellitus (n = 22 (13%)).

Pre-enrolment biological treatment

Biologics applied in the pre-enrolment period were etanercept, adalimumab, infliximab, ustekinumab, efalizumab, alefacept and onercept. Alefacept and onercept were exclusively applied before enrolment. The mean total duration of exposition to biologics (i.e. pre-enrolment and postenrolment biological treatment) was 2.7 ± 1.6 years (median 2.7 years (range 4 days - 7.4 years)) (Table 2).

Postenrolment biological treatment

The registry contains data of etanercept, adalimumab, efalizumab, infliximab and ustekinumab treatment episodes (Table 4). Single biological treatment regimens applied from the moment of enrolment consisted of etanercept (n = 94), adalimumab (n = 13), efalizumab (n = 3), infliximab (n = 3) and ustekinumab (n = 2). Twenty-four patients (14%) were treated with etanercept followed by adalimumab. The other 34 patients (20%) were treated with variable consecutive biological treatment regimens. In 79 patients (46%), etanercept was the only biologic ever applied. For 22 patients (13%), etanercept and subsequently adalimumab were the only biologics they had ever received. The mean duration of registry follow-up was 2.3 ± 1.6 years (median 2.3 years (range 4 days - 5.2 years)) (Table 2). The total number of patient-years in the registry was 409. Dosing information is provided in Table 4.

Table 5. Numbers and percentages of psoriasis patients treated with biologics with at least one adverse event in a category.

Adverse events	n = 173 n (%)
(Pre)malignancies, total	18 (10)
Actinic keratosis	11 (6)
Basal cell carcinoma	4 (2)
Squamous cell carcinoma	4 (2)
Cervix carcinoma in situ	1 (1)
Metastatic colon cancer*	1 (1)
Bowen disease	1 (1)
Breast cancer	1 (1)
Oesophageal carcinoma	1(1)
Cardiovascular diseases/complaints, total	22 (13)
Skin diseases/complaints, total	103 (60)
Endocrine diseases/complaints, total	8 (5)
Gastro-intestinal diseases/complaints, total	52 (30)
Infections, total	133 (77)
Upper respiratory tract infections	98 (57)
Lower respiratory tract infections	15 (9)
Gastrointestinal infections	16 (9)
Genital infections	2 (1)
Influenza/influenza-like symptoms	65 (38)
Skin infections	34 (20)
Latent tuberculosis	1 (1)
Urinary tract infections	16 (9)
Diseases/complaints of the musculoskeletal system, total	79 (46)
Diseases/complaints of the nervous system, total	48 (28)
Diseases/complaints of the genitourinary system, total	14 (8)
Eye diseases/complaints, total	29 (17)
Ear diseases/complaints, total	13 (8)
Mental diseases/complaints, total	13 (8)
Pulmonary diseases/complaints, total	25 (14)
Other, total	125 (72)

*Poorly differentiated metastatic cancer, possibly originated in the colon.

Safety

A total of 169 patients reported 1530 adverse events (Table 5). Common adverse events (reported by 20% of patients or more) were upper respiratory tract infections, skin infections, pruritus, joint complaints, flu-like symptoms, gastrointestinal complaints, headache and fatigue.

Serious adverse events

Forty-nine patients (28%) reported 88 SAEs (Table 6). Twenty-one events (24% of SAEs)

Table 6. Numbers of psoriasis patients treated with biologics with at least one serious adverse event in a category.

Serious adverse events	No. of patients	Treatment
Malignancies		
Basal cell carcinoma	4	ETN (n = 3), ADA (n = 1)
Squamous cell carcinoma	4	ETN (n = 3), EFZ (n = 1)
Breast cancer	1	ETN
Oesophageal carcinoma	1	ETN
Metastatic colon cancer[a]	1	ETN
Infections		
Erysipelas	1	ETN
Pneumonia	1	ETN
Asthmatic bronchitis exacerbation[b]	1	ETN
Cardiovascular events		
Myocardial infarction	2	ETN
Angina pectoris	2	ETN
Congestive cardiomyopathy	1	ETN
Atrial fibrillation	2	ETN
Perimesencephalic haemorrhage	1	ETN
Gastro-intestinal diseases/complaints		
Cholecystectomy (cholecystitis)	1	ETN
Hernia cicatricialis surgery	1	ETN
Hernia inguinalis surgery	1	ETN
Liver cirrhosis	1	ADA
Stomach complaints	1	ETN
Peri-anal fistula	1	ETN
Oesophageal varices bleeding	1	ADA
Diseases/complaints of the musculoskeletal system		
Arthritis	1	EFL
Shoulder enthesopathy	1	ETN
Traumatic bone fracture	3	ETN (n = 2), ADA (n = 1)
Joint complaints	1	EFL
Diseases of the genitourinary system		
Cystocele surgery	1	ETN
Nefrolithiasis	1	ADA
Hysterectomy (polyps)	1	ETN
Exacerbation of psoriasis	17	ETN (n = 13), ADA (n = 3), EFL (n = 5), INF (n = 2)[c]
Other		
Leg abscess	1	ETN
Infusion reaction	1	INF
Knee surgery	3	ETN
Spontaneous abortion	1	ETN
Child born with patent ductus arteriosus	1	ETN
Malaise, joint complaints, weight loss	1	ADA
Death	4	ETN (n = 3), ADA (n = 1)
Total	49	

[a]Poorly differentiated metastatic cancer, possibly originated in the colon. [b]Triggered by an airway infection. [c]Three patients experienced psoriasis exacerbations during different biological therapies. ADA, adalimumab; EFL, efalizumab; ETN, etanercept; INF, infliximab.

Table 7. Malignancies.

Malignancy	No. of malignancies in category	Rx	Time to event (months)	Relevant pretreatment	Relevant medical history
BCC					
Patient 1	5	ETN	2, 2, 4, 30, 33	UVB 138 J/cm^2, PUVA 1982 J/cm^2, CsA 1.5 yr, azathioprine 0.5 yr, MTX	-
Patient 2[a]	2	ETN	5	UVB, PUVA > 30 months, MTX 3 yr	SCC, multiple BCCs
Patient 3	1	ETN[b]	3	CsA, PUVA (low dose), MTX	-
Patient 4	2	ADA	3	CsA[c], MTX, UVB 7 treatments, PUVA (high dose), ETN 4 months	-
SCC					
Patient 1[d]	3	ETN	4	UVB 2 treatments, PUVA, CsA[c], MTX	-
Patient 2[a]	1	ETN	6	UVB, PUVA > 30 months, MTX 3 yr	SCC, multiple BCCs
Patient 3	1	ETN	17	UVB 6 months, PUVA > 330 J, CsA 1.9 yr, MTX	-
Patient 4	5	EFL	27	PUVA (high dose), UVB, CsA, MTX, alefacept	-
Breast cancer	1	ETN	30	CsA 2.5 yr, MTX 1.5 yr	-
Oesophageal carcinoma[d]	1	ETN	10	CsA[c], MTX	-
Metastatic colon cancer[e]	1	ETN	35	CsA 6.5 yr, azathioprine 4 months, EFL 1 yr, MTX	-

[a]This patient was diagnosed with 2 BCCs and one SCC. [b]1.5 months concomitant CsA. [c]< 3 months. [d]This patient was diagnosed with 3 SCCs and an oesophageal carcinoma. [e]Poorly differentiated metastatic cancer, possibly originated in the colon. ADA, adalimumab; BCC, basal cell carcinoma; CsA, ciclosporin A; EFL, efalizumab; ETN, etanercept; MTX, methotrexate; Rx, treatment; SCC, squamous cell carcinoma of the skin.

were considered possibly related and one event (infusion reaction) was certainly causally related to the biologic.

Four patients died during biological treatment. Two patients died from a sudden cardiac arrest after 12 and 15 months of etanercept treatment, respectively. One of these patients had a history of hypertension and stroke and the other patient suffered from chronic obstructive pulmonary disease. The third patient was diagnosed with alcoholic liver cirrhosis and died from an internal bleeding after 9 months of adalimumab treatment. In our opinion, a causal relation between the biological treatment and these deaths was unlikely. In the fourth patient, a myocardial infarction was revealed at autopsy after 4 days of etanercept treatment, which made a relation possible.

Table 8. Expected and observed numbers of malignancies, serious infections and serious cardiovascular events per 409 patient-years in the cohort of 173 psoriasis patients.

	Expected[a]	Observed[b]	RR (95% CI)[c]
Malignancies			
Breast cancer	0.4	1	2.7 (0.1 – 15.1)
Upper digestive tract	0.2	1	4.3 (0.1 – 23.8)
Lower digestive tract	0.4	1	2.4 (0.1 – 13.3)
Basal cell carcinoma	0.8[d]	10	12.2 (5.9 – 22.5)
Squamous cell carcinoma	0.1	10	81.4 (39.0 – 149.8)
Infections			
Erysipelas	2.2	1	0.5 (0.1 – 2.6)
Pneumonia	4.5	1	0.2 (0.1 – 1.2)
Asthmatic bronchitis exacerbation	4.0	1	0.2 (0.1 – 1.4)
Cardiovascular			
Myocardial infarction	1.3	2	1.5 (0.2 – 5.6)
Cerebrovascular accident	1.3	1	0.8 (0.1 – 4.2)
Heart failure	0.7	1	1.4 (0.1 – 7.7)
Angina pectoris	1.3	2	1.6 (0.2 – 5.6)
Atrial fibrillation	1.2	2	1.7 (0.2 – 6.1)

[a]Expected number of events based on the general population incidence rate (CMR). [b]Observed number of events in the psoriasis cohort. [c]RR (95% CI), relative rate (95% confidence interval). [d]Expected number of skin malignancies other than SCC and melanoma (almost always BCCs).

Malignancies

Eleven malignancies were found in 9 patients (Table 7). A 48-year-old man was diagnosed with three squamous cell carcinomas (SCCs) of the skin and an oesophageal carcinoma during etanercept therapy. Another patient had 2 basal cell carcinomas (BCCs) and one SCC of the skin within half a year after the start of etanercept. All patients with skin malignancies had an extensive history of UVB and/or PUVA exposure and were previously treated with immunosuppressive drugs, including a biologic in two cases. In all patients with skin malignancies but three patients with BCCs, the biologic was discontinued.

Moreover, a 66-year-old female patient on etanercept was diagnosed with an invasive ductal carcinoma of the breast. Recently, a 76-year-old male patient on etanercept was diagnosed with a poorly differentiated metastatic cancer, possibly originated in the colon. Biological treatment was discontinued in the patient with the oesophageal carcinoma, but continued in the patient with breast cancer and the patient with metastatic cancer, because of the significant negative impact of withdrawal of the biologic on their quality of life and only after informed consent of the patient and approval of the treating oncologist. The incidence of breast cancer, oesophageal carcinoma and colon carcinoma in our cohort was not increased compared with the rate expected from the CMR (Table 8). The observed rate of skin malignancies was higher than in the CMR.

Biological treatment in patients with previous malignancies

A patient with a history of breast cancer more than 10 years before the start of biological treatment was treated with alefacept, etanercept and adalimumab for a total duration of 5.7 years. Another patient diagnosed with breast cancer more than 8 years before the start of etanercept was treated with this agent for 3 months. Again another patient with a history of a bladder carcinoma more than 9 years before the start of etanercept was treated with etanercept followed by adalimumab for a total period of 2.7 years. No recurrences of solid tumours were seen.

A 65-year-old female patient with a history of a SCC of the skin and multiple BCCs 11 years and 3 years before the initiation of etanercept, respectively, was diagnosed with another SCC of the skin and 2 BCCs during etanercept treatment (Table 7). We did not see any recurrences or new skin malignancies in two other patients with a history of BCCs and one patient with a history of a SCC of the skin.

Infections

A total of 412 infections were reported in 133 patients (Table 5). Upper respiratory tract infections, influenza/influenza-like symptoms and skin infections occurred most frequently.

Serious infections concerned an exacerbation of asthmatic bronchitis (triggered by an airway infection) (n = 1), erysipelas (n = 1) and pneumonia (n = 1) (Table 6). The rate of serious infections was comparable with the CMR. In one patient, latent tuberculosis was detected during treatment. Etanercept was discontinued and isoniazid was started. Five patients were prophylactically treated with isoniazid, because of suspected latent or old healed tuberculosis. A chronic hepatitis B carrier was treated with etanercept and antiretroviral therapy for 0.8 years. No reactivation of hepatitis B occurred during the study period.

Cardiovascular events

Twenty-nine cardiovascular events were recorded in 22 patients. A 64-year-old male patient with a history of myocardial infarction was diagnosed with heart failure due to congestive cardiomyopathy after 3.5 years of etanercept treatment (Table 6). Another 53-year-old male patient with a history of a cerebrovascular accident was admitted with myocardial infarction after 2.9 years of etanercept treatment and another 61-year-old female patient died from a myocardial infarction after 4 days of etanercept treatment.

Another 61-year-old male patient had a perimesencephalic haemorrhage after 10 months of etanercept treatment. Two patients required a PTCA procedure for angina pectoris after 3 months and 1.3 years of etanercept treatment, respectively. All but one of abovementioned patients had cardiovascular risk factors. A relation with the etanercept

Table 9. Number of dermatological events in a category and percentages of patients with at least one adverse event in a category.

Dermatological event	No. of events (%)	No. of patients (%)	Biologic	Time to event (months)	
				Median	Range
Pruritus	70 (21.7)	55 (44.7)	ETN 47, A 14, EFZ 8, I 1	3.0	0.0 – 46.5
Skin infection	58 (18.0)	38 (30.9)	ETN 45, EFZ 5, A 3, I 4, U 1	9.9	0.1 – 54.2
Injection site reaction	29 (9.0)	27 (22.0)	ETN 26, A 2, EFZ 1	0.5	0.0 – 32.2
Benign skin tumour	23 (7.1)	21 (17.1)	ETN 19, EFZ 3, A 1	17.8	0.7 – 54.2
Malignant skin tumour	20 (6.2)	7 (5.7)	ETN 13, EFZ 5, A 2	4.6	1.1 – 33.1
Premalignant skin tumour	15 (4.7)	12 (9.8)	ETN 11, EFZ 3, A 1	7.2	1.2 – 38.0
Eczema	11 (3.4)	10 (8.1)	ETN 8, A 2, U 1	9.4	0.8 – 38.8
Hair loss	9 (2.8)	9 (7.3)	ETN 5, EFZ 2, A 1, U 1	4.8	1.1 – 40.9
Morphological change in psoriasis	8 (2.5)	8 (6.5)	ETN 7, EFZ 1	10.9	1.6 – 32.2
Xerosis cutis	7 (2.2)	7 (5.7)	ETN 3, A 4	15.3	0.5 – 48.2
Leg ulcer	5 (1.6)	5 (4.1)	ETN 4, A 1	18.3	3.7 – 41.5
Prurigo	4 (1.2)	4 (3.3)	ETN 3, A 1	26.0	0.5 – 51.7
Acneiform dermatosis	4 (1.2)	3 (2.4)	ETN 3, I 1	5.2	0.5 – 28.9
Drug eruption	5 (1.6)	5 (4.1)	ETN 3, A 1, EFZ 1	0.9	0.0 – 8.8
Seborrheic dermatitis	2 (0.6)	2 (1.6)	A 2	2.8; 4.8	-
Stasis dermatitis	2 (0.6)	2 (1.6)	ETN 2	0.2; 26.4	-
CVI/varices	2 (0.6)	2 (1.6)	ETN 1, EFZ 1	2.0; 19.5	-
Porokeratosis	2 (0.6)	2 (1.6)	ETN 1, A 1	5.7; 56.0	-
Worsening of hidradenitis suppurativa	2 (0.6)	2 (1.6)	ETN 2	7.0; 36.9	-
Photodermatosis	1 (0.3)	1 (0.8)	ETN	7.7	-
Grover disease	1 (0.3)	1 (0.8)	ETN	2.1	-
Vitiligo	1 (0.3)	1 (0.8)	ETN	23.0	-
Interstitial granulomatous dermatitis	1 (0.3)	1 (0.8)	A	17.2	-
Lichenoid dermatitis	1 (0.3)	1 (0.8)	ETN	1.4	-
Alopecia areata	1 (0.3)	1 (0.8)	ETN	17.4	-
Dyshidrosis lamellosa sicca	1 (0.3)	1 (0.8)	EFZ	33.9	-
Other	37 (11.5)	27 (22.0)		5.6	0.1 – 47.2
Total	322 (100)	123 (100)		5.7	0.0 – 56.0

A, adalimumab; ETN, etanercept; EFZ, efalizumab; I, infliximab; U, ustekinumab.

use was considered unlikely, except for the perimesencephalic haemorrhage and the early cases of angina pectoris and myocardial infarction, which were considered possibly related. The rate of serious cardiovascular events was comparable with the CMR.

Dermatological conditions

A total of 123 patients reported 322 dermatological events (Table 9). Common dermatological events were pruritus (n = 55) and skin infections (n = 38), consisting of 18 bacterial, 17 fungal, 14 viral and 9 nonspecified infections. Injection site reactions occurred frequently during the first 6 months of biological treatment. Eczema diagnosis comprised allergic contact dermatitis (n = 1), asteatotic eczema (n = 1), irritant contact dermatitis (n = 2), nonspecified cases of eczema (n = 5) and hand eczema (n = 1). Forty-eight dermatological events were classified as serious, comprising skin malignancies, exacerbations of psoriasis and one case of erysipelas. Seventeen patients required 27 hospital admissions because of an exacerbation of their psoriasis due to abrupt discontinuation of other systemic antipsoriatic treatments at the start of biological treatment, interruptions because of infections or suboptimal efficacy or loss of efficacy of the biologic.

In two patients on etanercept, a worsening of their concomitant hidradenitis suppurativa was seen. Eight patients experienced a morphological change in psoriasis, e.g. inverse psoriasis (n = 3), pustular psoriasis (n = 3), palmoplantar pustulosis (n = 1) and suberythrodermia (n = 1). One hundred and twenty-three dermatological events were considered possibly related, comprising among others, 58 skin infections and 36 reports of pruritus. Two drug eruptions were considered probably related and 29 reports of injection site reactions were considered certainly related.

Musculoskeletal events

Seventy-nine patients (46%) reported at least one musculoskeletal adverse event. Serious musculoskeletal events comprised arthritis (n = 1), tendon rupture (n = 1), traumatic bone fractures (n = 3) and one case of nonspecified joint complaints (Table 6). All were considered unlikely causally related. Fifty-one patients of the total group of patients (29%) had psoriatic arthritis. Of the patients who reported musculoskeletal adverse events, 26 (33%) had psoriatic arthritis.

Other adverse events

Pregnancy: Three healthy children were born to a parent taking etanercept. In two cases, the father was taking etanercept and in the other case the mother was taking etanercept at the time of conception. In the latter patient, etanercept was discontinued after 4 weeks of pregnancy. One male patient had a child born with a patent ductus arteriosus during etanercept treatment (Table 6). The child recovered completely.

Uveitis: One patient developed bilateral uveitis after 3.8 years of etanercept use. Etanercept was unlikely causally involved.

Laboratory: Significant changes in laboratory measurements were occasionally seen, but were often transient or pre-existent or could be explained by concomitant medication or comorbidity. Laboratory abnormalities did not lead to permanent withdrawal of biological treatment.

Discussion

In this study, we investigated the safety of biologic therapy for psoriasis applied in real-world practice for 5 years. The number of patient-years of follow-up was the highest for etanercept (319 patient-years), as this was one of the first biologics registered for the treatment of psoriasis (Table 4). To provide a complete overview, efalizumab was described as well, although the marketing authorization has been withdrawn.

The assessment of the relationship between an adverse event and the biologic was based on the investigator's judgment, taking into account the time relationship and the patient's comorbidity and/or comedication. This cohort of 173 psoriasis patients had an extensive medical history, with a mean number of 4.4 comorbidities per patient. Fifty-five patients (32%) received concomitant systemic antipsoriatic treatment. Additional morbidity caused by biological treatment can have a further negative impact on the quality of life of patients with psoriasis.

The mild adverse events were of the same nature as described in our previous articles and other studies and hardly ever outweighed the benefits of continuing the biologic.[2, 3, 5-7] The incidence of upper respiratory tract infections and flu-like symptoms was much higher in our cohort compared with the CMR. This will at least in part be the result of surveillance bias, as our cohort was followed more closely than the general population. In addition, the expected number of serious adverse events in our cohort was calculated using 10-year-age-group incidence rates from the CMR, which may have caused under- or overestimation of the expected rate for sharp age-related diseases in case of clustering at the top or the bottom of the 10-year-age-groups in our cohort.

The incidence of SAEs was comparable with the CMR, except for skin malignancies. Apart from exposition to biologics, the significantly higher number of skin malignancies in the psoriasis cohort could also be explained by previous exposure to UV phototherapy and immunosuppressive drugs, a higher awareness for skin malignancies among dermatologists than among general practitioners and by the fact that some patients in our cohort had several skin tumours, which were all registered as separate incident cases for comparison with the CMR.
With respect to skin malignancies in rheumatoid arthritis patients treated with TNF-antagonists, data are inconsistent. Some studies have found an increased risk of nonmelanoma skin cancer as well.[13-15] As these patients have not previously been treated with phototherapy, TNF-antagonists might play a role in this.

Two Swedish studies found an increased risk of SCCs of the skin in patients hospitalized for psoriasis compared with the general population.[16, 17] The relative rate of SCCs of the

skin in the present study was higher than that in the Swedish studies. However, in these studies only the first SCC in a patient was registered, in contrast to the present study and the CMR where all SCCs were registered. Selection bias might influence the incidence of malignancies during biologic therapy in a positive way, as past malignancies are a relative contraindication for biologic therapy.[18]

Nine malignancies were diagnosed within the first 10 months of biological treatment. This period of time is probably too short for the biologic to play a role in the pathogenesis of the tumour, although the drug could have accelerated the process of malignant degeneration.[18]
The oesophageal carcinoma concerned an adenocarcinoma in a Barrett oesophagus and was therefore probably not related to biological treatment but to reflux disease.
Malignancies are a relative contraindication for a TNF-antagonist and ustekinumab.[2, 3] We did not see any recurrences of malignancies in patients with previous malignancies.

Infections were mainly mild. Only three serious infections occurred. Guidelines recommend to avoid biologics in chronic hepatitis B carriers because of the risk of reactivation.[2, 3] No reactivation of hepatitis B occurred in a chronic hepatitis B carrier during 0.8 years of monitored etanercept treatment in combination with antiretroviral therapy.

A relation between the majority of serious cardiovascular events and the biologic was considered unlikely in view of the medical history, the presence of cardiovascular risk factors and the time relationship. The incidence of serious cardiovascular events was comparable with the CMR, but the prevalence of cardiovascular risk factors in our cohort was high compared with the CMR. Attention should be paid to these pre-existent cardiovascular risk factors.

The most common dermatological adverse event encountered in our cohort was pruritus, which was hardly ever reported by the RA patients. Skin infections were frequently seen in both our cohort as well as the RA cohort. Eczema was the second most common event in the RA cohort, but was less frequently seen in our cohort. A possible explanation given for eczema occurring in RA patients on anti-TNFα therapy was a shift of the Th1/Th2 balance towards a Th2-dominated immune response.[4] Why this occurs to a much lesser extent in psoriasis needs further investigation.
Paradoxical events were seen in the form of worsening of hidradenitis suppurativa, uveitis and morphological changes or exacerbations of psoriasis. Paradoxical events have been described before.[2] This phenomenon needs further investigation.

A child with a patent ductus arteriosus was born from a father taking etanercept, which we considered probably unrelated to the biologic. This congenital anomaly has been

described earlier but as part of a probable VACTERL association in a mother taking adalimumab.[19] As pregnancy safety data are still sparse, female patients should still be strongly advised to prevent pregnancy during biological treatment.[2]

In conclusion, in this cohort the safety of biological therapy for psoriasis was favourable with a low incidence of therapy-related SAEs. This especially holds for etanercept. Continuing long-term follow-up in registries and reporting of rare adverse events by physicians (inter)nationally is very important to substantiate data further and to detect adverse events for which cumulative exposition may play a role.

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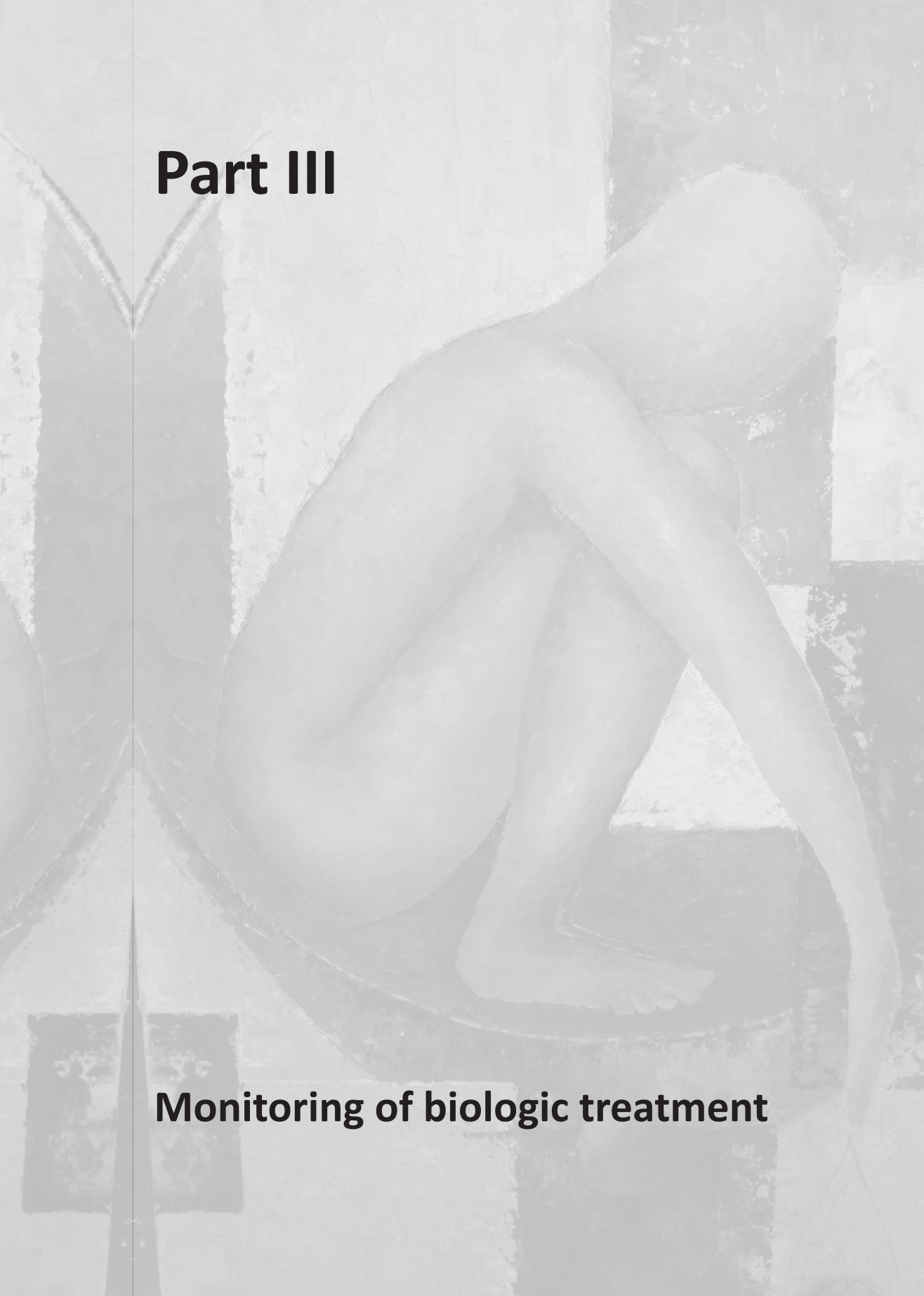

Part III

Monitoring of biologic treatment

Chapter 8

Nonmelanoma skin cancer during treatment with TNF-inhibitors in psoriasis patients probably relates to prior exposure to phototherapy

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Abstract

Background

Concerns exist about a risk of NMSC in psoriasis patients and rheumatoid arthritis (RA) patients treated with TNF-inhibitors. However, current data also show that in some psoriasis patients, NMSC is diagnosed relatively short after the start of TNF-inhibitors, which suggests that these NMSC can be explained by previous therapies like phototherapy instead of by TNF-inhibitor therapy. We hypothesized that if NMSC during TNF-inhibitor therapy can be attributed to phototherapy, the time until first NMSC will be shorter and the incidence of NMSC will be higher in psoriasis compared with RA.

Objective

To investigate whether there was a difference in time until first NMSC and the incidence of NMSC between psoriasis and RA patients on TNF-inhibitors.

Methods

Time until first NMSC and the rate of NMSC were compared between psoriasis and RA patients from the same region treated with TNF-inhibitors and followed-up for at least one year in prospective cohort studies, by using Cox regression and Poisson regression. Both analyses were corrected for confounders (age, gender, disease duration, prior NMSC and duration of anti-TNFα and other systemic therapies).

Results

The NMSC risk was significantly higher in the psoriasis group (fully adjusted HR 6.0 (1.6 – 22.4 95%CI)) with a shorter time until first NMSC in psoriasis compared with RA. By Poisson regression, psoriasis patients had a 5.5 (2.2 – 13.4 95%CI) higher rate of NMSC.

Conclusion

The risk of developing NMSC was significantly higher in psoriasis compared with RA with a shorter time until first NMSC in psoriasis. This indicates that disease related factors like phototherapy may be an important contributing factor to NMSC diagnosed in psoriasis patients treated with TNF-inhibitors.

Introduction

Concerns exist about a possible increased risk of malignancies, including nonmelanoma skin cancer (NMSC), in psoriasis and RA patients treated with TNF-inhibitors.[1-3] However, current data also show that in some psoriasis patients, NMSC is diagnosed relatively short after the start of TNF-inhibitor therapy[2, 4-9], which suggests that these NMSC can be explained by previous therapies like phototherapy instead of by TNF-inhibitor therapy.
To investigate the influence of phototherapy, the occurrence of NMSC in a group of psoriasis patients treated with TNF-inhibitors would ideally be compared with a group of psoriasis patients who have received TNF-inhibitor therapy and other immunosuppressive therapies, but no phototherapy. However, as TNF-inhibitors can only be prescribed to patients who failed on phototherapy in most countries, such a group of patients is not available. Therefore, a comparison with a group of RA patients who were treated with TNF-inhibitors therapy and other immunosuppressive therapies but no prior phototherapy, provides valuable information.
Patients with psoriasis or RA have all been treated with immunosuppressive therapies like methotrexate, ciclosporin, prednisone and azathioprine before the start of TNF-inhibitor therapy. Corrections can be carried out for differences in previous treatments and demographic characteristics. This means that after statistical corrections, an important difference between the psoriasis and the RA group, is the fact that the psoriasis patients have received phototherapy (UVB and/or PUVA) whereas the RA patients have not received phototherapy.

Our hypothesis was that, if the occurrence of NMSC is attributable to phototherapy in psoriasis patients, the time from start of anti-TNFα treatment to first NMSC is expected to be shorter and the incidence of NMSC is expected to be higher in psoriasis compared with RA. Therefore the objective of this study was to investigate whether there is a difference in time to first NMSC and the incidence of NMSC between psoriasis patients and RA patients treated with TNF-inhibitors.

Methods

Patients

First, all available patients with plaque psoriasis initiated on etanercept, adalimumab and/or infliximab at the department of Dermatology of the Radboud university medical centre (Radboudumc) and the department of Dermatology of the Academic Medical Centre (AMC) of the University of Amsterdam between February 2005 and November 2011 with a follow-up of at least one year after the start of anti-TNFα therapy and enrolled in their respective registries, were selected.[10, 11]

Second, a group of RA patients initiated on the same TNF-inhibitors at the department of Rheumatic Diseases of the Radboudumc with a follow-up of at least one year between 2001 and November 2011 was selected. The number of available RA patients was higher than the number of available psoriasis patients, but all RA patients were selected for analysis (instead of a random selection). As the number of NMSC in the RA population was expected to be lower than in the psoriasis cohort, selecting all available RA patients would gain sufficient power.
Patients were not always treated with TNF-inhibitors for at least one year, due to possible interruptions of therapy. Effects of etanercept, adalimumab and infliximab were analysed, as these agents are prescribed for psoriasis as well as RA. Exposure to TNF-inhibitors in other contexts (participation in trials or treatment in nonacademic hospitals) before enrolment in the registries was taken into account as well.

The protocol of the prospective study performed at the department of Dermatology and Rheumatic Diseases of the Radboudumc was presented to the institutional review board (IRB). A formal IRB procedure and obtaining informed consent was considered unnecessary by the board because of the noninterventional character of the studies. The prospective study performed at the AMC was approved by the IRB of the AMC and patients registered in this database gave informed consent for registration.

Available data

Data were extracted from three prospective registries in which psoriasis or RA patients starting biological therapy in daily practice are enrolled.[10-12] All three registries covered the same time period and contained prospectively collected data about patient characteristics, exposure to biologic therapies and prior (systemic) therapies, concomitant therapies, adverse events and effectiveness. The psoriasis and RA patients were expected to be comparable with regard to the degree of sun exposure as all 3 registries cover parts of the Netherlands.

Information about NMSC and histology data were obtained from PALGA, the Dutch national histo- and cytopathology database and verified with data from the registries and (electronic) patient records.[13] This study focused on the most common types of NMSC, i.e. basal cell carcinoma (BCC) and SCC of the skin. Keratoacanthomas were considered as SCCs. Only primary skin tumours were included for analysis.

Statistical analysis

The primary analysis was a Cox proportional hazard regression analysis with time until occurrence of first NMSC after the start of anti-TNFα therapy as dependent variable and ‘disease’ (psoriasis or RA) as independent variable. For patients who were not diagnosed with NMSC after the start of anti-TNFα therapy, follow-up ended at November 2011 or

the date of loss of follow up or death, whichever was first (censoring date). As anti-TNFα therapy may continue to influence the risk of NMSC after its cessation, follow-up time in patients who discontinued anti-TNFα treatment before November 2011 was included in the analysis until November 2011 or another censoring date, if applicable. This is further named the 'ever exposed to anti-TNF analysis' and was considered the main analysis of this study. In the Cox regression analysis, only the first NMSC diagnosed after the start of TNF-inhibitor therapy contributes to the results. Time until first NMSC is presented by Kaplan-Meier survival curves.

The secondary analysis is a Poisson regression analysis with the rate of NMSC (number of events of NMSC divided by observation time in patient-years) as dependent variable and 'disease' as independent variable. This analysis was done to support the results of the Cox regression analysis. A rate ratio (RR) was calculated by dividing the rate of NMSC in the psoriasis group by the rate of NMSC in the RA group. For this analysis, observation time started at the time of initiation of the first anti-TNFα agent and ended at November 2011 or another censoring date, if applicable. In the Poisson regression analysis, all NMSC diagnosed after the start of TNF-inhibitor therapy contribute to the results. This Poisson regression model was built using the Generalized Linear Models procedure with a binominal distribution and a logit link function.

It was foreseen that the psoriasis and RA patients would differ at important prognostic factors for getting NMSC, like for instance a difference in ciclosporin use. Both analyses were corrected for those possible confounders: age, gender, disease duration (as an intermediate variable for severity of the disease), history of NMSC before the start of anti-TNFα therapy, cumulative duration of anti-TNFα therapy, cumulative duration of MTX, ciclosporin, prednisone and azathioprine therapy and the cumulative duration of treatment with biologics with a mechanism of action other than TNF-α blockade. Correction for immunosuppressive therapies was applied for those therapies which have in some studies been shown to increase the risk of developing NMSC.[14-20]

As our hypothesis was based on the assumption of equal duration of exposition to anti-TNFα therapy and because follow-up time was longer than the duration of exposition to anti-TNFα therapy in the 'ever exposed to anti-TNF analysis', 'cumulative duration of anti-TNFα therapy' was included in this analysis independent of the presence of a significant difference in the univariate analysis. The other candidate confounding variables were tested univariately between the psoriasis and RA groups with the unpaired student's t-test, Mann-Whitney U test, chi-square test or Fisher's exact test. Variables with a p-value < 0.1 were all included in the multivariate analysis. The number of UVB and PUVA treatments per patient was calculated. In case only the start date and stop date of UVB or PUVA were known, UVB and PUVA were expected to be applied 3 times a week.

Table 1. Demographics and treatment characteristics.

	Psoriasis n = 280	**Rheumatoid arthritis** n = 448	**p-value**
Male gender, n (%)	181 (65)	144 (32)	< 0.001
Age, years, mean ± SD	46.8 ± 11.9	56.3 ± (12.9)	< 0.001
Disease duration, years, median (range)	19.7 (1.1 – 64.4)	9.7 (0 – 51.3)	< 0.001
Psoriatic arthritis, n (%)	77 (28)	0 (0)	N.A.
NMSC prior to anti-TNFα therapy, n (%)	6 (2.1)	5 (1.1)	0.4
Phototherapy (unspecified), % (n)[a]	99% (275/279)[c]	UNK	N.A.
UVB, % (n)[a]	92% (254/276)[d]	UNK	N.A.
PUVA, % (n)[a]	58% (160/275)[e]	UNK	N.A.
Methotrexate use, n (%)[a]	270 (96)	439 (98)	0.2
Duration of methotrexate use, years, median (range)[b]	1.3 (0 – 27.3)	4.4 (0 – 28.6)	< 0.001
Ciclosporin use, n (%)[a]	217 (78)	23 (5)	< 0.001
Duration of ciclosporin use, years, median (range)[b]	0.5 (0 – 10.2)	0 (0 – 2.1)	< 0.001
Prednisone use, n (%)[a]	25 (9)	270 (60)	< 0.001
Duration of prednisone use, years, median (range)[b]	0 (0 – 2.7)	0.5 (0 – 33.4)	< 0.001
Azathioprine use, n (%)[a]	3 (1)	160 (36)	< 0.001
Duration of azathioprine use, years, median (range)[b]	0 (0 – 0.6)	0 (0 – 30.4)	< 0.001
Duration of anti-TNFα therapy[b], years, median (range)	3.7 (0.2 – 8.1)	4.1 (0.1 – 14.9)	0.3
Duration of non anti-TNFα biological therapy[b], years, median (range)	0 (0 – 3.7)	0 (0 – 4.3)	0.009

[a]Number and percentages represent patients ever exposed to the respective therapy. [b]Duration of use until date of first diagnosis of NMSC, November 2011 or the date of loss of follow-up or death ('ever exposed to anti-TNF analysis'). N.A.; not applicable. UNK; unknown. [c]1 missing, [d]4 missing,[e]5 missing,

In addition to the 'ever exposed to anti-TNF analysis', a sensitivity analysis was done to support the results of the main 'ever exposed to anti-TNF analysis', analyzing time until occurrence of first NMSC (Cox regression) and rates of NMSC (Poisson regression) between the start date of the first anti-TNFα agent and the discontinuation date of the last anti-TNFα agent ('on drug analysis'). For patients who were not diagnosed with NMSC, follow-up ended at the discontinuation date of the last anti-TNFα agent, November 2011 if the patient was still on anti-TNFα therapy or another censoring date, whichever was first. Patients were included for analysis when the time between the start date of the first anti-TNFα agent and the discontinuation date of the last anti-TNFα agent or another censoring date comprised at least one year. In the 'on drug analysis', cumulative duration of anti-TNFα therapy was not included as a confounder. All analyses as described above were repeated for the 'on drug analysis'. Analyses were done using PASW statistics 18®.

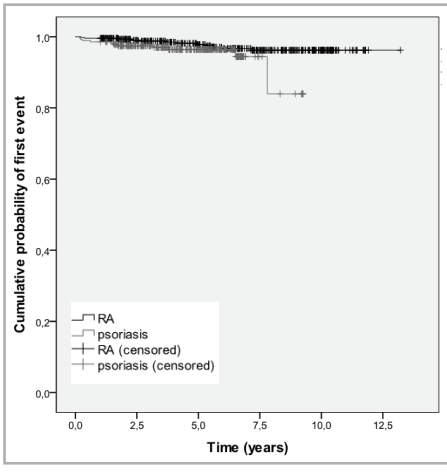

Figure 1. Time until first NMSC in all psoriasis and RA patients.

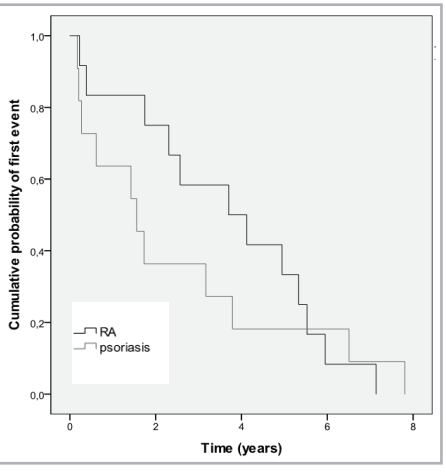

Figure 2. Time until first NMSC in psoriasis and RA patients with an event.

As NMSC prior to the start of TNF-inhibitor therapy was a strong predicting factor for being diagnosed with NMSC after the start of TNF-inhibitor therapy, a second sensitivity analysis excluding patients with prior NMSC was performed.

Results

Patients

Demographics and treatment characteristics

Two hundred and eighty psoriasis patients and 448 RA patients were included in the 'ever exposed to anti-TNF analysis' (Table 1). One patient with psoriasis was excluded because of insufficient information about the treatment history.

The median follow-up of the psoriasis patients in the 'ever exposed to anti-TNF analysis' was 4.8 (range 1.0 – 9.3) years. In the RA patients, this was 6.6 (range 1.0 – 14.9) years. The median follow-up in the 'on drug analysis' was 4.5 (range 1.0 – 9.3) years in de psoriasis group and 5.3 (range 1.0 – 14.9) years in the RA group. In the psoriasis cohort, 27 patients (9.6%) were lost to follow-up. In the RA group, this concerned 14 patients (3.1%).

The median exposition (censored) to anti-TNFα therapy in the psoriasis group was 3.7 (range 0.2 – 8.1) years. In the RA group, this was 4.1 (range 0.1 – 14.9) years.

The two groups differed significantly at important demographic characteristics, but were representative of a group of psoriasis patients or RA treated with biologic agents (Table 1).[12, 21] The psoriasis group contained a significantly higher proportion of males. In the psoriasis group, the mean age and disease duration at the start of anti-TNFα therapy was significantly lower, respectively longer. Ninety-nine percent of the psoriasis patients

Patient	NMSC	Total duration of anti-TNFα, (unadjusted, months)[a]	N° of NMSC during anti-TNFα[b]	N° of NMSC after anti-TNFα[c]
1	SCC	ETN[g] (101)	1	0
2	SCC BCC	ETN (12)	3 2	1 3
3	BCC	ETN, ADA[j] (17)	2	0
4	BCC	ETN, ADA (80)	1	0
5	SCC	ETN (39)	1	1
6	BCC	ETN (70)	5	0
7	BCC	ETN (63)	1	0
8	SCC	ETN, ADA (81)	1	0
9	BCC	ETN (67)	1	0
10	BCC	ETN (73)	1	0
11	SCC	ETN, ADA (76)	14	0

Table 2. Patients with psoriasis diagnosed with NMSC after the initiation of TNF-inhibitor therapy.
[a]Duration of therapy expressed as time (months) between the date of initiation of the first TNF-inhibitor and the date of discontinuation of the last TNF-inhibitor. [b]NMSC diagnosed between the date of initiation of the first TNF-inhibitor and the date of discontinuation of the last TNF-inhibitor. [c]NMSC diagnosed after the cessation of TNF-inhibitor therapy until November 2011 or the date of loss of follow up or death, whichever was first. [d]Time (months) between the date of initiation of TNF-inhibitor therapy and NMSC diagnosis. [e]Duration of treatment until the date of the first diagnosis of NMSC. [f]Skin cancer history before the initiation of TNF-inhibitor therapy. [g]ETN; etanercept, [h]MTX; methotrexate, [i]CsA; ciclosporin A, [j]ADA; adalimumab; [k]AZA; azathioprine. [l]KA; keratoacanthoma.

had been treated with phototherapy (UVB and/or PUVA). For the RA patients, information about phototherapy was lacking. However, when only considering psoriasis as an indication for phototherapy, the percentage of RA patients that had been treated with phototherapy was expected to be low, as only 5.6% of the RA patients had a history of psoriasis. Twenty-eight percent of the psoriasis patients had psoriatic arthritis and none had a concomitant diagnosis of RA. For 154 psoriasis patients, the number of UVB treatments was known and for 76 psoriasis patients, the number of PUVA treatments was known. In these patients, the median number of UVB treatments (censored) was 75 (range 2 – 490) and the median number of PUVA treatments (censored) was 65 (range 4 – 936).

Time to event (months) during anti-TNFα[d]	Time to event (months) after anti-TNFα[d]	Treatments, duration (censored, years)[e]	Skin cancer history[f]
94	N.A.	UVB (0.5), MTX[h] (1.4), CsA[i] (0.01), ETN (3.1)	-
2, 6, 10 5, 5	16 14, 14, 16	UVB, PUVA (>2.5), MTX (3), ETN (0.2)	4 BCC 2 KA[l]
7, 7	N.A.	UVB 7 courses, MTX (5.6), CsA (0.6), ETN (0.4), ADA (0.2)	-
78	N.A.	UVB 213 J, PUVA 2 courses, MTX (0.4), ETN (3.7), ADA (2.6)	-
38	51	UVB (0.5), PUVA (>0.9), MTX (5.6), CsA (1.9), ETN (1.4)	-
2, 2, 4, 30, 33	N.A.	UVB 138 J/cm^2, PUVA 1982 J/cm^2, MTX, CsA (1.5), AZA[i] (0.5), ETN (0.2)	-
3	N.A.	PUVA, MTX (0.3), CsA (0.4), ETN (0.3)	-
17	N.A.	UVB, MTX (1.2), CsA (0.4), alefacept (0.2), ETN (0.7)	-
45	N.A.	UVB >74 J/cm^2, PUVA, MTX (5.8), CsA (0.1), ETN (3.5)	-
21	N.A.	UVB, PUVA, MTX (1), ETN (1.6)	-
19, 31, 31, 40, 45, 49, 50, 50, 50, 59, 69, 69, 74, 74	N.A.	UVB, PUVA 12 courses, MTX (5.3), CsA (10.2), ETN (1.4)	5 BCC, 4 SCC, 1 KA[l], 1 melanoma in situ

The proportion of RA patients that had ever used prednisone or azathioprine was significantly higher and the duration of these therapies (censored) was significantly longer than in the psoriasis group (Table 1). In contrast, the proportion of patients that had ever used ciclosporin and the duration of ciclosporin therapy (censored) were significantly higher respectively longer in the psoriasis group. The dose of ciclosporin in the psoriasis patients was been between 2.5 and 3 mg per kg per day, according to Dutch guidelines. The proportion of patients that had used methotrexate did not differ significantly. The duration of methotrexate therapy (censored) was significantly longer in the RA group.
In the psoriasis group, 249 patients (89%) were treated with etanercept, 132 with adalimumab (47%) and 10 with infliximab (4%). In the RA group, 228 patients (51%) were treated with etanercept, 226 (50%) with adalimumab and 188 (42%) with infliximab.

Skin malignancies

Ever exposed to anti-TNF analysis

In the group of psoriasis patients, 11 patients (3.9%) were diagnosed with at least one NMSC after the start of TNF-inhibitor therapy (Table 2). In the group of RA patients, this concerned 12 patients (2.7%) (Table 3). The total number of NMSC was 38 (16 BCCs and 22 SCCs) in the psoriasis group and 27 (20 BCCs and 7 SCCs) in the RA group. One case of

Patient	NMSC	Total duration of anti-TNFα, (unadjusted, months)[a]	N° of NMSC during anti-TNFα[b]	N°of NMSC after anti-TNFα[c]
1	BCC	INF[g] (6)	0	3
2	BCC	INF, ETN[k], ADA[l] (113)	1	0
3	SCC BCC	ETN (107)	6 1	0 0
4	BCC	ADA (10)	0	3
5	BCC	ADA (69)	1	0
6	SCC	ADA (16)	0	1
7	BCC	INF, ETN, (11)	0	1
8	BCC	INF (16)	0	2
9	BCC	ETN, ADA (49)	0	1
10	BCC	INF, ETN, ADA (94)	1	0
11	BCC	INF (96)	1	0
12	BCC	ETN (12)	5	0

Table 3. Patients with RA diagnosed with NMSC after the initiation of TNF-inhibitor therapy.
[a]Duration of therapy expressed as time (months) between the date of initiation of the first TNF-inhibitor and the date of discontinuation of the last TNF-inhibitor. [b]NMSC diagnosed between the date of initiation of the first TNF-inhibitor and the date of discontinuation of the last TNF-inhibitor. [c]NMSC diagnosed after the cessation of TNF-inhibitor therapy until November 2011 or the date of loss of follow up or death, whichever was first. [d]Time (months) between the date of initiation of TNF-inhibitor therapy and NMSC diagnosis. [e]Duration of treatment until the date of the first diagnosis of NMSC. [f]Skin cancer history before the initiation of TNF-inhibitor therapy. [g]INF; infliximab, [h]MTX; methotrexate, [i]CsA; ciclosporin A, [j]AZA; azathioprine, [k]ETN; etanercept, [l]ADA; adalimumab.

BCC in the psoriasis group showed locally transition to a basosquamous carcinoma, which was considered as a BCC. No forms of NMSC other than BCC and SCC were diagnosed.

In the psoriasis group, six patients (2.1%) had a history of NMSC before the start of anti-TNFα therapy (Table 1). In the RA group, this concerned 5 patients (1.1%). Of the 11 psoriasis patients who were diagnosed with NMSC after the start of anti-TNFα therapy, 36% (4/11) received this diagnosis within the first year after the start of anti-TNFα therapy and 18% (2/11) had a history of NMSC before the start of TNF-inhibitor therapy. In the RA group, 17% (2/12) received a NMSC diagnosis within the first year and 17% (2/12) had a history of NMSC.
Apart from an SCC, patient 1 from the psoriasis group was also diagnosed with a superficial

Time to event (months) during anti-TNFα[d]	Time to event (months) after anti-TNFα[d]	Treatments, duration (censored, years)[e]	Skin cancer history[f]
N.A.	21, 53, 126	MTX[i] (2.2), CsA[i] (1), prednisone (8), AZA[k] (2), INF (0.5)	3 BCCs
28	N.A.	MTX (4.3), prednisone (5), INF (2.3)	-
5, 32, 58, 67, 70, 82 45	N.A. N.A.	MTX (2.3), prednisone (9), AZA (6), ETN (0.4)	-
N.A.	31, 31, 56	MTX (0.7), prednisone (13), AZA (1), ADA (0.9)	-
64	N.A.	MTX (0.1), prednisone (17), AZA (5), ADA (5.3)	-
N.A.	86	MTX (11.3), prednisone (10), ADA (1.1)	-
N.A.	66	MTX (1.8), prednisone (6), AZA (1), INF (0.6), ETN (0.3), rituximab (0.2)	-
N.A.	59, 61	MTX (28.6), prednisone (22), AZA (5), INF (1.3), abatacept (0.7)	-
N.A.	49	MTX (1.6), ETN (2.0), ADA (0.5)	-
44	N.A.	MTX (4.0), prednisone (2), AZA (1), INF (0.7), ETN (2.8),	6 BCCs
71	N.A.	MTX (10.8), prednisone (1), AZA (9), INF (6.0)	-
3, 3, 3, 3, 3	N.A.	MTX (0.1), prednisone (0.1), ETN (0.2)	-

spreading melanoma (Breslow thickness 0.3 mm, Clark level 3) after 101 months of TNF-inhibitor therapy.

The BCC:SCC ratio in the psoriasis group was 0.7:1 (16:22). In the RA group, this was 2.9:1 (20:7). After excluding patient 11 of the psoriasis group who had multiple SCCs, the BCC:SCC ratio was 2:1 (16:8).

Cox regression analysis

Figure 1 and Figure 2 show the time until first NMSC after the start of anti-TNFα therapy in all patients and in patients with an event only, respectively. The estimated mean time until first NMSC in all patients was 8.8 years in the psoriasis group and 12.9 years in the RA group. In patients with an event only, the median time until event was 1.6 years in the psoriasis patients and 3.7 years in the RA patients. The unadjusted hazard ratio (HR) of developing NMSC in the psoriasis group compared with the RA group was 2.0 (0.9 – 4.7 95%CI) (raw model, Table 4). The fully adjusted HR was 6.0 (1.6 – 22.4 95%CI) (corrected model). Correction for the duration of azathioprine therapy was not possible due to the low number of psoriasis patients that had used azathioprine.

The sensitivity analysis with exclusion of patients with NMSC prior to the start of TNF-inhibitor therapy showed an unadjusted HR of 2.1 (0.8 – 5.4 95%CI) and an adjusted HR of 13.4 (2.9 – 63.0 95%CI).

Table 4. Results of the Cox regression analysis ('ever exposed to anti-TNF analysis').

Variable	B	HR (exp B)	95% CI
Raw model			
Diagnosis	0.689	1.992	0.853-4.656
Corrected model			
Diagnosis	1.788	5.977	1.596-22.385
Age	0.053	1.054	1.011-1.099
Gender	0.381	1.464	0.586-3.660
Disease duration	0.010	1.010	0.997-1.023
NMSC prior to anti-TNFα therapy	1.843	6.316	1.698-23.499
Duration of anti-TNFα therapy	-0.013	0.988	0.982-0.993
Duration of non anti-TNFα biological therapy	-1.324	0.266	0.037-1.907
Duration of ciclosporin therapy	0.029	1.030	0.794-1.336
Duration of prednisone therapy	0.034	1.035	0.956-1.120
Duration of methotrexate therapy	-0.058	0.944	0.862-1.034

Poisson regression analysis

In the psoriasis patients a total number of 38 NMSC was reported in 1306 patient-years, resulting in an event rate of 2.9 (2.1-4.0 95%CI) per 100 patient-years; in the RA patients the event rate was 0.9 (0.6-1.3 95%CI) per 100 patient-years (27 events in 2863 patient-years). By Poisson regression, this resulted in an unadjusted rate ratio of 4.1 (2.3-7.0 95%CI). Corrected for confounders, by Poisson regression, psoriasis patients had a 5.5 (2.2 – 13.4 95%CI) higher rate of NMSC compared with RA patients. The model fit statistics showed that the Poisson model fitted the data well.

The sensitivity analysis with exclusion of patients with NMSC prior to the start of TNF-inhibitor therapy showed an unadjusted rate ratio of 2.1 (1.0 – 4.1 95%CI) and an adjusted rate ratio of 7.0 (2.3 – 21.5 95%CI).

On drug analysis

For this analysis, 397 RA patients and 279 psoriasis patients could be included. In the 'on drug' analysis, 11 psoriasis patients (3.9%) and 6 RA patients (1.5%) were diagnosed with NMSC (Table 2-3). The total number of NMSC was 33 (13 BCCs and 20 SCCs) in the psoriasis group and 16 (10 BCCs and 6 SCCs) in the RA group.

Cox regression analysis

The estimated mean time until first NMSC in all patients was 8.7 years in the psoriasis group and 12.9 years in the RA group. In patients with an event only the median time until event was 1.6 years in the psoriasis patients and 7.8 years in the RA patients.

The unadjusted HR of developing NMSC in the psoriasis group compared with the RA group was 6.8 (2.1-22.1 95%CI) (raw model, see Table 5) and the fully adjusted HR was 7.5 (1.7-33.6 95%CI) (corrected model).

Table 5. Results of the Cox regression analysis ('on drug analysis').

Variable	B	HR (exp B)	95% CI
Raw model			
Diagnosis	1.910	6.752	2.064-22.094
Corrected model			
Diagnosis	2.021	7.544	1.692-33.633
Age	0.091	1.095	1.041-1.151
Gender	0.803	2.233	0.736-6.776
Disease duration	0.013	1.013	0.993-1.033
NMSC prior to anti-TNFα therapy	2.561	12.943	2.696-62.138
Duration of non anti-TNFα biological therapy	-4.197	0.015	0.000-48.898
Duration of ciclosporin therapy	0.072	1.074	0.810-1.426
Duration of prednisone therapy	0.005	1.005	0.895-1.129
Duration of methotrexate therapy	-0.126	0.882	0.768-1.012

Poisson regression analysis

In the psoriasis patients a total number of 33 NMSC was reported in 1240 patient-years, resulting in an event rate of 2.7 (1.8-3.7 95%CI) per 100 patient-years; in the RA patients the event rate was 0.7 (0.4-1.2 95%CI) per 100 patient-years (16 events in 2193 patient-years). By Poisson regression, this resulted in an unadjusted rate ratio of 5.9 (2.8-12.3 95%CI). Corrected for confounders, by Poisson regression, psoriasis patients had a 3.0 (1.1 – 8.4 95%CI) higher rate of NMSC compared with RA patients. The model fit statistics showed that the Poisson model fitted the data well.

Discussion

In this study, it was hypothesized that, if the occurrence of NMSC is attributable to phototherapy in psoriasis patients, the time from start of anti-TNFα treatment to first NMSC is expected to be shorter and the incidence of NMSC is expected to be higher in psoriasis patients compared with RA patients. We can confirm this hypothesis by our results. In the 'ever exposed to anti-TNF analysis', which was the main analysis of this study, the adjusted hazard ratio of developing NMSC was significantly higher in the psoriasis group with a shorter time until first NMSC (HR 6.0 (1.6 – 22.4 95%CI)), after correction for differences in previous treatments and demographic characteristics. In addition, the total event rate was 5.5 (2.2 – 13.4 95%CI) times higher in the psoriasis group.

Two other findings support these results. Firstly, the proportion of patients diagnosed with NMSC within the first year after the start of anti-TNFα therapy was higher in psoriasis (36%) compared with RA (17%), which supports pointing towards phototherapy

as a contributing factor. Secondly, the low BCC:SCC ratio found in the psoriasis group in this study also supports our hypothesis. In the general population, BCC:SCC ratios of 4:1 are reported.[22-24] As it is known that the incidence of SCC may be more affected by phototherapy than BCC, the low BCC:SCC ratio found in this study supports an influence of phototherapy.

To support the abovementioned results, a sensitivity analysis was performed ('on drug analysis'). In this analysis, the time until first NMSC was also significantly shorter (HR 7.5 (1.7-33.6 95%CI) and the rate of NMSC was also significantly higher in de psoriasis group (rate ratio 3.0 (1.1 – 8.4 95%CI)) compared with the RA group. To our knowledge, this was the first observational study comparing the occurrence of NMSC in psoriasis patients with RA patients. Other studies comprised meta-analyses of RCTs with relatively short treatment durations or open label extension studies lacking a control group or comparing NMSC rates with expected NMSC rates in the general population.[4-9, 25]
The difference in the incidence of NMSC found could, apart from phototherapy, be influenced by differences in patient characteristics and previous immunosuppressive treatments. However, differences in patient characteristics and the use of ciclosporin, methotrexate and prednisone were corrected for in the Cox proportional hazard and Poisson regression analyses.
NMSC prior to the start of TNF-inhibitor therapy was shown to be a strong predicting factor for being diagnosed with NMSC after the start of TNF-inhibitor therapy. We corrected for this confounder (history of NMSC before the start of anti-TNFα therapy) in the Cox proportional hazard regression analysis and the Poisson regression analysis. In addition, a sensitivity analysis excluding patients with prior NMSC was performed which showed similar results.

This study has some limitations. Firstly, the absolute number of NMSC was small. However, despite the small number of NMSC, statistically significant differences between the psoriasis and the RA group were detected. In addition, the fact that the number of NMSC was small, is reassuring with respect to the risk of NMSC associated with treatment with TNF-antagonists.
Secondly, correction for important risk factors for developing NMSC such as skin type and sun exposure was not possible, as skin type information was only available for a part of the psoriasis patients and not for the RA patients. Information on sun exposure was not available. However, as both groups cover the Netherlands and the same time period, the degree of sun exposure and skin cancer trends were expected to be the same for both groups. Nevertheless, psoriasis patients could have higher recreational sun exposure as this often improves their psoriasis.
Thirdly, detection bias may have played a role in the psoriasis group due to more regular skin assessments by dermatologists. In addition, the actual number of NMSC may have

been higher due to treatment of in particular superficial BCCs without taking a biopsy. However, as both groups were treated in academic hospitals where is common practice to take a biopsy before initiating treatment, this influence is expected to be small. Furthermore, the follow-up was shorter in the psoriasis patients compared with the RA patients. This could be a bias in a setting where NMSC takes time to become clinically detectable.[26]

In addition, acitretin treatment in combination with immunosuppressive treatments in renal transplant recipients may be protecting against NMSC.[27, 28] In psoriasis, concomitant acitretin may have the same effect. In this study, 150 psoriasis patients (54%) had ever used acitretin but only 16 patients (5.7%) used acitretin concomitantly with TNF-inhibitors. The influence of acitretin is therefore expected to be small.

Another limitation is the fact that 28% of the patients also had psoriatic arthritis, which theoretically should be analysed as a separate group with its own NMSC risk.

In addition, the difference in the incidence of NMSC found, could be influenced by the specific disease. Ideally, the current psoriasis group would have been compared with a group of psoriasis patients who had received anti-TNFα therapy and conventional systemic antipsoriatic therapies but no phototherapy. However, as TNF-inhibitors can only be prescribed to patients who failed to respond to phototherapy in the largest part of the world, this group of patients is not available.

In conclusion, the risk of developing NMSC was significantly higher in the psoriasis group compared with the RA group with a shorter time until first NMSC. This indicates that disease related factors like phototherapy may be an important contributing factor to NMSC diagnosed in psoriasis patients treated with TNF-inhibitors.

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Chapter 9

Relevance of laboratory investigations in monitoring patients with psoriasis on etanercept or adalimumab

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Abstract

Background

Guidelines concerning biological treatment of patients with psoriasis recommend different pretreatment and monitoring laboratory panels in variable frequencies to monitor treatment.

Objectives

To investigate the relevance of laboratory investigations in monitoring patients with psoriasis on etanercept or adalimumab.

Methods

A prospective cohort study over 5 years was conducted in all consecutive patients with psoriasis on etanercept or adalimumab. All laboratory investigations performed for monitoring treatment were analysed. Laboratory abnormalities were graded according to the Common Terminology Criteria for Adverse Events v4.03. The primary endpoint was the percentage of patients with a grade 3 or grade 4 laboratory abnormality. The secondary endpoints were defined as: (i) significant changes in laboratory parameters during etanercept or adalimumab treatment and (ii) the percentage of patients having a laboratory abnormality requiring discontinuation of etanercept or adalimumab treatment.

Results

Laboratory parameters were available for 162 patients treated with etanercept and/or adalimumab. The number of treatment episodes was 155 for etanercept and 58 for adalimumab. Follow-up was 316 patient-years for etanercept and 54 patient-years for adalimumab. Thirty-eight of 146 patients treated with etanercept (26%) had one or more grade 3 and/or grade 4 laboratory abnormalities. For adalimumab, this was 8 of 58 (14%). These were predominantly considered unrelated to biologic therapy.

For both biologics, significant changes were observed in mean laboratory parameters during treatment compared with pretreatment as well as significant trends. However, mean values during treatment remained within normal ranges. Laboratory abnormalities did not lead to permanent discontinuation of biologic treatment in any patient.

Conclusions

In this cohort, the incidence of biologic therapy-related serious laboratory abnormalities was low. Our findings do not support a need for routine laboratory testing in patients with psoriasis on etanercept or adalimumab beyond the laboratory testing required for concomitant therapies or comorbidities.

Introduction

Patients with psoriasis treated with biologics are monitored routinely with laboratory investigations according to existing guidelines.[1-8] Several laboratory investigations including analysis of clinical chemistry (liver and kidney function tests) and haematology (full blood cell counts), urinalysis, hepatitis B/C and human immunodeficiency virus (HIV) serology, analysis of autoantibodies and a pregnancy test are recommended before the initiation of treatment. During biologic treatment, laboratory investigations are repeated periodically with variable panels and frequencies.[1-8] Most guidelines advise laboratory investigations at pretreatment, after the start of therapy at 4-12 weeks and at 3-6-monthly intervals thereafter.[7, 8]

However, the clinical relevance of these laboratory investigations remains to be determined. Moreover, a venipuncture is an invasive procedure for the patient and this procedure and the laboratory investigations involve health-care costs. Therefore, the objectives of this study were to investigate (i) how frequently serious abnormal laboratory parameters were observed during etanercept or adalimumab treatment, (ii) significant changes in laboratory parameters during etanercept or adalimumab treatment and (iii) the percentage of patients having a laboratory abnormality requiring discontinuation of etanercept or adalimumab treatment. In addition, we investigated the relationship between serious abnormal laboratory parameters and the use of etanercept or adalimumab.

To meet the objectives, all laboratory investigations of a prospective cohort consisting of all consecutive patients with psoriasis treated with etanercept and/or adalimumab between February 2005 and April 2010 were analysed.

Patients and methods

Patients

All consecutive patients starting biological treatment for psoriasis in the Dermatology outpatient clinic of the Radboud University Nijmegen Medical Centre are enrolled in a prospective patient registry, in which daily practice efficacy and pharmacovigilance data, including laboratory investigations, are collected. In the Netherlands, biological treatment was approved for the treatment of patients with psoriasis who had not responded to phototherapy, methotrexate and ciclosporin, or who had contraindications to or did not tolerate these therapies. Furthermore, a Psoriasis Area and Severity Index (PASI) of at least 10 was required.[9]

Table 1. Pretreatment and monitoring laboratory investigations.

Chemistry	Haematology	Additional
Creatinine	Haemoglobin	Antinuclear antibodies[a]
C-reactive protein (CRP)	Haematocrit	Hepatitis B/C serology[a]
Direct bilirubin	White blood cell count	Serum pregnancy test[a]
Total bilirubin	White blood cell differentiation	
Alkaline phosphatase (ALP)	Platelet count	
Alanine aminotransferase (ALT)		
γ-Glutamyl transferase (GGT)		
Cholesterol[a]		
Triglycerides[a]		
Urinalysis[a]		

[a]These laboratory tests were only performed at pretreatment. The other tests were performed at pretreatment, week 6 and 12 and every 12 weeks afterwards.

Laboratory investigations

At pretreatment, laboratory investigations included routine clinical chemistry and haematology analyses, determination of antinuclear antibodies (ANA), hepatitis B and C serology, a serum pregnancy test if applicable and a urinanalysis. General laboratory investigations were repeated at week 6 and 12, every 12 weeks afterwards and at other occasions when indicated (Table 1). Additional laboratory analyses were performed according to clinical signs and concomitant medication. All laboratory investigations were performed at the department of Laboratory Medicine or Medical Microbiology of the Radboud University Nijmegen Medical Centre.

Methods

Treatments were analysed as separate treatment episodes. A treatment episode was defined as a new course of biological treatment or a restart after an interruption of at least 6 months. In patients who were treated with both etanercept and adalimumab, laboratory investigations were analysed separately. In cases where patients had more than one treatment episode with the same biologic, laboratory investigations were analysed per treatment episode of that biologic.

For categorizing laboratory abnormalities, the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) of the National Cancer Institute of the U.S.A. were used (Table 2).[10] Where the CTCAE criteria did not provide a classification, a grading scale was designed at our own discretion, as described in Table 2.

The primary endpoint was the percentage of patients having a grade 3 or grade 4 laboratory abnormality. The secondary endpoints were defined as 1) significant changes

Table 2. Grading scale for abnormal laboratory parameters.

Laboratory parameter	Grade			
	1[a]	2[b]	3[c]	4[d]
Creatinine (µmol/L) increased*	♂ >110 - 165 ♀ >90 - 135	♂ >165 - 330 ♀ >135 - 270	♂ >330 - 660 ♀ >270 - 540	♂ >660 ♀ >540
C-reactive protein (CRP) (mg/L) increased**	≥10 - 29	≥30 - 49	≥50 - 99	≥100
Direct bilirubin (µmol/L) increased*	>5 - 7.5	>7.5 - 15	>15 - 50	>50
Total bilirubin (µmol/L) increased*	≥17 - 25	≥26 - 50	≥51 - 169	≥170
Alkaline phosphatase (ALP) (U/L) increased*	>120 - 300	>300 - 600	>600 - 2400	>2400
Alanine aminotransferase (ALT) (U/L) increased*	≥45 - 112	≥113 - 224	≥225 - 899	≥900
y-Glutamyl transferase (GGT) (U/L) increased*	♂ ≥50 - 124 ♀ ≥35 - 87	♂ ≥125 - 249 ♀ ≥88 - 174	♂ ≥250 - 999 ♀ ≥175 - 699	♂ ≥1000 ♀ ≥700
Haemoglobin (mmol/L) decreased*	♂ <8.1 - 6.2 ♀ <7.3 - 6.2	♂ <6.2 - 4.9 ♀ <6.2 - 4.9	♂ <4.9 - 4.0 ♀ <4.9 - 4.0	♂ <4.0 ♀ <4.0
White blood cell count ($x10^9$/L) increased White blood cell count ($x10^9$/L) decreased	>11.0 - 14.0** <3.5 - 3.0*	>14.0 - 17.0** <3.0 – 2.0*	>17.0 - 20.0** <2.0 - 1.0*	>20.0** <1.0*
Neutrophils (%) increased** Neutrophils (%) decreased**	>70 – 75 <40 – 35	>75 – 80 <35 – 30	>80 – 85 <30 – 25	>85 <25
Lymphocytes (%) increased** Lymphocytes (%) decreased**	>40 – 45 <20 – 15	>45 – 50 <15 – 10	>50 – 55 <10 – 5	>55 <5
Monocytes (%) increased** Monocytes (%) decreased**	>13 – 15 <4 – 3	>15 – 17 <3 – 2	>17 – 19 <2 – 1	>19 <1
Eosinophils (%) increased**	>6 - 8	>8 - 10	>10 - 12	>12
Basophils (%) increased**	>2 - 4	>4 - 6	>6 - 8	>8
Platelet count ($x10^9$/L) increased Platelet count ($x10^9$/L) decreased	>350.0 – 400.0** <120.0 – 75.0*	>400.0 – 450.0** <75 – 50.0*	>450.0 – 500.0** <50.0 – 25.0*	>500.0** <25.0*

*CTCAE v4.03 grading scale. **Grading scale designed at our own discretion. [a]Grade 1; mild AE. [b]Grade 2; moderate AE. [c]Grade 3; severe AE. [d]Grade 4; life-threatening or disabling AE.

in laboratory parameters during etanercept or adalimumab treatment and 2) the percentage of patients having a laboratory abnormality requiring discontinuation of etanercept or adalimumab treatment.

Laboratory parameters were analysed and represented separately for men and women when the grading scale differed for the two genders. The white blood cell differentiation into neutrophils, lymphocytes, monocytes, eosinophils and basophils was reported as percentages, as the percentage distribution of the different types of leukocytes should stay constant, irrespective of the absolute leukocyte count. Because of increased coefficients of analytical variation below the lower detection limits, C-reactive protein (CRP) results below 5 mg/L, direct bilirubin results below 5 µmol/L and total bilirubin

Table 3. Patient characteristics.

Patient characteristics	n = 162
Male gender, n (%)	103 (64)
Age (years), mean ± SD	50.9 (12.1)
Duration of psoriasis (years), mean ± SD	26.4 (12.9)
Psoriatic arthritis, n (%)	46 (28)

results below 10 µmol/L were not specified and were imputed as being 5, 5, and 10, respectively.

Alanine aminotransferase (ALT) results were analysed for all patients, and separately for the group of patients who were not on concomitant methotrexate or acitretin. In addition, CRP results were analysed for all patients and for the group of patients with and without concomitant psoriatic arthritis. Serum cholesterol and triglycerides were measured under nonfasting conditions and were used as indicators for further investigation.

Differences in mean laboratory parameters before the start of biologic treatment and during biologic treatment were analysed in all patients who were not on biologic treatment at the time they were screened for etanercept or adalimumab. In addition, trends in the course of the laboratory parameters were analysed using linear regression.

Statistics

Paired t-tests were performed for comparison of mean pretreatment laboratory results and mean results during treatment. $P < 0.05$ was considered statistically significant. Linear regression was used to calculate regression coefficients with 95% confidence intervals (CI).

Results

Patient characteristics and treatment

Laboratory results were available for 162 patients with psoriasis who were treated with etanercept and/or adalimumab and were collected by 2077 different venipunctures. One hundred and three patients (64%) were male (Table 3). The mean age (± SD) was 50.9 (± 12.1) years and the mean duration of psoriasis (± SD) was 26.4 (± 12.9) years. Forty-six patients (28%) had psoriatic arthritis.

One hundred and forty-six patients were treated with etanercept and 58 patients with adalimumab (Table 4). Forty-two patients had been treated with both etanercept and adalimumab. Five patients were treated with etanercept during two separate treatment episodes and two patients had three etanercept treatment episodes. The total number of

Table 4. Treatment characteristics.

Treatment characteristics	Etanercept	Adalimumab
Patients (n)	146	58
Treatment episode (n)	155	58
Treatment episode duration (years)		
Mean ± SD	2.0 (1.5)	0.9 (0.5)
Median (range)	1.8 (0.07 – 5.2)	0.9 (0.02 – 1.9)
Patient-years	316.6	54.1
Mean weekly dose (mg)	60.0	25.2

treatment episodes was 155 for etanercept and 58 for adalimumab. The mean treatment episode duration (± SD) was 2.0 (± 1.5) years for etanercept and 0.9 (± 0.5) years for adalimumab; the number of patient-years of follow-up was 316 for etanercept and 54 for adalimumab. The mean weekly dose was 60.0 mg for etanercept and 25.2 mg for adalimumab.

From 155 etanercept treatment episodes, 118 consisted of etanercept monotherapy, 26 consisted of etanercept combined with methotrexate (24 patients) and 11 consisted of etanercept combined with acitretin (11 patients). From 58 adalimumab treatment episodes, 43 consisted of adalimumab monotherapy, 13 consisted of adalimumab combined with methotrexate (13 patients) and 2 consisted of adalimumab with acitretin (2 patients).
Patients used concomitant methotrexate or acitretin as bridge therapy when transitioning from the classic systemic treatment to biologic treatment, or as add-on therapy during the course of biologic treatment because of unsatisfactory efficacy. Methotrexate and acitretin as bridge therapies were applied for variable lengths of time, varying from 2 weeks to continuously throughout the course of biologic treatment.

Severe laboratory abnormalities during biologic treatment

All laboratory investigations categorized as grade 3 or 4 adverse events observed during etanercept or adalimumab treatment are represented in Table 5. Thirty-eight patients of 146 etanercept-treated patients (26%) had one or more grade 3 and/or grade 4 laboratory abnormalities. For adalimumab, this number was 8 of 58 (14%).
In all patients with grade 3 or grade 4 laboratory abnormalities of CRP, total bilirubin, ALT and GGT, the abnormal results were pre-existent, (largely) transient or considered more likely related to comorbidity or the concomitant use of methotrexate.
In 13 etanercept-treated patients (9%), severe haematological laboratory abnormalities were considered possibly or probably interrelated (grade 3 and/or 4 lymphocytosis (n = 10), grade 3 lymphocytosis (n = 1), grade 4 thrombocytosis (n = 1), grade 3 leucopenia and grade 3 thrombocytopenia (n = 1)). In two patients on adalimumab (3%) the grade 3

Table 5. Number of patients with grade 3 and grade 4 abnormal laboratory parameters during etanercept or adalimumab treatment.

	Etanercept (n = 146)		**Adalimumab** (n = 58)	
	Grade 3	Grade 4	Grade 3	Grade 4
CRP increased	2[a]	0	2[b]	2[b]
Total bilirubin increased	3[c]	0	0	0
Alanine aminotransferase increased	2[d]	0	1[e]	0
γ-Glutamyl transferase increased ♂	2[f]	2[g]	1[i]	1[j]
♀	0	1[h]	1[i]	0
Leucocytosis	3	0	0	1
Leucopenia	1[k]	0	0	0
Neutrophilia	8	0	1	1
Neutropenia	0	1	0	0
Lymphocytosis	13	5	2	0
Lymphopenia	1	0	1	0
Monocytosis	1[k]	1	0	0
Monocytopenia	1	0	0	1
Eosinophilia	0	3	1	0
Thrombocytosis	3	3	1	1
Thrombocytopenia	1[k]	0	0	0

[a]One patient had an exacerbation of psoriasis, recent erysipelas, urinary tract infection and arthritis. The second patient had a nonspecified infection. [b]Grades 3 and 4 increased CRP were found in the same patients. One of these patients had an active arthritis and psoriasis. In the other patient the increased CRP was assessed as possibly related to active psoriasis at one occasion and at the other occasion the patient had gastroenteritis. [c]In all three patients the increased total bilirubin levels were pre-existing and transient. [d]Patient 1: pre-existent abnormal ALT activity, history of nonalcoholic fatty liver disease and alcohol use, partially transient. Patient 2: probably related to concomitant methotrexate use, partially transient after discontinuation of methotrexate. [e]Probably related to concomitant methotrexate use, partially transient after lowering the dose of methotrexate. [f]Patient 1: possibly related to alcohol use, partially transient. Patient 2: certainly related to alcohol abuse. [g]Patient 1: transient and probably related to alcohol use. Patient 2: pre-existing, partially transient and possibly related to fatty liver disease and diabetes mellitus. [h]Transient and probably related to alcohol use. [i]Grades 3 and 4 abnormal GGT activities were found in the same patient, certainly related to alcohol abuse. [j]Pre-existing, partially transient, medical history of liver fibrosis. [k]In patient with Felty's syndrome.

lymphocytosis that developed during treatment was considered possibly related. Clinical consequences of these laboratory abnormalities are described in the section entitled 'Laboratory abnormalities with clinical consequences'.

Laboratory parameters during etanercept treatment

Mean CRP, alkaline phosphatase (ALP), platelet counts and neutrophil percentages were significantly lower during etanercept treatment than at pretreatment (Table 6). ALP and

Table 6. The effect of etanercept on laboratory parameters.

	Etanercept					
Laboratory parameter	No. of treatment episodes[a]	Pre-treatment[b]	During treatment[c]	P-value[d]	No. of treatment episodes[e]	Regression coefficient (95% CI)[f]
Creatinine (µmol/L)	125	79 (1)	79 (1)	0.780	152	0.05 (-0.04-0.13)
C-reactive protein (mg/L)	123	9.0 (0.8)	6.4 (0.3)	<0.001	152	-0.03 (-0.06-0.0008)
Direct bilirubin (µmol/L)	96	5.0 (0.02)	5.0 (0.003)	0.276	150	-0.0002 (-0.0006-0.0001)
Total bilirubin (µmol/L)	124	12.1 (0.5)	12.1 (0.4)	0.960	152	0.007 (-0.01-0.02)
Alkaline phosphatase (U/L)	71	86 (3)	76 (2)	<0.001	135	-0.26 (-0.45, -0.07)
Alanine amino-transferase (U/L)	124	35 (2)	40 (2)	<0.001	152	0.08 (0.007- 0.16)
y-Glutamyl transferase (U/L)	92	40 (4)	38 (3)	0.306	146	-0.19 (-0.40-0.01)
Haemoglobin (mmol/L)	125	8.9 (0.1)	9.0 (0.1)	<0.001	152	-0.001 (-0.008-0.006)
White blood cell count ($x10^9$/L)	125	7.9 (0.2)	7.6 (0.2)	0.073	152	0.006 (-0.005-0.02)
Neutrophils (%)	124	65 (1)	58 (1)	<0.001	152	-0.12 (-0.20, -0.04)
Lymphocytes (%)	124	25 (1)	32 (1)	<0.001	152	0.12 (0.03 – 0.21)
Monocytes (%)	124	6.2 (0.2)	6.3 (0.1)	0.597	152	-0.01 (-0.03-0.005)
Eosinophils (%)	124	2.6 (0.2)	2.6 (0.1)	0.975	152	0.002 (-0.005-0.009)
Basophils (%)	124	0.5 (0.04)	0.7 (0.03)	0.002	152	0.001 (-0.002-0.004)
Platelet count ($x10^9$/L)	125	265 (7)	244 (6)	<0.001	152	-0.08 (-0.51-0.35)

[a]Number of treatment episodes available for comparison of mean pretreatment laboratory results and mean results during treatment. [b]Values are mean pretreatment values ± SEM. [c]Values are mean values during treatment ± SEM. [d]P-value for difference between pretreatment value and value during treatment. [e]Number of treatment episodes available for linear regression. [f]Linear regression coefficients with 95% confidence intervals.

neutrophil percentages also showed a significant declining trend.

Mean ALT, haemoglobin, lymphocyte and basophil percentages were significantly higher during etanercept treatment compared with pretreatment. For ALT activities and lymphocyte percentages, a significant increasing trend was also detected.

During etanercept therapy, all mean levels of laboratory parameters that were significantly different compared with pretreatment remained within normal reference ranges (Table 6).

In the group of patients who were not on concomitant methotrexate or acitretin treatment, mean (± SEM) ALT values also increased from 35 (± 2) U/L at pretreatment to 41 (± 2) U/L during etanercept therapy and linear regression also showed a significant incline (regression coefficient 0.11 (95% CI 0.03 - 0.19).

Laboratory parameters during adalimumab treatment

Mean ALP and neutrophil percentages were significantly lower during adalimumab

treatment than at pretreatment. Mean haemoglobin and lymphocyte percentages were significantly higher during adalimumab treatment than at pretreatment. No significant trends were observed. During adalimumab therapy, all mean levels of laboratory parameters with a significant difference in pretreatment and treatment values remained within normal reference ranges.

Laboratory abnormalities with clinical consequences

Laboratory abnormalities did not lead to permanent discontinuation of biologic treatment in any patient. Biologic treatment was temporarily interrupted in patients presenting with an infection clinically with or without elevated infection parameters. Elevated infection parameters during biologic treatment without clinical signs of infection occasionally led to temporary discontinuation.

Two patients (1%) required a temporary interruption of biologic treatment due to severe haematological laboratory abnormalities. One patient had a leucopenia (grade 1), neutropenia (grade 2) and lymphocytosis (grade 3) 4 months after the start of adalimumab treatment per label. Consequently, adalimumab was temporarily discontinued for 4 weeks, during which time the laboratory abnormalities returned to normal. The laboratory abnormalities did not recur during the subsequent year of adalimumab treatment.

Etanercept was interrupted temporarily in a patient with Felty's syndrome due to a grade 3 leucopenia and a grade 3 thrombocytopenia 5 months after the start of etanercept at a dosage of 25 mg twice a week, which were considered possibly related. The laboratory abnormalities were partially transient.

C-reactive protein

Mean CRP was significantly lower during biologic treatment than at pretreatment, both in the group of patient with psoriatic arthritis and the group of patients without psoriatic arthritis. In the group of patients with psoriatic arthritis mean (± SEM) CRP decreased from 9.5 (± 1.2) mg/L at pretreatment to 6.4 (± 0.7) mg/L during biologic treatment ($p < 0.05$). In the group of patients without psoriatic arthritis mean (± SEM) CRP decreased from 8.5 (± 0.9) mg/L at pretreatment to 6.4 (± 0.3) mg/L during treatment ($p < 0.01$).

Antinuclear antibodies

Etanercept

Seroconversion occurred in four patients during etanercept treatment, from negative to weakly positive in two patients, from negative to cytoplasmic dot pattern in one patient and from negative to 3+ in the fourth patient. None of these patients showed clinical signs of lupus erythematosus or other connective tissue diseases.

In two patients on etanercept, ANA was weakly positive at the time of screening for

Table 7. The effect of adalimumab on laboratory parameters.

	Adalimumab					
Laboratory parameter	No. of treatment episodes[a]	Pre-treatment[b]	During treatment[c]	P-value[d]	No. of treatment episodes[e]	Regression coefficient (95% CI)[f]
Creatinine (µmol/L)	17	75 (4)	72 (3)	0.226	54	0.001 (-0.1-0.1)
C-reactive protein (mg/L)	17	7.6 (1.1)	6.0 (0.4)	0.095	54	0.008 (-0.07-0.09)
Direct bilirubin (µmol/L)	16	5.1 (0.1)	5.1 (0)	0.164	53	0.001 (-0.004-0.006)
Total bilirubin (µmol/L)	17	11.5 (1.1)	10.4 (0.7)	0.129	54	-0.04 (-0.1-0.02)
Alkaline phosphatase (U/L)	17	73 (2)	68 (2)	0.022	54	-0.02 (-0.2-0.2)
Alanine amino-transferase (U/L)	18	38 (4)	36 (5)	0.451	54	-0.1 (-0.4-0.08)
y-Glutamyl transferase (U/L)	17	35 (6)	34 (7)	0.816	54	-0.5 (-1.3-0.3)
Haemoglobin (mmol/L)	17	8.6 (0.2)	8.8 (0.2)	0.025	54	0.03 (-0.004-0.06)
White blood cell count ($x10^9$/L)	17	8.3 (0.6)	7.9 (0.5)	0.296	54	0.009 (-0.04-0.05)
Neutrophils (%)	16	65 (2)	58 (2)	0.003	54	-0.1 (-0.3-0.1)
Lymphocytes (%)	16	26 (2)	34 (2)	<0.001	54	0.1 (-0.07-0.3)
Monocytes (%)	16	5.8 (0.6)	5.2 (0.4)	0.357	54	-0.02 (-0.06-0.02)
Eosinophils (%)	16	2.1 (0.3)	1.9 (0.4)	0.587	54	-0.006 (-0.03-0.02)
Basophils (%)	16	0.5 (0.1)	0.5 (0.1)	0.872	54	0.009 (-0.009-0.03)
Platelet count ($x10^9$/L)	17	258 (18)	247 (13)	0.165	54	0.1 (-0.5-0.7)

[a]Number of treatment episodes available for comparison of mean pretreatment laboratory results and mean results during treatment. [b]Values are mean pretreatment values ± SEM. [c]Values are mean values during treatment ± SEM. [d]P-value for difference between pretreatment value and value during treatment. [e]Number of treatment episodes available for linear regression. [f]Linear regression coefficients with 95% confidence intervals.

etanercept, but became 1+ positive (nucleoli and dot, respectively) during etanercept treatment. These patients did not have any signs or symptoms of autoimmune disease either.

In a third patient, autoimmune antibody patterns changed from positive anti-SS-A at screening to positive anti-SS-A and anti-SS-B during etanercept treatment. This patient turned out to have Sjögren's disease in combination with psoriasis. The relation between this seroconversion and etanercept therapy was uncertain, and etanercept was continued. No other autoimmune antibodies or symptoms developed afterwards.

Adalimumab

Seroconversion occurred in two patients during adalimumab treatment from negative to weakly positive and from negative to 1+, respectively, without signs of autoimmune disease.

Discussion

Recommendations about laboratory testing in patients with psoriasis treated with biologics should be based on a consideration of the potential risks and benefits. To justify the patient burden of repeated venipunctures, possible further investigations and the use of healthcare resources, abnormal laboratory parameters should have clinical consequences and early detection and adjustment of treatment should result in a better outcome.[6]

In the present cohort, 38 patients treated with etanercept (26%) and eight patients treated with adalimumab (14%) had one or more grade 3 and/or grade 4 laboratory abnormalities. Severe laboratory abnormalities were mainly considered unrelated to the biologic therapy and changes in mean values remained within normal reference ranges.
Two patients (1%) required a temporary interruption of biologic treatment due to severe haematological laboratory abnormalities. Laboratory abnormalities did not lead to complete discontinuation of treatment, whereas a patient's clinical signs and symptoms of, for example, infection without laboratory testing did lead to interruption or discontinuation of biologic treatment.

Confounders in this study were comorbidity and comedication, which were taken into account when assessing the relation between serious laboratory abnormalities and the biologic therapy. Severe laboratory abnormalities were mainly considered unrelated to the biologic, although a causal relation could not be excluded with certainty.

Laboratory panels for monitoring biologic therapy vary between guidelines, between guidelines and daily practice and between physicians. In addition, the frequency of testing differs considerably.[1-8]
In a literature review (using the Cochrane databases and MEDLINE) evaluating the evidence for screening and monitoring tests in patients with psoriasis on biologic therapy, the authors were unable to make definitive recommendations either in favour or against them based on the available literature.[2] Current recommendations for laboratory screening and monitoring are mainly based on short-term clinical trials and literature reviews, rather than cohort studies examining the relevance of different laboratory screening and monitoring strategies.[2]
This study was based on prospectively collected laboratory data from a cohort of patients with psoriasis treated with biologics in daily practice for 5 years. As most patient-years of follow-up were available for etanercept and adalimumab, these therapies were evaluated.

A distinct finding in this study was a significant reduction in neutrophil counts for etanercept as well as adalimumab. This has been previously described in patients with

inflammatory arthritides with a few patients developing a serious infection. In our cohort, no serious infections associated with neutropenia were seen.[11]

In the literature, elevated liver enzymes have been reported for anti-TNFα treatments.[12-14] In the present cohort, a significant increase of mean ALT during etanercept treatment was found as well, but mean ALT activities did not exceeding normal reference ranges. In the investigator's judgement, severely elevated ALT activities in our cohort were more likely due to concomitant therapy or comorbid disorders than to the biologic treatment.
Renal impairment has commonly been reported during adalimumab treatment in clinical trials,[13] but was not found in our cohort.

CRP decreased during biologic treatment in patients with and without psoriatic arthritis. This has been reported in several studies in the literature.[15, 16] Also, a correlation with the PASI score has been reported. With the CRP assay used (Architect; Abbott, Abbott Park, IL, U.S.A.), levels below 5 mg/L were not specified and were imputed as 5. Still, a significant decrease was measured during biologic treatment. The relevance of low levels of CRP could be discussed, although Ridker et al.[17] showed that achieving CRP levels of < 2 mg/L is associated with a significant improvement in event-free survival in patients with acute coronary syndrome in their history, regardless of their levels of low-density lipoprotein cholesterol.

The purpose of laboratory investigations before starting treatment with biologics is to detect pre-existent abnormalities which form contraindications or risk factors for starting biologic therapy and to provide a baseline value. Baseline laboratory parameters are important for interpreting abnormal laboratory test results which evolve during biologic treatment in terms of clinical significance and causality. We therefore propose that the pretreatment laboratory panel should at least encompass the laboratory parameters assessed during treatment.

During treatment, the monitoring of ALT, GGT and CRP can be considered. ALT testing seems useful, as a small but statistically significant increase in ALT was detected during etanercept treatment. ALT and GGT testing is also important because of common comorbidities in patients with psoriasis affecting liver function tests, such as nonalcoholic fatty liver disease, diabetes and alcohol use. CRP testing can be considered to detect infections, although most patients have infections in the interval between hospital visits. Monitoring of the full blood cell count and white blood cell differentiation can also be considered, as some severe haematological abnormalities and statistically significant declining trends were observed in our cohort. Previously these adverse effects have also been described in the literature and in the Summary of Product Characteristics of etanercept and adalimumab.[12, 13]

In the present study no (biologic therapy-related) severe laboratory abnormalities or clinically significant changes of creatinine, direct and total bilirubin and ALP were found during treatment. Hence, routine laboratory monitoring of these parameters does not seem useful.

A positive ANA is nonspecific and does not preclude a patient from starting biologic therapy. However, in our opinion, it is important to have a baseline test result, as seroconversion of ANA during TNF-α blocking therapy is a known phenomenon and rarely patients with a lupus-like syndrome have been reported in the literature.[18] ANA can then be reassessed in case of signs or symptoms of lupus erythematosus.
A pregnancy test performed at pretreatment is recommended, as data on the use of biologic therapies during pregnancy are still sparse, together with data associating TNF-antagonists with VACTERL.[8]
HIV testing is recommended to be performed at screening only in patients at risk and hepatitis B and C testing is recommended to be performed in all patients at screening, although there is insufficient evidence to support this.[1, 2, 4, 5, 7, 8]
The literature review of Huang et al.[2] recommended against a standard urinalysis. Although not analysed in this study, we would suggest evaluating urine by strip analysis before starting treatment to have a baseline value and to repeat urinalysis only when there is clinical suspicion and symptoms of a urinary tract infection.

This study does not support routine laboratory testing in patients with psoriasis treated with biologics beyond the laboratory testing required for concomitant antipsoriatic systemic medication or comorbidities. Routine testing every 3 months may not be necessary either. However, this has not been investigated in other prospective studies. Additional evidence in a larger group of patients with_a longer follow-up and future implementation studies could provide more evidence as to which laboratory panels and intervals are appropriate.
At least as important as laboratory testing is obtaining an appropriate history and physical examination to estimate potential risks for the individual patient when deciding on treatment and monitoring strategies.

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Part IV

Chapter 10

Summary and Discussion

Main study objective

The objective of the present thesis was to prospectively investigate the long-term efficacy and safety of biologics in the treatment of patients with moderate to severe psoriasis in daily clinical practice. The majority of the data analysed were extracted from a prospective registry, named the Bio-CAPTURE registry. In this registry, all consecutive patients with psoriasis starting biological therapy in routine clinical practice are enrolled.

The registry reflects to some extent the history of the introduction of biologics. Etanercept was one of the first biologics registered for psoriasis. Therefore, at the beginning of the biological era, etanercept was the first biological therapy for many patients. In case of insufficient efficacy of etanercept or adverse events during etanercept therapy, patients mainly switched to adalimumab. Therefore, most efficacy and safety data in this thesis concern etanercept and adalimumab. Efalizumab safety data are presented in **chapter 7**, although this agent has been withdrawn from the market in 2009 because of serious safety concerns.

The registry also reflects the logistic organization of our department. In our department, infliximab is reserved for patients with very severe psoriasis who require rapid improvement and for patients who failed to respond to other biologics. This is due to the facilities required for the administration of infliximab and the infusion reactions sometimes observed. Therefore, infliximab has not been widely used in our department. Ustekinumab was registered for psoriasis in 2009. At the time the studies outlined in this thesis were performed, experience with ustekinumab was limited. **Chapter 7** presents the data available in our registry on the long-term safety of infliximab and ustekinumab.
After having clarified these historical and logistical aspects, we will now revert to the research questions as defined in **chapter 1**. We will discuss the questions and come to conclusions based on these discussions as well as the studies presented in **chapter 2-9**.

Research question 1: What is the long-term efficacy of biologics for psoriasis in daily practice?

Efficacy or effectiveness

Efficacy and effectiveness are two terms that are both used for describing the effect of a certain treatment. However, these terms have different meanings. Efficacy describes the effect of a treatment in the controlled setting of an RCT, whereas effectiveness describes the effect in a real life clinical setting.[1-3] In this thesis, the term efficacy is used mostly to describe the effects of biological therapies in daily practice, whereas the term effectiveness would actually have been more appropriate. To be consistent, the term efficacy will continued to be used in this chapter.

Long-term efficacy of etanercept and adalimumab

Etanercept and adalimumab therapy for moderate to severe psoriasis in daily practice were effective in the long-term. In **chapter 6**, the long-term efficacy of etanercept in patients with a mean treatment duration of 2.7 years is shown to be substantial. In **chapter 4**, it is shown that the efficacy of adalimumab in patients with a mean treatment duration of 1.4 years was well maintained.

Considering the results of the intention-to-treat (ITT) analysis with last observation carried forward (LOCF) and modified nonresponder imputation (modified NRI) in **chapter 6** (Figures 2-4), there appears to be a gradual loss of efficacy of etanercept. This was already shown in open-label extension studies.[4, 5] The phenomenon responsible for loss of efficacy has not been elucidated yet. Possible explanations could be biological adaptation to chronic TNF-α blockade (not by antibody formation in case of etanercept), decreased TNF-α dependency of the disease, increased metabolic clearance or compliance problems.[5-7]

Open-label extension studies and daily practice experience have shown that there can be loss of efficacy with adalimumab therapy as well.[8, 9] Explanations for loss of efficacy with adalimumab therapy include those mentioned for etanercept plus antibody formation against adalimumab, which has been shown to be associated with impaired treatment outcomes.[10]

Indirect comparisons between the long-term efficacy of etanercept and adalimumab should be made with caution due to differences in patient populations and dosing regimens.

Daily clinical practice versus randomized controlled trials

The long-term efficacy of etanercept and adalimumab in our daily practice studies was lower than in RCTs and open-label extension studies of RCTs.[5, 9, 11-22] However, it has to be kept in mind that comparisons between RCTs and daily practice are seriously hampered by differences in patient populations, outcome measures, time points of assessment, methods of analysis and dosing regimens used.

A few explanations can be given for the lower PASI 75 response rates in our study compared with RCTs. Firstly, our study concerned patients treated in a university hospital. Patients who are referred to a tertiary care centre probably are more therapy-resistant. Secondly, patients in daily practice have to fulfil strict reimbursement criteria, which is not an eligibility criterion for RCTs. This may also lead to the selection of more therapy-resistant patients in real-world practice. Thirdly, patients included in RCTs are in general 'healthy' patients, who fulfil strict inclusion and exclusion criteria, whereas patients in daily practice generally have comorbidities and concomitant medication. Furthermore, washout periods are applied in RCTs, leading to a high baseline PASI. As a result, some patients will be enrolled based on high PASI scores, that are not representative of their mean PASI. This favours a phenomenon called 'regression to the mean'. In addition, investigators may have

the tendency to measure psoriasis severity using the higher end of the subjective range of the scale of the PASI at initial assessment visits, when eligibility for a clinical trial is determined. This phenomenon is called 'eligibility creep'. These two phenomena may also partly explain the considerable placebo effects seen in psoriasis clinical trials.[23]
Other explanations for the lower efficacy found in daily practice may be compliance problems, inadequate use of the biologic and interruptions of treatment due to infections or elective surgery. On the other hand, treatment strategies applied in daily practice like the concomitant use of topical or classical systemic therapies and dose escalation of biologics, may bias efficacy in a positive way.

In conclusion: etanercept and adalimumab therapy for moderate to severe psoriasis in daily practice are effective in the long term. Daily clinical practice and RCTs differ in many aspects, which implies that daily practice studies provide important complementary information to RCTs.

PASI as outcome measure

PASI 50/75/90/100 are the outcome measures most frequently used in clinical trials and daily practice studies, which permits comparisons of study results. However, absolute outcome measures reflecting static psoriasis severity, like for example the static Physician's Global Assessment (PGA), may be more reasonable for use in long-term studies than outcome measures that reflect change in relation to baseline, which is the focus of RCTs.[24, 25]
An important limitation of the PASI is that it does not include quality of life, psoriasis in 'high-impact' sites (visible areas/scalp/genital) and nail involvement.[26, 27] There is a need for a composite outcome measure that includes all relevant aspects of psoriasis. Another inherent limitation of the PASI is the low responsiveness in case of small areas of involvement.

Selection of the baseline PASI

As shown in **chapter 2-6**, efficacy is highly dependent on the baseline PASI used and the methodological approach chosen to analyse long-term efficacy. The influence of methodological approaches will be discussed later.
In **chapter 3**, the response to adalimumab is evaluated in relation to the baseline PASI before the start of adalimumab (course baseline PASI) and the baseline PASI before the start of etanercept (original baseline PASI). In **chapter 4**, the response to adalimumab is evaluated in relation to the baseline PASI before the start of adalimumab (course baseline PASI) and the first available baseline PASI before the start of a biological therapy at the moment of enrolment in the registry (original baseline PASI). This was done because of a potential carry-over effect of the previous therapy, which often leads to a lower course baseline PASI than the original baseline PASI.

The current gold standard outcome measure PASI 75 is a measure of relative improvement with respect to baseline. In view of residual psoriasis that is frequently seen and the low responsiveness of the PASI in case of small areas of involvement, a PASI 75 response is difficult to attain starting from a low baseline PASI.

In conclusion: efficacy results depend on which baseline PASI is used, when relative outcome measures are used (e.g. PASI 75). It is important to consider this for correctly interpreting efficacy results. An alternative could be the additional use of an absolute outcome measure.

Treatment goals

In 2011, a European consensus group published treatment goals for the treatment of moderate to severe plaque psoriasis with systemic therapies, on the analogy of treatment goals for other chronic diseases like diabetes mellitus.[28] These treatment goals include the severity of psoriasis measured with the PASI and quality of life measured with the Dermatology Life Quality Index (DLQI). The use of treatment goals involves regular assessments of treatment response after the induction phase and during the maintenance phase, to see if treatment goals are met. In case treatment goals are not met, the treatment regimen should be modified. Treatment goals may help dermatologists in providing high-quality care for psoriasis patients and may lead to less undertreatment. The studies outlined in this thesis were largely performed before the publication of these treatment goals.

In rheumatoid arthritis (RA), treating-to-target or so called tight control treatment, showed better treatment results compared with standard care.[29, 30] The efficacy of treatments for psoriasis could improve as well by using tight control approaches. However, before treatment goals are implemented for psoriasis, the added value should first be demonstrated. In addition, although treatment goals may be applied to all patients with moderate to severe psoriasis in the future, treatment modifications should still be personalized.[31]

In the first years after the registration of biological therapies for psoriasis, the treatment goal in the Netherlands, although not defined as such, was a PASI reduction of at least 50% (PASI 50) at week 12 to get approval for continued treatment and reimbursement. The Dutch psoriasis guideline (2003, updated in 2005 and 2009) also required a PASI 50 response at week 12 for etanercept and efalizumab and a PASI 50 response at week 8 for infliximab.[32] The current gold standard treatment goal is PASI 75.[33, 34] This may be changed into PASI 90 or even PASI 100 with the advent of highly effective therapies.

In conclusion: treatment goals offer the possibility for standardized tight control treatment. Further studies in daily practice have to show which treatment goal correlates best with an optimal improvement from the perspective of the patient.

The clinical utility of observational studies

In the future, the efficacy and safety of biological therapies for psoriasis will be compared with data from a similar observational study performed in our department investigating the efficacy and safety of methotrexate for psoriasis (MTX-CAPTURE). A limitation of such a comparison and of observational studies in general is that there is nonrandom assignment to treatment leading to confounding by indication, e.g. when the patients treated with biologics have more severe psoriasis than the patients treated with methotrexate. Confounding by indication is a well-known limitation of comparisons using observational data. Confounding by indication occurs when the outcome of interest is related to the factors that determine the indication for treatment. However, results of observational studies can be confirmed in other studies and can lead to important modifications in clinical practice.

In conclusion: notwithstanding the methodological restrictions of observational studies, this form of research offers a valuable approach to assessing the efficacy and safety of biological therapies for psoriasis in daily practice.

Research question 2: Is consecutive treatment with a second biologic therapy effective and safe? Is there an influence of biologic-naïvety versus non-naïvety on the efficacy results?

In **chapter 3**, switching from etanercept to adalimumab is shown to be effective and safe in patients who were naïve to biologics at the time of initiation of etanercept. On the analogy of studies in RA and a few studies in psoriasis, patients in this study were categorized as primary nonresponders to etanercept (patients not achieving PASI 50 at week 12), secondary nonresponders to etanercept (patients with loss of response after achieving PASI 50 at week 12) and patients who discontinued etanercept therapy due to adverse events (categorized as 'intolerance').

Studies in RA have shown that the efficacy of a second TNF-inhibitor is less than the efficacy of the first TNF-inhibitor and that the response to a second TNF-inhibitor depends on the reason for discontinuation of the first TNF-inhibitor. This decline in efficacy with a second TNF-antagonist is suggested to be a result of a class effect or the selection of patients with more severe disease.[35] Gniadecki et al. also showed that the drug survival of anti-TNFα agents for psoriasis, which is an indicator of treatment success, was higher

in anti-TNFα-naïve patients compared with patients who previously experienced lack of efficacy of one more anti-TNFα agents.[36]
In our study outlined in **chapter 3**, response rates to adalimumab compared with the original baseline PASI were generally better (although not statistically significant) than those previously achieved with etanercept. Irrespective of the reason for discontinuation of etanercept, the chance of having a primary response on adalimumab (defined as achieving PASI 50 at week 12) was higher than the chance of primary failure. This suggests that TNF-inhibitors demonstrate unique agent-specific profiles rather than 'class effects',[37] although the percentage of patients achieving a primary response was higher among the secondary nonresponders to etanercept (11 out of 14 (79%)) than among the primary nonresponders to etanercept (6 out of 11 (55%)).

In **chapter 4**, it is shown that the PASI 75 response rates on adalimumab during 48 weeks were only significantly higher in biologic-naïve versus non-naïve patients at week 12. These findings are supported by a study from Ortonne et al., who found only modestly decreased efficacy of adalimumab in patients with prior exposure to one or more TNF-antagonists compared with patients without prior exposure to TNF-antagonists.[38] Additional studies with larger numbers of patients are needed to address this further.
The efficacy of adalimumab in patients who failed to respond to etanercept may be explained by differences in molecule structure, mechanism of action or pharmacogenetics. The observation that adalimumab, in contrast with etanercept, is an effective therapy for granulomatous diseases, supports different biological properties of these two anti-TNFα agents.[39]
In **chapter 3**, it is shown that previous treatment with etanercept did not increase the adverse event rate nor change the nature of the adverse events during subsequent adalimumab therapy up until 48 weeks.

In conclusion, switching from etanercept to adalimumab is effective and safe, irrespective of the reason for discontinuation of etanercept. Further studies are needed to investigate whether previous treatment with biologics results in decreased efficacy of the subsequent biologic therapy in psoriasis patients.

Research question 3: What is the efficacy and safety of adalimumab dose escalation or combination therapy with methotrexate?

In case of insufficient efficacy of a biological agent, a treatment modification strategy can consist of dose escalation, the addition of another (systemic) therapy (combination therapy) or transition to another drug or modality.[28] However, before switching to another treatment, one may want to use the full potential of a biological therapy, as switching reduces the

number of available treatment options. Dose escalation and combination therapy are not approved for use in psoriasis. However, both treatment strategies are used in daily practice. Dose escalation includes increasing the amount of the biological agent per single dose or shortening the dosing interval. In patients with a very good response, dose reduction is sometimes tried. Dose reduction includes reducing the amount of the biologic per single dose or lengthening the dosing interval. A substantial proportion of the patients in the studies described in this thesis was (temporarily) treated with an escalated dose of adalimumab or etanercept or with combination therapy. Only some patients received a reduced dose of adalimumab or etanercept.

Chapter 5 describes the efficacy and safety of adalimumab dose escalation (to 40 mg per week) and combination therapy (adalimumab 40 mg every other week combined with methotrexate). In addition, the efficacy and safety of both treatment strategies applied at the same time was investigated. It is shown that a subgroup of patients with an insufficient response to adalimumab 40 mg every other week benefits from dose escalation or combination therapy (25% of first treatment episodes of adalimumab dose escalation resulted in PASI 50 at week 12 and 9% of treatment episodes with combination therapy with methotrexate resulted in PASI 50 at week 12). In a small number of patients both treatment strategies were applied at the same time with variable results.
Leonardi et al. found comparable results in their study: one quarter of patients benefited from adalimumab dose escalation (27% achieved PASI 75 within 12 weeks).[8] However, in the study of Leonardi et al., a responder was defined as a patient achieving PASI 75 relative to the baseline PASI of their first psoriasis study, whereas in our study, a responder was defined as a patient achieving PASI 50 in relation to the PASI at the start of the treatment modification. A phase II study also showed that a subgroup of patients can benefit from adalimumab dose escalation.[11] In contrast, in RA, it was shown that there is no significant change in disease activity with adalimumab dose escalation.[40]
Leonardi et al. retrospectively identified three patient characteristics that predicted a beneficial response to adalimumab dose escalation: secondary nonresponders, relatively low weight and relatively short disease duration.[8] Additional studies are needed to identify patient characteristics that predict which patients will benefit from which treatment strategy, from the point of view of optimization of treatment and the high costs of adalimumab dose escalation.

In patients receiving combination therapy with methotrexate, the dose of methotrexate was relatively low. In addition, in some patients the duration of combination therapy was short. Addition of methotrexate in a higher dose and for a longer period of time may lead to better results. Data on adalimumab combined with methotrexate for psoriasis in the literature are limited to studies with small numbers of patients successfully treated with combination therapy.[22, 41, 42]

Both adalimumab dose escalation and combination therapy with methotrexate were well tolerated. No therapy-related SAEs occurred. Safety data on non-standard dosing regimens with escalated doses of adalimumab and etanercept in the literature are limited. Up until now, there has been no evidence that treatment regimens with an escalated dose lead to increased adverse event rates.[5, 8, 11, 13, 14, 43, 44] Further large and long-term studies are needed to confirm the absence of safety issues with dose escalation or combination therapy in psoriasis.

The efficacy and safety of etanercept dose escalation or combination therapy of etanercept with a classical systemic therapy was not specifically addressed in this thesis, but has been described in the literature. Two studies investigated etanercept dose escalation to 50 mg twice weekly in patients with an insufficient response to etanercept 50 mg once weekly.[13, 45] Both studies showed greater efficacy with the escalated dose. With respect to combination therapy, most evidence is available for the combination of etanercept and methotrexate.[46-51] Combining etanercept with methotrexate in patients with an insufficient response to etanercept monotherapy increased efficacy and had acceptable tolerability in these studies.[46, 48]

In conclusion: dose escalation of adalimumab and combination therapy with methotrexate enhance the efficacy of adalimumab in a subgroup of psoriasis patients and were safe in this study.

Research question 4: What is the influence of different analytical methods on the efficacy results?

RCTs are most often analysed according the intention-to-treat (ITT) principle. An ITT analysis includes all randomized patients in the groups to which they were randomly assigned, regardless of the treatment they actually received and regardless of early withdrawal from the study or deviation from the protocol.[2, 52, 53] In the Bio-CAPTURE study, patients are not randomized. However, the term ITT analysis is used in **chapter 4-6**, as all patients were analysed for the full period of analysis. This has also been done in other observational studies.[17, 54]

As the duration of a study increases, the number of patients continuing in the study usually declines, leading to missing data.[52] Data can be missing for a variety of reasons, including withdrawal from the study due to lack or loss of efficacy or adverse events.[2, 52, 53, 55]

Different approaches for providing an estimated value for missing data exist, commonly referred to as 'imputation' of missing data (Table 1). In our study, the efficacy outcome measures are PASI 50, PASI 75 and PASI 90. Imputation methods commonly used in RCTs are last observation carried forward (LOCF) and nonresponder imputation (NRI).

Table 1. Description of different approaches for the analysis of data in clinical studies.[52]

Approach	Abbreviation	Description	Equivalent terminology
Populations			
Intention-to-treat	ITT	All randomized patients in the groups to which they were randomly assigned	
Per-protocol	PP	All patients who did not deviate from the protocol	Adherers only
Intention-to-observe	ITO	All patients entering the observational phase of a long-term study	Maintenance ITT
Imputation of missing data			
Missing equals succes	MES	Missing values are assigned as a success	
Missing equals failure	MEF	Missing values are assigned as a failure	Nonresponder imputation
Missing equals excluded	MEX	Missing values are excluded from the analysis	As-treated
Missing completely at random	MCAR	The missingness of data does not depend on the previously observed or current unobserved outcomes	
Missing at random	MAR	The missingness of data depends on the previously observed values, but not the current unobserved values	
Missing not at random	MNAR	The missingness of data depends on the current unobserved outcomes	
Last observation carried forward	LOCF	The previous observation is used for the missing value	

With LOCF, the previous available value is used for the subsequent missing value(s). Although criticized by statisticians, LOCF is the most commonly used imputation method in RCTs. It is generally considered to provide a conservative estimate of efficacy.[52]
The most conservative approach is NRI. With NRI, a patient with a missing value is regarded as a nonresponder, also referred to as 'missing equals failure' (MEF). In an as-treated analysis, missing values are excluded from the analysis, which is also referred to as 'missing equals excluded' (MEX).[2, 53, 56] The as-treated analysis is sometimes also called observed values analysis (**chapter 2**) and is mainly being used in observational studies and open-label extension studies from RCTs.[4, 56, 57]

Based on the research question, different analytical methods can be chosen. The as-treated analysis gives an idea of maximum efficacy. However, if one wants to know what treatment efficacy is under less ideal conditions, including patients who discontinue treatment due to insufficient efficacy, an ITT analysis will provide better information.[2] As shown in **chapter 6**, the methodological approach used has a major influence on the efficacy results. In our study, efficacy could double when the as-treated approach was used instead of the modified NRI approach.
Using NRI in an observational cohort study is problematic, as the inclusion of patients is continuously ongoing. Applying NRI for patients who were still using etanercept at the time of analysis, but did not reach all time points of analysis due to an insufficient duration

of follow-up, was considered inappropriate. Therefore, a less conservative modification of the NRI approach, named the modified NRI approach, was used in **chapter 6**.[56]

The influence of missing data on the efficacy outcomes of a study depends on the reasons for missing data. As shown in Figure 1 in **chapter 6**, the most frequent reason for discontinuing etanercept treatment in our study was loss of efficacy or a combination of loss of efficacy and adverse events.[55] For this reason and for reason of the prolonged treatment duration of responders, the as-treated analysis gives a too positive view of the efficacy of etanercept. On the other hand, nonresponder imputation would probably give a too negative view of the efficacy of etanercept, as a substantial number of treatment episodes had missing data for other reasons than loss of efficacy or a combination of loss of efficacy and adverse events. The modified NRI method may underestimate the efficacy of etanercept as well, as some patients who discontinued etanercept due to lack of efficacy or a combination of lack of efficacy and adverse events, actually were PASI 75 responders (Figure 3). This means that a PASI 75 response is not always a sufficient response for patients and/or dermatologists.

A way to overcome the bias introduced by each statistical method, is the use and development of other outcome measures. A possible outcome measure could be the amount of time patients continue to take a particular drug, which is also referred to as 'drug survival'. Drug survival is an indirect measure of drug efficacy. However, drug survival is also dependent on side effects, general satisfaction with the treatment and the availability of other therapies.[36, 55] An alternative outcome measure could be represented by a biomarker that measures psoriasis activity instead of an outcome measure that measures psoriasis severity like the PASI. However, reliable biomarkers are not available at this moment.

In conclusion: every method of analysis has its advantages and disadvantages and can introduce a bias. As the method of analysis used has a large influence, we support the use of different methods of analysis.

Research question 5: What is the safety profile of biologic treatment for psoriasis with extended exposure?

Chapter 7 shows that the safety profile of biological therapies was favourable in patients with prolonged treatment with one biologic or consecutive biological agents during 5 years of follow-up. The incidence of serious adverse events was low. This corresponds with data from RCTs, meta-analyses and open-label extension studies.[58]
Most safety data in this thesis concern etanercept and adalimumab. **Chapter 7** presents the available safety data on efalizumab, ustekinumab and infliximab. Data on the safety

of ustekinumab and infliximab are also available in the literature. The long-term safety of ustekinumab up to five years has been shown in a long-term extension study from RCTs.[59] The intermediate-term safety of infliximab in psoriasis has been shown in an RCT with 50 weeks duration, an RCT with an open-label extension phase lasting 78 weeks and a retrospective study in patients treated with infliximab for a minimum of one year and a mean follow-up of 2.2 years.[58, 60-62]
As described in **chapter 7**, adverse events in our study were mainly mild and were of the same nature as described in earlier reports from our registry and in other studies. Twenty-eight percent of the patients reported at least one SAE. However, only 24% of SAEs was considered to be possibly therapy-related, taking into account the time relationship and the patient's medical history. Only one serious adverse event (infusion reaction) was considered to be certainly causally related to infliximab treatment.

Criteria for determining causality in epidemiological studies have been established, the so called Bredford-Hill criteria.[63] In addition, WHO causality categories exist.[64] However, the best way to attribute causality in adverse events detected or to measure their magnitude, is to make a comparison with a control group.[65] In the study described in **chapter 7**, observed numbers of malignancies, serious infections and serious cardiovascular events are compared with the expected rate in the general population. It is shown that the incidence of these serious adverse events was comparable with the population incidence rate, except for nonmelanoma skin cancer (NMSC). However, the number of patients was too small to detect possible differences in the incidence of other less frequent SAEs. The increased incidence of NMSC could also be explained by previous phototherapy and nonbiologic systemic agents or a higher awareness for skin malignancies among dermatologists than among general practitioners. It was shown that 5 out of 7 psoriasis patients with NMSC were diagnosed with their first NMSC within 5 months after the start of biological treatment, which suggests that these NMSC cases can be explained by previous therapies like phototherapy instead of by the biological therapy.

All biologics were analysed as one group, as the majority of patient-years of follow-up concerned etanercept and because some adverse effects like malignancies may appear after a long latency period, which makes it difficult to attribute them to a specific therapy. However, ideally all biological agents should be analysed separately, as inter-class and even intra-class differences in the risk of inducing SAEs may exist. TNF-inhibitors as a class for example, have been associated with reactivation of latent tuberculosis, development or worsening of heart failure, demyelinating diseases and drug-induced lupus erythematosus.[26, 34]

The incidence of SAEs observed with adalimumab therapy in daily practice (0.23 SAEs per patient-year (**chapter 4**)) was higher than the incidence of SAEs reported with

adalimumab therapy in the REVEAL randomized controlled trial (0.06 SAEs per patient-year), an open-label extension study (0.07 SAEs per patient-year) and a comprehensive analysis of all adalimumab exposure in all clinical trials (0.09 events per patient-year).[9, 16, 66] However, the number of SAEs, the number of patients and the number of patient-years of follow-up in our study were too low to draw definitive conclusions.
A possible explanation for the higher morbidity associated with adalimumab therapy in our study could be that daily practice patients have more comorbidity and concomitant medication. This is supported by a study from Garcia-Doval et al., who showed that 30% of patients receiving systemic therapy (biologic and nonbiologic) for psoriasis in daily practice were not eligible for RCTs and that the risk of SAEs in these patients was higher than in patients eligible for RCTs.[67]

Biologics are currently seen as third-line therapies after topical therapies, phototherapy and conventional nonbiologic systemic agents, due to remaining concerns about their long-term safety and their high cost. Present intermediate-term data show a favourable risk-benefit profile, but there is not yet enough insight into the safety of biological therapies for psoriasis in the very long term. There are still long-term concerns regarding the possibility of certain adverse events like malignancies with possible long latency periods, although up until now, there have been no signs of cumulative toxicity with the currently available biologics.[58]
In 2009, the EMA withdraw the market authorization of efalizumab, due to three fatal cases of progressive multifocal leucoencephalopathy (PML) in patients who had been treated with efalizumab for 3 years or longer.[26] PML is related to reactivation of the John Cunningham (JC) virus in immunosuppressed persons. This emphasizes the importance of continuous pharmacovigilance of biological therapies. If longer-term follow-up continuous to show a good safety profile, biologics might become second-line alternative treatments options when only considered from the safety perspective.

TNF-inhibitors have been in use longer for RA and inflammatory bowel disease than for psoriasis. However, safety data from these other patient populations cannot just be extrapolated to psoriasis. Patients with psoriasis differ from patients with RA with respect to gender distribution, BMI, previous exposure to phototherapy, comorbidity, dosing regimens and the concomitant use of other immunosuppressive drugs.[6, 26, 34, 68]
Other challenges encountered in biologics safety research include the rarity of some adverse events, the choice of comparator groups, inconsistent coding of adverse events and reporting bias.[43] Large-scale registries, postmarketing surveillance databases and pooling of data are essential for providing information on the long-term safety of biologics and possible rare adverse events. Registries are preferred over postmarketing data, as the latter face underreporting and the lack of an internal control group.[69]

So far the safety concerns about long-term treatment with biologics have decreased and at present, the limited safety concerns associated with biologic treatment can be interpreted in the light of the high benefits of these agents in patients with moderate to severe psoriasis. However, in daily practice, the choice for a certain biologic is often not only based on efficacy and safety. The choice for a certain biologic will be determined by the overall picture of short-term and long-term efficacy, safety, the severity of psoriasis, the presence or absence of psoriatic arthritis, costs, the way of administration, injection frequency, comorbidity, the possibility of interrupted therapy in relation to antibody formation and patient preference.

In conclusion: in this cohort, the long-term safety of biological therapies for psoriasis was favourable with a low incidence of therapy-related serious adverse events.

Research question 6: Is there a difference in time to first NMSC and the incidence of NMSC between patients with psoriasis and patients with rheumatoid arthritis treated with TNF-inhibitors?

In the study presented in **chapter 8**, it is shown that the risk of developing NMSC was significantly higher in the psoriasis group compared with the RA group with a shorter time until first NMSC in the psoriasis group. The results also indicate that disease related factors like phototherapy may be an important contributing factor to NMSC diagnosed in psoriasis patients treated with TNF-inhibitors.
Ideally, a comparison would have been made with a group of psoriasis patients (instead of a group of RA patients) who have received TNF-inhibitor therapy and conventional systemic antipsoriatic therapies but no phototherapy, as the incidence of NMSC could be influenced by the specific disease (i.e. psoriasis or RA). However, as TNF-inhibitors can only be prescribed to patients who failed to respond to phototherapy in the largest part of the world, this control group is not available.
A comparison with a group of psoriasis patients who have been treated with phototherapy and conventional systemic therapies but no anti-TNFα therapy would be an adequate approach to investigate the influence of TNF-inhibitors on NMSC development. However, this was not possible as this group of patients was not available. A comparison with data from the literature has many limitations due to differences in study procedures, differences in the classification of adverse events, different time periods covered with increasing skin cancer rates over time and differences in the degree of sun exposure with latitude, as was shown in the studies from Burmester et al. and Pariser et al.[44, 70] These studies and the studies presented in this thesis show that comparisons should preferably be made with an internal control cohort with a parallel follow-up.

In conclusion: the risk of developing NMSC was significantly higher in psoriasis compared with RA with a shorter time until first NMSC in psoriasis. Disease related factors like phototherapy may be an important contributing factor to NMSC diagnosed in psoriasis patients treated with TNF-inhibitors.

Research question 7: Is monitoring with regard to laboratory investigations needed in patients with psoriasis with extended exposure to etanercept or adalimumab?

Patients with psoriasis treated with biologics are monitored routinely with laboratory investigations according to existing guidelines. However, to justify the invasiveness of a venipuncture and the costs of this procedure and possible further investigations, abnormal laboratory values should have clinical consequences and should result in a better outcome.

In the literature, cytopenias and elevated liver enzymes have been reported for TNF-inhibitors.[71, 72] In our study only, two patients (1%) experienced clinical consequences of abnormal haematological laboratory values in terms of a temporary interruption of treatment due to severe abnormalities. A significant increase of mean alanine aminotransferase (ALT) during etanercept treatment was also found, but the mean value did not exceed normal reference ranges. Severely elevated ALT activities (grade 3 and grade 4) were probably due to the concomitant use of methotrexate or comorbidities.

Statistically significant changes in mean values during treatment compared with pretreatment as well as significant trends were also detected for certain other haematology and chemistry parameters. However, mean values during treatment remained within normal reference ranges.

Biological treatment was temporarily interrupted in patients presenting with an infection clinically with or without laboratory testing and with or without elevated infection parameters.

Further studies in other groups of patients, preferably with a longer follow-up, and implementation studies could provide more evidence as to which laboratory panels and intervals are appropriate. At least as important as laboratory testing is to instruct patients to contact their dermatologist when health problems, including infections, occur in between hospital visits.

In conclusion: in this cohort, the incidence of biological therapy-related serious laboratory abnormalities was low. Our findings do not support a need for routine laboratory testing during etanercept or adalimumab treatment in psoriasis patients beyond the laboratory testing required for concomitant therapies, comorbidities or symptoms. Further studies could provide more evidence as to which laboratory panels

and intervals are appropriate. Screening tests before the start of biological treatment are necessary to detect contraindications or risk factors and to provide a baseline value.

Future directions

There is a need for direct comparisons of various aspects of biological therapies and other systemic therapies for psoriasis in daily practice. By using information from the Bio-CAPTURE registry and the MTX-CAPTURE registry, comparisons can be made of the efficacy, safety, cost-effectiveness, quality of life and treatment satisfaction of the biological therapies and methotrexate.
Most efficacy and safety data in this thesis concern etanercept and adalimumab. Data on the use of ustekinumab in routine practice will be analysed in the near future.
In our studies, etanercept and adalimumab showed lower efficacy in a daily practice setting compared with RCTs. It would be interesting to evaluate the efficacy of biological agents in daily practice patients who are eligible and patients who are ineligible for RCTs. In RA, it was shown that patients eligible for RCTs had higher response percentages and responses more similar to RCTs than ineligible patients.[73]
In RA, it was also shown that treating according to treatment goals improved efficacy compared with standard care.[29, 30] A prospective implementation study, investigating treatment according to treatment goals compared with routine outpatient care, can be performed in psoriasis patients from the Bio-CAPTURE registry.
The Bio-CAPTURE network offers the opportunity to compare the efficacy of biological agents between academic and nonacademic patients and to perform safety analyses in a larger group of patients.

The development of algorithms of care would be helpful for dermatologists to help them decide which treatment modifications to implement in case of insufficient efficacy of a biological agent. To establish these algorithms of care, more information is needed. In the future, the effect of dose escalation or combination therapy with a traditional systemic agent can be compared in a larger group of patients. The duration of dose escalation and the duration and dose of combination therapy needed, can also be further characterized. Furthermore, the effect of switching to a biologic agent with the same mechanism of action can be compared with switching to a biologic with a different mode of action.

From the point of view of the high costs of biological therapies and remaining concerns about the safety of biological therapies in the very long term, it would be interesting to investigate the efficacy and safety of dose reduction, intermittent therapy and a possible biologic-sparing effect of combination therapy. At present, the number of patients treated with reduced doses is too low to analyse. Interruption of therapy has been done

in patients with infections, patients undergoing invasive surgery and patients with a desire for pregnancy. The efficacy and safety of intermittent therapy can be analysed in this group of patients to begin with. Interrupted therapy or discontinuation of a biological agent is at present not considered in other patients, as there are no biomarkers for remission of psoriasis. In addition, interrupted therapy has a risk of disease rebound, antibody formation and possibly also decreased efficacy with retreatment.

Perspective

Psoriasis is a chronic disease and every patient has his or her own psoriasis. A scientific approach to the treatment of psoriasis in daily clinical practice is important to develop tools for a personalized approach to the long-term treatment of psoriasis. Stratification of patients based on patient characteristics, clinical characteristics, pharmacogenetics and biomarkers will result in individualized long-term management of psoriasis, utilizing available therapies and new treatment options. Registries with detailed information on patient and treatment characteristics are essential for developing the personalized healthcare of the future.

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Chapter 11

Samenvatting en Discussie

Doelstelling

Het doel van dit proefschrift was het prospectief onderzoeken van de lange termijn effectiviteit en veiligheid van biologicals bij de behandeling van patiënten met matige tot ernstige psoriasis in de dagelijkse praktijk. Het merendeel van de geanalyseerde gegevens werd verkregen uit een prospectieve database (registry), de Bio-CAPTURE registry. In deze registry worden gegevens verzameld over alle patiënten met psoriasis die starten met een biological in de dagelijkse praktijk.

De registry weerspiegelt in zekere mate de geschiedenis van de introductie van biologicals. Etanercept was een van de eerste biologicals die geregistreerd werd voor psoriasis. Etanercept was daarom de eerste biological voor veel patiënten. In het geval van onvoldoende effectiviteit of adverse events tijdens behandeling met etanercept, switchten patiënten met name naar adalimumab. Dit proefschrift bevat daarom met name gegevens over de effectiviteit en veiligheid van etanercept en adalimumab. Veiligheidsgegevens over efalizumab zijn beschreven in **hoofdstuk 7**, hoewel efalizumab in 2009 van de markt is gehaald vanwege een risico op ernstige bijwerkingen.

De registry weerspiegelt ook de logistieke organisatie van onze afdeling. Op onze afdeling wordt behandeling met infliximab alleen toegepast bij patiënten met zeer ernstige psoriasis, waarbij een snelle respons vereist is en bij patiënten waarbij andere biologicals onvoldoende effectief waren. Dit heeft te maken met de faciliteiten die nodig zijn voor de toediening van infliximab en de infusiereacties die soms voorkomen. Behandeling met infliximab is daarom niet veelvuldig toegepast op onze afdeling. Ustekinumab is geregistreerd voor psoriasis sinds 2009. Op het moment dat de onderzoeken beschreven in dit proefschrift werden uitgevoerd, was de ervaring met ustekinumab nog beperkt. In **hoofdstuk 7** zijn de beschikbare gegevens over de lange termijn veiligheid van infliximab en ustekinumab beschreven.
Na deze historische en logistieke aspecten te hebben verduidelijkt, zullen nu de onderzoeksvragen zoals geformuleerd in **hoofdstuk 1** worden bediscussieerd en zullen conclusies worden geformuleerd gebaseerd op deze discussies en de onderzoeken beschreven in **hoofdstuk 2-9**.

Onderzoeksvraag 1: Wat is de lange termijn effectiviteit van biologicals bij de behandeling van psoriasis in de dagelijkse praktijk?

De begrippen efficacy en effectiveness

De Engelse termen 'efficacy' en 'effectiveness' worden beide gebruikt om het effect van een bepaalde behandeling te beschrijven. Deze twee termen hebben echter een verschillende

betekenis. In het Nederlands bestaan geen aparte termen voor deze twee begrippen. Efficacy duidt op het effect van een behandeling in de context van een gerandomiseerde gecontroleerde trial (randomized controlled trial (RCT)), terwijl effectiveness duidt op het effect van een behandeling in de dagelijkse praktijk.[1-3] In dit proefschrift is meestal de term efficacy gebruikt voor het beschrijven van het effect van biologicals in de dagelijkse praktijk, terwijl de term effectiveness eigenlijk geschikter zou zijn geweest.

Lange termijn effectiviteit van etanercept en adalimumab

Behandeling met etanercept en adalimumab voor matige tot ernstige psoriasis in de dagelijkse praktijk was effectief op de lange termijn. De resultaten beschreven in **hoofdstuk 6** laten zien dat de lange termijn effectiviteit van etanercept bij patiënten met een gemiddelde behandelduur van 2,7 jaar aanzienlijk is. In **hoofdstuk 4** is beschreven dat de effectiviteit van adalimumab behouden blijft bij patiënten met een gemiddelde behandelduur van 1,4 jaar.

Wanneer men kijkt naar de resultaten van de intention-to-treat (ITT) analyse met last observation carried forward (LOCF) en gemodificeerde nonresponder imputation (modified NRI) in **hoofdstuk 6** (Figuur 2-4), dan lijkt er sprake te zijn van een geleidelijke afname van de effectiviteit van etanercept. Dit is ook beschreven in open-label extensie onderzoeken.[4, 5] Het is niet bekend waardoor deze geleidelijke afname van de effectiviteit veroorzaakt wordt. Mogelijke verklaringen zouden kunnen zijn: biologische adaptatie aan chronische blokkade van TNF-α (door een ander mechanisme dan antistofvorming in het geval van etanercept), verminderde afhankelijkheid van de ziekte van TNF-α, verhoogde metabole klaring of compliance problemen.[5-7]

Op basis van de resultaten van open-label extensie onderzoeken en vanuit de dagelijkse praktijk is bekend dat er ook tijdens behandeling met adalimumab sprake kan zijn van verlies van effectiviteit.[8, 9] Mogelijke verklaringen hiervoor zijn dezelfde als hierboven beschreven voor etanercept. Voor adalimumab geldt daarnaast dat antistofvorming tegen adalimumab geassocieerd is met een slechtere effectiviteit.[10]

Een indirecte vergelijking van de lange termijn effectiviteit van etanercept en adalimumab kan niet goed gemaakt worden, vanwege verschillen in patiëntengroepen en gebruikte doseringen.

Dagelijkse praktijk vergeleken met RCT's

De lange termijn effectiviteit van etanercept en adalimumab in onze onderzoeken in de dagelijkse praktijk was lager dan in de RCT's en open-label extensie onderzoeken van RCT's.[5, 9, 11-22] RCT's en onderzoeken uit de dagelijkse praktijk kunnen echter niet zomaar vergeleken worden, vanwege verschillen in patiëntenpopulaties, uitkomstmaten, analysemethoden en gebruikte doseringen. Daarnaast verschillen de tijdstippen waarop de effectiviteit wordt beoordeeld.

Er zijn een aantal factoren die de lagere PASI 75 respons in ons onderzoek vergeleken met RCT's kunnen verklaren. Ten eerste zijn de patiënten uit ons onderzoek behandeld in een academisch ziekenhuis. Patiënten die verwezen worden naar een tertiair centrum hebben waarschijnlijk een hogere therapieresistentie. Ten tweede moeten patiënten in de dagelijkse praktijk voldoen aan strenge vergoedingscriteria, hetgeen niet geldt voor patiënten die deelnemen aan RCT's. Ook dit kan leiden tot de selectie van patiënten met een hogere therapieresistentie in de dagelijkse praktijk. Daarnaast zijn patiënten die geïncludeerd worden in RCT's over het algemeen 'gezond', omdat ze voldoen aan strenge inclusie- en exclusiecriteria. Patiënten in de dagelijkse praktijk daarentegen hebben over het algemeen comobiditeit en comedicatie.
Tevens worden in RCT's 'washout' periodes toegepast, hetgeen leidt tot een hoge PASI bij aanvang van de RCT (baseline PASI). Als gevolg hiervan worden sommige patiënten geïncludeerd op basis van een hoge PASI, die niet representatief is voor hun gemiddelde PASI. Dit leidt tot een fenomeen dat 'regressie naar het gemiddelde' wordt genoemd. Daarnaast kunnen onderzoekers op het moment dat bepaald wordt of een patiënt kan deelnemen aan een RCT de neiging hebben om bij het scoren van de subjectieve items van de PASI de hoogst passende score te kiezen, een fenomeen dat 'eligibility creep' wordt genoemd. Deze twee fenomenen kunnen mogelijk ook deels de grote placebo-effecten in RCT's bij psoriasis verklaren.[23]
Andere verklaringen voor de lagere effectiviteit in de dagelijkse praktijk zijn compliance problemen, inadequaat gebruik van de biological en onderbrekingen van de behandeling als gevolg van infecties of electieve operaties. Aan de andere kant kunnen behandelstrategieën die toegepast worden in de dagelijkse praktijk, zoals het gelijktijdig gebruik van lokale of klassieke systemische therapieën en dosisverhogingen van biologicals, leiden tot een hogere effectiviteit.

Conclusie: behandeling met etanercept en adalimumab voor matige tot ernstige psoriasis in de dagelijkse praktijk is effectief op de lange termijn. Er zijn veel verschillen tussen de dagelijkse praktijk en RCT's, hetgeen impliceert dat onderzoeken in de dagelijkse praktijk belangrijke informatie verschaffen als aanvulling op de informatie die beschikbaar is vanuit RCT's.

PASI als uitkomstmaat

PASI 50/75/90/100 zijn de meest gebruikte uitkomstmaten in klinische trials en onderzoeken in de dagelijkse praktijk, hetgeen vergelijkingen van onderzoeksresultaten mogelijk maakt. Absolute uitkomstmaten die de ernst van de psoriasis op een bepaald moment weergeven, zoals bijvoorbeeld de statische Physician's Global Assessment (PGA), zijn echter mogelijk geschikter voor gebruik in lange termijn onderzoeken dan uitkomstmaten die de verandering ten opzichte van baseline weergeven. Dit laatste is

de focus van onderzoek in RCT's.[24, 25] Een belangrijke beperking van de PASI is dat deze uitkomstmaat geen rekening houdt met de invloed van psoriasis op de kwaliteit van leven, de lokalisatie van de psoriasis (zichtbare plekken/behaarde hoofd/genitaal) en het wel of niet aanwezig zijn van nagelpsoriasis.[26, 27] Er is behoefte aan een samengestelde uitkomstmaat, waarin alle relevante aspecten van psoriasis aan bod komen. Een andere beperking van de PASI is dat de score bij een klein aangedaan lichaamsoppervlak weinig veranderlijk is.

Selectie van de baseline PASI

In **hoofdstuk 2-6** wordt getoond dat de effectiviteit erg afhangt van welke baseline PASI en welke analysemethode gebruikt wordt. De invloed van de gebruikte analysemethode zal later bediscussieerd worden.

In **hoofdstuk 3** is de respons op adalimumab berekend in relatie tot de baseline PASI voor de start van adalimumab (course baseline PASI) en de baseline PASI voor de start van etanercept (original baseline PASI). In **hoofdstuk 4** is de respons op adalimumab berekend in relatie tot de baseline PASI voor de start van adalimumab (course baseline PASI) en de eerste beschikbare baseline PASI voor de start van een biological op het moment van inclusie in de registry (original baseline PASI). Dit is gedaan vanwege het feit dat de course baseline PASI meestal lager is dan de original baseline PASI, als gevolg van het effect van de voorafgaande behandeling.

De huidige gouden standaard uitkomstmaat PASI 75 is een relatieve uitkomstmaat, die de verbetering van de PASI ten opzichte van baseline weergeeft. Omdat patiënten vaak restplekken overhouden en omdat de PASI weinig veranderlijk is bij een klein aangedaan lichaamsoppervlak, is een PASI 75 respons moeilijk te bereiken wanneer een behandeling gestart wordt bij een lage baseline PASI.

Conclusie: resultaten voor effectiviteit zijn afhankelijk van welke baseline PASI gebruikt wordt, wanneer gebruikt wordt gemaakt van relatieve uitkomstmaten (bijv. PASI 75). Het is belangrijk dat men zich dit realiseert voor een correcte interpretatie van resultaten. Een alternatief zou kunnen zijn het gebruik van een absolute uitkomstmaat in combinatie met een relatieve uitkomstmaat.

Treatment goals

In 2011 publiceerde een Europese consensusgroep treatment goals (behandeldoelen) voor de behandeling van matige tot ernstige plaque psoriasis met systemische therapieën, naar analogie van treatment goals voor andere chronische ziekten zoals diabetes mellitus.[28] Deze treatment goals omvatten de ernst van de psoriasis (gemeten met de PASI) en de kwaliteit van leven (gemeten met de Dermatology Life Quality Index (DLQI)). Het gebruik van treatment goals houdt in dat de respons op een behandeling

na de inductiefase en tijdens onderhoudsbehandeling regelmatig geëvalueerd wordt, om te zien of de treatment goals gehaald worden. Wanneer de treatment goals niet gehaald worden, moet de behandeling aangepast worden. Het gebruik van treatment goals zou dermatologen kunnen helpen bij het leveren van hoge kwaliteit van zorg aan psoriasis patiënten en zou kunnen leiden tot minder onderbehandeling. De onderzoeken beschreven in dit proefschrift zijn grotendeels uitgevoerd vóór de publicatie van deze treatment goals.

In onderzoeken bij patiënten met reumatoïde artritis (RA) is aangetoond dat het gebruik van treatment goals leidt tot betere behandelresultaten vergeleken met reguliere behandeling.[29, 30] Het gebruik van treatment goals zou ook bij psoriasis kunnen leiden tot betere behandelresultaten. Echter, voordat er treatment goals geïmplementeerd kunnen worden voor psoriasis, moet de toegevoegde waarde van het gebruik van treatment goals eerst aangetoond worden. Daarnaast geldt dat ook wanneer patiënten behandeld worden volgens treatment goals, het aanpassen van de behandeling maatwerk blijft.[31]

In de eerste jaren na de registratie van biologicals voor psoriasis was de treatment goal in Nederland, alhoewel niet als zodanig genoemd, het bereiken van een PASI 50 respons na 12 weken behandeling ter verkrijging van goedkeuring voor vergoeding van voortgezette behandeling. De Nederlandse psoriasis richtlijn (2003, update in 2005 en 2009) vereiste ook een PASI 50 respons na 12 weken voor etanercept en efalizumab en een PASI 50 respons na 8 weken voor infliximab.[32] De huidige gouden standaard treatment goal is PASI 75.[33, 34] Mogelijk komen er in de toekomst dusdanig effectieve behandelingen op de markt dat dit veranderd kan worden in PASI 90 of PASI 100.

Conclusie: het gebruik van treatment goals maakt het mogelijk om het effect van een behandeling strak te monitoren. Vervolgonderzoek in de dagelijkse praktijk moet aantonen welke treatment goal het best overeenkomt met een optimale verbetering vanuit het perspectief van de patiënt.

Het belang van observationeel onderzoek

In de toekomst zal de effectiviteit en veiligheid van biologicals bij de behandeling van psoriasis vergeleken worden met gegevens uit een vergelijkbaar onderzoek van onze afdeling naar de effectiviteit en veiligheid van methotrexaat bij de behandeling van psoriasis (MTX-CAPTURE). Een beperking van een dergelijke vergelijking en van observationele onderzoeken in het algemeen, is dat patiënten niet op basis van toeval een bepaalde behandeling voorgeschreven krijgen (nonrandom assignment to treatment). Dit leidt tot een verschijnsel genaamd confounding by indication, hetgeen zich bijvoorbeeld voordoet wanneer patiënten die met biologicals behandeld worden een ernstigere

psoriasis hebben dan patiënten die behandeld worden met methotrexaat. Confounding by indication is een bekende beperking van vergelijkingen waarbij gebruik gemaakt wordt van observationele data. Confounding by indication doet zich voor wanneer de uitkomstmaat waarin men geïnteresseerd is, gerelateerd is aan factoren die de indicatie voor de behandeling bepalen. Resultaten van observationele onderzoeken kunnen echter in andere onderzoeken bevestigd worden en kunnen leiden tot belangrijke veranderingen in de dagelijkse praktijk.

Conclusie: observationeel onderzoek kent methodologische beperkingen, maar is zeer waardevol bij het onderzoeken van de effectiviteit en veiligheid van biologicals bij de behandeling van psoriasis in de dagelijkse praktijk.

Onderzoeksvraag 2: Is behandeling met een tweede biological effectief en veilig? Heeft voorafgaande behandeling met biologicals invloed op de effectiviteit van de volgende biological?

De resultaten van het onderzoek beschreven in **hoofdstuk 3** laten zien dat switchen van etanercept naar adalimumab effectief en veilig is bij patiënten die nog niet eerder met een biological waren behandeld (naïef waren voor behandeling met biologicals) op het moment dat ze startten met etanercept. Naar analogie van onderzoeken bij patiënten met RA en een paar onderzoeken bij patiënten met psoriasis, werden patiënten in dit onderzoek ingedeeld in 3 categorieën: primaire nonresponders op etanercept (patiënten die geen PASI 50 respons halen in week 12), secundaire nonresponders op etanercept (patiënten met verlies van effectiviteit na het behalen van een PASI 50 respons in week 12) en patiënten die gestopt waren met etanercept vanwege adverse events (categorie 'intolerance').
Onderzoeken bij patiënten met RA hebben laten zien dat de effectiviteit van een tweede TNF-antagonist lager is dan de effectiviteit van de eerste TNF-antagonist en dat de respons op een tweede TNF-antagonist afhangt van de reden voor het stoppen van de eerst TNF-antagonist. De afname van de effectiviteit bij een tweede TNF-antagonist zou het gevolg kunnen zijn van een klasse-effect of van de selectie van patiënten met ernstigere RA.[35] Gniadecki et al. vonden in hun onderzoek bij psoriasis patiënten ook dat de drug survival van TNF-antagonisten (hetgeen een indicator is voor de effectiviteit van een behandeling) hoger was bij patiënten die naïef waren voor behandeling met TNF-antagonisten, vergeleken met patiënten die eerder behandeld waren met één of meerdere TNF-antagonisten en hiermee gestopt waren i.v.m. onvoldoende effectiviteit.[36]
Hoofdstuk 3 laat zien dat in ons onderzoek de respons op adalimumab vergeleken met de originele baseline PASI over het algemeen beter was (hoewel niet statistisch significant) dan de voorafgaande respons op etanercept. Onafhankelijk van de reden voor staken

van etanercept was de kans op het bereiken van een primaire respons op adalimumab (PASI 50 in week 12) hoger dan de kans op primair falen. Dit pleit tegen een klasse-effect van TNF-antagonisten,[37] hoewel het percentage patiënten met een primaire respons op adalimumab hoger was onder de secundaire nonresponders op etanercept (11 van de 14 (79%)) dan onder de primaire nonresponders op etanercept (6 van de 11 (55%)).

Hoofdstuk 4 laat zien dat het percentage patiënten met een PASI 75 respons tijdens behandeling met adalimumab gedurende 48 weken alleen in week 12 significant hoger was bij patiënten die naïef waren voor biologicals vergeleken met patiënten die niet naïef waren voor biologicals. Deze bevindingen worden ondersteund door een onderzoek van Ortonne et al., waarin slechts een geringe afname van de effectiviteit van adalimumab werd gevonden bij patiënten die eerder behandeld waren met één of meerdere TNF-antagonisten vergeleken met patiënten die naïef waren voor behandeling met TNF-antagonisten.[38] Meer onderzoeken met grotere aantallen patiënten zijn nodig om dit verder te onderzoeken.
Het feit dat adalimumab effectief was bij het merendeel van de patiënten die gefaald hadden op etanercept, kan mogelijk verklaard worden door verschillen in molecuulstructuur of werkingsmechanisme of door farmacogenetische verschillen. Het feit dat adalimumab in tegenstelling tot etanercept effectief is bij de behandeling van granulomateuze aandoeningen, pleit voor verschillende biologische eigenschappen van deze twee biologicals.[39]
Hoofdstuk 3 laat zien dat voorafgaande behandeling met etanercept niet leidde tot meer adverse events of andere adverse events tijdens behandeling met adalimumab gedurende 48 weken.

Conclusie: switchen van etanercept naar adalimumab is effectief en veilig, onafhankelijk van de reden voor staken van etanercept. Verder onderzoek is nodig om de vraag te beantwoorden of voorafgaande behandeling met biologicals leidt tot verminderde effectiviteit van de volgende biological bij patiënten met psoriasis.

Onderzoeksvraag 3: Wat is de effectiviteit en veiligheid van dosisverhoging van adalimumab of combinatietherapie met methotrexaat?

Wanneer een biological onvoldoende effectief is, kan de behandeling op verschillende manieren aangepast worden. De dosis van de biological kan verhoogd worden, er kan een andere (systemische) therapie toegevoegd worden (combinatietherapie) of er kan geswitcht worden naar een ander geneesmiddel of een andere modaliteit.[28] Omdat switchen het aantal behandelingsmogelijkheden verkleint, kan men er voor kiezen om eerst de werking van de biological volledig te proberen te benutten door middel van dosisverhoging of combinatietherapie. Dosisverhoging en combinatietherapie zijn

niet geregistreerd voor psoriasis, maar worden in de dagelijkse praktijk wel toegepast. Dosisverhoging betekent het verhogen van de dosis van de biological per toediening of verkorting van het toedieningsinterval. Bij patiënten met een zeer goede respons wordt soms geprobeerd om de dosis te verlagen. Dosisverlaging houdt in het verlagen van de dosis van de biological per toediening of verlenging van het toedieningsinterval. In de onderzoeken beschreven in dit proefschrift is bij een substantieel deel van de patiënten (tijdelijk) dosisverhoging van adalimumab of etanercept of combinatietherapie toegepast. Slechts bij enkele patiënten is dosisverlaging van adalimumab of etanercept toegepast.

Hoofdstuk 5 beschrijft de effectiviteit en veiligheid van dosisverhoging van adalimumab (naar 40 mg per week) en combinatietherapie (adalimumab 40 mg om de week gecombineerd met methotrexaat). Daarnaast is de effectiviteit en veiligheid onderzocht wanneer beide behandelstrategieën tegelijkertijd worden toegepast. De resultaten laten zien dat een subgroep van patiënten met een onvoldoende respons op adalimumab 40 mg om de week, baat heeft bij dosisverhoging of combinatietherapie (27% van de eerste behandelepisodes met dosisverhoging resulteerde in PASI 50 na 12 weken en 9% van de behandelepisodes met combinatietherapie resulteerde in PASI 50 na 12 weken). Bij een klein aantal patiënten werden beide behandelstrategieën tegelijkertijd toegepast. Hierbij werden wisselende resultaten gezien.
Leonardi et al. vonden een vergelijkbaar resultaat: een kwart van de patiënten had baat bij dosisverhoging van adalimumab (27% behaalde PASI 75 binnen 12 weken).[8] In het onderzoek van Leonardi et al. was een responder echter gedefinieerd als een patiënt die een PASI 75 respons behaalt vergeleken met de baseline PASI van het eerste psoriasis onderzoek waar de patiënt aan deelgenomen had. In ons onderzoek was een responder gedefinieerd als een patiënt die een PASI 50 respons behaalt ten opzichte van de PASI op het moment dat de dosis van adalimumab werd verhoogd of methotrexaat werd toegevoegd. In een fase II onderzoek met adalimumab werd ook gevonden dat een subgroep van patiënten baat kan hebben bij dosisverhoging.[11] Bij patiënten met RA daarentegen is gevonden dat dosisverhoging van adalimumab niet leidt tot een significante verbetering van de ziekte-activiteit.[40]
In het onderzoek van Leonardi et al. werden retrospectief drie patiëntkarakteristieken geïdentificeerd, die voorspellend waren voor een goede respons op dosisverhoging van adalimumab. Dit waren: secundaire nonresponders, een relatief laag lichaamsgewicht en een relatief korte ziekteduur. Vervolgonderzoek is nodig om patiëntkarakteristieken te identificeren waarmee voorspeld kan worden welke patiënten baat zullen hebben bij welke behandelstrategie. Dit is belangrijk om patiënten een optimale behandeling te kunnen bieden en vanwege de hoge kosten van dosisverhoging.

De dosering van methotrexaat bij patiënten die behandeld werden met combinatietherapie was relatief laag. Daarnaast was de duur van combinatietherapie bij

sommige patiënten slechts kort. Het toevoegen van methotrexaat in een hogere dosering en gedurende een langere periode zou kunnen leiden tot betere resultaten. Gegevens over combinatietherapie van adalimumab met methotrexaat bij psoriasis in de literatuur blijven beperkt tot publicaties over kleine groepen patiënten die succesvol zijn behandeld met combinatietherapie.[22, 41, 42]
Zowel bij dosisverhoging van adalimumab als bij combinatietherapie werden weinig adverse events gezien. Er traden geen ernstige adverse events op die gerelateerd waren aan de behandeling. Er zijn weinig gegevens over de veiligheid van dosisverhoging van adalimumab en etanercept in de literatuur. Tot nu toe zijn er geen aanwijzingen dat dosisverhoging leidt tot meer adverse events.[5, 8, 11, 13, 14, 43, 44] Vervolgonderzoeken met grote aantallen patiënten zijn nodig om de veiligheid van dosisverhoging en combinatietherapie bij psoriasis te bevestigen.

In dit proefschrift is geen specifieke aandacht besteed aan de effectiviteit en veiligheid van dosisverhoging van etanercept of combinatietherapie van etanercept met een klassieke systemische therapie. Dit is wel beschreven in de literatuur. In twee onderzoeken is het effect van dosisverhoging van etanercept naar 2 keer 50 mg per week onderzocht bij patiënten die onvoldoende gereageerd hadden op etanercept 1 keer 50 mg per week.[13, 45] Beide onderzoeken lieten zien dat dosisverhoging leidt tot een verhoogde effectiviteit. Wat betreft combinatietherapie is het meeste bewijs voorhanden voor de combinatie van etanercept en methotrexaat.[46-51] Combinatietherapie met methotrexaat bij patiënten met een onvoldoende respons op etanercept monotherapie leidde in deze onderzoeken tot een betere effectiviteit en ging gepaard met weinig bijwerkingen.[46, 48]

Conclusie: dosisverhoging van adalimumab en combinatietherapie met methotrexaat verhogen de effectiviteit van adalimumab bij een subgroep van psoriasis patiënten. Beide behandelstrategieën waren veilig in dit onderzoek.

Onderzoeksvraag 4: Wat is de invloed van verschillende analysemethoden op de effectiviteit?

RCT's worden meestal geanalyseerd volgens het intention-to-treat (ITT) principe. In een ITT analyse worden patiënten geanalyseerd in de groep waarin ze zijn gerandomiseerd. Dit gebeurt onafhankelijk van de behandeling die patiënten daadwerkelijk gekregen hebben, vroegtijdige beëindiging van deelname aan het onderzoek of schendingen van het onderzoeksprotocol.[2, 52, 53] In het Bio-CAPTURE onderzoek wordt geen randomisatie toegepast. De term ITT analyse wordt in **hoofdstuk 4-6** echter wel gebruikt, omdat alle patiënten voor de volledige duur van de geanalyseerde periode zijn meegenomen in de analyse. Dit is ook zo gedaan in andere observationele onderzoeken.[17, 54]

Met de toename van de duur van een onderzoek neemt het aantal patiënten dat uitvalt uit het onderzoek meestal toe, hetgeen leidt tot ontbrekende onderzoeksgegevens.[52] Gegevens kunnen ontbreken om verschillende redenen, waaronder het beëindigen van het onderzoek vanwege onvoldoende effectiviteit of adverse events.[2, 52, 53, 55]
Onbrekende gegevens kunnen op verschillende manieren benaderd en ingevuld worden, ook wel 'imputation' genoemd (Tabel 1). De uitkomstmaten voor effectiviteit in ons onderzoek zijn PASI 50, PASI 75 en PASI 90. Imputation methoden die vaak gebruikt worden in RCT's, zijn last observation carried forward (LOCF) en nonresponder imputation (NRI). Bij LOCF wordt de laatst beschikbare waarde gebruikt voor het invullen van de hier op volgende ontbrekende waarde(n). Ondanks kritiek van statistici op de LOCF methode is dit de meest gebruikt methode in RCT's. De LOCF methode wordt over het algemeen beschouwd als een conservatieve methode.[52]
De meest conservatieve methode is de NRI methode. Bij de NRI methode wordt een patiënt in het geval van een ontbrekende waarde beschouwd als een nonresponder. Dit wordt ook wel 'missing equals failure' (MEF) genoemd. In een 'as-treated' analyse worden ontbrekende gegevens niet meegenomen in de analyse. Dit wordt ook wel 'missing equals excluded' (MEX) genoemd.[2, 53, 56] De 'as-treated' analyse wordt soms ook wel 'observed values' analyse genoemd (**hoofdstuk 2**) en wordt voornamelijk gebruik in observationele onderzoeken en open-label extensie onderzoeken van RCT's.[4, 56, 57]

Afhankelijk van de onderzoeksvraag kunnen verschillende analysemethoden gebruikt worden. Een as-treated analyse geeft een idee van de maximale effectiviteit. Als men echter een reëler beeld wil hebben van de effectiviteit, waarbij patiënten die uitvallen vanwege onvoldoende effectiviteit meegenomen worden in de analyse, kan beter voor een ITT analyse gekozen worden.[2] De resultaten in **hoofdstuk 6** laten zien dat de gebruikte analysemethode een grote invloed heeft op de resultaten; de effectiviteit kan verdubbelen wanneer de as-treated methode gebruikt wordt in plaats van de modified NRI methode.
De NRI methode is problematisch bij observationele onderzoeken, omdat er voortdurend nieuwe patiënten geïncludeerd worden. Het toepassen van NRI bij patiënten met nog maar een korte follow-up waarbij waarden voor veel tijdenstippen in de analyse nog ontbreken, beschouwden wij als incorrect. Daarom is in **hoofdstuk 6** gebruik gemaakt van een minder conservatieve gemodificeerde NRI methode, de 'modified NRI' methode genaamd.[56]

De invloed van ontbrekende gegevens op de effectiviteit hangt af van de redenen voor het ontbreken van gegevens. Figuur 1 in **hoofdstuk 6** laat zien dat verlies van effectiviteit of een combinatie van verlies van effectiviteit en adverse events de meest voorkomende redenen waren voor het stoppen van etanercept.[55] Daarom en vanwege de lange behandelduur van patiënten die goed reageren op behandeling met etanercept, geeft de as-treated analyse de effectiviteit van etanercept te positief weer. De NRI methode

Tabel 1. Beschrijving van verschillende methoden voor de analyse van gegevens in klinisch onderzoek.[52]

Approach	Abbreviation	Description	Equivalent terminology
Populations			
Intention-to-treat	ITT	All randomized patients in the groups to which they were randomly assigned	
Per-protocol	PP	All patients who did not deviate from the protocol	Adherers only
Intention-to-observe	ITO	All patients entering the observational phase of a long-term study	Maintenance ITT
Imputation of missing data			
Missing equals succes	MES	Missing values are assigned as a success	
Missing equals failure	MEF	Missing values are assigned as a failure	Nonresponder imputation
Missing equals excluded	MEX	Missing values are excluded from the analysis	As-treated
Missing completely at random	MCAR	The missingness of data does not depend on the previously observed or current unobserved outcomes	
Missing at random	MAR	The missingness of data depends on the previously observed values, but not the current unobserved values	
Missing not at random	MNAR	The missingness of data depends on the current unobserved outcomes	
Last observation carried forward	LOCF	The previous observation is used for the missing value	

daarentegen zou de effectiviteit van etanercept waarschijnlijk te negatief weergeven, aangezien bij een substantieel deel van de behandelepisodes gegevens ontbraken om andere redenen dan verlies van effectiviteit of een combinatie van verlies van effectiviteit en adverse events. De gemodificeerde NRI methode geeft mogelijk ook een onderschatting van de effectiviteit van etanercept, aangezien sommige patiënten die gestopt waren met etanercept vanwege onvoldoende effectiviteit of een combinatie van onvoldoende effectiviteit en adverse events, in werkelijkheid PASI 75 responders waren (Figuur 3). Dit betekent dat een PASI 75 respons niet altijd als een voldoende respons beschouwd wordt door patiënten en/of dermatologen.

Een manier om de bias die elke statistische methode met zich meebrengt te omzeilen, is het gebruik en de ontwikkeling van andere uitkomstmaten, zoals bijvoorbeeld 'drug survival'. De term drug survival staat voor de duur van het gebruik van een bepaald geneesmiddel, hetgeen een indirecte maat is voor de effectiviteit van het geneesmiddel. De drug survival van een geneesmiddel is echter niet alleen afhankelijk van de effectiviteit, maar ook van bijwerkingen, algemene tevredenheid over het geneesmiddel en de beschikbaarheid van andere geneesmiddelen.[36, 55] Een alternatief zou kunnen zijn het gebruik van een biomarker, die de activiteit van de psoriasis weergeeft in plaats van de ernst van de psoriasis, zoals bijvoorbeeld weergegeven wordt door de PASI. Betrouwbare biomarkers zijn op dit moment echter niet beschikbaar.

Conclusie: elke analysemethode heeft voor- en nadelen en kan leiden tot vertekende resultaten. Omdat de invloed van de gebruikte analysemethode groot is, ondersteunen wij het gebruik van verschillende analysemethoden.

Onderzoeksvraag 5: Wat is het veiligheidsprofiel van biologicals bij de behandeling van psoriasis bij langdurige behandeling?

In **hoofdstuk 7** is beschreven dat het veiligheidsprofiel van biologicals bij patiënten die langdurig behandeld waren met één biological of opeenvolgende verschillende biologicals gunstig was gedurende 5 jaar follow-up. De incidentie van ernstige adverse events was laag. Dit komt overeen met resultaten uit RCT's, meta-analyses en open-label extensie onderzoeken.[58]
Het merendeel van de gegevens over adverse events in dit proefschrift heeft betrekking op etanercept en adalimumab. In **hoofdstuk 7** zijn de beschikbare gegevens over de veiligheid van efalizumab, ustekinumab en infliximab beschreven. Gegevens over de veiligheid van ustekinumab en infliximab zijn tevens beschikbaar in de literatuur. Behandeling met ustekinumab in een open-label extensie onderzoek van RCT's was veilig gedurende 5 jaar follow-up.[59] Behandeling met infliximab bij psoriasis was veilig in een RCT met een duur van 50 weken, een RCT met een open-label extensiefase met een duur van 78 weken en een retrospectief onderzoek bij patiënten die minimaal één jaar behandeld waren met infliximab en een gemiddelde follow-up hadden van 2,2 jaar.[58, 60-62]
In **hoofdstuk 7** is beschreven dat de adverse events in ons onderzoek met name mild van aard waren en niet verschilden van de adverse events beschreven in eerdere publicaties over onze registry en in andere onderzoeken. Achtentwintig procent van de patiënten meldde één of meer ernstige adverse events. Slechts 24% van deze ernstige adverse events beschouwden wij echter als mogelijk gerelateerd aan de behandeling, op basis van de tijdsrelatie en de medische voorgeschiedenis van de patiënt. Slechts één ernstige adverse event (infusiereactie) beschouwden wij als zeker gerelateerd aan de behandeling met infliximab.

Er zijn criteria opgesteld voor het bepalen van causaliteit in epidemiologische studies, de zogenaamde Bredford-Hill criteria.[63] Daarnaast bestaan er categorieën voor causaliteit van de WHO.[64] Echter de beste manier om te bepalen of er een causaal verband is tussen een geneesmiddel en een bepaalde adverse event, is het maken van een vergelijking met een controlegroep.[65] In het onderzoek beschreven in **hoofdstuk 7** is het aantal geobserveerde maligniteiten, ernstige infecties en ernstige cardiovasculaire gebeurtenissen vergeleken met het aantal dat verwacht werd op basis van gegevens over de algemene bevolking. De incidentie van deze ernstige adverse events was vergelijkbaar met de incidentie die verwacht werd op basis van gegevens over de algemene bevolking, met uitzondering

van nonmelanoma huidmaligniteiten. Het aantal patiënten was echter te klein om eventuele verschillen te kunnen ontdekken in de incidentie van andere minder frequent voorkomende ernstige adverse events.
De verhoogde incidentie van nonmelanoma huidmaligniteiten zou ook verklaard kunnen worden door voorafgaande lichttherapie en klassieke systemische therapieën of doordat dermatologen bekwamer zijn in het diagnosticeren van huidmaligniteiten dan huisartsen. Bij 5 van de 7 psoriasis patiënten met nonmelanoma huidkanker werd de eerste huidmaligniteit gediagnosticeerd binnen 5 maanden na de start van de biological. Dit suggereert dat deze gevallen van nonmelanoma huidkanker verklaard kunnen worden door voorafgaande behandelingen zoals lichttherapie en niet het gevolg zijn van behandeling met biologicals.
Alle biologicals zijn als één groep geanalyseerd, aangezien het merendeel van de patiëntjaren follow-up etanercept betrof en omdat bepaalde bijwerkingen zoals bijvoorbeeld maligniteiten, mogelijk pas na een lange latentieperiode optreden en daardoor lastig toe te schrijven zijn aan een bepaalde behandeling. Idealiter worden alle biologicals apart geanalyseerd, aangezien er verschillen bestaan tussen klassen biologicals en zelfs binnen klassen met betrekking tot het risico op bepaalde ernstige adverse events. De klasse van TNF-antagonisten is bijvoorbeeld geassocieerd met reactivatie van latente tuberculose, het ontstaan of verergeren van hartfalen, demyeliniserende aandoeningen en lupus erythematosus.[26, 34]

De incidentie van ernstige adverse events tijdens behandeling met adalimumab in de dagelijkse praktijk (0.23 ernstige adverse events per patiëntjaar (**hoofdstuk 4**)) was hoger dan de incidentie van ernstige adverse events tijdens behandeling met adalimumab in de RCT REVEAL (0.06 ernstige adverse events per patiëntjaar), een open-label extensie onderzoek (0.07 ernstige adverse events per patiëntjaar) en een analyse van alle klinische trials met adalimumab (0.09 ernstige adverse events per patiëntjaar).[9, 16, 66] Het aantal ernstige adverse events, het aantal patiënten en het aantal patiëntjaren follow-up in ons onderzoek was echter te klein om definitieve conclusies te kunnen trekken.
De hogere morbiditeit tijdens behandeling met adalimumab in ons onderzoek zou mogelijk verklaard kunnen worden door meer comorbiditeit en comedicatie bij patiënten in de dagelijkse praktijk. Dit wordt ondersteund door een onderzoek van Garcia-Doval et al., waarin aangetoond werd dat 30% van de psoriasis patiënten die behandeld werden met systemische therapieën (biologicals of klassieke systemische therapieën) in de dagelijkse praktijk niet voldeden aan de inclusiecriteria voor RCT's en dat het risico op ernstige adverse events bij deze patiënten hoger was dan bij patiënten die wel voldeden aan de inclusiecriteria voor RCT's.[67]

Biologicals worden op dit moment beschouwd als derdelijns behandelingen na lokale therapieën, lichttherapie en klassieke systemische therapieën. Dit is een gevolg van

resterende onzekerheid over de veiligheid van biologicals op de lange termijn en de hoge kosten van biologicals. De op dit moment beschikbare gegevens tonen een gunstige verhouding tussen werking en bijwerkingen. Het is op dit moment echter nog onduidelijk of er risico's verbonden zijn aan zeer langdurige behandeling met biologicals, zoals bijvoorbeeld het ontstaan van maligniteiten, eventueel na een lange latentietijd. Tot op heden zijn er bij de op dit moment beschikbare biologicals echter geen aanwijzingen voor cumulatieve toxiciteit.[58]
In 2009 werd efalizumab van de markt gehaald door de EMA, nadat 3 patiënten die gedurende 3 jaar of langer behandeld waren met efalizumab waren overleden aan progressieve multifocale leukoencefalopathie (PML).[26] PML is gerelateerd aan reactivatie van het John Cunningham (JC) virus bij immuungecompromitteerde personen. Deze gebeurtenis onderschrijft het belang van continue farmacovigilantie met betrekking tot biologicals. Indien het veiligheidsprofiel van zeer langdurige behandeling met biologicals gunstig blijft, zouden biologicals tot de tweedelijns behandelingen kunnen gaan behoren wanneer alleen gekeken wordt naar het veiligheidsaspect.

Behandeling met TNF-antagonisten wordt al langer toegepast bij RA en inflammatoire darmziekten dan bij psoriasis. Veiligheidsgegevens van deze andere patiëntenpopulaties kunnen echter niet zomaar vertaald worden naar psoriasis. Patiënten met psoriasis verschillen bijvoorbeeld van patiënten met RA wat betreft geslachtsverdeling, BMI, voorafgaande blootstelling aan lichttherapie, comorbiditeit, gebruikte doseringen en het gelijktijdig gebruik van andere immunosuppressiva.[6, 26, 34, 68]
Andere uitdagingen van het onderzoek naar de veiligheid van biologicals zijn de zeldzaamheid van sommige adverse events, de keuze van controlegroepen, inconsistente codering van adverse events en verschillen in rapportage van adverse events (reporting bias).[43] Grote registries, postmarketing surveillance databases en het combineren van gegevens uit verschillende onderzoeken zijn belangrijk om meer inzicht te krijgen in de lange termijn veiligheid van biologicals, inclusief mogelijke zeldzame adverse events. Registries hebben de voorkeur boven postmarketing surveillance, aangezien postmarketing surveillance databases geen eigen controlegroep hebben en hierbij sprake is van onderrapportage.[69]

Op dit moment kunnen de beperkte zorgen wat betreft de veiligheid van biologicals gezien worden in het licht van de grote voordelen die patiënten met matige tot ernstige psoriasis ondervinden van deze behandelingen. De keuze voor een bepaalde biological is in de dagelijkse praktijk echter vaak niet alleen gebaseerd op effectiviteits- en veiligheidsaspecten. De keuze is gebaseerd op het totaalplaatje van effectiviteit op de korte en lange termijn, veiligheid, de ernst van de psoriasis, de aan- of afwezigheid van artritis psoriatica, kosten, toedieningswijze, injectiefrequentie, comorbiditeit, de mogelijkheid van het onderbreken van de behandeling in relatie tot antistofvorming en de voorkeur van de patiënt.

Conclusie: het lange termijn veiligheidsprofiel van biologicals bij de behandeling van psoriasis was gunstig in dit cohort met een lage incidentie van ernstige adverse events gerelateerd aan de behandeling.

Onderzoeksvraag 6: Is er een verschil in tijd tot het optreden van de eerste nonmelanoma huidmaligniteit en de incidentie van nonmelanoma huidmaligniteiten tussen patiënten met psoriasis en patiënten met reumatoïde artritis die behandeld worden met TNF-antagonisten?

Het onderzoek beschreven in **hoofdstuk 8** laat zien dat het risico op het ontwikkelen van nonmelanoma huidmaligniteiten (nonmelanoma skin cancer; NMSC) significant hoger was in de psoriasis groep vergeleken met de RA groep en dat de tijd tot het optreden van de eerste NMSC korter was in de psoriasis groep. De resultaten geven ook aan dat ziektegerelateerde factoren zoals lichttherapie een belangrijke bijdrage zouden kunnen leveren aan NMSC die gediagnosticeerd worden bij psoriasis patiënten die behandeld worden met TNF-antagonisten.
Idealiter zou een vergelijking zijn gemaakt met een groep psoriasis patiënten (in plaats van een groep RA patiënten) die behandeld zijn met TNF-antagonisten en klassieke systemische therapieën maar niet met lichttherapie, omdat de specifieke ziekte (d.w.z. psoriasis of RA) van invloed zou kunnen zijn op de incidentie van NMSC. Deze controlegroep is echter niet beschikbaar, omdat biologicals in het grootste deel van de wereld alleen voorgeschreven kunnen worden aan patiënten die gefaald hebben op lichttherapie.
Om de invloed van TNF-antagonisten op het ontwikkelen van NMSC te onderzoeken, zou een vergelijking moeten worden gemaakt met een groep psoriasis patiënten die behandeld zijn met lichttherapie en conventionele systemische therapieën, maar niet met TNF-antagonisten. Dit was echter niet mogelijk, omdat deze groep patiënten niet beschikbaar was. Het maken van een vergelijking met gegevens uit de literatuur kent vele beperkingen vanwege verschillen in de opzet van onderzoeken, verschillen in classificatie van adverse events, verschillende onderzoeksperiodes bij een toenemende incidentie van NMSC en verschillen in de incidentie van NMSC op basis van de breedtegraad, zoals beschreven in de onderzoeken van Burmester et al. en Pariser et al.[44, 70] Deze onderzoeken en de onderzoeken in dit proefschrift laten zien dat een vergelijking bij voorkeur gemaakt wordt met een interne controlegroep met een parallelle follow-up.

Conclusie: het risico op het ontwikkelen van NMSC was hoger en de tijd tot de diagnose van de eerste NMSC was korter bij psoriasis vergeleken met RA. Ziektegerelateerde factoren zoals lichttherapie zouden een belangrijke bijdrage kunnen leveren aan NMSC die gediagnosticeerd worden bij psoriasis patiënten die behandeld worden met TNF-antagonisten.

Onderzoeksvraag 7: Is bloedonderzoek bij patiënten met psoriasis die langdurig worden behandeld met etanercept of adalimumab nodig?

Bij patiënten met psoriasis die behandeld worden met biologicals wordt regelmatig bloedonderzoek gedaan volgens de huidige richtlijnen. Een venapunctie is echter invasief, gaat gepaard met kosten en kan leiden tot onnodig vervolgonderzoek. Om deze nadelige aspecten van een venapunctie te kunnen rechtvaardigen, moeten abnormale labwaarden klinische consequenties hebben en leiden tot een betere uitkomst voor de patiënt.
In de literatuur is beschreven dat cytopenieën en verhoogde leverenzymen voorkomen tijdens behandeling met TNF-antagonisten.[71, 72] In ons onderzoek hadden abnormale hematologische parameters slechts bij 2 patiënten (1%) klinische consequenties. Bij deze patiënten werd de behandeling tijdelijk onderbroken vanwege ernstige afwijkingen van het bloedbeeld. De gemiddelde alanine aminotransferase (ALAT) waarde tijdens behandeling met etanercept was significant hoger dan de gemiddelde waarde voor de start van etanercept, maar bleef wel binnen de normale range. Ernstig verhoogde ALAT waarden (graad 3 en graad 4) waren waarschijnlijk gerelateerd aan het gelijktijdig gebruik van methotrexaat of comorbiditeit.
Statistisch significante veranderingen van gemiddelde labwaarden tijdens behandeling vergeleken met voor de start van de behandeling evenals significante trends werden ook gevonden voor een aantal andere hematologische en chemische parameters. De gemiddelde waarden tijdens behandeling bleven echter allemaal binnen de normale range. De behandeling met biologicals werd tijdelijk onderbroken bij patiënten die zich presenteerden met klachten passend bij een infectie, met of zonder het verrichten van bloedonderzoek en met of zonder verhoogde infectieparameters.
Vervolgonderzoeken in andere patiëntengroepen, bij voorkeur met een langere follow-up, en implementatieonderzoeken zouden meer bewijs kunnen leveren voor de benodigde frequentie van bloedonderzoek en de te bepalen laboratoriumwaarden. Minstens zo belangrijk als bloedonderzoek is de instructie aan patiënten om contact op te nemen met hun dermatoloog wanneer zich gezondheidsproblemen, inclusief infecties, voordoen tussen ziekenhuisbezoeken door.

Conclusie: de incidentie van ernstig afwijkende laboratoriumwaarden gerelateerd aan de behandeling was laag in dit cohort. Op basis van de resultaten van dit onderzoek lijkt routinematig bloedonderzoek tijdens behandeling met etanercept of adalimumab bij patiënten met psoriasis niet nodig. Bloedonderzoek dat nodig is in verband met gelijktijdig gebruikte medicatie, comorbiditeit of klachten dient wel plaats te vinden. Vervolgonderzoek zou meer bewijs kunnen leveren voor de benodigde frequentie van bloedonderzoek en de te bepalen laboratoriumwaarden. Screening voor de start van een biological is nodig om contraindicaties of risicofactoren op te sporen en om uitgangswaarden te bepalen.

Vervolgonderzoek in de toekomst

Er is behoefte aan directe vergelijkingen van verschillende aspecten van behandeling met biologicals en andere systemische therapieën voor psoriasis in de dagelijkse praktijk.
Met behulp van gegevens uit de Bio-CAPTURE registry en de MTX-CAPTURE registry kunnen in de toekomst de effectiviteit, veiligheid, kosteneffectiviteit, kwaliteit van leven en tevredenheid over de behandeling van verschillende biologicals vergeleken worden en kan een vergelijking gemaakt worden met methotrexaat.
In dit proefschrift zijn met name effectiviteits- en veiligheidsgegevens over etanercept en adalimumab beschreven. Gegevens over het gebruik van ustekinumab in de dagelijkse praktijk zullen in de nabije toekomst geanalyseerd worden.
De effectiviteit van etanercept en adalimumab in de dagelijkse praktijk was lager dan in RCT's. Het zou interessant zijn om een vergelijking te maken van de effectiviteit van biologicals bij patiënten in de dagelijkse praktijk die voldoen aan de inclusiecriteria voor RCT's en patiënten die hier niet aan voldoen. In een onderzoek bij patiënten met RA werd bij patiënten die voldeden aan de inclusiecriteria voor RCT's een hoger responspercentage gevonden vergeleken met patiënten die hier niet aan voldeden.[73]
In onderzoeken bij RA is ook aangetoond dat behandeling volgens treatment goals leidt tot een betere effectiviteit vergeleken met standaardzorg.[29, 30] Behandeling volgens treatment goals vergeleken met standaardzorg kan in een prospectief implementatieonderzoek bij psoriasis patiënten uit de Bio-CAPTURE registry onderzocht worden.
Het Bio-CAPTURE netwerk biedt de mogelijkheid om een vergelijking te maken van de effectiviteit van biologicals bij patiënten die behandeld worden in een academisch ziekenhuis en patiënten die in een niet-academisch ziekenhuis behandeld worden. Tevens kan de veiligheid van de biologicals onderzocht worden in een grotere patiëntengroep.

De ontwikkeling van een behandelalgoritme zou dermatologen kunnen helpen bij het nemen van beslissingen omtrent het aanpassen van de behandeling in het geval van onvoldoende effectiviteit van een biological. Er zijn echter meer gegevens nodig voordat een dergelijk behandelalgoritme opgesteld kan worden. In de toekomst kan het effect van dosisverhoging of combinatietherapie met een klassieke systemische therapie vergeleken worden in een grotere patiëntengroep. Tevens kunnen de benodigde duur van dosisverhoging en de benodigde duur en dosering van combinatietherapie vastgesteld worden. Daarnaast kan het effect van switchen naar een biological met hetzelfde werkingsmechanisme vergeleken worden met switchen naar een biological met een ander werkingsmechanisme.

Vanuit het oogpunt van de hoge kosten van biologicals en resterende onzekerheid over de veiligheid van biologicals op de lange termijn, zou het interessant zijn om de effectiviteit en veiligheid van dosisverlaging, intermitterende behandeling en een mogelijk

'biological sparend' effect van combinatietherapie te onderzoeken. Op dit moment is het aantal patiënten waarbij dosisverlaging is toegepast nog te klein. Onderbreking van de behandeling is toegepast bij patiënten met infecties, patiënten die een electieve operatie moesten ondergaan en bij patiënten met een zwangerschapswens. De effectiviteit en veiligheid van intermitterende behandeling kan om te beginnen worden onderzocht in deze groep patiënten. Intermitterende behandeling of het stoppen van de behandeling met een biological wordt op dit moment niet bij andere patiënten toegepast, omdat er geen biomarkers voor remissie van psoriasis bestaan. Daarnaast bestaat bij intermitterende behandeling het risico op een rebound van de psoriasis, antistofvorming en verminderde effectiviteit bij herbehandeling.

Perspectief

Psoriasis is een chronische ziekte en elke patiënt heeft zijn of haar eigen psoriasis. Een wetenschappelijke benadering van de behandeling van psoriasis in de dagelijkse praktijk is belangrijk om gezondheidszorg op maat te kunnen bieden bij de lange termijn behandeling van psoriasis. Het stratificeren van patiënten op basis van patiëntkarakteristieken, klinisch beeld, farmacogenetica en biomarkers zal leiden tot geïndividualiseerde lange termijn behandeling van psoriasis, waarbij gebruik gemaakt kan worden van de bestaande behandelingen en nieuwe behandelingsmogelijkheden. Registries met gedetailleerde informatie over patiënt- en behandelkarakteristieken zijn essentieel voor het ontwikkelen van gezondheidszorg op maat.

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Curriculum Vitae
List of Publications
Dankwoord

Curriculum Vitae

Pauline Petronella Maria (roepnaam Paula) van Lümig werd geboren op 28 januari 1984 in Weert. Haar jeugd bracht ze door in Roggel. In 2002 behaalde ze haar gymnasium diploma aan Scholengemeenschap Sint Ursula in Horn. In hetzelfde jaar begon ze aan de studie geneeskunde aan de Radboud Universiteit Nijmegen.
Na het behalen van het artsexamen in 2008 werkte ze gedurende 9 maanden als ANIOS (arts niet in opleiding tot specialist) interne geneeskunde in het Elkerliek ziekenhuis in Helmond voor de specialismen interne geneeskunde, cardiologie, longziekten en neurologie op de spoedeisende hulp en de afdeling interne geneeskunde.
Nadat haar interesse voor de dermatologie was gewekt, begon ze in juni 2009 aan haar promotieonderzoek naar de effectiviteit en veiligheid van biologicals bij de behandeling van psoriasis in de dagelijkse praktijk, onder begeleiding van mw. dr. E.M.G.J. de Jong en prof. dr. dr. P.C.M. van de Kerkhof. In januari 2012 is ze gestart met haar opleiding tot dermatoloog.

List of Publications

Switching from etanercept to adalimumab is effective and safe: results in 30 patients with psoriasis with primary failure, secondary failure or intolerance to etanercept.

van Lümig PPM, Lecluse LLA, Driessen RJB, Spuls PI, Boezeman JBM, van de Kerkhof PCM, de Jong EMGJ. *Br J Dermatol. 2010;163(4):838-46.*

Relevance of laboratory investigations in monitoring patients with psoriasis on etanercept or adalimumab.

van Lümig PPM, Driessen RJB, Roelofs-Thijssen MAMA, Boezeman JBM, van de Kerkhof PCM, de Jong EMGJ. *Br J Dermatol. 2011;165(2):375-82.*

Safety of treatment with biologics for psoriasis in daily practice: 5-year data.

van Lümig PPM, Driessen RJB, Berends MAM, Boezeman JBM, van de Kerkhof PCM, de Jong EMGJ. *J Eur Acad Dermatol Venereol. 2012;26(3):283-91.*

Long-term efficacy of etanercept for psoriasis in daily practice.

van Lümig PPM, Driessen RJB, Boezeman JBM, van de Kerkhof PCM, de Jong EMGJ. *Br J Dermatol. 2012;166(2):445-7.*

Adalimumab therapy for psoriasis in real-world practice: efficacy, safety and results in biologic-naïve vs. non-naïve patients.

van Lümig PPM, van de Kerkhof PCM, Boezeman JBM, Driessen RJB, de Jong EMGJ. *J Eur Acad Dermatol Venereol. 2013;27(5):593-600.*

Results of three analytical approaches on long-term efficacy of etanercept for psoriasis in daily practice.

van Lümig PPM, Driessen RJB, Kievit W, Boezeman JBM, van de Kerkhof PCM, de Jong EMGJ. *J Am Acad Dermatol. 2013;68(1):57-63.*

Effectiveness of adalimumab dose escalation, combination therapy of adalimumab with methotrexate, or both in patients with psoriasis in daily practice.

van den Reek JMPA, van Lümig PPM, Kievit W, Zweegers J, van de Kerkhof PCM, Seyger MMB, de Jong EMGJ. *J Dermatolog Treat. 2013;24(5):361-8.*

Nonmelanoma skin cancer during treatment with TNF-inhibitors in psoriasis patients probably relates to prior exposure to phototherapy.

van Lümig PPM, Menting SP, van den Reek JMPA, Spuls PI, van Riel PLCM, van de Kerkhof PCM, Fransen J, Kievit W, de Jong EMGJ. *Submitted.*

Extent and consequences of antibody formation against adalimumab in patients with psoriasis: one-year follow-up.
Menting SP, van Lümig PPM, de Vries ACQ, van den Reek JMPA, van der Kleij D, de Jong EMGJ, Spuls PI, Lecluse LLA. *JAMA Dermatol. 2013 Dec 18. Epub ahead of print.*

Determinants of drug-survival of etanercept for psoriasis in a long-term daily practice cohort.
van den Reek JMPA, van Lümig PPM, Driessen RJB, van de Kerkhof PCM, Seyger MMB, Kievit W, de Jong EMGJ. *Br J Dermatol. 2013 Sep 30. Epub ahead of print.*

Increased incidence of squamous cell carcinoma of the skin after long-term treatment with azathioprine in patients with auto-immune inflammatory rheumatic diseases.
van den Reek JMPA, van Lümig PPM, Janssen M, Schers HJ, Hendriks JCM, van de Kerkhof PCM, Seyger MMB, de Jong EMGJ. *J Eur Acad Dermatol Venereol. 2014;28(1):27-33.*

Satisfaction with medication is high for biologics in psoriasis*. Results from the Bio-CAPTURE network.*
van den Reek JMPA, van Lümig PPM, Otero ME, Zweegers J, van de Kerkhof PCM, Ossenkoppele PM, Njoo MD, Mommers JM, Koetsier MIA, Arnold WP, Sybrandy-Fleuren BAM, Kuijpers ALA, Andriessen MPM, Seyger MMB, Kievit W, de Jong EMGJ. *Accepted.*

Predictors of adalimumab drug survival in psoriasis depend on reasons for discontinuation. *Long term results from a prospective daily practice cohort*.
van den Reek JMPA, Tummers M, Zweegers J, Seyger MMB, van Lümig PPM, Driessen RJB, van de Kerkhof PCM, Kievit W, de Jong EMGJ. *Submitted.*

Dankwoord

Dit proefschrift is het resultaat van veel gezamenlijke inspanning. Een aantal mensen wil ik in het bijzonder bedanken voor hun hulp bij de totstandkoming van dit proefschrift.

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