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Effects and side effects of biological treatment for severe psoriasis in daily practice

Rieke Driessen
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Effects and side effects of biological treatment for severe psoriasis in daily practice.

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“Jean-Claude Salgueira creates his own universe in pictures and objects using acrylic paint. Dots, blots, grids and streams. They are eruptions of colour and energy. Repetitions and structure are important elements in his work. Always accompanied however by flowing chaos. Though the paint drips off the panels and glistens in the light, the image is never polished. Jean-Claude’s work is always about layers. Literally. In the end the images are what they are. Meditations in paint. Besides his paintings, Jean-Claude is also working on digital images that clearly reveal the origins of his work...” www.salgueira.com

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Effects and side effects of biological treatment for severe psoriasis in daily practice

Een wetenschappelijke proeve op het gebied van de Medische Wetenschappen

Proefschrift

ter verkrijging van de graad van doctor aan de Radboud Universiteit Nijmegen

op gezag van de rector magnificus prof. mr. S.C.J.J. Kortmann,

volgens besluit van het college van decanen in het openbaar te verdedigen op maandag 25 oktober 2010 om 13.30 uur precies

door

Rieke Johanna Bernardina Driessen

geboren op 14 juli 1982 te Nijmegen
Promotor: Prof. dr. dr. P.C.M. van de Kerkhof

Co-promotor: Mevr. dr. E.M.G.J. de Jong

Manuscriptcommissie: Prof. dr. J.B.M.J. Jansen
                       Prof. dr. P.L.C.M. van Riel
                       Mevr. dr. Ph.I. Spuls (Universiteit van Amsterdam)

Paranimfen: Mevr. drs. M.E.A. de Jager
             Mevr. A.J.M. Driessen
Voor mijn ouders
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## LIST OF ABBREVIATIONS

<table>
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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>ACR 20</td>
<td>20% reduction in the ACR criteria relative to baseline</td>
</tr>
<tr>
<td>AGA</td>
<td>American Gastroenterological Association</td>
</tr>
<tr>
<td>ANA</td>
<td>Antinuclear antibody</td>
</tr>
<tr>
<td>AS</td>
<td>Ankylosing spondylitis</td>
</tr>
<tr>
<td>ATI</td>
<td>Antibodies to infliximab</td>
</tr>
<tr>
<td>AU</td>
<td>Arbitrary units</td>
</tr>
<tr>
<td>BAD</td>
<td>British Association of Dermatologists</td>
</tr>
<tr>
<td>BCC</td>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CASPAR</td>
<td>Classification criteria for psoriatic arthritis</td>
</tr>
<tr>
<td>CD</td>
<td>Cluster of differentiation</td>
</tr>
<tr>
<td>CD</td>
<td>Crohn's disease (Chapter 14)</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>DAS-28</td>
<td>Disease activity score in 28 joints</td>
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<tr>
<td>DMARD</td>
<td>Disease-modifying antirheumatic drug</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>ECCO</td>
<td>European Crohn's and Colitis Organisation</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>EMEA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>HACA</td>
<td>Human anti-chimeric antibodies</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>HLA</td>
<td>Human leukocyte antigen</td>
</tr>
<tr>
<td>ICAM</td>
<td>Intercellular adhesion molecule</td>
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<tr>
<td>Ig</td>
<td>Immunoglobulin</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>IL12B</td>
<td>Interleukin-12 subunit beta</td>
</tr>
<tr>
<td>IL23R</td>
<td>Interleukin-23 receptor</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to treat</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
</tbody>
</table>
Kg  Kilogram
L   Litre (Liter)
LABAG  Landelijke Beoordeling Aanvragen Geneesmiddelen
LCE  Late cornified envelope
LFA  Lymphocyte function-associated antigen
LOCF Last observation carried forward
µg  Microgram
M   Meter
MDD  Mean daily dose
Mg  Milligram
MI  Millilitre (milliliter)
NAPSI  Nail psoriasis severity index
NICE National Institute for Health and Clinical Excellence
NSAID Nonsteroidal anti-inflammatory drug
OTC  Over-the-counter
PASI  Psoriasis area and severity index
PASI 50  50% reduction in PASI relative to baseline
PASI 75  75% reduction in PASI relative to baseline
PASI 90  90% reduction in PASI relative to baseline
PASI 100 100% reduction in PASI relative to baseline
PCD  Pediatric Crohn’s disease
PIIIINP Amino-terminal propeptide of type III procollagen
PML  Progressive multifocal leukoencephalopathy
POR  Probability of response
PP  Per protocol
PPPY  Per patient per year
Ps  Psoriasis
PsA  Psoriatic arthritis
PSORS  Psoriasis susceptibility
PUVA  Psoralen-Ultraviolet A
QOL  Quality of life
RA  Rheumatoid arthritis
RCT Randomized controlled trial
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>SAPASI</td>
<td>Self-administered psoriasis area and severity index</td>
</tr>
<tr>
<td>SC</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>SCC</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>SCORAD</td>
<td>Scoring atopic dermatitis</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SEM</td>
<td>Standard error of the mean</td>
</tr>
<tr>
<td>Th1</td>
<td>Type 1 helper T cells</td>
</tr>
<tr>
<td>Th17</td>
<td>Type 17 helper T cells</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
</tr>
<tr>
<td>TNFR</td>
<td>Tumor necrosis factor receptor</td>
</tr>
<tr>
<td>TSQM</td>
<td>Treatment satisfaction questionnaire for medication</td>
</tr>
<tr>
<td>U</td>
<td>Units</td>
</tr>
<tr>
<td>UC</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>UV</td>
<td>Ultraviolet</td>
</tr>
<tr>
<td>UVB</td>
<td>Ultraviolet B</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>Yrs</td>
<td>Years</td>
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PROLOGUE

Since 2005, new pharmaceuticals called ‘biologics’ or ‘biological therapies’ have been registered and reimbursed in The Netherlands for the treatment of patients with moderate to severe plaque psoriasis. The introduction of these drugs heralded an entirely new era in the management of psoriasis. Recent improvement in the knowledge of the pathogenesis of psoriasis was fundamental for the development of these novel targeted treatment options. At the same time, the utilization of these drugs lead to new insights in the pathogenesis of different immune-mediated inflammatory diseases, including psoriasis.

Biologics were implemented in daily clinical practice after years of thorough investigation on the efficacy and safety of these drugs in randomized controlled trials. The introduction of biological therapies provided new perspectives for patients with severe, recalcitrant psoriasis (‘high-need’ population), but also created new challenges for dermatologists. Despite extensive research on these therapies in randomized controlled trials, the implementation of these drugs in daily clinical practice gave rise to many uncertainties. Are these biologics as effective as claimed in publications on randomized controlled trials? What do we know about the safety of these products on longer term? What happens when I treat a patient with biologics who is not as ‘healthy’ as a clinical trial participant? What do the high medication costs mean for the society as a whole? And last but not least: What are the implications of these therapies for my routine as a dermatologist?

To be able to study these themes, a patient registry was set up by investigators of the Radboud University Nijmegen Medical Centre department of dermatology, enabling the collection of efficacy and safety data on biological therapies for the treatment of patients with psoriasis. The purpose of this registry was to follow all patients with psoriasis treated with biological therapies in daily clinical practice. The content of this thesis is largely based on the data collected in the registry. Specific themes were studied, including efficacy, safety, costs, procedures en comorbidities.
GENERAL INTRODUCTION
INTRODUCTION
INTRODUCTION

TABLE I
Epidemiology, pathogenesis and clinical features of psoriasis

Introduction
Psoriasis is a common chronic skin disease, characterized by sharply demarcated, erythematous, scaly plaques. It often has a significant negative impact on the physical, emotional and psychosocial wellbeing of affected patients. Furthermore, psoriasis has a major impact on health care systems and on society in general. Although the exact pathogenesis of psoriasis is still not entirely demystified, research has demonstrated scientific evidence for a role for genetic, environmental and immunological factors. This chapter describes the epidemiology, pathogenesis and clinical and histological features of psoriasis.
PART I

Epidemiology
Psoriasis was recognised as being a specific clinical entity that was different from leprosy by Robert Willan in the beginning of the 19th century. In the 1840s, Ferdinand von Hebra laid the foundation for the classification of psoriasis in its current form.1 The prevalence of psoriasis in various locations throughout the world has been estimated 0.6 to 4.8%. In a recent study from the United States, a prevalence in adults of approximately 3% was demonstrated.2 Although some studies find minor deviations, psoriasis is equally common in males and females. Psoriasis can present at any age, but is most likely to appear between the ages of 15 and 30 years.3

Pathogenesis
Psoriasis is supposed to be initiated by an interplay between genetic, environmental, and immunological factors, eventually leading to the evolution of psoriatic lesions.

Genetic factors
Population studies clearly indicate that the incidence of psoriasis is greater among first-degree and second-degree relatives of patients than among the general population. Moreover, the risk of psoriasis is two to three times as high among monozygotic twins as among dizygotic twins. Nevertheless, the mode of inheritance of psoriasis is complex. Classic linkage analysis and genomewide association scans have identified different genes associated with psoriasis. The strongest associations have been observed in the psoriasis susceptibility 1 (PSORS1) region, which probably accounts for 35 to 50% of the heritability of the disease.4 Other major psoriatic gene variants include the genes encoding the interleukin-23 receptor (IL23R) and the untranslated region of the interleukin-12B (IL12B).5,6 Recent findings indicate that both genomic copy number variation at the β-defensin cluster and deletion of the late cornified envelope (LCE) genes may be risk factors for psoriasis as well.7,8

Environmental factors
Multiple environmental factors have been implicated in the pathogenesis of psoriasis. Some of these appear to be able to trigger the disease, including streptococcal throat infections, medications, trauma to the skin, stressful life events and smoking. These factors, as well as many others, have also been shown to exacerbate or modify the disease in different patients. Other relevant environmental factors that may influence the disease course of psoriasis are human immunodeficiency virus (HIV) infection, obesity, alcohol, and ultraviolet (UV) radiation.3
**Immunological factors**

Key cells and mediators in the immunopathogenesis of psoriasis include keratinocytes, dendritic cells, T lymphocytes, and cytokines. Before the mid-1980s, research into the pathogenesis of psoriasis mainly focused on the differentiation and proliferation of keratinocytes. However, the observation of dramatic clearing of psoriasis by ciclosporin, a T-cell inhibitor, was highly suggestive of a pivotal role for T cells in psoriasis development. This hypothesis was confirmed more than a decade later, when the efficacy of psoriasis treatment with biologically engineered T-cell modulators, including alefacept and efalizumab, was established. Besides, the impressive response of psoriasis to tumor necrosis factor α (TNF-α) and interleukin-12 (IL-12)/ interleukin-23 (IL-23) blocking drugs indicate an important role for cytokines as well. (See Chapter 2: Biological therapies)

A proposed schema of the evolution of psoriatic lesions is provided in Figure 1. Initial triggers such as physical trauma or bacterial products start a cascade of events that lead to the activation of myeloid dermal dendritic cells through production of key cytokines (TNF-α, interferon-α, interferon-y, interleukin-1β, and interleukin-6) by innate immune cells. Activated dendritic cells present antigens and secrete mediators such as interleukin-12 and interleukin-23, leading to the differentiation of type 1 and type 17 helper T cells (Th1 and Th17), respectively. T cells, in turn, secrete mediators (e.g., interleukin-17A, interleukin-17F, and interleukin-22) that activate keratinocytes and induce the production of antimicrobial peptides (e.g., LL-37 cathelicidin and β-defensins), proinflammatory cytokines (TNF-α, interleukin-1β, and interleukin-6), chemokines (CXCL8 through CXCL11 and CCL20) and S100 proteins. These soluble mediators feed back into the proinflammatory disease cycle and shape the inflammatory infiltrate.

**Clinical and histological features**

**Clinical features**

Psoriasis is characterized by sharply demarcated, erythematous, scaly plaques of different sizes. Plaques are usually distributed symmetrically, and occur most commonly on the extensor aspects of elbows and knees, scalp, lumbosacral region, and umbilicus. Psoriasis vulgaris is the commonest type of psoriasis, accounting for 90% of all cases. Other types include flexural (inverse) psoriasis, guttate psoriasis, generalised pustular psoriasis (von Zumbusch), and palmoplantar pustulosis. About 50% of patients with psoriasis have distinctive nail changes, most commonly observed in patients with psoriatic arthritis.
Figure 1. Proposed (simplified) scheme of the evolution of psoriatic lesions. (Modified from Nestle FO, Kaplan DH, Barker J. Psoriasis.4)

PSORS1, Psoriasis Susceptibility 1; LCE, Late Cornified Envelope; TNF, Tumor Necrosis Factor; Th1, type 1 helper T-cell; Th17, type 17 helper T-cell.
Histological features

Fully developed clinical plaques show marked epidermal hyperplasia with regular elongation of epidermal rete ridges. There is marked hyperkeratosis, often composed of alternating orthokeratosis and parakeratosis. The inflammatory infiltrate consists mainly of T cells, dendritic cells and macrophages. T cells in psoriatic lesions are polarized as type 1 helper T cell (Th1; CD4+) and cytotoxic T cell (Tc1; CD8+) subsets, but probably also include a separate population of type 17 helper T cells (Th17). CD11c+ dendritic cells are detected mainly in the upper part of the epidermis. Collections of neutrophils within the parakeratosis (Munro’s microabscesses) are present in most cases and less commonly within the spinous layer (spongiform pustules of Kogoj). Furthermore, psoriatic epidermis expresses high levels of host defense proteins, especially human β-defensin-2.
PART I

References

CHAPTER 2

Treatment of psoriasis

Introduction
Psoriasis can be treated with many different therapies, singly or in combination. In general, three therapeutic modalities are available, i.e. topical agents, UV therapy (phototherapy) and systemic medications. A few years ago, a new class of systemic pharmaceuticals, called “biologics” or “biological therapies” have been introduced into the therapeutic arsenal for psoriasis. The “psoriasis treatment ladder” refers to the concept that medications with the least potential for adverse reactions should preferentially be employed and that therapies with greater potential toxicity are used only if the treatment goal is not achieved by the former treatment. This step up scheme respectively includes topical therapies, phototherapy and (conventional) systemic therapies. Whether biological therapies are part of the third step, or must be reserved for therapy resistant patients, remains an issue of debate, as long-term safety and efficacy data on these therapies are sparse. This chapter describes different treatment modalities for psoriasis, with special emphasis on methotrexate and biological therapies.
Topical therapy
Topical monotherapy remains the mainstay of treatment for most patients with psoriasis, especially those with limited disease. Topical therapies commonly used for psoriasis include corticosteroids, vitamin D analogues, calcineurin inhibitors, dithranol and coal tar. The most widely prescribed topical therapies are corticosteroids, which are available in classes with different potency. Vitamin D analogues show lower initial clinical responses than higher potency corticosteroids, but their longer-term safety profile makes them valuable for maintenance therapy.¹

Phototherapy
Phototherapy denotes treatment with UV radiation in different wavelength spectra. Types of phototherapy used for psoriasis are broadband UVB, narrow-band UVB and Psoralen-UVA (PUVA). Broadband UVB has lost its popularity nowadays, although it is still used in some units. UV radiation induces growth arrest of keratinocytes and influences the pathologic immune response in the skin, leading to a significant improvement of psoriasis symptoms.²

Conventional systemic therapies
A wide range of systemic drugs are registered for the treatment of psoriasis. Frequently used traditional therapies are methotrexate, ciclosporin, acitretin, and fumaric acid esters. Except for methotrexate, these therapies will not be outlined further.

Methotrexate
Methotrexate has been one of the most frequently prescribed therapies for psoriasis for more than 50 years. Although biological therapies have recently demonstrated to be highly effective in psoriasis, methotrexate has remained popular for the treatment of patients with psoriasis. In contrast to biologics, methotrexate is a cheap drug with a well-known long-term efficacy and safety profile. Therefore, most guidelines for the use of biological therapies for psoriasis recommend to use methotrexate prior to biologics, and to use biological therapies only in patients in whom methotrexate treatment is ineffective, contraindicated, or causes side effects. Furthermore, the combination of biologics with methotrexate has proven highly beneficial, especially in rheumatic diseases.³

Methotrexate competitively inhibits the enzyme dihydrofolate reductase, thus decreasing the synthesis of folate cofactors needed to produce nucleic acids. This leads to inhibition of epidermal proliferation, but more importantly, of proliferation of lymphoid tissue. The latter supports the concept that the therapeutic effect of low-dose methotrexate in psoriasis is a
result of its effects on the immune system.4 The use of methotrexate is restricted by the risk of organ toxicity, in particular myelosuppression, pulmonary fibrosis, and hepatotoxicity. To prevent the development of serious liver injury, routine performance of liver biopsies is advocated for all patients using methotrexate. However, this recommendation has been an issue of debate, as rheumatologists deem the liver biopsy as unnecessary in their patients.5 Therefore, current research focuses on potentially alternative markers for liver injury associated with lower morbidity and mortality compared to liver biopsies. One of these markers is amino-terminal propeptide of type III procollagen (PIIINP), which has proven to effectively reduce the requirement for liver biopsies.6

Biological therapies
The term “biologics” or “biological therapies” is used for a class of pharmaceuticals that are produced by means of biological processes involving recombinant deoxyribonucleic acid (DNA) technology. DNA is isolated from natural sources, including animals and humans. For psoriasis, two types of biological therapies are available nowadays, either receptor fusion proteins or monoclonal antibodies. Receptor fusion proteins currently used for psoriasis treatment are alefacept and etanercept, recognizable by a generic name with the suffix “-cept”. Monoclonal antibodies used in psoriasis are efalizumab, infliximab, adalimumab and ustekinumab, recognizable by a generic name with the suffix “-mab”. As reflected in Table 1, biological therapies are named following specific guidelines based on structural classification of molecules.7

Table 1. Nomenclature of biological therapies.7

<table>
<thead>
<tr>
<th>Suffix</th>
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<tbody>
<tr>
<td>-cept</td>
<td>Receptor molecules</td>
</tr>
<tr>
<td>-mab</td>
<td>Monoclonal antibodies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infix preceding suffix</th>
<th>Used for</th>
</tr>
</thead>
<tbody>
<tr>
<td>-u-</td>
<td>Human</td>
</tr>
<tr>
<td>-xi-</td>
<td>Chimera</td>
</tr>
<tr>
<td>-zu-</td>
<td>Humanized</td>
</tr>
<tr>
<td>-kin-</td>
<td>Interleukins</td>
</tr>
<tr>
<td>-li(m)-</td>
<td>Immunomodulators</td>
</tr>
<tr>
<td>-ner-</td>
<td>Tumor necrosis factor</td>
</tr>
<tr>
<td>-lefa-</td>
<td>Lymphocyte function-associated antigen</td>
</tr>
</tbody>
</table>

Additionally, biological therapies can be classified according to their mechanism of action. Two types of biologics are used for the treatment of patients with psoriasis, i.e. T-cell
inhibitors and cytokine inhibitors. T-cell inhibitors include alefacept and efalizumab. Cytokine inhibitors include etanercept, infliximab, and adalimumab, which are inhibitors of TNF-α, and ustekinumab, which inhibits both IL-12 and IL-23 (Figure 1).8

Figure 1. Pathogenesis-based targeted therapy for psoriasis. (Modified from Nestle FO, Kaplan DH, Barker J. Psoriasis.8)

The efficacy and safety of biological therapies has been thoroughly investigated in randomized, controlled trials (RCTs). However, few studies directly compare active treatments for psoriasis, and only one head-to-head RCT comparing biological agents has been performed yet.9 Therefore, until more data from head-to-head trials are available, comparative estimates of treatment efficacy and safety must be derived from systematic literature reviews and meta-analyses (Table 2). For the current introduction, data on the efficacy of biological therapies (ustekinumab excluded) were adapted from a systematic review and meta-analysis by Bansback et al.10
Psoriasis Area and Severity Index
The primary efficacy measure in most RCTs is the percentage reduction in Psoriasis Area and Severity Index (PASI) compared to baseline. The PASI is a composite score of erythema, induration, and desquamation of plaques, multiplied by a score for the affected body surface area in different regions, i.e. head, trunk, arms and legs. Scores range from 0.0 (no disease) to 72.0 (maximal disease). In most RCTs on biological therapies for psoriasis, only patients with a PASI of at least 10 at baseline are eligible for study participation. Likewise, most national guidelines state that treatment of psoriasis with biologics in daily practice is indicated only for patients with a PASI of at least 10 at screening. Many RCTs focus on a specific primary efficacy outcome, i.e. the number of patients achieving a 50%, 75%, 90% or 100% reduction in PASI relative to baseline (PASI 50, PASI 75, PASI 90 and PASI 100, respectively).

T-cell inhibitors

Alefacept (Amevive®)
Alefacept is a dimeric fusion protein that consists 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 lymphocyte activation by specifically binding to the lymphocyte antigen CD2, thereby inhibiting LFA-3/CD2 interaction. The recommended dose of alefacept is 7.5 milligram (mg) given once weekly as an intravenous (IV) bolus or 15 mg given once weekly as an intramuscular (IM) injection. In RCTs, a PASI 50 at week 14 was achieved by 24% of patients with psoriasis using alefacept 15 mg IM weekly. In the same trials, a PASI 75 was achieved by 9 to 21% of patients using the same dosage and route of administration (Table 2). Common adverse events in RCTs investigating alefacept in patients with psoriasis were pharyngitis, chills, headache, pruritus and infections. The incidence of serious adverse events was greater in IV-dosed patients and lower in IM-dosed patients compared with placebo. Alefacept is approved as monotherapy for the treatment of moderate to severe psoriasis vulgaris only in the United States of America, Australia, Canada, Argentina, Switzerland, Kuwait, and Israel.

Efalizumab (Raptiva®)
Efalizumab is a recombinant humanized monoclonal antibody that binds specifically to the CD11a subunit of lymphocyte function-associated antigen-1 (LFA-1). By this mechanism, efalizumab inhibits the binding of LFA-1 to intercellular adhesion molecule-1 (ICAM-1),
Table 2. Efficacy of biological therapies for moderate to severe psoriasis. Results from a systematic review and meta-analysis.
(Adapted from Bansback et al. Efficacy of systemic treatments for moderate to severe psoriasis: systematic review and meta-analysis.10)

<table>
<thead>
<tr>
<th>Therapy Description</th>
<th>PASI 50 Range</th>
<th>Trial Data</th>
<th>Meta-Analysis POR (95% CI)</th>
<th>PASI 75 Range</th>
<th>Trial Data</th>
<th>Meta-Analysis POR (95% CI)</th>
<th>PASI 90 Range</th>
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<td>29 (24-34)</td>
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<td>81 (75-86)</td>
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<td>37-51^c</td>
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</table>

Presented numbers indicate the percentage of patients (range) and the probability of achieving a specific PASI response. POR, Probability of response; CI, Confidence Interval; IV, Intravenous; IM, Intramuscular; SC, Subcutaneous; EOW, Every Other Week. ^a Dose administered every 8 weeks following doses at 0, 2 and 6 weeks. ^b Dose administered at week 0 and 4. ^c Adapted from the PHOENIX 1 (Leonardi et al.) and PHOENIX 2 (Papp et al.) study.
which interferes with T lymphocytes adhesion to other cell types. The recommended
dose of efalizumab for psoriasis is an initial single subcutaneous (SC) injection of 0.7 mg/
kilogram (kg) followed by weekly SC injections of 1.0 mg/kg.14

In RCTs, a PASI 50 at week 12 was achieved by 52 to 61% of patients with psoriasis using
efalizumab 1 mg/kg SC weekly. A PASI 75 and PASI 90 was achieved by 22 to 39% and
4 to 12% of patients, respectively (Table 2).10 The most common adverse events were
headaches, infections and chills. The pooled relative risk for incidence of one or more
serious adverse events in efalizumab-treated patients was 1.43, which was not statistically
significant in a comprehensive analysis of five trials.13

In February 2009, the European Committee for Medicinal Products for Human Use
recommended the suspension of the marketing authorisation of efalizumab, because
its benefits in the treatment of psoriasis were modest, while there was a risk of serious
side effects in patients receiving the medicine, including the occurrence of progressive
multifocal leukoencephalopathy (PML). Consequently, the Marketing Authorisation Holder
for efalizumab (Raptiva®, Serono Europe Limited) voluntarily withdrew the marketing
authorisation for the product.

Cytokine inhibitors

Etanercept (Enbrel®)

Etanercept is a dimeric fusion protein consisting of the 75-kilodalton (p75) tumor necrosis
factor receptor-2 (TNFR2) linked to the Fc domain of human IgG1. Etanercept competitively
inhibits TNF-binding to its cell surface receptors, thereby inhibiting the biological activity
of both TNF-α and lymphotoxin-α (TNF-β). The recommended dose of etanercept for
psoriasis is 25 mg SC twice a week or 50 mg SC once a week.15 Alternatively, 50 mg may
be given twice a week for up to 12 weeks, followed by 25 mg twice a week or 50 mg once
a week.15

In RCTs, a PASI 50 at week 12 was achieved by 74 to 77% of patients with psoriasis using
etanercept 50 mg SC twice weekly. A PASI 75 and PASI 90 was achieved by 47 to 49%
and 21 to 22% of patients using the same dosage and route of administration, respectively
(Table 2).10 The most common adverse events reported were injection-site reactions,
headache and upper respiratory tract infections. The most common serious adverse events
were malignancies, serious infections and worsening psoriasis.13 Etanercept is currently
approved for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis,
psoriatic arthritis, ankylosing spondylitis, and adult and paediatric plaque psoriasis.
PART I

**Infliximab (Remicade®)**

Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF-α, but not to lymphotoxin-α, thereby inhibiting the functional activity of TNF-α. The recommended dose of infliximab for psoriasis is 5 mg/kg given as an IV infusion over a two-hour period, followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. In RCTs, a PASI 50, PASI 75 and PASI 90 at week 10 was achieved by 82 to 97%, 76 to 88% and 45 to 58%, respectively, of patients with psoriasis using infliximab 5 mg/kg IV at week 0, 2 and 6 (Table 2). The most common adverse events in RCTs studying infliximab in patients with psoriasis were upper respiratory tract infections, headache, increased hepatic enzymes and infections. Some of the most common serious adverse events reported were malignancies, serious infections, serious infusion reactions and lupus-like syndrome. Infliximab is currently approved for the treatment of rheumatoid arthritis, adult and paediatric Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis.

**Adalimumab (Humira®)**

Adalimumab is a recombinant human monoclonal antibody, which binds specifically to TNF-α and neutralizes the biological function of TNF-α by blocking its interaction with the p55 and p75 cell surface TNF receptors. The recommended dose of adalimumab 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. In RCTs, a PASI 50 at week 12 or 16 was achieved by 76 to 88% of patients with psoriasis using adalimumab 40 mg SC every other week. In the same trials, a PASI 75 and PASI 90 was achieved by 53 to 80% and 24 to 52% of patients, respectively (Table 2). The most common adverse events in RCTs were nasopharyngitis, injections site reactions and headache. The most frequently reported serious adverse events were malignancies and serious infections. Adalimumab is currently approved for the treatment of rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease and psoriasis.

**Ustekinumab (Stelara®) / ABT-874 (briakinumab)**

Ustekinumab is a fully human IgG1κ monoclonal antibody that binds with high affinity and specificity to the p40 protein subunit of the human cytokines IL-12 and IL-23. Ustekinumab inhibits the activity of human IL-12 and IL-23 by preventing these cytokines from binding to their IL-12Rβ1 receptor protein expressed on the surface of immune cells. ABT-874
(briakinumab), which is now under investigation for the treatment of psoriasis, exhibits the same mechanism of action. The recommended dose of ustekinumab is 45 mg SC administered at week 0, followed by 45 mg SC at week 4, then every 12 weeks thereafter. For patients with a body weight above 100 kg the dose is 90 mg SC administered at week 0, followed by 90 mg SC at week 4, then every 12 weeks thereafter.

Currently, two RCTs have been published in which the efficacy and safety of ustekinumab for psoriasis was investigated. In these studies, 84% of patients using ustekinumab 45 mg SC at week 0 and 4 achieved a PASI 50 at week 12. A PASI 75 and PASI 90 was achieved by 67% and 42% of patients, respectively (Table 2). Commonly reported adverse events were upper respiratory tract infections, nasopharyngitis, headache, arthralgias, cough, and injection site erythema. Rates of serious infections and malignancies were low.

Ustekinumab is currently approved for the treatment of psoriasis.
PART I

References


Comorbidities in psoriasis

Introduction
Psoriasis is associated with comorbidities of different nature, although the origin of the associations is often complex. Psoriasis is related to immune-mediated inflammatory diseases, such as psoriatic arthritis and Crohn’s disease. Furthermore, psoriasis is associated with impaired quality of life (QOL), which may lead to depression and psychosocial problems. Since the introduction of biological therapies, psoriasis has been considered a chronic systemic inflammatory disease, predisposing patients to cardiovascular disease. However, the cardiovascular risk of patients with psoriasis may also be increased by unhealthy lifestyle behaviour, such as smoking and alcohol consumption. Additionally, psoriasis therapies may cause specific health related problems, such as hypertension and liver fibrosis, induced by ciclosporin and methotrexate, respectively. This chapter describes common comorbidities in psoriasis, including psoriatic arthritis, cardiovascular disease and emotional, psychosocial and socioeconomic problems.
Psoriatic arthritis

Psoriatic arthritis (PsA) is a rheumatoid factor seronegative arthritis associated with psoriasis. Typical clinical features are distal interphalangeal joint involvement, asymmetric distribution, dactylitis, enthesitis, spinal involvement, and the association with human leukocyte antigen B27 (HLA-B27). Based on these characteristics, PsA has been classified with the HLA-B27-associated spondyloarthropathies. Historically, the principle classification criteria for PsA have been the Moll and Wright criteria. In 2006, new classification criteria for PsA have been developed, known as the CASPAR (ClASsification criteria for Psoriatic Arthritis) criteria. The estimated prevalence of PsA in patients with psoriasis varies extremely between different studies; a recent national survey in Germany revealed a prevalence of 19%. PsA can be treated with nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs) or biological therapies.

Cardiovascular disease

Studies on cardiovascular diseases suggest that the risk of incident myocardial infarction, angina pectoris, atherosclerosis, peripheral vascular disease and stroke is increased in patients with psoriasis. The cardiovascular risk of patients with psoriasis may be influenced by the high incidence of cardiovascular risk factors, e.g. hypertension, diabetes mellitus, obesity, and dyslipidaemia, as well as by unhealthy lifestyle behaviour. However, there seems to be an increased risk of mortality due to psoriasis independent of major risk factors, especially in severely affected patients.

There has currently been much debate about whether it is beneficial to induce systemic anti-psoriatic therapies in an early phase to reduce cardiovascular morbidity and mortality. Large prospective studies are needed to confirm this concept. On the other hand, knowledge about comorbidities including cardiovascular diseases is required for an adequate choice and dosing of systemic medication.

Emotional, psychosocial and socioeconomic problems

In 1999, Rapp et al. found that health-related QOL was markedly reduced in patients with psoriasis, and that the impact of psoriasis on QOL was comparable to that seen in cancer, arthritis, hypertension, heart disease, diabetes, and depression. Prominent sequelae of psoriasis are embarrassment, shame, impaired self-image, low self-esteem, self-consciousness and stigmatisation. Moreover, the prevalence of mood disorders including depression in patients with psoriasis is high. Physical and emotional problems associated with psoriasis may lead to behavioural avoidance, and may influence a patient's potential to earn income and gain full
Consequently, psoriasis has a major economic impact on the society as a whole, as a result of direct health care costs and indirect costs due to production losses.\textsuperscript{21-23}
References


17. Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with


CHAPTER 4

Observational studies

Introduction
When new therapies are introduced, randomized controlled trials (RCTs) are needed to study the efficacy and safety of these therapies, as RCTs provide the most robust estimate of causal effects. Randomization enables an unbiased allocation of treatment and the application of statistical theory on the basis of random sampling. In contrast, after approval and implementation of new therapies in daily practice clinical care, observational studies may provide additional information on these therapies which cannot be acquired by RCTs. When studying psoriasis therapies, especially biologics, the treatment course in clinical practice is different from the setting in which trials are conducted. In clinical practice, the aim is to provide an optimal treatment for an individual patient. Dose adjustments, treatment interruptions or combinations with other antipsoriatic therapies are instrumental to reach this goal. Clinical practice, therefore, is principally different from the artificial situation of clinical trials with predefined inclusion, exclusion and discontinuation criteria. In the current thesis, the outcomes of observational studies on biological treatment for severe psoriasis in daily practice are described. Most study data are obtained from a patient registry, in which efficacy and safety data on biological therapies for psoriasis were prospectively collected.
Patient registries
Following the licensing of the first biological therapy for the treatment of severe rheumatoid arthritis, several countries initiated independent registries for the long-term evaluation of the efficacy and safety of this new generation of drugs. Today, many small or large, national or international registries exist on biological therapies for different indications. These registries are useful drug surveillance tools, as they allow long-term follow-up of large groups of patients in a natural setting, which is important for the assessment of rare and long-term outcomes. Furthermore, registration of efficacy and safety data regarding systemic therapies for different indications gives the opportunity to compare the outcomes of these therapies in different diseases. Besides, the systematic collection of patient and treatment data directly reflects a patient’s treatment course, which may invite the physician to critically consider his proceedings.

Continuous Assessment of Psoriasis Treatment Use Registry (CAPTURE)
Immediately after the registration and reimbursement of etanercept and efalizumab for the treatment of patients with moderate to severe psoriasis in The Netherlands, a patient registry was set up by investigators of the Radboud University Nijmegen Medical Centre department of dermatology, enabling the collection of efficacy and safety data on biological therapies for the treatment of patients with psoriasis in daily clinical practice. All patients with psoriasis treated with biologics were included in this registry, and each patient was followed prospectively. The first patient was included in February 2005; nowadays, the registration of patients is still operational. In 2008, after additional inclusion of therapies for childhood psoriasis, the registry was nominated “CAPTURE”, an acronym for Continuous Assessment of Psoriasis Treatment Use Registry.
References


CHAPTER 5

Outline of the thesis

Introduction
In this chapter, the outline of the thesis is described, representing study objectives and related questions.
Study objectives
This thesis includes the outcomes of observational studies on psoriasis in daily clinical practice. The objective of these studies was:

1. To prospectively investigate the effects and side effects of biological treatment in patients with severe psoriasis in daily practice.

Specific themes were studied, including:

a. The efficacy and safety of biological therapies in daily practice compared with RCTs.

b. The influence of clinical strategies and patient characteristics on treatment outcome.

c. The influence of combining etanercept with methotrexate on treatment outcome.

d. The influence of antibody formation against adalimumab on treatment outcome.

2. To investigate the economic impact of psoriasis and psoriasis treatment, including biological therapies.

3. To investigate procedures on prescription and application of biological therapies in daily practice.

4. To investigate the occurrence of comorbidities in patients with (severe) psoriasis.

Questions
With respect to these objectives, attempt was made to answer the following questions:

I. Which differences can be established when comparing the efficacy and safety of biological therapies for severe psoriasis in daily clinical practice with the outcomes of RCTs?

II. Are treatment outcomes influenced by specific factors, such as patient and treatment characteristics, addition or withdrawal of concomitant (systemic) therapies, antibody formation and comorbidities?

III. Has the total cost-of-illness of severe psoriasis changed since the introduction of
PART I

biologics? Can the introduction of biological therapies be cost neutral or cost saving compared with the period before introduction of biological therapies for certain patients?

IV. How are procedures on prescription and application of biological therapies implemented in daily practice health care? Which information about physicians’ prescription behaviour and treatment efficacy do these data provide?

V. How often do cardiovascular, rheumatological and hepatic comorbidities occur in patients with severe psoriasis? What is the relevance of these comorbidities for systemic treatment of patients?
PROSPECTIVE COHORT MONITORING OF PATIENTS WITH SEVERE PSORIASIS: EFFECTS AND SIDE EFFECTS OF BIOLOGICAL TREATMENT IN DAILY PRACTICE

PART II
ENGLISH MONITORING OF BIODIVERSITY
CHAPTER 6

Etanercept and efalizumab treatment for high-need psoriasis. Effects and side effects in a prospective cohort study in outpatient clinical practice

Abstract

Background: Since the beginning of 2005, etanercept and efalizumab are officially registered and reimbursed for the treatment of recalcitrant psoriasis in The Netherlands. Objective: The evaluation of the efficacy, safety and adverse events of etanercept and efalizumab treatment in daily practice.

Methods: A prospective cohort study was carried out for patients treated with etanercept or efalizumab between February 2005 and March 2006.

Results: Over the past 13 months, 45 individuals were treated with etanercept and 17 subjects were treated with efalizumab. The cohort represented a high-need population. At week 12, 82% of the subjects treated with 2 x 50 mg etanercept per week and 71% of the subjects treated with 2 x 25 mg etanercept per week reached a 50% improvement in Psoriasis Area and Severity Index relative to baseline. Efficacy of etanercept treatment was comparable to the results of clinical trials. For efalizumab, efficacy in responding patients was also comparable to clinical trial data, but the percentage of dropouts was substantial. During biological treatment, safety was preserved and mainly mild adverse events were reported.

Conclusion: Etanercept and efalizumab are effective and safe therapies for patients with psoriasis, even for a high-need population. Etanercept was able to sustain the clinical improvement throughout 24 weeks, whereas efalizumab was not in 47% of subjects.

PART II

Introduction

Etanercept and efalizumab belong to the newest antipsoriatic therapies, known as biologics. These drugs became of particular interest for the treatment of psoriasis after discovering the high potential combined with assumed fewer side effects than regular systemic antipsoriatic therapies.

In September 2004, the European Union approved etanercept and efalizumab for the treatment of adult patients with moderate to severe plaque psoriasis who failed to respond to, or have a contraindication to, or are intolerant of other systemic therapies. In The Netherlands, these pharmaceuticals have been reimbursed by health insurance since the beginning of 2005. Etanercept binds specifically to tumor necrosis factor α (TNF-α) and blocks its interaction with cell surface TNF-α receptors. Efalizumab binds to human CD11a, the α-subunit of leukocyte function antigen-1 (LFA-1), thereby inhibiting the adhesion of leukocytes to other cell types.

Many well-designed trials have been performed to study the efficacy of biologics in considerable numbers of patients. The use in daily practice, however, is different from the setting in which trials are conducted. From February 2005 until March 2006, we started with biological therapy in 62 individuals with recalcitrant psoriasis in our outpatient clinic. In this report we describe the first year of experience in treating patients in daily clinical practice with moderate to severe plaque psoriasis with etanercept and efalizumab. Evaluating the efficacy and safety of biological agents in clinical practice rather than in clinical trials provides relevant additional information about these new therapeutic strategies in the day-to-day care of psoriasis.

Patients and methods

Patients

Data were collected prospectively, using a standard form at each visit for all patients treated with etanercept or efalizumab between February 2005 and March 2006. Patients came into consideration for one of these treatments if they had failed to respond to phototherapy, methotrexate and ciclosporin in the past, or if they had a contraindication to, or were intolerant of one of these treatments. At the same time, patients had to have a minimum Psoriasis Area and Severity Index (PASI) of 10 at the time of screening, as stated in the guidelines of the Dutch Society of Dermatology and Venereology (Nederlandse Vereniging voor Dermatologie en Venereologie, NVDV).

Charts were reviewed for demographics and baseline characteristics, including age, sex, existence of psoriatic arthritis, duration of psoriasis, baseline PASI, previous dermatological
treatments and the number of concomitant non-dermatological drugs.

Protocol

Before treatment, a chest X-ray and a Mantoux skin test were performed to exclude tuberculosis. Patients were treated with etanercept or efalizumab, depending on the physician’s preference. For etanercept, two dosing regimens were used randomly, either 50 milligram (mg) subcutaneously (SC) twice weekly for 12 weeks, followed by 25 mg SC twice weekly for 12 weeks (dosage schedule 1), or 25 mg SC twice weekly for 24 weeks (dosage schedule 2). After 24 weeks, patients interrupted etanercept treatment for an indefinite period according to the approved European Medicines Agency (EMEA) label. Efalizumab was given in a single conditioning dose of 0.7 mg/kilogram (kg) SC, followed by 1.0 mg/kg weekly (up to a maximum single dose of 200 mg).

Contraindications for etanercept treatment were an active infection or increased susceptibility for infections (including immunocompromised individuals), a history of tuberculosis, the existence of a demyelinating disease and pregnancy. Relative contraindications were the existence of cardiac decompensation, a blood dyscrasia, a malignancy in recent history, the presence of an antinuclear antibody (ANA) positive autoimmune disease or chronic exposition to actinic radiation in the past.

Contraindications for therapy with efalizumab were the presence of pustular, guttate or erythrodermic psoriasis during screening, a previous malignancy (basal cell carcinomas excluded), active infection or increased susceptibility for infections (including immunocompromised individuals), active tuberculosis, and pregnancy. Relative contraindications were the existence of leukocytosis, lymphocytosis or thrombocytopenia, the presence of an ANA positive autoimmune disease or chronic exposition to actinic radiation in the past.

Patients were allowed to use topical dermatological therapies during biological treatment. An effort was made to confine the use of concomitant systemic dermatological therapies in cases of unsatisfactory effectiveness of etanercept or efalizumab. Termination of other non-dermatological drugs was found unnecessary. Visits were scheduled every 4 weeks during the first 12 weeks, every 6 weeks until week 24 and every 12 weeks thereafter. At each visit, the PASI and adverse events were documented. Furthermore, laboratory tests were conducted, including haematological analysis, serum chemistry, urinalysis and ANA. After 12 weeks of therapy, the treatment protocol required an improvement in PASI of at least 50% for both etanercept- and efalizumab-treated patients. Patients who did not meet this criterion were excluded from therapy according to the reimbursement guidelines. In some of these cases, treatment
PART II

with the other available biological agent was started thereafter. The administration of etanercept or efalizumab was discontinued if patients developed a serious infection; therapy was restarted after recovery. Likewise, therapy was interrupted in cases of elective surgical procedures.

Analysis

Data from charts and forms were transported to a database and analysed to define treatment efficacy by means of PASI, with primary efficacy endpoints including the achievement of an improvement in PASI relative to baseline of at least 50% or 75% (PASI 50 and PASI 75, respectively). Efficacy analysis of the first 12 weeks of treatment was made according to the intention to treat principle. Missing PASI at given time points were imputed using the last observation carried forward (LOCF). Because there were large differences in the follow-up periods of subjects, efficacy of the next 12 weeks was measured by means of a per protocol analysis. Reported adverse events and abnormal laboratory values were summarized. If patients received both etanercept and efalizumab treatment, chart analysis was performed twice. Multiple occurrences of the same adverse event in a single subject were counted once.

Results

Demographics

Over the past 13 months, 45 subjects were treated with etanercept, of whom 28 received a dose of 50 mg SC twice weekly for 12 weeks, followed by 25 mg SC twice weekly for 12 weeks (dosage schedule 1) and 17 received a dose of 25 mg SC twice weekly for 24 weeks (dosage schedule 2).

Seventeen subjects were treated with efalizumab. Overall, 55% was male, the mean age was 50.9 years and the mean duration of psoriasis was 21.6 years. Of all the subjects, 18 suffered from psoriatic arthritis. The mean PASI at baseline was 19.8. Patients had previously received 4 to 10 different dermatological therapies, with an average of 6.7 treatments per patient. The mean number of systemic therapies that patients had used before the start of biological treatment was 3.3, indicating a high-need population. Some patients had even used biological agents in the past, mostly in the context of clinical trials. These included etanercept, alefacept, efalizumab, infliximab and oncept. The mean number of concomitant non-dermatological drugs was 2.2 (Table 1).

Patients were treated for various periods. The overall mean duration of treatment was 26 weeks (interruptions after 24 weeks or for other reasons excluded), with a range of 5-46
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<td></td>
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<td>Range, total</td>
<td>4-10</td>
<td>4-9</td>
<td>4-9</td>
<td>4-10</td>
</tr>
<tr>
<td>Range, systemic treatments</td>
<td>1-6</td>
<td>2-6</td>
<td>2-5</td>
<td>1-6</td>
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<tr>
<td>Mean, total (±SEM)</td>
<td>6.8 (0.3)</td>
<td>6.4 (0.3)</td>
<td>6.8 (0.3)</td>
<td>6.7 (0.2)</td>
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<tr>
<td>Mean, systemic treatments (±SEM)</td>
<td>3.5 (0.2)</td>
<td>3.0 (0.2)</td>
<td>3.4 (0.3)</td>
<td>3.3 (0.2)</td>
</tr>
<tr>
<td><strong>Types of previous treatments used, no. (%)</strong></td>
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<td></td>
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</tr>
<tr>
<td>Topical steroids/ vitamin D analogues</td>
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<td>17 (100)</td>
<td>17 (100)</td>
<td>62 (100)</td>
</tr>
<tr>
<td>Dithranol</td>
<td>19 (68)</td>
<td>12 (71)</td>
<td>14 (82)</td>
<td>45 (73)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>28 (100)</td>
<td>17 (100)</td>
<td>16 (94)</td>
<td>61 (98)</td>
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<td>UVB</td>
<td>25 (89)</td>
<td>14 (82)</td>
<td>15 (88)</td>
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</tr>
<tr>
<td>PUVA</td>
<td>21 (75)</td>
<td>14 (82)</td>
<td>11 (65)</td>
<td>46 (74)</td>
</tr>
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<td>Acitretin</td>
<td>20 (71)</td>
<td>12 (71)</td>
<td>13 (76)</td>
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<tr>
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<td>13 (75)</td>
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<td>Infliximab</td>
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<td>2 (12)</td>
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</tr>
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<td><strong>Concomitant non-dermatological drugs, no.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0-9</td>
<td>0-6</td>
<td>0-9</td>
<td>0-9</td>
</tr>
<tr>
<td>Mean (±SEM)</td>
<td>2.5 (0.5)</td>
<td>1.7 (0.4)</td>
<td>2.1 (0.6)</td>
<td>2.2 (0.3)</td>
</tr>
</tbody>
</table>

Dosage schedule 1, 50 mg SC twice weekly for 12 weeks, followed by 25 mg SC twice weekly; Dosage schedule 2, 25 mg SC twice weekly; SEM, Standard Error of the Mean; PASI, Psoriasis Area and Severity Index; UVB, Ultraviolet B; PUVA, Psoralen-Ultraviolet A.
weeks in the etanercept dosage schedule 1 group, 11-49 weeks in the etanercept dosage schedule 2 group and 6-32 weeks in the efalizumab-treated group.

Efficacy
Twenty-three subjects (82%) in the etanercept dosage schedule 1 group, 12 subjects (71%) in the etanercept dosage schedule 2 group and 10 subjects (59%) in the efalizumab group achieved a PASI 50 at week 12. At the same time, respectively 39%, 24% and 6% achieved a PASI 75 (Figure 1).

Figure 1. Efficacy results after 12 weeks of biological therapy (intention to treat analysis).

Dosage schedule 1, 50 mg SC twice weekly for 12 weeks, followed by 25 mg SC twice weekly; Dosage schedule 2, 25 mg SC twice weekly; PASI, Psoriasis Area and Severity Index; PASI 50, 50% reduction in PASI relative to baseline; PASI 75, 75% reduction in PASI relative to baseline.

For 14 subjects in the etanercept dosage schedule 1 cohort, 14 subjects in the dosage schedule 2 cohort and 4 subjects in the efalizumab cohort, PASI at 24 weeks of treatment were available. After per protocol analysis, data revealed the achievement of a PASI 50 in respectively 71%, 79% and 100% of these subjects. Nevertheless, these efficacy percentages are calculated by dividing on the remaining number of subjects at week 24. In the efalizumab cohort, the dropout rate due to lack of efficacy at week 24 was high, i.e.
Table 2. Efficacy results after 18 and 24 weeks of biological therapy (per protocol analysis).

<table>
<thead>
<tr>
<th></th>
<th>Etanercept Dosage schedule 1</th>
<th>Etanercept Dosage schedule 2</th>
<th>Efalizumab</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients at baseline</td>
<td>28</td>
<td>17</td>
<td>17</td>
<td>62</td>
</tr>
<tr>
<td>No. of patients with unfinished follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At week 18</td>
<td>10</td>
<td>1</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>At week 24</td>
<td>13</td>
<td>0</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>No. of dropouts due to lack of efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At week 18</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>At week 24</td>
<td>1</td>
<td>3</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Remaining no. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At week 18</td>
<td>17</td>
<td>14</td>
<td>5</td>
<td>36</td>
</tr>
<tr>
<td>At week 24</td>
<td>14</td>
<td>14</td>
<td>4</td>
<td>32</td>
</tr>
<tr>
<td>≥ 50% improvement in PASI, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At week 18</td>
<td>15 (88)</td>
<td>11 (79)</td>
<td>5 (100)</td>
<td>31 (86)</td>
</tr>
<tr>
<td>At week 24</td>
<td>10 (71)</td>
<td>11 (79)</td>
<td>4 (100)</td>
<td>25 (78)</td>
</tr>
<tr>
<td>≥ 75% improvement in PASI, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At week 18</td>
<td>8 (47)</td>
<td>9 (64)</td>
<td>1 (20)</td>
<td>18 (50)</td>
</tr>
<tr>
<td>At week 24</td>
<td>7 (50)</td>
<td>8 (57)</td>
<td>1 (25)</td>
<td>16 (50)</td>
</tr>
<tr>
<td>&lt; 50% improvement in PASI, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At week 18</td>
<td>2 (12)</td>
<td>3 (21)</td>
<td>0 (0)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>At week 24</td>
<td>4 (29)</td>
<td>3 (21)</td>
<td>0 (0)</td>
<td>7 (22)</td>
</tr>
</tbody>
</table>

Dosage schedule 1, 50 mg SC twice weekly for 12 weeks, followed by 25 mg SC twice weekly; Dosage schedule 2, 25 mg SC twice weekly; PASI, Psoriasis Area and Severity Index.

For 18 of all the etanercept-treated subjects, a PASI beyond 24 weeks was available. Analysis of the effect of treatment interruption, after 24 weeks according to EMEA guidelines or due to other reasons, on PASI in this group showed that these patients encountered a mean increase in PASI of 2.97 (Standard Error of the Mean ±1.07) during interruption, with a mean increase of 0.65 per week (Figures 2 and 3). Currently, 12 of these subjects have reached a PASI 50 and 8 have achieved a PASI 75. The only subject in the efalizumab group, who was treated beyond 24 weeks, has currently achieved an improvement in PASI relative to baseline of 69.5%.

Despite a considerable reduction in the severity of disease in many patients, the effects of biological therapy were unsatisfactory several times. In these cases, concomitant use
PART II

of other antipsoriatic therapies was necessary. In 91% of all etanercept-treated patients and 82% of all efalizumab-treated patients, topical corticosteroids or vitamin D analogues were used in addition to biological treatment. Other concomitant therapies included methotrexate, dithranol, acitretin and fumaric acid. Five subjects in the etanercept dosage schedule 1 cohort, one subject in the etanercept dosage schedule 2 cohort and one patient in the efalizumab cohort used one of these therapies.

Figure 2. Effect of etanercept interruption at week 24 in 18 subjects.

In general, etanercept and efalizumab treatment was well tolerated, and mainly mild adverse events were reported. The most common side effects reported (with an overall incidence of more than 20%) were upper respiratory infections, flu-like symptoms and gastrointestinal symptoms. No subjects were diagnosed with tuberculosis, although after the marker study period we discovered three patients with possible latent tuberculosis who had to be prophylactically treated with isoniazid. Malignancies were found in two subjects. One 48-year-old man was diagnosed with an oesophageal carcinoma, as well as with three squamous cell carcinomas and Bowen’s disease during etanercept therapy. Another etanercept-treated patient developed a basal cell carcinoma and a squamous cell carcinoma. Both patients were treated with phototherapy in the past.

Side effects

PASI, Psoriasis Area and Severity Index.
Infections were reported 38 times. These included upper and lower respiratory infections, skin infections, eye infections, urinary tract infections and oral infections. Eye infections were seen four times in the etanercept group and none in the efalizumab group (Table 3). Etanercept therapy was interrupted 12 times: seven times because of upper or lower respiratory infections, twice because of flu-like symptoms and three times due to an elective surgical procedure. Efalizumab treatment was only interrupted once, due to the scheduling of surgery. Five patients required hospital admission: once because of severe arthralgia in combination with a high increase in the C-reactive protein (CRP, 118 milligram/litre [mg/l]) value and four times through severe exacerbation of psoriasis. Exacerbations were seen after abrupt discontinuation of other systemic antipsoriatic treatments before the start of biological therapy, and consecutively a poor response on biological treatment; after the occurrence of infection during biological therapy, that caused discontinuation of biological therapy; or both. Four of the subjects, who needed admission to hospital, were treated with efalizumab at that time, including the patient with arthralgia.

Seven efalizumab-treated patients (41%) reported changes in the morphologic pattern of psoriasis since the start of treatment. Such morphologic changes did not occur in the etanercept cohort.

Routine laboratory monitoring did reveal leukocytosis (white blood cell count > 11 x 10⁹/
Table 3. Adverse events.

<table>
<thead>
<tr>
<th></th>
<th>Etanercept Dosage schedule 1</th>
<th>Etanercept Dosage schedule 2</th>
<th>Efalizumab</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections, no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infections</td>
<td>13 (46)</td>
<td>6 (35)</td>
<td>2 (12)</td>
<td>21 (34)</td>
</tr>
<tr>
<td>Lower respiratory infections</td>
<td>2 (7)</td>
<td>2 (12)</td>
<td>1 (6)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Skin infections</td>
<td>2 (0)</td>
<td>2 (12)</td>
<td>2 (12)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Eye infections(\textsuperscript{a})</td>
<td>0 (0)</td>
<td>4 (24)</td>
<td>0 (0)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>1 (4)</td>
<td>2 (12)</td>
<td>0 (0)</td>
<td>3 (5)</td>
</tr>
<tr>
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<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>(Pre)malignancies, no. (%)</strong></td>
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<td></td>
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<td>1 (6)</td>
<td>1 (6)</td>
<td>3 (5)</td>
</tr>
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<td>0 (0)</td>
<td>2 (3)</td>
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<tr>
<td>Bowen’s disease</td>
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<td>0 (0)</td>
<td>1 (2)</td>
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<tr>
<td>Basal cell carcinoma</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Oesophageal carcinoma</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>Skin reactions, no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Skin reactions(\textsuperscript{b})</td>
<td>6 (21)</td>
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<td>3 (5)</td>
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<td>2 (3)</td>
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<td><strong>Miscellaneous, no. (%)</strong></td>
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<td>Flu-like symptoms(\textsuperscript{c})</td>
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<td>4 (24)</td>
<td>6 (35)</td>
<td>15 (24)</td>
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<td>Gastrointestinal symptoms(\textsuperscript{d})</td>
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<td>4 (24)</td>
<td>5 (29)</td>
<td>14 (23)</td>
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<td>4 (24)</td>
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<td>2 (12)</td>
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<td>1 (6)</td>
<td>0 (0)</td>
<td>2 (3)</td>
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<td><strong>Any</strong></td>
<td>23 (82)</td>
<td>17 (100)</td>
<td>14 (82)</td>
<td>54 (87)</td>
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</table>

Dosage schedule 1, 50 mg SC twice weekly for 12 weeks, followed by 25 mg SC twice weekly; Dosage schedule 2, 25 mg SC twice weekly. \(\textsuperscript{a}\)Such as blepharitis, conjunctivitis; \(\textsuperscript{b}\)Such as drug eruption, prurigo nodularis, photodermatosis, mollusca contagiosa, mycosis, urticaria, eczema, pseudofolliculitis barbae; \(\textsuperscript{c}\)Such as myalgia, fatigue, chills, sweating; \(\textsuperscript{d}\)Such as nausea, vomiting, diarrhea, abdominal pain, loss of appetite, rectal bleeding.

_litre_ in 23 patients at one or more moments during therapy. Twelve of these patients were in the etanercept cohort (27%) and 11 patients were in the efalizumab group (65%).
Fourteen times leukocytosis was combined with an increased CRP (CRP > 10 mg/l): six times in the etanercept group and eight times in the efalizumab group. However, only seven patients reported clinical signs of infection (etanercept: n = 4, efalizumab: n = 3), principally diagnosed as mild upper respiratory infections and skin infections. Thrombocytopenia was seen three times, one in every treatment group. No other notable changes in laboratory markers were found during therapy.

Current status
At the beginning of March 2006, 48 subjects were still on biological treatment, including three subjects who had temporarily discontinued therapy. Of the efalizumab cohort, 47% discontinued therapy because of lack of efficacy. On the contrary, only six subjects (13%) terminated etanercept treatment. One of these six subjects (i.e. the patient with the oesophageal carcinoma and squamous cell carcinomas) discontinued therapy because of these adverse events, diagnosed at week 44.

Discussion
Our aim was to evaluate the efficacy, safety and adverse events of etanercept and efalizumab treatment in the outpatient clinic. Data were obtained from a one-year follow up of 62 patients. The cohort represented a high-need population, concerning the treatment of psoriasis.

A total of 82% of the subjects in the etanercept dosage schedule 1 group and 71% of the subjects in the etanercept dosage schedule 2 group achieved a PASI 50 at week 12, 39% and 24%, respectively, achieved a PASI 75 at this point. These efficacy data are comparable with the results of several clinical trials. During the next 12 weeks, the efficacy of etanercept treatment remained stable.

Efalizumab efficacy data were much less satisfying. A total of 59% of all subjects achieved a PASI 50, but only 6% achieved a PASI 75 at week 12. Furthermore, after 24 treatment weeks, eight of the 17 efalizumab-treated patients discontinued therapy because of lack of efficacy. In addition, four subjects in this cohort needed hospital admission during therapy. This is in contrast with efalizumab clinical trial data, which show significant PASI improvements in large numbers of patients.

It has to be kept in mind that these data are presumably influenced by the use of concomitant antipsoriatic therapies. More than 80% of all subjects needed concomitant use of topical steroids or vitamin D analogues, and in seven of all the subjects, the use of other systemic antipsoriatic treatments or dithranol was even necessary. It is an important goal to investigate further the effect of combining biologics with other antipsoriatic treatments.
PART II

Combining etanercept with methotrexate has already been found to be more effective in the treatment of rheumatoid arthritis than etanercept monotherapy.\textsuperscript{11} Abrupt cessation of other systemic antipsoriatic treatments before starting with biologics could possibly influence the efficacy of these drugs in a negative manner. Likewise, interruption of etanercept treatment after 24 weeks, as we did according to the EMEA label, appears to elicit a substantial fall in treatment benefits. Taking this into account, we recommend a gradual tapering of systemic antipsoriatic treatments before starting biological therapy, or partially overlapping biological therapy with conventional systemic therapies. In addition, continuing treatment after 24 weeks instead of interrupting therapy at that point would be of benefit to the patient.

Both etanercept and efalizumab were well tolerated. Fifty-four patients reported one or more side effects, but those were mainly mild. The most frequently reported side effects were upper respiratory infections, flu-like symptoms and gastrointestinal symptoms. Eye infections were only seen in the etanercept cohort, as well as eye irritation. Recently, Taban et al. accomplished a literature review about inflammatory eye disease associated with etanercept therapy, and found that ocular inflammation is a potential adverse event following the use of etanercept.\textsuperscript{12} Of significance as well are the nine subjects in the etanercept cohort reporting arthralgias. Only two of these subjects suffered from psoriatic arthritis. Physical examination of the other subjects by a rheumatologist did not reveal a significant arthritis.

Changes in the morphologic pattern of psoriasis since the start of treatment were reported by 41% of the efalizumab-treated patients. In some cases this meant the manifestation of psoriasis in regions that were not affected earlier; in other cases, the plaque-type psoriasis appeared to change in another type, such as guttate or pustular psoriasis. This phenomenon was also seen in other trials, although an incidence of 3.2% was mentioned.\textsuperscript{13} As leukocytosis is often seen during treatment with efalizumab, it should not be used as an infection parameter. Therefore, to monitor infections, physicians should pay attention to the clinical symptoms of infection reported by patients. Furthermore, as latent tuberculosis was found three times in our cohort, we recommend performing tuberculosis screening in all patients who are candidates for biological therapy.

In conclusion, prospective cohort monitoring of patients with high-need psoriasis on systemic treatments, especially on biologics, is worthwhile. Information about treatment with these new drugs in daily clinical practice is important for adjusting treatment schedules and guidelines.
References


CHAPTER 7

Psoriasis treatment with etanercept and efalizumab: clinical strategies influencing treatment outcome

Abstract

Background: Multiple trials have been conducted in which the safety and efficacy of different biological therapies for psoriasis have been studied. However, the treatment course in clinical practice is different from the setting in which trials are conducted.

Objectives: The evaluation of the efficacy, safety and adverse events of etanercept and efalizumab treatment in daily practice and the investigation of interfering clinical strategies that could be of influence on treatment outcome.

Methods: A prospective cohort consisting of 101 patients with high-need psoriasis was followed for two years and analysed. Patients were treated with etanercept or efalizumab between February 2005 and May 2007. Efficacy, safety and adverse events were investigated. Furthermore, all accompanying factors of which an influence on treatment efficacy outcome was suspected were registered, including treatment interruptions, dosage adjustments and combinations of therapies.

Results: Etanercept and efalizumab treatment was effective and safe in most patients. However, in many cases the treatment course was characterized by unsatisfactory efficacy (83%), necessitating combination therapies or dosage adjustments. Treatment interruptions occurred in 56% (etanercept 2x50 mg group), 84% (etanercept 2x25 mg group) and 10% (efalizumab-treated patients).

Conclusions: Treatment of patients with high-need psoriasis in daily practice is highly different from treatment courses in clinical trials. Frequently applied clinical strategies such as treatment interruptions, dosage adjustments and combinations of treatments influence treatment outcome in routine treatment in comparison with randomized controlled trials. Information about treatment with these new drugs in daily clinical practice is important for adjusting treatment schedules and guidelines.

CHAPTER 7

Introduction
In recent years, multiple trials have been conducted in which the safety and efficacy of different biological therapies for psoriasis have been studied. Examples of these therapies are etanercept, alefacept, efalizumab, infliximab and adalimumab. In Europe, etanercept, efalizumab, infliximab and adalimumab are currently approved for the treatment of moderate to severe plaque psoriasis. Etanercept and efalizumab are now routinely used in outpatient clinical practice. However, the treatment course in clinical practice is different from the setting in which trials are conducted. In clinical practice, the aim is to provide an optimal treatment for an individual patient. Dose adjustments, treatment interruptions or combinations with other antipsoriatic therapies are instrumental to reach this goal. Clinical practice, therefore, is principally different from the artificial situation of clinical trials with predefined inclusion, exclusion and discontinuation criteria.

From February 2005 (start of reimbursement) all patients with psoriasis who have been treated with biologics in the outpatient clinic were followed prospectively. The first analysis of the accompanying data was performed after one year. During this period, 62 patients were treated with either etanercept or efalizumab. In most cases, biological therapy was effective and safe, although the drop-out rate in the efalizumab-treated group was substantial (47%). After 2.5 years of therapy, a new data analysis of the extended cohort was performed. The number of patients treated with biologics increased up to 101.

In this report we describe the experience in treating a cohort of 101 patients with high-need psoriasis with etanercept and efalizumab in daily clinical practice during two years. The objective of this study is to report efficacy and safety data of etanercept and efalizumab in the context of real world practice. Special attention has been paid to frequently used clinical strategies to provide the best result for the individual patient, including treatment interruptions, dosage adjustments and combinations of therapies.

Patients and methods

Patients
Data were collected prospectively, using a standard form at each visit for all patients treated with etanercept or efalizumab between February 2005 and May 2007. Patients came into consideration for one of these treatments if they had failed to respond to phototherapy, methotrexate and ciclosporin in the past, or if they had a contraindication to, or were intolerant of, these treatments. At the same time, patients had to have a minimum Psoriasis Area and Severity Index (PASI) of 10 at the time of screening.

Charts and forms were reviewed for demographics and baseline characteristics, including
PART II

age, sex, existence of psoriatic arthritis and other joint complaints, duration of psoriasis, baseline PASI, previous dermatological treatments and concomitant drugs.

Protocol

Before treatment, a chest X-ray and a Mantoux skin test were performed to exclude tuberculosis. Patients were treated with etanercept or efalizumab, depending on which therapy was most suitable for a patient according to the physician's opinion. For etanercept, two dosing regimens were used, either 50 milligram (mg) subcutaneously (SC) twice weekly for 12 weeks, followed by 25 mg SC twice weekly for 12 weeks (2x50 mg group), or 25 mg SC twice weekly for 24 weeks (2x25 mg group). In the beginning of the etanercept treatment period, the etanercept label stated to initiate treatment with 25 mg twice weekly; later on, insights changed and most patients were initiated on 50 mg etanercept twice weekly for 12 weeks. After 24 weeks, patients interrupted etanercept treatment for an indefinite period according to the approved European Medicines Agency (EMEA) label. Therapy was resumed if needed. Efalizumab was given in a single conditioning dose of 0.7 milligram/kilogram (mg/kg) SC followed by 1.0 mg/kg weekly (up to a maximum single dose of 200 mg).

Contraindications for etanercept treatment were an active infection or increased susceptibility for infections (including immunocompromised persons), a history of tuberculosis, the existence of a demyelinating disease or pregnancy. Relative contraindications were the existence of cardiac decompensation, a blood dyscrasia, a recent malignancy, the presence of an antinuclear antibody (ANA) positive autoimmune disease or chronic exposure to actinic radiation in the past.

Contraindications for therapy with efalizumab were the presence of pustular, guttate or erythrodermic psoriasis during screening, a malignancy in the medical history (basal cell carcinomas (BCCs) excluded), active infection or increased susceptibility for infections (including immunocompromised persons), active tuberculosis and pregnancy. Relative contraindications were the existence of leucocytosis, lymphocytosis or thrombocytopenia or chronic exposure to actinic radiation in the past.

Patients were allowed to use topical dermatological therapies during biological treatment if desired. An effort was made to limit the use of concomitant systemic dermatological therapies in cases of unsatisfactory effectiveness of etanercept or efalizumab. Termination of other non-dermatological drugs was considered unnecessary.

Visits were scheduled every 4 weeks during the first 12 weeks, every 6 weeks until week 24 and every 12 weeks thereafter. At each visit, PASI and adverse events were documented. Laboratory tests were conducted, including haematological analysis, serum
chemistry, urinalysis and ANA. After 12 weeks of therapy, the treatment protocol required an improvement in PASI of at least 50% for both etanercept- and efalizumab-treated patients. Patients who did not meet this criterion were excluded from therapy according to the reimbursement guidelines. In some of these cases, treatment with the other available biological agent was started thereafter. The administration of etanercept or efalizumab was discontinued if patients developed a serious infection; therapy was resumed after recovery.

Analysis
All patients treated with etanercept or efalizumab in the outpatient clinic were included for analysis. Descriptive statistics were used to reproduce study results as percentages, means and standard error of the mean (SEM).

Treatment efficacy was analysed by calculation of the PASI, the percentage improvement in PASI from baseline at different time points, and by the number of patients with an improvement in PASI relative to baseline of at least 50%, 75% or 90% (PASI 50, PASI 75 and PASI 90, respectively). Population PASI scores were calculated for weeks 4, 8, 12, 18, 24 and every 12 weeks thereafter, until follow-up data for no fewer than three patients in each treatment group were available. Due to logistical reasons the individual visits were not always exactly at these fixed time points. If so, the interpolated PASI between most nearby visits was included in the analysis.

Measurement of treatment efficacy was done by means of an intention to treat (ITT) principle. Furthermore, those patients who responded satisfactorily and therefore could be treated for an unrestricted period of time were analysed separately. This analysis is designated as ‘per protocol’ (PP).

Accompanying factors, of which an influence on treatment efficacy outcome was suspected, including dose adjustments, concomitant medication and treatment interruptions, were considered. Reported adverse events and abnormal laboratory values were summarized. If patients received etanercept as well as efalizumab treatment, each biological therapy was analysed separately.

Results

Demographics
Over the past 27 months, 101 patients were treated with either etanercept or efalizumab. Overall, 61% of patients were male, the mean age was 49.0 years and the mean duration of psoriasis was 21.3 years. Of all patients, 62 reported joint complaints, of which 28 suffered
from psoriatic arthritis. The mean PASI at baseline was 18.6. Age and sex distribution were comparable for each treatment. At baseline, joint complaints were more common in the etanercept-treated group than in the efalizumab-treated group. The duration of psoriasis was longest in the etanercept 2x25 mg group. Mean baseline PASI was highest for the etanercept 2x50 mg treated patients (Table 1).

Table 1. Baseline demographic data and disease characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Etanercept 2x50 mg (n = 61)</th>
<th>Etanercept 2x25 mg (n = 19)</th>
<th>Efalizumab (n = 21)</th>
<th>All (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>21-72</td>
<td>28-69</td>
<td>27-71</td>
<td>21-72</td>
</tr>
<tr>
<td>Mean (±SEM)</td>
<td>48.2 (1.4)</td>
<td>51.5 (2.5)</td>
<td>48.9 (2.7)</td>
<td>49.0 (1.1)</td>
</tr>
<tr>
<td>Sex, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39 (64)</td>
<td>11 (58)</td>
<td>12 (57)</td>
<td>62 (61)</td>
</tr>
<tr>
<td>Female</td>
<td>22 (36)</td>
<td>8 (42)</td>
<td>9 (43)</td>
<td>39 (39)</td>
</tr>
<tr>
<td>Psoriasis, no (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With joint complaints</td>
<td>39 (64)</td>
<td>13 (68)</td>
<td>10 (48)</td>
<td>62 (61)</td>
</tr>
<tr>
<td>With psoriatic arthritis</td>
<td>20 (33)</td>
<td>3 (16)</td>
<td>5 (24)</td>
<td>28 (28)</td>
</tr>
<tr>
<td>Without joint complaints</td>
<td>22 (36)</td>
<td>6 (32)</td>
<td>11 (52)</td>
<td>39 (39)</td>
</tr>
<tr>
<td>Duration of psoriasis, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>3-42</td>
<td>4-46</td>
<td>3-40</td>
<td>3-46</td>
</tr>
<tr>
<td>Mean (±SEM)</td>
<td>20.5 (1.2)</td>
<td>25.6 (2.8)</td>
<td>19.8 (2.4)</td>
<td>21.3 (1.0)</td>
</tr>
<tr>
<td>Baseline PASI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (±SEM)</td>
<td>20.1 (1.3)</td>
<td>16.9 (1.4)</td>
<td>15.8 (1.3)</td>
<td>18.6 (0.9)</td>
</tr>
</tbody>
</table>

SEM, Standard Error of the Mean; PASI, Psoriasis Area and Severity Index.

Patients received 3-11 different categories of dermatological therapies before the start of biological treatment, with an average of 7.0 treatments per patient. The mean number of different systemic therapies that patients used before the start of biological treatment was 3.4, indicating a ‘high-need’ population. Some patients had used biological agents in the past, mostly in the context of clinical trials. These included etanercept, alefacept, efalizumab, infliximab and onercept (Table 2).

Eighty patients were treated with etanercept, of whom 61 received a dose of 50 mg SC twice weekly for 12 weeks, followed by 25 mg SC twice weekly for 12 weeks (2x50 mg group) and 19 received a dose of 25 mg SC twice weekly for 24 weeks (2x25 mg group). Twenty-one patients were treated with efalizumab.

Patients were treated for various periods. The overall mean duration of treatment was 58
weeks, with a range of 6-107 weeks in the etanercept 2x50 mg group, 11-117 weeks in the etanercept 2x25 mg group and 6-88 weeks in the efalizumab-treated group.

Table 2. Previous treatments.

<table>
<thead>
<tr>
<th>Topical, no. (%)</th>
<th>Etanercept 2x50 mg (n = 61)</th>
<th>Etanercept 2x25 mg (n = 19)</th>
<th>Efalizumab (n = 21)</th>
<th>All (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroid/ Vitamin D analogue</td>
<td>61 (100)</td>
<td>19 (100)</td>
<td>21 (100)</td>
<td>101 (100)</td>
</tr>
<tr>
<td>Dithranol</td>
<td>45 (74)</td>
<td>15 (79)</td>
<td>17 (81)</td>
<td>77 (76)</td>
</tr>
<tr>
<td>Coal tar</td>
<td>14 (23)</td>
<td>7 (37)</td>
<td>4 (19)</td>
<td>25 (25)</td>
</tr>
<tr>
<td>Calcineurin inhibitor</td>
<td>4 (7)</td>
<td>0 (0)</td>
<td>2 (10)</td>
<td>6 (6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Light, no. (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>UVB</td>
<td>53 (87)</td>
<td>17 (89)</td>
<td>16 (76)</td>
<td>86 (85)</td>
</tr>
<tr>
<td>PUVA</td>
<td>40 (66)</td>
<td>15 (79)</td>
<td>15 (71)</td>
<td>70 (69)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic, no. (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>58 (95)</td>
<td>19 (100)</td>
<td>20 (95)</td>
<td>97 (96)</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>47 (77)</td>
<td>11 (58)</td>
<td>17 (81)</td>
<td>75 (74)</td>
</tr>
<tr>
<td>Retinoidsb</td>
<td>43 (70)</td>
<td>14 (74)</td>
<td>15 (71)</td>
<td>72 (71)</td>
</tr>
<tr>
<td>Fumaric acid</td>
<td>35 (57)</td>
<td>5 (26)</td>
<td>8 (38)</td>
<td>48 (48)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>9 (15)</td>
<td>2 (11)</td>
<td>4 (19)</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Alefacept</td>
<td>9 (15)</td>
<td>3 (16)</td>
<td>4 (19)</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Onercept</td>
<td>4 (7)</td>
<td>2 (11)</td>
<td>1 (5)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>11 (18)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

*Tacrolimus, pimecrolimus; b Acitretin, bexarotene, liarozole. UVB, Ultraviolet B; PUVA, Psoralen-Ultraviolet A.

Efficacy

Forty patients (66%) in the etanercept 2x50 mg group, 13 patients (68%) in the etanercept 2x25 mg group and 12 patients (57%) in the efalizumab group achieved a 50% PASI reduction at week 12. At the same time, respectively, 20%, 21% and 10% achieved a PASI 75, and 8%, 5% and 0% achieved a PASI 90 (Figure 1).

The response on etanercept treatment as well as efalizumab treatment levelled out after approximately 24 weeks. At that time point, the mean PASI reduction was 59% (SEM 5.0) in the etanercept 2x50 mg group, 60% (SEM 8.4) in the etanercept 2x25 mg group and 51% (SEM 8.8) in the efalizumab group, according to the ITT analysis (Figure 2). PP analysis shows a mean reduction in PASI of 59% (SEM 5.3), 58% (SEM 8.9) and 58% (SEM 5.9), respectively, at week 24 (Figure 3).
At the beginning of May 2007, 71 patients were still on biological treatment. Of the efalizumab cohort, 62% discontinued therapy because of lack of efficacy, adverse events or both. On the contrary, 17 patients (21%) have terminated etanercept treatment (Table 3).

Table 3. Current therapy status.

<table>
<thead>
<tr>
<th>Current therapy status, no. (%)</th>
<th>Etanercept 2x50 mg (n = 61)</th>
<th>Etanercept 2x25 mg (n = 19)</th>
<th>Efalizumab (n = 21)</th>
<th>All (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued due to lack of efficacy</td>
<td>4 (7)</td>
<td>1 (5)</td>
<td>6 (29)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Discontinued due to adverse events</td>
<td>3 (5)</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Discontinued due to lack of efficacy and adverse events</td>
<td>2 (3)</td>
<td>4 (21)</td>
<td>6 (29)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Dead</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Discontinued treatment (total)</td>
<td>11 (18)</td>
<td>6 (32)</td>
<td>13 (62)</td>
<td>30 (30)</td>
</tr>
<tr>
<td>Continued treatment</td>
<td>50 (82)</td>
<td>13 (68)</td>
<td>8 (38)</td>
<td>71 (70)</td>
</tr>
</tbody>
</table>
Figure 2. Treatment efficacy, intention to treat (ITT).

Figure 3. Treatment efficacy, per protocol (PP).

PASI, Psoriasis Area and Severity Index.
Response-modifying strategies

Despite a considerable reduction in the severity of disease in many patients, biological therapy did not induce an improvement that was entirely satisfactorily in 84 (83%) of all patients. In these cases, concomitant antipsoriatic therapies were started or therapy dose was increased temporarily. In 81% of all etanercept-treated patients and 71% of all efalizumab-treated patients, topical corticosteroids or vitamin D analogues were used in addition to biological treatment. Other concomitant therapies included coal tar, dithranol, tacrolimus, methotrexate, ciclosporin, acitretin, prednisone, fumaric acid and mycofenolate mofetil (Table 4).

Table 4. Concomitant medication.

<table>
<thead>
<tr>
<th>Topical, no. (%)</th>
<th>Etanercept 2x50 mg (n = 61)</th>
<th>Etanercept 2x25 mg (n = 19)</th>
<th>Efalizumab (n = 21)</th>
<th>All (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroid/ Vitamin D analogue</td>
<td>49 (80)</td>
<td>16 (84)</td>
<td>15 (71)</td>
<td>80 (79)</td>
</tr>
<tr>
<td>Coal tar</td>
<td>5 (8)</td>
<td>3 (16)</td>
<td>4 (19)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Dithranol</td>
<td>3 (5)</td>
<td>2 (11)</td>
<td>1 (5)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>5 (8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>12 (20)</td>
<td>0 (0)</td>
<td>2 (10)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>Ciclosporine</td>
<td>5 (8)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Acitretin</td>
<td>4 (7)</td>
<td>1 (5)</td>
<td>2 (10)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Fumaric acid</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Mycofenolate mofetil</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

In 11 patients systemic therapies were introduced after the start of biological therapy, if biological monotherapy was insufficient. Seventeen patients were already using systemic therapies before biological therapy was started, and in 10 of these cases these pharmaceuticals were tapered during biological therapy. Patients who used concomitant systemic antipsoriatic treatments did not generally present better efficacy results compared with the group that did not use concomitant systemic therapies (Figure 4).

In 24 of all etanercept-treated patients who had an unsatisfactory response on therapy, the weekly dose was increased to 2x50 mg for varying periods, mostly 2-4 weeks. Patients who used higher dosages of etanercept during their treatment period achieved the same ultimate PASI reduction but at a higher cumulative dose of etanercept (Figure 5).
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Figure 4. Influence of concomitant systemic therapy on biological treatment efficacy.

Figure 5. Influence of dose increase on etanercept treatment efficacy.

PASI, Psoriasis Area and Severity Index.
PART II

Treatment interruptions occurred in 34 (56%) of the etanercept 2x50 mg treated patients, 16 (84%) of the etanercept 2x25 mg treated patients and two (10%) of the efalizumab-treated patients. Etanercept was interrupted predominantly because of adherence to the EMEA label at week 24. Other reasons for treatment interruption were adverse events, such as infections, problems with distribution of medication or patients’ decisions (Table 5). For 27 of all etanercept-treated patients, data about the effect of treatment interruption after 24 weeks of conforming to EMEA guidelines were available. Analysis of these data demonstrated that 19 of these patients encountered an increase in PASI during interruption, with a mean PASI increase of 4.0 per patient. The mean duration of interruption was 25 days (range 3-92 days) (Figure 6).

Table 5. Response-modifying strategies.

<table>
<thead>
<tr>
<th></th>
<th>Etanercept 2x50 mg (n = 61)</th>
<th>Etanercept 2x25 mg (n = 19)</th>
<th>Efalizumab (n = 21)</th>
<th>All (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accompanying factors, no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose increase</td>
<td>21 (34)</td>
<td>3 (16)</td>
<td>0 (0)</td>
<td>24 (24)</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical</td>
<td>49 (80)</td>
<td>17 (89)</td>
<td>15 (71)</td>
<td>81 (80)</td>
</tr>
<tr>
<td>Systemic</td>
<td>23 (38)</td>
<td>1 (5)</td>
<td>5 (24)</td>
<td>29 (29)</td>
</tr>
<tr>
<td>Treatment interruption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>34 (56)</td>
<td>16 (84)</td>
<td>2 (10)</td>
<td>52 (51)</td>
</tr>
<tr>
<td>More than 2 weeks cumulative</td>
<td>20 (33)</td>
<td>15 (79)</td>
<td>1 (5)</td>
<td>36 (36)</td>
</tr>
<tr>
<td>More than 2 weeks consecutive</td>
<td>17 (28)</td>
<td>13 (68)</td>
<td>0 (0)</td>
<td>30 (30)</td>
</tr>
</tbody>
</table>

Adverse events
In general, etanercept and efalizumab treatment was well tolerated, and mainly mild adverse events were reported. The most reported adverse events (with an overall incidence of more than 20%) were upper respiratory infections, pruritus, arthralgia, gastrointestinal complaints and flu-like symptoms (Table 6).

Infections
Infections were reported 77 times. These included upper and lower respiratory infections, skin infections, eye infections, urinary tract infections, gastrointestinal infections and oral infections. No patients were diagnosed with tuberculosis during treatment, although, after the marker study period, we discovered 4 patients with possible latent tuberculosis who had to be treated prophylactically with isoniazid.
Malignancies

Malignancies were found in 4 etanercept-treated patients. A 48-year-old man was diagnosed with an oesophageal carcinoma, as well as with three squamous cell carcinomas (SCCs) and Bowen’s disease during etanercept therapy. Another patient developed a BCC as well as a SCC. In the other two patients BCCs were diagnosed. All skin malignancies were noticed after less than half a year of biological treatment. The patients in question had been treated extensively with phototherapy in the past. Furthermore, a female patient had to discontinue etanercept treatment because of a cervix carcinoma in situ. No malignancies were found in the efalizumab-treated group.

Serious adverse events

Eleven patients required hospital admission during treatment. In 8 of these patients (5 treated with etanercept and three treated with efalizumab) their psoriasis was aggravated and an intensifying of therapy was needed. Psoriasis aggravation was seen after abrupt discontinuation of other systemic antipsoriatic treatments before the start of biological therapy, and consecutively a poor response on biological treatment; after the occurrence of infection during biological therapy, which caused discontinuation of biological therapy; or both. One etanercept-treated patient was admitted with pneumonia. Two other admitted
### Table 6. Adverse events.

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Etanercept 2x50 mg (n = 61)</th>
<th>Etanercept 2x25 mg (n = 19)</th>
<th>Efalizumab (n = 21)</th>
<th>All (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections, no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infections</td>
<td>27 (44)</td>
<td>12 (63)</td>
<td>4 (19)</td>
<td>43 (43)</td>
</tr>
<tr>
<td>Skin infections</td>
<td>4 (7)</td>
<td>3 (16)</td>
<td>3 (14)</td>
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</tr>
<tr>
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</tr>
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</tr>
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<td>(Pre)malignancies, no. (%)</td>
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<td><strong>Skin reactions, no. (%)</strong></td>
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<tr>
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<td>12 (20)</td>
<td>8 (42)</td>
<td>7 (33)</td>
<td>27 (27)</td>
</tr>
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<td>3 (14)</td>
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<td>2 (11)</td>
<td>2 (10)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (13)</td>
<td>6 (32)</td>
<td>2 (10)</td>
<td>16 (16)</td>
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<td><strong>Muscle and joint complaints, no. (%)</strong></td>
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<td>7 (37)</td>
<td>3 (14)</td>
<td>20 (20)</td>
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<td>Pain</td>
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<td>4 (21)</td>
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<tr>
<td><strong>Miscellaneous, no. (%)</strong></td>
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<td></td>
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<td>Flu-like symptoms</td>
<td>15 (25)</td>
<td>7 (37)</td>
<td>6 (29)</td>
<td>28 (28)</td>
</tr>
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<td>Gastrointestinal complaints</td>
<td>13 (21)</td>
<td>5 (26)</td>
<td>5 (24)</td>
<td>23 (23)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (8)</td>
<td>4 (21)</td>
<td>10 (48)</td>
<td>19 (19)</td>
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<tr>
<td>Fatigue</td>
<td>9 (15)</td>
<td>4 (21)</td>
<td>2 (10)</td>
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<tr>
<td>Coughing</td>
<td>5 (8)</td>
<td>2 (11)</td>
<td>3 (14)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Eye complaints</td>
<td>3 (5)</td>
<td>5 (26)</td>
<td>2 (10)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Dead</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (2)</td>
</tr>
<tr>
<td><strong>Any</strong></td>
<td>55 (90)</td>
<td>19 (100)</td>
<td>20 (95)</td>
<td>94 (93)</td>
</tr>
</tbody>
</table>

Represented are numbers and percentages of patients having at least one adverse event in a predefined category.
patients suffered from severe joint complaints; both were being treated with efalizumab at that moment. Two female patients of our cohort died of sudden cardiac arrest during etanercept treatment. One had a history of hypertension and stroke; the other suffered from chronic obstructive pulmonary disease.

Dermatological adverse events
Dermatological adverse events are represented in Table 7. Pruritus, injection site reactions and skin infections (including erysipelas, mycosis, folliculitis, herpes zoster and wound infections) were reported most frequently.

Miscellaneous
Two patients reported vision impairment during etanercept treatment. Because optic neuritis was suspected, etanercept therapy was discontinued and patients were referred to an ophthalmologist or neurologist. In neither patient could the diagnosis be confirmed. Besides vision impairment, other eye complaints were common. These included eye infections, such as chalazion and conjunctivitis, and other complaints, such as dryness, redness and irritation of the eyeball (Table 6).

Laboratory abnormalities
Routine laboratory monitoring revealed a newly developed leucocytosis (white blood cell count > 11x10^9/litre [l]) in 12 patients (15%) on etanercept therapy and 19 patients (90%) on efalizumab therapy. In these cases, a concurrent increase in C-reactive protein was monitored in three and 10 patients, respectively. A significant leucopenia (white blood cell count < 4x10^9/l) was found in one etanercept-treated patient. Three efalizumab-treated patients (14%) and 8 etanercept-treated patients (10%) developed a thrombocytopenia (platelet count < 150x10^9/l). In 18 (23%) patients on etanercept and 5 (24%) patients on efalizumab, alanine amino transferase values increased above 45 units/litre (U/l) during treatment. Other laboratory changes were pre-existent or were considered clinically insignificant.

Discussion
The aim of the present prospective cohort study was to evaluate the efficacy, safety and adverse events of etanercept and efalizumab treatment in the outpatient clinic and to investigate accompanying factors that influenced treatment outcome. We present data from a 27-month follow-up of 101 patients treated with etanercept or efalizumab.
Table 7. Dermatological adverse events.

<table>
<thead>
<tr>
<th>Dermatological conditions, no (%)</th>
<th>Etanercept 2x50 mg (n = 61)</th>
<th>Etanercept 2x25 mg (n = 19)</th>
<th>Efalizumab (n = 21)</th>
<th>All (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>12 (20)</td>
<td>8 (42)</td>
<td>7 (33)</td>
<td>27 (27)</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>10 (16)</td>
<td>3 (16)</td>
<td>3 (14)</td>
<td>12 (12)</td>
</tr>
<tr>
<td>Skin infections</td>
<td>4 (7)</td>
<td>3 (16)</td>
<td>10 (10)</td>
<td></td>
</tr>
<tr>
<td>Oedema</td>
<td>1 (2)</td>
<td>5 (25)</td>
<td>3 (14)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Hair loss</td>
<td>1 (2)</td>
<td>2 (11)</td>
<td>2 (10)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Actinic keratosis</td>
<td>2 (3)</td>
<td>1 (5)</td>
<td>2 (10)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>2 (3)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Morphological changes in psoriasis</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Drug eruption</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>5 (5)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1 (2)</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (2)</td>
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<tr>
<td>Bowen’s disease</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Black hairy disease</td>
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<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Eczema</td>
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</tr>
<tr>
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<td>1 (5)</td>
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<tr>
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<td>1 (5)</td>
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<tr>
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<tr>
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<td>0 (0)</td>
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<td>Grover’s disease</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Leg ulcer</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

The cohort represented a high-need population: only patients with a PASI of at least 10 who did not respond sufficiently to phototherapy, methotrexate and ciclosporin were included. Safety and efficacy of biologics in randomized controlled trials (RCTs) and initial experiences with biologics in clinical practice are described in literature.\textsuperscript{3-15} RCTs in which etanercept and efalizumab were investigated show a mean PASI reduction between approximately 50% and 60% at week 12. In the present study, comparable efficacy results are found for etanercept-treated patients. In the efalizumab-treated group, efficacy results for week 12 are lower. Moreover, PASI 75 and PASI 90 responses are less high than RCT data for both etanercept- and efalizumab-treated patients.\textsuperscript{3,5-10,12,14,15} A few explanations for this can be given.

Firstly, the present population differs from study populations used in RCTs in many respects. The cohort is composed only of patients who were not responsive or contraindicated to three systemic therapies. Secondly, it may be the fact that a certain number of the patients...
making the transition from conventional therapy to biological treatment without washout do not have a representative baseline PASI, and that they are starting from a point of partial response. Thirdly, the individualized approach of permitting combination treatments and dose adjustments makes comparison with RCTs difficult. Furthermore, data about patients with extremely poor response on therapy have great impact on all (ITT) efficacy results. Nevertheless, it is possible that there actually is a discrepancy between efficacy of biologics in real life practice versus RCTs. Additional reasons for this could be non-compliance or inadequate use of medication.

According to the represented efficacy data, it may be concluded that the higher dose of etanercept is equally or less effective than etanercept 25 mg twice weekly. However, based on practical clinical experience, this seems not to be the case. Several explanations for the lower efficacy results for the 2x50 mg etanercept group can be given. First of all, mean baseline PASI was highest for the etanercept 2x50 mg group (Table 1), reflecting a severely affected subgroup. Secondly, patients initially treated with 2x50 mg etanercept used more different types of antipsoriatic therapies in history (Table 2), reflecting a degree of therapy resistance. Furthermore, the mean follow-up period was longer for the etanercept 2x25 mg group than for the 2x50 mg group. This may imply that some 2x50 mg treated patients require treatment for a longer time to achieve the maximum response on therapy.

The response on biological treatment in this cohort showed a maximum effect after approximately 6 months. For this reason we believe that efficacy in daily practice can best be analysed after half a year, in contrast to the current guidelines of reimbursement, for which an analysis after 12 weeks is demanded. A study by Krueger et al. demonstrated that patients with psoriasis who initially had an incomplete response or did not respond to etanercept treatment in RCTs had meaningful improvement with continued treatment.\textsuperscript{16} The etanercept dose was increased temporarily in 24 of 80 cases. This indicates that the use of 2x25 mg weekly may not be sufficient throughout the whole treatment period for a high-need psoriasis cohort. No influence of these dosage adjustments was seen on safety parameters.

 Interruption of etanercept treatment after 24 weeks, as carried out according to the EMEA label, appears to elicit a substantial fall in treatment benefits. Taking this into account, continuing treatment after 24 weeks instead of interrupting therapy at that point would be of benefit to the patient.

 In routine practice, combination treatment may imply a classical drug to which a biologic is added subsequently, or the reverse: a biologic with subsequent combination with a classical drug. Further studies on various combination schedules are indicated. In this
PART II

study, a combination of therapies did not lead to increased toxicity or altered safety profiles during the time they were applied.

Both etanercept and efalizumab were well tolerated. Ninety-four patients reported one or more adverse events, but those were mainly mild. Two female patients died of a sudden cardiac arrest during the treatment follow-up period, but this was presumably not related to the use of etanercept, according to the opinion of the general practitioner. Common adverse events were upper respiratory infections, pruritus, joint complaints, gastrointestinal complaints and flu-like symptoms. Thirty-seven patients reported muscle and joint complaints: 30 of these patients already had such complaints before biological treatment was started.

As optic neuritis is a potential serious side effect of etanercept, special attention needs to be paid to all patients with vision impairment. In our patients with complaints of reduced vision, no signs of demyelinating disease were found. Apart from vision impairment, other eye complaints occurred in our cohort as well. Taban et al. undertook a literature review about inflammatory eye disease associated with etanercept therapy, and found that ocular inflammation is a potential adverse event following the use of etanercept. Skin malignancies were seen in low frequencies in this cohort. All were recorded in the first 6 months of treatment with biologics. Therefore, it is more likely that these malignancies are caused by previous antipsoriatic therapies such as ciclosporin and phototherapy than biologics. To reduce actinic overexposure, the eligibility criteria for use of biologics should state a failure to respond to either phototherapy or ciclosporin.

In conclusion, prospective cohort monitoring of patients with high-need psoriasis on systemic treatments, especially on biologics, is worthwhile. The course of treatment in general practice is highly different from treatment schedules in clinical trials, and it is worth noting that clinical trials on selected healthy individuals lack external validity in some cases. Frequently applied clinical strategies such as treatment interruptions due to concomitant illnesses or protocol definitions, dosage adjustments and combination of treatments influence treatment outcome in routine treatment in comparison with RCT research data. Therefore, information about treatment with these new drugs in daily clinical practice is important for adjusting treatment schedules and guidelines.
References


CHAPTER 8

Three-year registry data on biological treatment for psoriasis: the influence of patient characteristics on treatment outcome

Abstract

Background: The course of biological treatment in clinical practice may be highly different from treatment schedules in clinical trials. Treatment modifications and patient characteristics may influence treatment safety and efficacy. So far, long-term results from the use of biological treatment in clinical practice are lacking.

Objectives: To report short- and long-term efficacy and safety data on biologics, especially etanercept, used in daily clinical practice. Special attention has been paid to patient characteristics that may have influenced the response to therapy.

Methods: Prospectively collected registry data of all patients with psoriasis treated with biologics in the Radboud University Nijmegen Medical Centre Department of Dermatology outpatient clinic were used for analysis. Patient and treatment characteristics were surveyed. Efficacy and safety of etanercept for up to three years were analysed. Moreover, the influence of patient characteristics on etanercept treatment response was studied.

Results: The analysed cohort, consisting of 118 patients, went through 142 treatment episodes in total. Patients treated with biologics had an extensive medical history. Optimization of biological treatment was established in various ways, including treatment switches and introduction of concomitant therapies. Short-term etanercept efficacy analysis showed a mean Psoriasis Area and Severity Index (PASI) improvement at week 24 of 59.7%. No significant influence of gender, age, baseline PASI, body mass index, number of previous systemic therapies or duration of psoriasis was found on week 24 efficacy results, although trends were discernible. The efficacy of etanercept remained stable for up to 156 weeks. Long-term daily practice treatment with etanercept was only occasionally accompanied by major safety concerns.

Conclusions: The current study demonstrates that etanercept is able to improve psoriasis symptoms for a considerable time, and that serious side effects are infrequent. The influence of patient characteristics on treatment response is limited.

PART II

Introduction
The safety and efficacy of biological treatments for psoriasis have been thoroughly studied in well designed clinical trials. Results of these trials founded the approval of four different biologics for psoriasis by the European Union: etanercept, efalizumab, infliximab and adalimumab. Now that biological therapies are accepted as a regular therapeutic option for psoriasis, knowledge about the use of these therapies in daily practice is growing. This has given rise to the compilation of new guidelines for the management of psoriasis.1-5 Recently, we performed a study in which the experience in treating a cohort of 101 patients with high-need psoriasis with etanercept and efalizumab in daily clinical practice during two years was described. In that study, we focused on different biological therapies, including treatment modifications which were suspected to influence treatment efficacy outcome. The course of biological treatment in general practice proved highly different from treatment schedules in clinical trials.6 In addition to treatment modifications induced by physicians, patient characteristics may also influence treatment safety and efficacy. Clinical trials make use of predefined inclusion, exclusion and discontinuation criteria, which leads to the selection of specific, in general ‘healthy’, patient categories. In clinical practice, however, an attempt is made to provide an optimal treatment for each individual patient, even though many have comorbidities, co-medication and an extensive psoriasis treatment history.

In the current report we describe the experience in treating a cohort of 118 patients with high-need psoriasis with biologics in daily clinical practice for up to three years. The objective of this study is to report short- and long-term efficacy and safety data on biologics, especially etanercept, in the context of real-world practice. Data are analysed from the perspective of individual patients. Special attention has been paid to patient characteristics that may have influenced the response to therapy.

Patients and methods

Patients
Data were extracted from a prospective observational cohort registry, including all patients with psoriasis treated with biologics between February 2005 and May 2008. Patients came into consideration for biological treatment if they had failed to respond to phototherapy, methotrexate and ciclosporin in the past, or if they had a contraindication to, or were intolerant of these treatments. At the same time, patients had to have a minimum Psoriasis Area and Severity Index (PASI)7 of 10 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 blood screening, including haematological analysis, serum chemistry and antinuclear antibodies (ANA), was performed in each patient. Patients were treated with a biologic that was most suitable in the physician’s opinion. As etanercept and efalizumab have been approved and reimbursed since the start of 2005, and consequently most experience is gained with these therapies, these drugs were preferred as initial treatment. Infliximab was used for patients with very severe psoriasis, who were unresponsive to etanercept or efalizumab. Adalimumab was approved, but not reimbursed, in December 2007. Therefore, adalimumab has been prescribed only in a few cases up until now.

Absolute contraindications for biological treatment were a known hypersensitivity to the constituents of the drug to be prescribed, an active infection or increased susceptibility for infections (including immunocompromised persons), a history of tuberculosis, and pregnancy. Furthermore, antitumor necrosis factor-α therapies (etanercept, infliximab, adalimumab) were contraindicated in patients with a demyelinating disease. Contraindications specific for therapy with efalizumab were the presence of pustular, guttate or erythrodermic psoriasis during screening and a history of malignancy (basal cell carcinomas excluded). Relative contraindications for biological treatment were cardiac decompensation, a blood dyscrasia, a recent history of malignancy (absolute contraindication for efalizumab), the presence of ANA-positive autoimmune disease or chronic exposure to actinic radiation in the past.

Patients were allowed to use topical dermatological therapies during biological treatment if desired. An effort was made to limit the use of concomitant systemic dermatological therapies in cases of unsatisfactory effectiveness of biological treatment. Termination of other non-dermatological drugs was considered unnecessary. Ideally, visits were scheduled every 4 weeks during the first 12 weeks, every 6 weeks until week 24 and every 12 weeks thereafter. Each visit, PASI and adverse events were documented. After 12 weeks of therapy (or 8 weeks for infliximab), the treatment protocol required an improvement in PASI of at least 50% for all treated patients. Patients who did not meet this criterion were excluded from therapy according to the reimbursement guidelines. In some of these cases, treatment with another available biological agent was started thereafter. The administration of a biologic was discontinued if patients developed a serious infection; therapy was restarted after recovery.
PART II

Analysis

All patients with psoriasis treated with biologics in the Radboud University Nijmegen Medical Centre Department of Dermatology outpatient clinic were included for analysis. Descriptive statistics were used to reproduce study results as percentages and mean ± standard error of the mean (SEM).

Patient characteristics were surveyed, including age, gender, duration of psoriasis, PASI at first screening, duration of follow-up, number of biological treatment episodes and therapy status at analysis. General medical history was categorized by organ system or, in cases of high prevalence, by disease. Treatment characteristics, including nature of treatment, number of different treatment episodes, duration of treatment episodes and concomitant or intervening systemic therapies were outlined. The number of patients actively treated with biologics and the number of dropouts were counted.

As most patients of the current cohort were treated with etanercept, and most short- and long-term data were available from this group, efficacy analysis in this study was performed for etanercept-treated patients only. In the previous article, a maximal treatment response was observed after 24 weeks of therapy. Therefore, to study short-term efficacy of etanercept and the influence of patient characteristics on treatment response, only etanercept-treated patients of whom efficacy data of at least 24 weeks were available were included for analysis. Patients were stratified by gender, age, baseline PASI, body mass index (BMI), number of previous systemic therapies and duration of psoriasis. Mean percentage PASI improvement at week 24 was calculated for the entire group as well as for subgroups by means of interpolation. The number of patients with an improvement in PASI relative to baseline of at least 50%, 75% or 90% (PASI 50, PASI 75 and PASI 90, respectively) at week 24 was counted. To demonstrate the magnitude of differences between subgroups, an independent samples t-test was performed using SPSS 14.0.2 for windows (SPSS Inc., Chicago, IL, U.S.A.). All tests are two-tailed. $P < 0.05$ was considered statistically significant.

Long-term treatment efficacy was analysed by calculation of the absolute decrease in PASI. In this analysis, only patients treated with etanercept for at least 72 weeks were included. Mean weekly etanercept dosage was reflected. Mean population PASI values were calculated by interpolation of data, considering week 4, 8, 12, 18, 24 and every 12 weeks thereafter as fixed time points. Interpolation was performed until data about no fewer than 6 patients were available.

Adverse events of all patients treated with biologics were outlined. Represented were numbers of patients having at least one adverse event in a predefined category. Serious adverse events were defined as malignancies or adverse events that were immediately
life threatening, caused persistent disability, required hospital admission, or resulted in a patient's death.

Results

Patient characteristics

Between February 2005 and May 2008, 118 patients were treated with a biologic for at least one consecutive period. Mean ± SEM age of patients was 47.3 ± 1.0 years. Sixty-four percent of patients were male. Patients had had psoriasis for a mean ± SEM of 22.4 ± 0.9 years. Mean ± SEM PASI at first screening was 17.5 ± 0.8. Mean ± SEM duration of patient follow up in the registry was 1.7 ± 0.1 years. Fifteen percent of all patients were treated with more than one biologic.

At analysis in May 2008, 88 (75%) of all patients were still on biological therapy. The remaining 25% were lost to follow up, had discontinued therapy due to adverse events, lack of efficacy or desire to become pregnant, or had died (Table 1).

Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>n = 118</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(^a) (years), mean ± SEM</td>
<td>47.3 ± 1.0</td>
</tr>
<tr>
<td>Gender, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>76 (64)</td>
</tr>
<tr>
<td>Female</td>
<td>42 (36)</td>
</tr>
<tr>
<td>Duration of psoriasis(^a) (years), mean ± SEM</td>
<td>22.4 ± 0.9</td>
</tr>
<tr>
<td>PASI(^a), mean ± SEM</td>
<td>17.5 ± 0.8</td>
</tr>
<tr>
<td>Follow-up duration (years), mean ± SEM</td>
<td>1.7 ± 0.1</td>
</tr>
<tr>
<td>Biological treatment episodes, no. (%)</td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>100 (85)</td>
</tr>
<tr>
<td>Two</td>
<td>14 (12)</td>
</tr>
<tr>
<td>More than two</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Therapy status at analysis, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>88 (75)</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>11 (9)</td>
</tr>
<tr>
<td>Discontinued due to AE and lack of efficacy</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Discontinued due to AE</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Discontinued due to lack of efficacy</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Discontinued due to desire to become pregnant</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

\(^a\)At first screening. SEM, Standard Error of the Mean; PASI, Psoriasis Area and Severity Index; AE, Adverse Event.
PART II

Patients treated with biologics had an extensive medical history. More than 40% of all patients had undergone surgery for different reasons. A great proportion of patients had an unfavourable cardiovascular risk profile, considering the high prevalence of hypertension (36%), hyperlipidaemia (19%), diabetes (14%) and cardiological disease (14%). In addition, mean BMI was 28.8 kilograms/meters squared (kg/m²), and 44 (37%) patients were obese (defined as BMI > 30 kg/m²).

Treatment characteristics
The analysed cohort, consisting of 118 patients, went through a total of 142 treatment episodes. Mean ± SEM duration of a treatment episode was 1.8 ± 0.1 years. Eighty percent of patients were treated with etanercept only. Additionally, 9 patients were initially treated with efalizumab, but switched to etanercept later on. Another 10 patients were treated with efalizumab as well, of whom 4 were treated with etanercept before, and one was treated with infliximab thereafter. Four other patients went through more than two biological treatment episodes. One patient was initially treated with etanercept, followed by efalizumab, but due to lack of efficacy of both treatments infliximab was initiated. Another patient was treated with, respectively, etanercept and efalizumab as well, but preferred retreatment with etanercept. Likewise, one patient was treated with efalizumab, etanercept and retreated with efalizumab thereafter. A patient with very severe, therapy-resistant psoriasis underwent 5 different treatment episodes, including infliximab, efalizumab, etanercept, infliximab and adalimumab, respectively (Table 2).

Concomitant or intervening systemic therapies were introduced or maintained in 30 patients. These comprised methotrexate (n = 17), ciclosporin (n = 9), acitretin (n = 9), fumaric acid (n = 2), mycophenolate mofetil (n = 1), tacrolimus (n = 1), ultraviolet (UV) B (n = 1) and Psoralen-UVA (PUVA) (n = 1). Concomitant therapies were used to prevent patients from rebound or to improve treatment efficacy. Although unconventional, PUVA was used in a patient during a 10-month interruption period of infliximab. UVB was used to bridge a transition period from efalizumab to etanercept in another patient.

Short-term efficacy of etanercept and the influence of patient characteristics on treatment response
To evaluate the influence of patient characteristics on etanercept treatment response, 90 (81%) patients with available week 24 efficacy data were included for analysis. Mean PASI improvement at week 24 was 59.7%. PASI 50, PASI 75 and PASI 90 at week 24 was achieved by, respectively, 62 (69%), 35 (39%) and 16 (18%) patients. No significant influence of gender, age, baseline PASI, BMI, number of previous systemic therapies or
duration of psoriasis was found on week 24 efficacy results. Differences between efficacy data were most pronounced for subgroups stratified by baseline PASI above 20, BMI above 30 kg/m² and psoriasis duration longer than 20 years. Patients with a baseline PASI above 20 showed a greater mean percentage PASI reduction than patients with a baseline PASI below 20 (67.6% versus 54.9%, \( p = 0.072 \)). Furthermore, obese patients tended to demonstrate a lower efficacy response compared with patients with BMI beneath 30 kg/m² (53.0% versus 63.4%, \( p = 0.146 \)). A psoriasis duration of longer than 20 years was associated with a mean percentage PASI reduction of 64.1% at week 24, whereas patients with a shorter duration of psoriasis before biological treatment showed a mean percentage PASI reduction of 54.6% \( (p = 0.170) \) (Table 3). Obviously, patients with psoriasis duration of longer than 20 years were older than patients with a shorter psoriasis history (67.6 versus 54.9 years).

Table 2. Treatment characteristics.

<table>
<thead>
<tr>
<th>Treatment characteristics</th>
<th>n = 118</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nature of treatment, no. (%)</td>
<td></td>
</tr>
<tr>
<td>Etanercept only</td>
<td>94 (80)</td>
</tr>
<tr>
<td>Efalizumab, followed by etanercept</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Efalizumab only</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Etanercept, followed by efalizumab</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Infliximab only</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Efalizumab, followed by infliximab</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Number of treatment episodes</td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>112</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>24</td>
</tr>
<tr>
<td>Infliximab</td>
<td>5</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1</td>
</tr>
<tr>
<td>All</td>
<td>142</td>
</tr>
<tr>
<td>Duration of treatment episodes* (years), mean ± SEM</td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>1.6 ± 0.1</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Infliximab</td>
<td>0.7 ± 0.3</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1.0</td>
</tr>
<tr>
<td>All</td>
<td>1.8 ± 0.1</td>
</tr>
</tbody>
</table>

*Data are influenced by duration of follow-up and therapy status. SEM, Standard Error of the Mean.
PART II

Long-term efficacy of etanercept

Efficacy results of a 156-week etanercept treatment period are represented in Figure 1. Of all 111 etanercept-treated patients, 63 (57%) were treated for longer than 72 weeks. Mean PASI at baseline for this group was 16.6. Mean weekly dosage of etanercept was 60.4 milligram. After 24 weeks of treatment, an absolute decrease in PASI of approximately 10 points was established (interpolated mean week 24 PASI: 7.2). This effect remained stable during the next 132 weeks. At analysis, 9 patients of the surveyed subgroup had discontinued etanercept treatment as a result of lack of efficacy (n = 4), adverse events (n = 4) or both (n = 1). Furthermore, 6 patients were lost to follow up and one patient had temporarily interrupted etanercept therapy due to a desire to become pregnant.

Figure 1. Efficacy of three-year etanercept treatment.

Serious adverse events

Serious adverse events occurred in 22 patients. Fifteen patients were admitted to the hospital at least once. In total, 23 periods of hospital admission were required, i.e. as a result of an exacerbation of psoriasis (etanercept, n = 10; efalizumab, n = 4; infliximab, n = 3; adalimumab, n = 1), muscle and joint complaints (efalizumab, n = 2), cerebrovascular accident (etanercept, n = 1), pneumonia (etanercept, n = 1) and infusion reaction (infliximab, n = 1). Psoriasis exacerbations occurred as a result of erysipelas during etanercept
treatment \((n = 1)\), inefficacy of efalizumab \((n = 4)\), prolonged infliximab interruption period \((n = 1)\), or for no apparent reason \((n = 12)\).

### Table 3. Mean Psoriasis Area and Severity Index reduction at week 24 stratified by patient characteristics.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>No. of patients (%)</th>
<th>PASI reduction (%), mean ± SEM</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>59 (66)</td>
<td>61.6 ± 4.1</td>
<td>0.456</td>
</tr>
<tr>
<td>Female</td>
<td>31 (34)</td>
<td>56.1 ± 6.1</td>
<td></td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 50</td>
<td>44 (49)</td>
<td>58.4 ± 5.2</td>
<td>0.717</td>
</tr>
<tr>
<td>≤ 50</td>
<td>46 (51)</td>
<td>60.9 ± 4.9</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline PASI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 20</td>
<td>34 (38)</td>
<td>67.6 ± 4.9</td>
<td>0.072</td>
</tr>
<tr>
<td>≤ 20</td>
<td>56 (62)</td>
<td>54.9 ± 4.6</td>
<td></td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 30</td>
<td>32 (36)</td>
<td>53.0 ± 6.7</td>
<td>0.146</td>
</tr>
<tr>
<td>≤ 30</td>
<td>58 (64)</td>
<td>63.4 ± 3.8</td>
<td></td>
</tr>
<tr>
<td><strong>Previous systemic treatments, no.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 5</td>
<td>32 (36)</td>
<td>62.2 ± 5.9</td>
<td>0.588</td>
</tr>
<tr>
<td>≤ 5</td>
<td>58 (64)</td>
<td>58.3 ± 4.3</td>
<td></td>
</tr>
<tr>
<td><strong>Psoriasis duration, years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 20</td>
<td>48 (53)</td>
<td>64.1 ± 4.2</td>
<td>0.170</td>
</tr>
<tr>
<td>≤ 20</td>
<td>42 (47)</td>
<td>54.6 ± 5.6</td>
<td></td>
</tr>
</tbody>
</table>

PASI, Psoriasis Area and Severity Index; SEM, Standard Error of the Mean.

Eight episodes of malignancies were found in 6 patients, and included basal cell carcinomas (etanercept, \(n = 3\)), squamous cell carcinomas (etanercept, \(n = 2\); efalizumab, \(n = 1\)), breast cancer (etanercept) and an oesophageal carcinoma (etanercept). Two female patients died of a sudden cardiac arrest during etanercept treatment. One had a history of hypertension and stroke, and the other had chronic obstructive pulmonary disease. Whether the cardiac arrests were induced by a preceding myocardial infarction is unclear. Mild adverse events were of the same nature as outlined in the previous study,\(^6\) and are therefore not represented.

### Discussion

The aim of the current prospective observational cohort study was to present short- and long-term efficacy and safety data on biological treatment for patients with high-need
psoriasis in daily practice, and to investigate the influence of patient characteristics on therapy response. As most patients were treated with etanercept, and most long-term data were available from this group, efficacy analyses focused on etanercept therapy. In the current study, daily practice efficacy and safety results of etanercept treatment for up to three years were represented.

Long-term efficacy analysis showed a mean PASI improvement of approximately 57% after 24 weeks of etanercept treatment. Efficacy results may be overestimated, as only patients with available long-term efficacy data were included for analysis. The effect remained stable during the next 132 weeks of treatment, which leads to the conclusion that etanercept has the potential to improve psoriasis symptoms for a considerable time. However, although patients encountered a significant PASI improvement, an absolute PASI of approximately 7.0 remained. For patients expecting their psoriasis to be cleared by biological therapy, such a residual psoriasis could be a major disappointment. Moreover, a significant PASI residue makes addition of other topical or systemic antipsoriatic treatments necessary in some cases. Notifying patients about the chance that their psoriasis will not entirely be cleared by biological treatment is therefore essential.

Long-term daily practice treatment with etanercept was only occasionally accompanied by major safety concerns. Whether these are related to the use of etanercept is unclear, but a direct role for biologics on the incidence of serious adverse events seemed unlikely in most cases. Results of an integrated safety analysis showed that there were no signs of dose-related or cumulative toxicity over time with etanercept treatment for up to 144 weeks. In the current study, etanercept retained an apparently positive safety profile for up to 156 weeks.

No significant influence of gender, age, baseline PASI, BMI, number of previous systemic therapies or duration of psoriasis was found on week 24 efficacy results, although trends were discernible. Patients with a baseline PASI above 20 showed a greater mean percentage PASI reduction than patients with a baseline PASI below 20. This can be explained by the phenomenon called 'regression to the mean', as outlined by Wolfe et al. According to Hick and Feldman, this is caused by 'eligibility creep', the tendency for patients to have higher measured severity at initial assessment visits when eligibility is determined. Obese patients tended to demonstrate lower efficacy response compared with patients with BMI beneath 30 kg/m². Recently, Clark and Lebwohl concluded from a literature analysis that etanercept may have compromised efficacy in heavier individuals. Efficacy of etanercept was lower in patients with psoriasis duration shorter than 20 years compared with patients with a longer psoriasis duration. The hypothesis that an extensive systemic treatment history might lead to resistance for newly described systemic therapies
seems thus rejected. In contrast, some patients with psoriasis may be more resistant to systemic treatments than others, which leads to fast switches in systemic treatments, and consequently a shorter medication history until eligibility for biological treatment.

Patients treated with biologics had an extensive medical history, especially in the field of cardiovascular diseases. Although not investigated in the current study, the impact of these comorbidities (obesity excluded) on the course of biological treatment seems indifferent in daily practice. However, concurrent medical complaints related to pre-existing diseases may be wrongfully interpreted as side effects of biological treatment, sometimes leading to discontinuation of medication. Reviewing general health before and during biological therapy is therefore required.

In conclusion, this three-year analysis of biological treatment in patients with psoriasis shows that etanercept is able to produce a sustained efficacy in long-term clinical therapy up to 156 weeks. During long-term treatment, serious side effects are infrequent, and the influence of patient characteristics on treatment outcome is limited. As long-term efficacy and safety data of biological therapies are difficult to gain from randomized controlled trials, continuous, prospective registration of patient and treatment data in daily practice is essential.
PART II

References
Etanercept combined with methotrexate for high-need psoriasis

Abstract

Background: For some high-need psoriatic patients, the efficacy of etanercept monotherapy is insufficient. In these cases it might be indicated to combine etanercept with other conventional treatments.

Objectives: To provide daily practice safety and efficacy data for etanercept and methotrexate combination therapy.

Methods: Data were extracted from an existing database, which contains prospective safety and efficacy data of all patients who were treated with etanercept in clinical practice. A case was defined as a patient using etanercept and methotrexate simultaneously for an indefinite period during follow-up. For all cases, baseline data, Psoriasis Area and Severity Index (PASI), adverse events and laboratory values were investigated. Furthermore, the influence of introduction and discontinuation of methotrexate on these parameters was analysed.

Results: Fourteen patients with simultaneous use of etanercept and methotrexate were selected. In 6 patients, methotrexate was introduced after etanercept to avoid further psoriasis deterioration, which resulted in an improvement of psoriasis in 4 of these patients. Eight patients were on methotrexate therapy before start of etanercept. Discontinuation of methotrexate in 6 of these patients resulted in a decrease in PASI improvement in 5 patients. Etanercept combined with methotrexate was well tolerated, and only mild adverse events were reported. No clinically significant changes in laboratory parameters occurred.

Conclusions: Results show that combining etanercept with methotrexate is reasonable when efficacy of etanercept monotherapy is insufficient, or when rapid deterioration of psoriasis after abrupt discontinuation of methotrexate is expected. Laboratory values and adverse events were not different from what would have been expected when using methotrexate alone.

Introduction
Psoriasis is a common skin disease, affecting people in different ways, varying from a limited number of small erythematous plaques to lesions covering large body surface areas. Some severely affected patients have been designated as ‘high need’, defined by failure of at least two conventional systemic therapies due to lack of efficacy, intolerance or contraindication. These patients are eligible for biological treatment, such as etanercept. Etanercept is a human tumor necrosis factor (TNF) receptor p75 Fc fusion protein that blocks interaction of TNF-α with cell surface TNF receptors. Etanercept has been proven highly effective for the treatment of psoriasis. For some high-need patients, however, efficacy of etanercept monotherapy is insufficient. In these cases it might be indicated to switch to an alternative biological therapy or to combine etanercept with other conventional treatments. So far, however, no evidence-based data are available on efficacy and safety of combinations of biologics with other systemic therapies for psoriasis. The concomitant use of etanercept and methotrexate has already been studied for rheumatoid arthritis. In these studies, the combination of etanercept and methotrexate was significantly more effective than methotrexate or etanercept alone. For psoriasis, no such studies have been performed yet.

In this report we describe our experience in treating 14 high-need psoriatic patients with a combination of etanercept and methotrexate. The aim of this report is to provide daily practice safety and efficacy data for etanercept and methotrexate combination therapy.

Patients and methods
Data were extracted from an existing database. This database contains prospective, daily practice safety and efficacy data of all patients who were treated with etanercept at the Radboud University Nijmegen Medical Centre Department of Dermatology from February 2005. Patients were eligible for etanercept treatment if they had failed to respond to phototherapy, methotrexate and ciclosporin in the past, or if they had a contraindication to, or were intolerant of these treatments. At the same time, patients had to have a Psoriasis Area and Severity Index (PASI) of at least 10 at the time of screening.

In general, etanercept was given at a dosage of 50 milligram (mg) subcutaneously (SC) twice weekly for 12 weeks, followed by 25 mg SC twice weekly. Contraindications for etanercept treatment were an active infection or increased susceptibility for infections (including immunocompromised persons), a history of tuberculosis, the existence of a demyelinating disease and pregnancy. Relative contraindications were the existence of cardiac decompensation, a blood dyscrasia, a malignancy in recent history, the presence of an antinuclear antibody (ANA)-positive autoimmune disease or chronic exposure to...
actinic radiation in the past. Visits were scheduled every 4 weeks during the first 12 weeks, every 6 weeks until week 24 and every 12 weeks thereafter. Each visit, PASI and adverse events were documented. Laboratory tests were conducted, including haematological analysis, serum chemistry, urinalysis and ANA.

For this study, a case was defined as a patient using etanercept and methotrexate simultaneously for an indefinite period during follow-up. This implied either cases in which methotrexate was added to etanercept because of unsatisfactory response to etanercept monotherapy, or cases in which methotrexate was used and etanercept was started afterwards. The latter treatment schedule was obeyed to prevent severely affected patients from rebound after discontinuation of methotrexate. When etanercept was introduced successfully, an attempt was made to taper methotrexate.

For all cases, baseline data, PASI scores, adverse events and laboratory values were investigated retrospectively. Furthermore, the influence of introduction and discontinuation of methotrexate on these parameters was analysed.

**Results**

In total, 14 patients were treated simultaneously with etanercept and methotrexate. Six of these patients initially started on etanercept, and methotrexate was introduced later in the course of treatment due to insufficient efficacy of etanercept monotherapy (patients 1–6). In the other 8 patients, etanercept was introduced while patients were on methotrexate (patients 7–14). Patient 9 was treated with etanercept 25 mg twice weekly during the entire treatment period, in contrast to all other patients, who had initially been treated with etanercept 50 mg twice weekly for 12 weeks.

Baseline characteristics are represented in Table 1. Concomitant methotrexate dosages ranged from 2.5 to 35.0 mg per week (a maximum of 35.0 mg was used by a patient who accidentally raised the methotrexate dosage up to 14 tablets). The mean weekly dosage ranged from 7.5 to 21.4 mg in this group.

The influence of introduction of methotrexate during etanercept therapy on efficacy parameters is shown in Figure 1. In 6 patients (patients 1–6), methotrexate was introduced to avoid further psoriasis deterioration. This immediately resulted in an improvement of psoriasis, and therefore, better treatment efficacy outcomes in 4 of these patients (patients 2–4 and 6). Patient 1 preferred to cease etanercept shortly after the introduction of methotrexate to be able to start another antipsoriatic treatment. For patient 5, high-dose methotrexate was necessary to reverse the worsening of psoriasis. The mean duration of combination therapy was 40.8 weeks (range 6.0–73.9) (Figure 1).
PART II

Table 1. Baseline demographic data and disease characteristics.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yrs)</th>
<th>Gender</th>
<th>Psoriatic arthritis</th>
<th>Duration of psoriasis (yrs)</th>
<th>Baseline PASI</th>
<th>MTX weekly dosage, mean (mg)</th>
<th>MTX weekly dosage, range (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>Male</td>
<td>No</td>
<td>14</td>
<td>10.6</td>
<td>7.5</td>
<td>7.5</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>Female</td>
<td>No</td>
<td>4</td>
<td>31.8</td>
<td>14.2</td>
<td>15.0 - 12.5</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>Male</td>
<td>No</td>
<td>39</td>
<td>19.0</td>
<td>15.6</td>
<td>10.0 - 35.0</td>
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<td>4</td>
<td>42</td>
<td>Female</td>
<td>No</td>
<td>24</td>
<td>18.3</td>
<td>9.7</td>
<td>7.5 - 10.0</td>
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<tr>
<td>5</td>
<td>45</td>
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<td>25</td>
<td>19.8</td>
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<td>6</td>
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<td>-</td>
<td>-</td>
<td>22</td>
<td>24.1</td>
<td>12.4</td>
<td>-</td>
</tr>
<tr>
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<td>Male</td>
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<td>21</td>
<td>15.9</td>
<td>9.0</td>
<td>5.0 - 10.0</td>
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<td>7.5 - 20.0</td>
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<td>Male</td>
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<td>8</td>
<td>16.8</td>
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<td>2.5 - 22.5</td>
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<td>14</td>
<td>38</td>
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<td>22</td>
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<td>5.0 - 10.0</td>
</tr>
<tr>
<td>Mean 7-14</td>
<td>44</td>
<td>-</td>
<td>-</td>
<td>19</td>
<td>18.5</td>
<td>12.6</td>
<td>-</td>
</tr>
</tbody>
</table>

*At start of etanercept. Yrs, years; PASI, Psoriasis Area and Severity Index; MTX, methotrexate; Mg, milligram.

Figure 1. Influence of introduction of methotrexate on efficacy results.

Labels indicate patient number and moment of introduction of methotrexate. *Introduction of methotrexate 15 mg/week. **Introduction of methotrexate 25 mg/week. PASI, Psoriasis Area and Severity Index.
Patients 7–14 were on methotrexate therapy before start of etanercept. Methotrexate was discontinued in 6 of these patients (patients 7, 9, 10, 12–14). This resulted in a decrease in PASI improvement in 5 patients (patients 7, 9, 10, 12 and 13). For patient 8, efficacy of etanercept in combination with methotrexate was disappointing, and for this reason both therapies were ceased. Methotrexate tapering is still ongoing for patient 11. The mean period of treatment overlap was 42.7 weeks (range 1.6–99.4) (Figure 2).

**Figure 2. Influence of withdrawal of methotrexate on efficacy results.**

![Graph showing influence of withdrawal of methotrexate on efficacy results.](image)

Labels indicate patient number and moment of withdrawal of methotrexate. In patient 8, both etanercept and methotrexate were ceased. Methotrexate tapering is still ongoing for patient 11. PASI, Psoriasis Area and Severity Index. For more detailed figures, please see original article (Br.J.Dermatol. 2008; 159: 460-3).

Etanercept combined with methotrexate was well tolerated, and only mild adverse events were reported. Five patients had gastrointestinal complaints that possibly were related to the use of methotrexate, including the patient who used 35.0 mg of methotrexate. Diagnosed infections included folliculitis, herpes labialis and two urinary tract infections. Other infection-like symptoms, such as sore throat, common cold and influenza, were reported 12 times. Two patients showed actinic keratoses. No malignancies were seen, especially no skin malignancies.

Laboratory results demonstrated liver function abnormalities (increase in alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase or lactate dehydrogenase) in 5 patients. For three of these patients a relationship with the concomitant
use of methotrexate was suspected, but discontinuation of methotrexate was unnecessary in these cases. All other laboratory abnormalities were considered clinically insignificant.

Discussion
This case series shows efficacy and safety results of combination treatment of 14 patients with high-need psoriasis with etanercept and methotrexate in daily practice. Results show that combining etanercept with methotrexate is reasonable when efficacy of etanercept monotherapy is insufficient, even when methotrexate is introduced half way through the etanercept treatment course. Furthermore, overlapping with methotrexate while introducing etanercept treatment is useful when deterioration of psoriasis after abrupt discontinuation of methotrexate is expected. Laboratory values and adverse events for etanercept therapy combined with methotrexate are not different from what would have been expected when using methotrexate alone.

The improvement of efficacy results after introduction of methotrexate or the decrease in efficacy after discontinuation of methotrexate could be explained by the individual effects of methotrexate. However, all patients included in this report had been treated with methotrexate in the past, and this had been unsuccessful or unsatisfactory in all cases. Combination of etanercept and methotrexate has been proven more effective than methotrexate or etanercept alone for the treatment of rheumatoid arthritis.4-7 This is probably due to the additive effect of etanercept and methotrexate, as both therapies intervene in the pathogenesis of rheumatoid arthritis in different manners.9-11 Methotrexate was first introduced as an antiproliferative agent that inhibits the synthesis of purines and pyrimidines. Nowadays, it has become clear that many of the anti-inflammatory effects of methotrexate are mediated by adenosine.9 As the mechanism with which methotrexate induces the anti-inflammatory effect is different from that of etanercept, an additive effect of methotrexate on etanercept could be expected in psoriasis as well.

Risk profiles of etanercept and methotrexate are essentially different and no interactions between these drugs have been described. Use of methotrexate is associated with potentially serious side effects such as bone marrow toxicity, hepatotoxicity and nephrotoxicity, whereas use of etanercept is not.2,11,12 However, combining medicines that act on different components of the immune system could theoretically result in massive immune suppression, and consequently an increased risk for infections and malignancies. Furthermore, long-term use of methotrexate can lead to persistent organ damage as liver fibrosis, although this is relatively infrequent.13 This case series did not reveal serious infections, malignancies or other serious adverse events, not even in those patients who had combination therapy for a long period of time.
Whether the combination of etanercept and methotrexate is more effective for the treatment of psoriasis than etanercept or methotrexate alone needs further double-blind, controlled investigation in large groups of patients. Also, controlled trials are required to investigate safety issues of etanercept and methotrexate combination therapy. The present study describes the first case series in which combination of etanercept and methotrexate in patients with high-need psoriasis is evaluated.
References


CHAPTER 10

Extent and clinical consequences of antibody formation against adalimumab in patients with plaque psoriasis

Abstract

Objectives: To investigate the extent antibodies to adalimumab are formed in patients with plaque psoriasis and to study whether these antibodies have clinical consequences. Also, to examine the relationship between antibodies to adalimumab and adalimumab trough titers.

Design: Prospective observational cohort study.

Setting: Two Dutch dermatology departments in university hospitals.

Patients: All consecutive patients starting a regimen of adalimumab for chronic plaque psoriasis. Patients were screened and fulfilled the Dutch reimbursement criteria for adalimumab to treat psoriasis.

Intervention: Adalimumab treatment (per label).

Main outcome measure: The titer of antibodies to adalimumab, the adalimumab trough concentration, and the Psoriasis Area and Severity Index at weeks 12 and 24.

Results: Antibodies to adalimumab were detected in 13 of 29 patients (45%) during 24 weeks of treatment. Differences in response rates among patients with low, high and no titers of antibodies to adalimumab were significant at weeks 12 and week 24 ($p = 0.04$ and $p < 0.001$, respectively). The median adalimumab trough concentrations varied significantly among patients with low, high and no titers of antibodies to adalimumab (1.30 [range, 0.01-5.50], 0.0 [range 0.0-0.0], and 9.6 [range 0.0-22.6] mg/l, respectively; $p < 0.001$). At week 24, the median adalimumab trough concentrations differed significantly among good responders, moderate responders and non-responders (9.7 [range 0.0-22.6], 8.9 [range 3.2-12.6], and 0.0 [range 0.0-13.3] mg/l, respectively; $p = 0.01$).

Conclusion: Antibodies to adalimumab are associated with lower serum adalimumab trough concentrations and with non-response or loss of response to adalimumab in patients with plaque psoriasis.

PART II

Introduction
Antibodies to adalimumab have been associated with non-response or loss of initial response to adalimumab in a substantial portion of patients with rheumatoid arthritis and Crohn’s disease. Adalimumab is a fully humanized monoclonal immunoglobulin (Ig)G1 antibody and tumor necrosis factor α (TNF-α) antagonist; its indication was extended for treatment of moderate to severe chronic plaque psoriasis in 2008. Treatment of psoriasis with adalimumab has shown promising results in phase III trials. Some patients with plaque psoriasis do not respond to adalimumab, or they no longer respond to adalimumab treatment despite initial good results. The mechanism of antibody formation is assumed to have a role in these patients. Because adalimumab, with other biological agents, represents the end of the therapeutic spectrum for treatment-resistant moderate to severe plaque psoriasis, it is important to identify factors that may impair the clinical response. Further research may then lead to treatment optimization.

The objectives of this study were to investigate the extent antibodies to adalimumab are formed in patients with plaque psoriasis and to study whether these antibodies have clinical consequences. Another objective was to examine the relationship between antibodies to adalimumab and adalimumab trough titers. Therefore, we evaluated adalimumab trough concentration and concentration of antibodies to adalimumab relative to clinical response in a cohort of patients with plaque psoriasis and up to 24 weeks of adalimumab treatment.

Patients and Methods

Patients
This prospective observational cohort study in The Netherlands consisted of all consecutive patients with plaque psoriasis starting a regimen of adalimumab at the Departments of Dermatology of the Academic Medical Center in Amsterdam and the Radboud University Nijmegen Medical Centre in Nijmegen. Patients were treated with adalimumab 40 mg every other week after an initial dose of 80 mg and a dose of 40 mg the week thereafter. In patients with an inadequate response as judged by the treating physician, the dosing interval of adalimumab could be reduced to once weekly. The study was approved by the medical ethics committees of both hospitals and all patients gave written informed consent.

Clinical response
Disease severity was assessed at baseline, at week 12, and at week 24 using the Psoriasis Area and Severity Index (PASI), which is the most commonly used outcome measure in
trials of antipsoriatic agents.\textsuperscript{7} Response was measured as the percentage improvement in PASI compared with baseline. Patients were classified as non-responders (< 50% improvement in PASI compared with baseline [\(<\) PASI 50]), moderate responders (\(\geq\) PASI 50 to < PASI 75 improvement), or good responders (\(\geq\) PASI 75 improvement). The PASI assessment was performed before serum sample analysis.

\textit{Measurement of adalimumab concentrations}

Blood was drawn at an adalimumab trough concentration (just before administration of adalimumab) 12 and 24 weeks after initiation of treatment. The samples were frozen and analysed when all sampling was completed. The laboratory had no access to clinical data at the time of analysis. Adalimumab trough concentrations were measured by enzyme-linked immunosorbent assay (ELISA), based on the principle that adalimumab is captured through its ability to bind tumor necrosis factor. Adalimumab trough concentrations were quantified as described previously.\textsuperscript{2} Adalimumab binding was assessed by incubation with biotinylated rabbit IgG directed to the adalimumab idiotype. The detection limit of the assay is approximately 0.001 milligram/liter (mg/l).

\textit{Measurement of antibodies against adalimumab}

Concentrations of antibodies to adalimumab were measured using a radioimmunoassay. The assay measures specific high-avidity IgG antibodies to adalimumab by an antigen-binding test as described previously.\textsuperscript{2} Because the presence of adalimumab interferes with the assay, concentrations of antibodies to adalimumab in patients with high concentrations of adalimumab are underestimated or undetectable. Therefore blood was drawn at the adalimumab trough concentration. The antibody test was considered positive when the concentration of antibodies to adalimumab exceeded 12 arbitrary units/millilitre (AU/ml), which was previously shown to be the mean +6 standard deviations of the pretreatment values.\textsuperscript{2} In a previous study, the serum concentrations of antibodies to adalimumab showed two clusters, which could be separated at a cutoff value of 100 AU/ml.\textsuperscript{2} In our cohort, the concentrations of antibodies to adalimumab also naturally formed two clusters; therefore, we used the same cutoff points for titers of antibodies to adalimumab. A concentration between 12 and 100 AU/ml was considered a low titer of antibodies to adalimumab, and a concentration above 100 AU/ml was considered a high titer of antibodies to adalimumab.

\textit{Statistical analysis}

For differences between groups, we used independent samples t-test, chi-square test, the Mann-Whitney U test, or Kruskal-Wallis test, as appropriate. The threshold for significance
was set at $p < 0.05$. To analyse clinical response in patients with and without antibodies to adalimumab after 24 weeks of treatment for patients who stopped treatment, we used the last observation carried forward method.

Results

**Patient characteristics**

Most patients in the cohort were male (69% [20 of 29]), with a mean age of 44 years (Table 1). The mean disease severity on the PASI at baseline was 15.5, and the mean disease duration was 22 years. One patient scored only 3 on the PASI at baseline because she had switched from etanercept, to which her psoriasis responded, but her arthritis did not. Patients did not respond to a mean of 4.2 previous systemic therapies, including phototherapy. Among all patients, 17% (5 of 29) were also diagnosed as having psoriatic arthritis. At baseline, one patient used concomitant fumaric acid, one patient used concomitant acitretin, and three patients used concomitant methotrexate (mean dosage, 12 milligram/week). Most patients used concomitant topical therapies.

There were no significant differences between patients with and without antibodies to adalimumab in mean age, proportion of male sex, PASI at baseline, body mass index, proportion of patients with psoriatic arthritis, or number of previous systemic therapies. Table 1 gives the patient characteristics of the total cohort, and separated for patients with or without antibodies to adalimumab.

**Clinical response**

At week 12, 14 of 28 patients (50%) were moderate responders, 9 (32%) were good responders and 6 (21%) had even reached 90% improvement compared with baseline (data are missing for one patient). Twenty-seven of 29 patients were still receiving adalimumab at week 24.

Two patients discontinued receiving adalimumab because of its ineffectiveness as decided by the treating dermatologist after 14 and 16 weeks. At week 24, 16 of 29 patients (53%) were moderate responders, 10 (34%) were good responders, and 4 (14%) had reached 90% improvement compared with baseline. At week 24, half of the non-responders had reached 40% improvement compared with baseline.

Most patients who were good responders at week 12 ($n = 9$) were still good responders at week 24 ($n = 7$). Likewise, most of the non-responders at week 12 ($n = 14$) remained non-responders at week 24 ($n = 8$).
Table 1. Clinical characteristics of patients at baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total cohort (n = 29)</th>
<th>Antibodies to adalimumab Patients with (n = 13)</th>
<th>Patients without (n = 16)</th>
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</thead>
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<tr>
<td>Age, mean (SD), years</td>
<td>44 (11)</td>
<td>47 (13)</td>
<td>42 (10)</td>
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<tr>
<td>Male sex, no. (%)</td>
<td>20 (69)</td>
<td>8 (62)</td>
<td>12 (75)</td>
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<td>Disease duration, mean, years</td>
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<td>Psoriasis Area and Severity Index, mean</td>
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<td>16.2</td>
<td>14.9</td>
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<td>Body mass index×</td>
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<td>30</td>
<td>28</td>
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<tr>
<td>Diagnosed as having psoriatic arthritis, no (%)</td>
<td>5 (17)</td>
<td>3 (23)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Concomitant methotrexate, no (%)</td>
<td>3 (10)</td>
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<td>Previous systemic therapies, no (%)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
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<td>12 (92)</td>
<td>16 (100)</td>
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<td>Ciclosporin</td>
<td>19 (66)</td>
<td>9 (69)</td>
<td>10 (63)</td>
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<td>12 (92)</td>
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<td>PUVA</td>
<td>19 (66)</td>
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<td>Mean no. of previous therapies</td>
<td>4.2</td>
<td>4.6</td>
<td>3.9</td>
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</table>

No data differed significantly between patients with and without antibodies to adalimumab except for the proportion of patients previously treated with etanercept (p = 0.02). Last observation carried forward method was used in two patients; if applicable. ×Calculated as weight in kilograms divided by height in meters squared. SD, Standard Deviation; UVB, Ultraviolet B; PUVA, Psoralen-Ultraviolet A.

Concentrations of antibodies to adalimumab

During 24 weeks of follow-up, antibodies to adalimumab were detected in 13 of 29 patients (45%). Seven patients had antibodies to adalimumab at week 12, and another 6 patients at week 24. At week 12, 2 of 25 patients (8%) had a low titer of antibodies to adalimumab (range, 13-21 AU/ml), and 5 (20%) had a high titer of antibodies to adalimumab (range, 340-7300 AU/ml). At week 24, 6 of 29 patients (21%) had a low titer of antibodies to adalimumab (range, 15-54 AU/ml), and 7 (24%) had a high titer of antibodies to adalimumab (range, 1640-55700 AU/ml).

One patient with a high titer at week 12 (474 AU/ml) had a low titer at week 24 (30 AU/ml); he received adalimumab every week from weeks 8 through 24 and was treated with oral prednisone after week 12 for asthma. All other patients had increasing titers of antibodies to adalimumab over time. The three patients who took concomitant methotrexate did not develop antibodies to adalimumab.
Adalimumab trough concentrations

Adalimumab trough concentrations ranged from undetectable to 22.6 mg/l. In patients receiving adalimumab 40 mg every other week, the median adalimumab trough concentrations were 8.2 (range, 0.0-17.0) mg/l at week 12 and 4.8 (range, 0.0-22.6) mg/l at week 24. In Figure 1, the course of adalimumab trough concentrations is shown over 24 weeks in patients with and without antibodies to adalimumab. The median adalimumab trough concentrations varied significantly among patients with low, high, and no titers of antibodies to adalimumab (1.30 [range, 0.01-5.50], 0.0 [range, 0.0-0.0], and 9.6 [range, 0.0-22.6] mg/l, respectively; $p<0.001$).

Figure 1. Median adalimumab trough concentrations for patients with low, high and no titers of antibodies to adalimumab.

The median adalimumab trough concentrations were measured at weeks 12 and 24 for patients with low, high and no titers of antibodies to adalimumab. At weeks 12 and 24, the differences among the three groups were statistically significant ($p = 0.001$ and $p < 0.001$, respectively). For patients with high titers of antibodies to adalimumab, a positive adalimumab trough concentration could probably have been obtained shortly after baseline. The adalimumab trough concentration at baseline is assumed to be 0 based on previous studies and the fact that no patient had received adalimumab before baseline.

Increased dosing frequency of adalimumab

The adalimumab dosing interval was shortened in two patients at week 12 and in another seven patients between weeks 12 and 24 because of ineffectiveness as decided by the treating dermatologist. In these nine patients receiving adalimumab every week, the median adalimumab trough concentration was 1.7 (range, 0.0-13.3) mg/l at week 24. Adalimumab trough concentrations did not differ significantly between patients who used adalimumab every week versus every other week ($p = 0.54$). One patient was treated with adalimumab approximately once every 25 days between
weeks 12 and 24. This patient had no health care insurance and paid out of pocket for treatment. His adalimumab trough concentration was undetectable (without antibodies to adalimumab).

**Clinical response and concentrations of antibodies to adalimumab**

Among patients with a good response on the PASI at week 12, only one had detectable antibodies to adalimumab (13 AU/ml). Similarly, among patients with a moderate response, only one patient had detectable antibodies to adalimumab (21 AU/ml). At week 24, both patients had increased titers of antibodies to adalimumab and no longer responded to adalimumab treatment. Among patients with a good response on the PASI at week 24, there was again only one patient with detectable antibodies to adalimumab (41 AU/ml). Two patients who were moderate responders had detectable antibodies to adalimumab at week 24 (15 and 19 AU/ml). All patients with high titers of antibodies to adalimumab at weeks 12 or 24 were non-responders. However, not all non-responders had high titers of antibodies to adalimumab (Figure 2). Differences in response rates among patients with low, high and no titers of antibodies to adalimumab were significant at weeks 12 and week 24 \( (p = 0.043 \text{ and } p < 0.001, \text{ respectively}) \). Twelve of 17 patients (71%) without antibodies to adalimumab improved their response on the PASI between weeks 12 and 24, as opposed to 1 of 7 patients (14%) of patients with antibodies to adalimumab. Differences between responses at weeks 12 and 24 were not significant for either group.

**Clinical response and adalimumab trough concentration**

At week 12, non-responders had lower adalimumab trough concentrations than good responders (4.2 [range, 0.0-16.0] versus 11.0 [range, 1.0-17.0] mg/l; \( p = 0.046 \)). The median adalimumab trough concentration in moderate responders (4.4 [range, 1.0-10.0] mg/l) was not significantly different compared to the other groups. At week 24, the median adalimumab trough concentrations differed significantly among good responders, moderate responders, and non-responders (9.7 [range, 0-22.6], 8.9 [range, 3.2-12.6] and 0.0 [range, 0.0-13.3] mg/l, respectively, \( p = 0.01 \)) (Figure 3). Data from a patient with a typical antibody response are shown in Figure 4; as the level of antibodies to adalimumab increased, the PASI increased and the adalimumab trough concentration decreased.

**Discussion**

In this study, we have shown that antibodies to adalimumab are formed in a large portion of patients with plaque psoriasis; at the end of the study, 45% (13 of 29) of patients had developed antibodies to adalimumab. High titers of antibodies to adalimumab were
Figure 2. Percentages of non-responders, moderate responders, and good responders for patients with low, high and no titers of antibodies to adalimumab at week 24.

The difference among the three groups was statistically significant ($p < 0.001$).

particularly associated with undetectable adalimumab trough concentrations. We also showed that high titers of antibodies to adalimumab and low adalimumab trough concentrations were associated with impaired treatment outcome.

Response rates to adalimumab in this study are surprisingly lower than those in phase III trials, in which 53% and 71% of patients were good responders after 12 and 16 weeks, respectively, compared with 32% (9 of 28) of patients in our cohort after 12 weeks. At week 24, the percentages of good responders for the two phase III trials were 64% and 70%, compared with 35% (10 of 29) in our cohort. This might be the result of selected populations in phase III trials versus the ‘normal’ population with psoriasis having more comorbidities and concomitant medication. However, another factor may be the selection of patients in our cohort since they were treated in tertiary psoriasis referral centers, and some had previously failed other systemic therapies.

Twelve of 13 patients (92%) who developed antibodies to adalimumab had previously been treated with etanercept versus 8 of 16 patients (50%) who did not develop antibodies to adalimumab, which was a significant difference. This is a notable finding that needs further investigation. However, the test for antibodies to adalimumab is specific, and cross-
linking is unlikely. Furthermore, neutralizing antibodies to etanercept have not been demonstrated to date. As shown in patients receiving infliximab who develop antibodies to infliximab, we assume that adalimumab and antibodies to adalimumab form complexes. These complexes may be removed by the liver and the spleen. This would explain the undetectable serum adalimumab trough concentrations in patients with high titers of antibodies to adalimumab compared with the clearly detectable serum adalimumab trough concentrations in patients without antibodies to adalimumab.

Removal of the therapeutic agent by the formation of complexes would explain why all patients with high titers of antibodies to adalimumab were non-responders. It has been speculated that dose escalation may overload the capacity of the immune system to produce antibodies to adalimumab or may lead to immunological tolerance.
Figure 4. Data from a good responder at 12 weeks who developed a high titer of antibodies to adalimumab after week 12 and lost most response to treatment.

The proportion of our patients who developed antibodies to adalimumab is higher than that in other studies. In a phase III trial of patients treated with adalimumab for psoriasis...
that analysed antibody formation, only 8.8% of patients tested positive for antibodies to adalimumab.\textsuperscript{6} However, patients may have been tested for antibodies even if they had received only one dose of adalimumab. Furthermore, no specific details about the methods of antibody testing were given.

In a study by Bartelds et al.,\textsuperscript{17} 17% of patients with adalimumab-treated rheumatoid arthritis developed antibodies to adalimumab after 28 weeks.\textsuperscript{2} That study used the same assay and had practically the same set-up as in the present study. An explanation for the difference in results might be concomitant methotrexate use. Among patients with rheumatoid arthritis who used concomitant methotrexate, the percentage of patients with antibodies to adalimumab was significantly lower than the percentage of patients without antibodies to adalimumab (\( p = 0.003 \)). Of the patients using concomitant methotrexate (mean dosage, 19.4 mg/week), 12% developed antibodies to adalimumab versus 38% of patients receiving adalimumab monotherapy. Furthermore, concomitant low-dose methotrexate has been shown to reduce immunogenicity associated with infliximab treatment for rheumatoid arthritis.\textsuperscript{11} In our cohort, only three patients used concomitant methotrexate; none of these patients developed antibodies to adalimumab. However, the sample number is too small to statistically analyse the effect of methotrexate on development of antibodies to adalimumab in our cohort.

Another factor in antibody formation may be related to patient genetics.\textsuperscript{10} Further investigation of this theory is needed. Also requiring more study is the finding of non-responders to adalimumab therapy without evidence of antibody formation against adalimumab. The non-response of these patients cannot be explained based on current knowledge.

We analysed few patients in our study. However, the small sample size should not be considered a limitation because the data analysis demonstrated statistically significant differences. Nevertheless, multiple regression analysis with a larger cohort could detect factors that might affect antibody formation, such as concomitant methotrexate use and dosing interval changes.

In conclusion, antibodies to adalimumab are associated with lower serum adalimumab trough concentrations and with non-response or loss of response to adalimumab in patients with plaque psoriasis. We recommend testing for antibodies to adalimumab when patients lose response to adalimumab or do not respond at all, since spontaneous improvement is unlikely in the presence of high titers of antibodies to adalimumab. Further research is needed to identify risk factors for antibody development and factors affecting antibody development. Investigations are also needed to study how the effect of antibodies to adalimumab can be minimized.
PART II

References


ECONOMIC IMPACT OF PSORIASIS AND PSORIASIS TREATMENT

PART III
The economic impact of high-need psoriasis in daily clinical practice before and after the introduction of biologics

Abstract

Background: Although costs of biologics are high, effective treatment of patients with psoriasis may reduce the total health care costs, as it may limit the need for hospitalization.

Objective: To investigate the economic impact of psoriasis, including direct costs, before and after the introduction of biologics, with special focus on hospitalized patients, treatment effectiveness and patient satisfaction with medication.

Methods: A descriptive retrospective cohort study including 67 patients with high-need psoriasis was performed. Direct costs were investigated for the biological and pre-biological treatment period. Direct costs for a subgroup of hospitalized patients were analysed separately. Patient satisfaction with biological treatment was measured using the Treatment Satisfaction Questionnaire for Medication (TSQM) version II. Effectiveness of biological therapy was investigated by means of the Psoriasis Area and Severity Index (PASI).

Results: Mean total direct costs were €10,146.- per patient per year (PPPY) in the pre-biological treatment period, compared to €17,712.- PPPY in the biological treatment period. For 6 patients in the cohort, introduction of biologics lead to a reduction of direct costs, as these patients did not need long hospitalizations. Treatment with biologics led to a 66.4% decrease in PASI from 19.0 at start of biological therapy to 6.4 at analysis. Patient’s satisfaction with biologics was high, indicated by a mean TSQM score of 77.8.

Conclusions: Introduction of biological therapies may have cost-neutral or cost-saving effects for patients who otherwise require long hospitalization periods. Treatment with biologics proved effective and was accompanied by a high satisfaction for the patients.

PART III

Introduction

Psoriasis is a common chronic skin disease, which impairs patients' quality of life to a large extent.\(^1\) Several studies have indicated that psoriasis also has a relevant economic impact, generated by the expenditures for different treatments, diagnostic procedures, medical consultations and productivity losses.\(^2\) The economic impact of psoriasis seems to be larger as the severity of psoriasis increases.\(^7\) Recently, a cost-of-illness study in Italy revealed that the sum of direct and indirect costs for patients with severe psoriasis was €11,434.40 on average per year. As this study was performed before the introduction of biological therapies, none of the patients included had received such a therapy.\(^3\)

Since the beginning of 2005, biological therapies have been introduced for the treatment of moderate to severe psoriasis, including etanercept, efalizumab, infliximab, adalimumab and recently ustekinumab. These therapies have been proven highly effective, as they significantly improve patients' skin symptoms as well as quality of life.\(^8\) - \(^10\)

As a consequence of the high costs of biologics, strict reimbursement criteria for biological treatment are formulated in many countries. Nevertheless, direct medication costs for the treatment of immune-mediated diseases, have risen excessively since then. In The Netherlands, both etanercept and adalimumab are in the top 10 most expensive pharmaceuticals as well as in the top 10 pharmaceuticals with the biggest cost rise in 2008.\(^11\) However, effective treatment of patients with psoriasis may reduce other direct health care costs, as it potentially limits the need for labour-intensive and time-consuming treatments and hospital admissions. A longitudinal cohort study by Bhosle et al. showed that the introduction of a biologic resulted in a significant reduction in health care service utilization compared to the period before biological treatment.\(^12\)

In the current retrospective cohort study, the economic impact of psoriasis before and after the introduction of biologics was investigated. In contrast to most other pharmacoeconomic studies, this study was performed in a real life care setting. Direct costs for both the biological and pre-biological treatment period were calculated for the same patients with high-need psoriasis. The current study focussed specifically on direct costs for a subgroup of hospitalized patients. Furthermore, biological treatment effectiveness and patient satisfaction with biological therapies was evaluated.

Patients and methods

Setting and population

A retrospective cohort analysis comprised all patients with psoriasis treated with biologics...
at the Radboud University Nijmegen Medical Centre Department of Dermatology between February 2005 and February 2009. Patients were eligible for biological treatment if they had failed to respond to phototherapy, methotrexate and ciclosporin in the past, or if they had a contraindication to, or were intolerant of these treatments. At the same time, patients had to have a minimum Psoriasis Area and Severity Index (PASI)\textsuperscript{13} of 10 at the time of screening.

**Outcome measures**

Charts were reviewed from the very first hospital visit for psoriasis up to the final hospital visit (this latter taking place between October 2008 and February 2009) for demographic data, topical and systemic medication history, number of diagnostic procedures, and number and duration of in- and outpatient hospital visits. Episodes of clinical trial participation were not included. Measures that were determined before initiation of biological treatment were considered as belonging to the pre-biological treatment period; measures that were determined after this date were considered as belonging to the biological treatment period. The end of the biological treatment period was defined as the final documented hospital visit for psoriasis. At this visit, patients were asked to fill out the Treatment Satisfaction Questionnaire for Medication (TSQM) version II. The TSQM is a generic measure of treatment satisfaction for medication, including questions on effectiveness, side effects, convenience and global satisfaction, generating scores ranging from 0 (extremely dissatisfied) to 100 (extremely satisfied).\textsuperscript{14}

Efficacy of treatment in the biological therapy period was represented by the percentage decrease in PASI from baseline (start of biological therapy) at the final visit, and by the percentage of patients who achieved a 50% and 75% reduction in PASI (PASI 50 and PASI 75, respectively) relative to baseline. These measures were already prospectively collected in the light of a registry including the same patients.

**Analysis**

As costs for biological treatment are generally higher in the initial treatment phase compared with the maintenance phase, only patients who were treated with biologics for at least one year, and for whom data for at least one year of the pre-biological treatment period were available were included for analysis. Direct costs were calculated for both the biological and pre-biological treatment period by multiplying the quantity of medication used, the number of diagnostic procedures, and the number and duration of hospital visits by prices published by the Dutch Health Care Insurance Board (College Voor Zorgverzekeringen).\textsuperscript{15} Costs for topical therapies were estimated by multiplying the number of prescriptions by
the price of 60 grams of ointment. Emollients or over-the-counter (OTC) medicines were not included for analysis. Costs for ultraviolet (UV) therapies were calculated on the basis of a standard monthly price for treatment with a mean frequency of twice per week.\textsuperscript{16} The calculation of travelling expenses was performed through multiplication of the mean number of hospital visits a year by the travelling distance, multiplied by a fixed amount of €0.19 per kilometre. For each systemic therapy, the mean daily dose (MDD) in milligrams (mg) was determined. As the yearly expenses for biological treatment matched with the expenses for approximately 30 hospital admission days, the direct costs for patients who were admitted for more than 30 days per year on average in the pre-biological treatment period were analysed separately. 

All costs were presented as mean costs (in €) per patient per year (PPPY). Values were represented as mean (range; 95% confidence interval [CI]). Statistical analysis was carried out using descriptive statistics.

Results

Patient and treatment characteristics

In total, 140 charts of patients treated with biologics were reviewed. Of these charts, 67 were suitable for analysis, as patients were followed for at least one year before and after the introduction of biologics. Forty-four patients were male and 23 were female. Mean age at the start of the biological treatment period was 47.9 (range 21.7-71.8; 95% CI 45.1-50.7) years. Mean follow-up duration was 6.6 (range 1.0-35.5; 95% CI 5.1-8.2) years of the pre-biological treatment period and 2.6 (range 1.0-4.5; 95% CI 2.4-2.8) years of the biological treatment period. Mean PASI at start of the biological treatment period was 19.0 (range 5.9-45.2; 95% CI 16.8-21.2).

Of all patients, 64 were treated with etanercept, 20 with efalizumab, 12 with adalimumab, and 4 with infliximab (Table 1). Forty-two patients were treated with only one biologic, mostly etanercept; 19 were treated with two different biologics; 6 were treated with three or four different biologics. The final biological therapy before analysis comprised etanercept in 48 patients, adalimumab in 12 patients, efalizumab in 6 patients, and infliximab in one patient. Conventional systemic therapies included methotrexate, ultraviolet B (UVB), acitretin, ciclosporin, fumaric acid, psoralen-ultraviolet A (PUVA), hydroxyurea, mycofenolate mofetil and tacrolimus.

Mean daily dose of each therapy used is reflected in Table 1. With regard to biological therapies, this was 8.8 mg for etanercept, 17.9 mg for efalizumab, 3.8 mg for adalimumab, and 11.2 mg for infliximab (after extrapolation of the costs).
Table 1. Nature and costs of systemic therapies (daily clinical practice use).

<table>
<thead>
<tr>
<th></th>
<th>Pre-biological treatment period</th>
<th>Biological treatment period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>Mean costs/patient/year (€)</td>
</tr>
<tr>
<td>Conventional systemic therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>57</td>
<td>97</td>
</tr>
<tr>
<td>UVB</td>
<td>39</td>
<td>1,105</td>
</tr>
<tr>
<td>Acitretin</td>
<td>34</td>
<td>804</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>34</td>
<td>3,099</td>
</tr>
<tr>
<td>Fumaric acid</td>
<td>25</td>
<td>205</td>
</tr>
<tr>
<td>PUVA</td>
<td>11</td>
<td>1,160</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mycofenolate mofetil</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Biological therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etanercept</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infliximab</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Calculated as total costs/total period of actual drug use. †Costs for UV therapies were calculated on the basis of a standard monthly price for treatment in a mean frequency of twice per week. ‡Calculated on the basis of one ampoule of 125 milligrams per week. ‡Costs for infliximab were calculated by extrapolation of the costs for a year of therapy (actual treatment period was 157 days on average), and do not include costs for administration of infliximab. MDD (mg), Mean Daily Dose (milligram); UVB, Ultraviolet B; PUVA, Psoralen-Ultraviolet A.

Direct costs

Direct costs are outlined in Table 2. Mean total direct costs were €10,146.- (range 715-51,375; 95% CI 7,614-12,678) PPPY in the pre-biological treatment period, compared with €17,712.- (range 7,508-99,750; 95% CI 15,004-20,421) PPPY in the biological treatment period. This implies a significant mean rise in direct costs of €7,566.- PPPY. The rise in direct costs was mainly attributable to the expenses for biological therapies, i.e. €13,843.- (range 6,534-22,727; 95% CI 13,212-14,474) PPPY on average. The number of day care and hospital admission days per year was reduced by 94% (5.1 versus 0.3) and 64% (14.9 versus 5.4), respectively, after the introduction of biologics. Direct costs related to day-care admission decreased significantly during biological therapy (€1,167.- [range 0-6,903; 95% CI 827-1,506] PPPY versus €60.- [range 0-830; 95% CI 13-107] PPPY). When each patient was included for analysis, direct costs for hospitalization did not differ significantly. However, when excluding cost data on patient 10, which were much higher
Table 2. Direct costs.

<table>
<thead>
<tr>
<th></th>
<th>Pre-biological treatment period</th>
<th>Biological treatment period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volume^a</td>
<td>Costs^b</td>
</tr>
<tr>
<td>Treatment prescriptions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical therapies</td>
<td>21.7</td>
<td>138 (5-436; 113-163)</td>
</tr>
<tr>
<td>Conventional systemic therapies</td>
<td>1.1</td>
<td>607 (12-3,345; 438-775)</td>
</tr>
<tr>
<td>Biological therapies</td>
<td>0.0</td>
<td>0 (0-0; -)</td>
</tr>
<tr>
<td>Diagnostic procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>14.9</td>
<td>164 (20-1,203; 123-204)</td>
</tr>
<tr>
<td>Radiology</td>
<td>0.7</td>
<td>29 (0-129; 23-35)</td>
</tr>
<tr>
<td>Skin/liver biopsies</td>
<td>0.3</td>
<td>38 (0-286; 25-51)</td>
</tr>
<tr>
<td>Medical consultations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consultations of physician</td>
<td>7.6</td>
<td>757 (0-1,808; 677-837)</td>
</tr>
<tr>
<td>Day-care admission days</td>
<td>5.1</td>
<td>1,167 (0-6,903; 827-1,506)</td>
</tr>
<tr>
<td>Hospital admission days</td>
<td>14.9</td>
<td>7,098 (0-43,465; 4,675-9,522)</td>
</tr>
<tr>
<td>Travelling expenses</td>
<td>881.7^c</td>
<td>168 (0-1,196; 125-210)</td>
</tr>
<tr>
<td>Total direct costs</td>
<td>10,146</td>
<td>(715-51,375; 7,614-12,678)</td>
</tr>
</tbody>
</table>

^aMean volume per patient per year. ^bCosts are presented as means (in €) per patient per year (range; 95% confidence interval). ^cMean number of kilometres.
than for other patients (Table 3), a significant difference could be established (pre-biological
treatment period: €6,738.- [range 0-43,465; 95% CI 4,384-9,092], biological treatment
period: €1,475.- [range 0-21,517; 95% CI 564-2,385].

**Direct costs for subgroup of hospitalized patients**

As the yearly expenses for biological treatment matched with the expenses for
approximately 30 hospital admission days, direct costs for patients who were admitted
for more than 30 days per year on average in the pre-biological treatment period were
analysed separately. This subgroup comprised 12 patients. Median number of hospital
admission days was 53.0 PPPY in the pre-biological treatment period, compared with 5.3
PPPY in the biological treatment period. For 6 of the 12 patients the mean direct costs
per year declined after the introduction of biologics, as a consequence of the reduction
in hospital admission days. Five patients who were admitted for more than 30 days per
year on average in the pre-biological treatment period were not admitted during biological
therapy (Table 3). Patient 10 had an extremely severe therapy resistant psoriasis, and was
admitted frequently, even during biological therapy.

**Table 3. Direct costs for patients with hospital admission ≥ 30 days.**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Pre-biological treatment period</th>
<th>Biological treatment period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of daysa</td>
<td>Direct costsb</td>
</tr>
<tr>
<td>1</td>
<td>54.2</td>
<td>31,215</td>
</tr>
<tr>
<td>2</td>
<td>58.6</td>
<td>30,888</td>
</tr>
<tr>
<td>3</td>
<td>33.3</td>
<td>18,985</td>
</tr>
<tr>
<td>4</td>
<td>30.6</td>
<td>18,880</td>
</tr>
<tr>
<td>5</td>
<td>91.3</td>
<td>51,375</td>
</tr>
<tr>
<td>6</td>
<td>62.1</td>
<td>31,514</td>
</tr>
<tr>
<td>7</td>
<td>73.1</td>
<td>36,235</td>
</tr>
<tr>
<td>8</td>
<td>31.5</td>
<td>19,319</td>
</tr>
<tr>
<td>9</td>
<td>34.6</td>
<td>18,785</td>
</tr>
<tr>
<td>10</td>
<td>64.9</td>
<td>35,493</td>
</tr>
<tr>
<td>11</td>
<td>51.6</td>
<td>26,761</td>
</tr>
<tr>
<td>12</td>
<td>51.7</td>
<td>27,371</td>
</tr>
<tr>
<td>Median of 12 patients</td>
<td>53.0</td>
<td>29,130</td>
</tr>
</tbody>
</table>

*Mean number of hospital admission days per patient per year. *Mean costs (in €) per patient per year.
PART III

Patient satisfaction with biological therapy
Patients were highly satisfied with their biological therapies, reflected by the mean TSQM score for global satisfaction of 77.8 (range 0.0-100.0; 95% CI 72.3-83.4). Categorised TSQM questions on effectiveness, side effects and convenience showed a mean score of 71.3 (range 0.0-100.0; 95% CI 64.5-78.2), 95.5 (range 0.0-100.0; 95% CI 91.9-99.1) and 80.2 (range 50.0-100.0; 95% CI 76.5-83.9), respectively.

Effectiveness of biological treatment
The mean PASI at the start of the biological treatment period was 19.0 (range 5.9-45.2; 95% CI 16.8-21.2). This decreased to a score of 6.4 (range 0.0-26.6; 95% CI 5.1-7.6), indicating a mean improvement of 66.4%. Seventy-three percent of patients (n = 49) reached a PASI 50; forty-three percent (n = 29) reached a PASI 75.

Discussion
The current retrospective cohort study of the economic impact of psoriasis in a real life care setting shows that the direct costs, related to the treatment of high-need psoriasis in daily clinical practice, are significantly higher during the biological treatment period than during the period before. Although the direct costs for biological therapy were high (€13,843.- PPPY), there was a large decrease in costs for medical consultations during biological treatment, ultimately resulting in a mean rise in direct costs of €7,566.- PPPY (Table 2). The number of day care and hospital admission days in this period decreased by 94% and 64%, respectively. For 6 of the 67 patients in the cohort, introduction of biologics led to a reduction of direct costs, as these patients no longer needed long-term hospitalization. In accordance with previous studies, the introduction of biologics was accompanied by a distinct improvement of psoriasis signs, as reflected by a mean decrease in PASI of 66.4%. Moreover, patients appeared to be highly satisfied with biological treatment, as the TSQM score for global satisfaction was 77.8.

The outcomes are the results from an analysis of daily clinical practice data in patients with severe, classical-therapy resistant (high-need) psoriasis treated in a tertiary referral hospital with biologics for more than one year. Cost proportions may be different for patients with milder psoriasis and for treatment in primary or secondary care settings, as treatment schedules may be different. In the current study, the MDD for etanercept was 8.8 mg, i.e. 61.6 mg per week. Based on the mean follow-up duration of 2.6 years, the mean weekly etanercept dosage would normally be 54.4 mg, according to the dosage schedule of 50 mg twice weekly for 12
weeks followed by a dose of 25 mg twice weekly or 50 mg once weekly. The mean dosage of 61.6 mg per week equals this standard dosage regimen plus a dose increase from 50 mg to 100 mg for 20 weeks. So, in the current cohort the used etanercept dosage, and therefore the expense for biological therapy, is considerably higher than in randomized controlled trials. In a previous study we found that 35.5% of the patients, who were of the same cohort as that analysed currently, were obese. This may lead to an increase in the medication doses required for adequate therapy, and thus in medication costs.

Costs related to psoriasis comorbidities, such as psoriatic arthritis, were not included in the current analysis. In addition, OTC medicines were not taken into account, although a study by Javitz et al. revealed that the direct costs for OTC medication in psoriasis care are substantial. Direct costs may in fact be higher, though, both for the period before and the period after the introduction of biologics. Furthermore, specific OTC products may have antipsoriatic effects, thereby influencing ‘biological’ treatment effectiveness.

The design of the present study has certain limitations. Firstly, the retrospective design could give rise to inaccuracies during analysis. Obviously, a prospective study would have given more reliable data. It would be of great value if treatment effectiveness, quality of life and cost measures could be taken into account in prospective registries on systemic treatments for psoriasis in daily practice.

Secondly, only patients who received biologics for at least one year were included for analysis. For patients who did not continue treatment for at least one year, biological treatment may have been ineffective or not tolerated, which may influence the outcomes. However, only five of all 140 patients discontinued therapy before the period of one year as a result of ineffectiveness or intolerance. Other patients were lost to follow-up, or started biologics shortly before the analysis was performed.

Thirdly, the causality of biological treatment in the shifts of different cost aspects after the introduction of biological therapies is difficult to establish, as carryover effects may have taken place.

In conclusion, treatment of patients with psoriasis with biologics in daily practice is clinically effective with a substantial PASI decrease. It results in a rise in direct costs of €7,566.- PPPY on average. A small subgroup of patients who demonstrate a significant reduction in hospital admissions after the introduction of biologics even show a reduction in direct costs in this period. So, introduction of biological therapies for psoriasis may have cost-neutral or cost-saving effects for patients who otherwise require long hospitalizations. Additionally, treatment with biologics was accompanied by a high patient satisfaction.
PART III

References


Quintiles, Inc. at www.quintiles.com/TSQM or TSQM@quintiles.com.


PROCEDURES

VI TRAI

PROCEDURES ON RESEARCH APPLICATIONS IN DATA SURVEY
CHAPTER 12

Analysis of three-year national reimbursement application data on etanercept and efalizumab for psoriasis

Abstract

Background: Since September 2004, etanercept and efalizumab are approved by the European Union for the treatment of adult patients with moderate to severe plaque psoriasis. To obtain approval for reimbursement of these therapies, patients need to fulfil specific diagnostic, disease activity, and response criteria.

Objective: Aim of this analysis was to evaluate three-year Dutch reimbursement application data, which were applied for treatment of psoriasis with etanercept or efalizumab.

Methods: All applications for approval of treatment with etanercept and efalizumab between January 2005 and January 2008 were included. Data were analysed descriptively with regard to application characteristics, patient characteristics, disease activity measures, medication history, and response on therapy.

Results: Analysis was performed of 2,306 received applications, which included 1,197 patients with 1,327 initial treatment applications. 1,254 of all initial treatment applications and 812 of all follow-up applications were approved. According to the application data concerning medication history, phototherapy was used by most patients, followed by ciclosporin and methotrexate. A 50% reduction in Psoriasis Area and Severity Index after 12 weeks of treatment was achieved by 69.0% of all patients with an approved initial treatment application for etanercept, and by 50.0% of all patients with an approved initial treatment application for efalizumab.

Conclusions: The present analysis demonstrates that, as a consequence of strict adherence to reimbursement criteria, only 0.4% of Dutch patients with psoriasis are treated with etanercept or efalizumab. The question arises whether it is indicated to broaden these criteria, in particular considering the long-term and presumably safe control of psoriasis by biologics.

PART IV

Introduction
The past years have witnessed great advances in our knowledge of the pathogenesis of psoriasis, which has catalysed the development of targeted biological treatments, such as etanercept and efalizumab. Etanercept is a human tumor necrosis factor (TNF) receptor fusion protein, which competitively inhibits TNF-binding to its cell surface receptors and thereby inhibits the biological activity of TNF. Efalizumab is a recombinant humanized monoclonal antibody that inhibits the binding of lymphocyte function-associated antigen 1 (LFA-1) to intercellular adhesion molecule 1 (ICAM-1), which interferes with T lymphocytes adhesion to other cell types.

Since September 2004, etanercept and efalizumab are approved by the European Union for the treatment of adult patients with moderate to severe plaque psoriasis. As a consequence of the expense of these biological therapies, patients need to fulfil specific criteria to obtain approval for reimbursement in many countries. In The Netherlands, patients with psoriasis are considered for reimbursement of the cost of treatment with etanercept or efalizumab if they are unresponsive, intolerant or have contraindications to phototherapy, ciclosporin and methotrexate. Furthermore, a minimum Psoriasis Area and Severity Index (PASI) of 10 is required at the time of screening. A PASI between 8 and 10 in combination with a Skindex-29 of at least 35 is accepted as well. After 12 weeks of therapy, a PASI reduction of at least 50% (PASI 50) is necessary to demonstrate effectiveness of the prescribed drug and to get approval for long-term treatment and reimbursement.

Evaluation of these diagnostic, disease activity and response criteria in The Netherlands occurs centrally by a subcommittee of an independent foundation (Landelijke Beoordeling Aanvragen Geneesmiddelen [National Evaluation of Applications of Drugs], LABAG). This committee is appointed by health insurance companies and comprises representatives of dermatologists, rheumatologists, health insurance companies and the government.

Since the beginning of 2005, etanercept and efalizumab are reimbursed by Dutch health insurance companies for the treatment of patients with psoriasis. Therefore, reimbursement application data of three years are available at the moment.

Aim of this analysis was to evaluate three-year Dutch reimbursement application data, including diagnostic, disease activity, and response criteria, which were applied for treatment of psoriasis with etanercept or efalizumab.

Patients and methods

Requests for reimbursement of etanercept or efalizumab were made by dermatologists filling out an application form, which was submitted to the national committee (LABAG).
This application form contained patient’s demographic data, specific questions about phototherapy, methotrexate and ciclosporin use in history, baseline and follow-up PASI, and Skindex-29.

All applications for approval of treatment with etanercept and efalizumab between January 2005 and January 2008, submitted to LABAG, were included. Data were analysed descriptively with regard to application characteristics, patient characteristics and disease activity measures of involved patients, medication history, and response on therapy. Patient characteristics and medication history were analysed from the patient perspective. Response on therapy was analysed from the treatment perspective.

**Application characteristics**
The number of received application forms and the number of patients concerned was calculated. The percentage of approved initial and follow-up treatment applications was computed.

**Patient characteristics**
Patient characteristics included gender, age at application, and baseline PASI.

**Medication history**
Analysis of medication history comprised whether phototherapy, methotrexate and ciclosporin were used in history and the reason for treatment failure. According to the Dutch guideline, only patients with plaque psoriasis are eligible for biological therapies.

**Response on therapy**
To be eligible for treatment with etanercept or efalizumab, patients must be unresponsive, intolerant or have contraindications to phototherapy, ciclosporin and methotrexate. Response failure of phototherapy was defined as a less than 50% clearance of psoriasis after twice weekly treatment for 10 weeks. Response failure of ciclosporin was defined as a less than 50% clearance of psoriasis after treatment with a daily dosage of 3-5 milligrams/kilogram for 16 weeks. Response failure of methotrexate was defined as a less than 50% clearance of psoriasis after treatment with a weekly dosage of 22.5 milligrams for 16 weeks. Patients may not have reached the required maximum therapy dose as a consequence of contraindications or intolerance.

In some cases, it was difficult to distinguish contraindications and side effects. For example, actinic damage is a side effect of phototherapy, but also an (acquired) relative contraindication for phototherapy or ciclosporin treatment. In these cases, the reason for
treatment failure was defined as “adverse event AND contraindication”.

To study the response of therapy after three months, only patients with initial application approval were enclosed. PASI 50 response was calculated by comparing the number of approved applications for continuation after twelve weeks with the number of initial applications. Furthermore, the mean percentage improvement in PASI from baseline was calculated for each treatment in two ways. First, treatment efficacy was analysed for all patients with approved initial applications. In case of missing follow-up application forms and hence missing PASI, treatment was considered insufficient and the baseline PASI was carried forward to week 12 (although side effects could have been a reason for discontinuation of therapy as well). Second, mean percentage improvement in PASI from baseline was determined for ‘responding’ patients, i.e. patients with approved initial and follow-up applications.

Results

Application characteristics
From January 2005 to January 2008, 2,306 application forms were received by LABAG. These concerned 1,327 initial treatment applications (etanercept 1,014, efalizumab 313). From patient perspective, this comes down to 1,197 patients, including 884 patients with an application for etanercept, 183 patients with an application for efalizumab and 130 patients with two applications: one for etanercept and one for efalizumab. The last mentioned group failed to respond to the first applied biological therapy, and an application for an alternative biologic was submitted. In 62.3% (81) of the patients in this group, the first applied therapy was efalizumab; for 37.6% (49) the first submitted application was etanercept.

In 2005, 571 initial treatment applications were received, compared to 429 and 327 in 2006 and 2007, respectively. When analysing the number of received initial applications per month, no specific seasonal pattern was recognizable. In total, 1,254 (94.5%) of all initial treatment applications were approved by LABAG.

Patient characteristics
Of all patients, 729 (60.9%) were male, 452 (37.8%) were female, and of 16 (1.3%) the gender was not mentioned. Mean ± standard error of the mean (SEM) age was 49.0 ± 0.4 years (range 16.9-86.6). Mean baseline PASI at patients’ initial application was 22.5. Skindex-29 was applied only for 21 patients (1.7%). The mean Skindex-29 was 48.5. Date of primary diagnosis of psoriasis was not registered on the application forms, so disease
duration could not be calculated.

Medication history
Medication history and reason for treatment failure are presented in Table 1. According to the application forms, most people used phototherapy in history (1141, 95.3%). Ciclosporin was used at the required dosage and duration by 826 (69.0%) of all patients; methotrexate was only used at the required dosage and duration by less than half of the patients (531, 44.4%). Response on phototherapy was insufficient in 79.0% of all cases. On the contrary, ciclosporin and methotrexate had side effects or were contraindicated in more than 65% of the patients.

Table 1. Medication history of individual patients and reason for treatment failure.

<table>
<thead>
<tr>
<th></th>
<th>All patients, no. (%)</th>
<th>Insufficient, no. (%)</th>
<th>AE, no. (%)</th>
<th>AE and CI, no. (%)</th>
<th>CI, no. (%)</th>
<th>Unknown, no. (%)</th>
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<tr>
<td>Phototherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1141 (95.3)</td>
<td>935 (78.1)</td>
<td>69 (5.8)</td>
<td>36 (3.0)</td>
<td>52 (4.3)</td>
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<td>56 (4.7)</td>
<td>12 (1.0)</td>
<td>5 (0.4)</td>
<td>19 (1.6)</td>
<td>9 (0.8)</td>
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<tr>
<td>Ciclosporin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>826 (69.0)</td>
<td>327 (27.3)</td>
<td>151 (12.6)</td>
<td>291 (24.3)</td>
<td>7 (0.6)</td>
<td>50 (4.2)</td>
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<td>No</td>
<td>371 (31.0)</td>
<td>4 (0.3)</td>
<td>44 (3.7)</td>
<td>192 (16.0)</td>
<td>105 (8.8)</td>
<td>26 (2.2)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>531 (44.4)</td>
<td>242 (20.2)</td>
<td>97 (8.1)</td>
<td>118 (9.9)</td>
<td>8 (0.7)</td>
<td>66 (5.5)</td>
</tr>
<tr>
<td>No</td>
<td>666 (55.6)</td>
<td>40 (3.3)</td>
<td>243 (20.3)</td>
<td>281 (23.5)</td>
<td>60 (5.0)</td>
<td>42 (3.5)</td>
</tr>
</tbody>
</table>

Percentages are calculated by dividing by the total number of patients (1197). Yes/No are answers to specific questions on medication history: "Did the patient receive treatment with phototherapy twice weekly for 10 weeks?" "Did the patient receive treatment with ciclosporin at a daily dosage of 3-5 mg/kg for 16 weeks?" "Did the patient receive treatment with methotrexate at a weekly dosage of 22.5 mg for 16 weeks?" AE, Adverse Events; CI, Contraindication.

Response on therapy
In total, 1,254 of all initial treatment applications and 812 of all follow-up applications were approved by LABAG. The remaining 442 follow-up applications were not received or were rejected, mainly as a result of a < 50% decrease in PASI at week 12.

Age, gender, and baseline PASI were comparable for each treatment group. A PASI 50 response was achieved by 69.0% of all patients with an approved initial treatment application for etanercept, and by 50.0% of all patients with an approved initial treatment application for efalizumab. The mean reduction in PASI relative to baseline at week 12
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was 53.1% for etanercept, compared with 35.5% for efalizumab, after carrying forward the baseline PASI to week 12 in case of missing follow-up PASI. When analysing only 'responding' patients, mean reduction in PASI relative to baseline was 75.0% and 68.3% for etanercept and efalizumab, respectively (Table 2).

Table 2. Response on therapy of patients with approved initial treatment application.

<table>
<thead>
<tr>
<th></th>
<th>All approved applications (n = 1254)</th>
<th>Applications of responding patients (n = 812)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Etanercept (n = 972)</td>
<td>Efalizumab (n = 282)</td>
</tr>
<tr>
<td>Baseline PASI, mean ± SEM (range)</td>
<td>22.6 ± 0.4 (1.8-72.0)</td>
<td>21.7 ± 0.6 (0.9-63.3)</td>
</tr>
<tr>
<td>Follow-up PASI, mean ± SEM (range)</td>
<td>10.6 ± 0.3 (0.0-72.0)</td>
<td>14.0 ± 0.7 (0.0-63.3)</td>
</tr>
<tr>
<td>PASI reduction relative to baseline</td>
<td>53.1%</td>
<td>35.5%</td>
</tr>
<tr>
<td>PASI 50 responseb</td>
<td>Etanercept 69.0%</td>
<td>Efalizumab 50.0%</td>
</tr>
</tbody>
</table>

*Responding patients are defined as patients with approved initial and follow-up applications. b Calculated as number of responding patient divided by total number of patients in each treatment group. PASI, Psoriasis Area and Severity Index; SEM, Standard Error of the Mean; PASI 50, 50% reduction in PASI relative to baseline.

Discussion

This report presents three-year Dutch diagnostic, disease activity, and response criteria data, which were applied for reimbursement of treatment of psoriasis with etanercept or efalizumab. Analysed application forms comprised data of 1,197 patients, who were potentially eligible for biological therapy. As the estimated number of persons suffering from psoriasis in The Netherlands is 300,000, this is only 0.4% of the Dutch psoriasis population. Moreover, approximately 15% to 20% (i.e. 45,000 to 60,000) of psoriatic patients have a moderate to severe psoriasis that may require systemic therapy.6 Converted to these numbers, only 2% to 3% of patients with psoriasis requiring systemic treatment seemed eligible for biological therapy. Obviously, the number of patients using biological treatment will increase in the following years, although the number of new applications per year declined during the studied period. Nevertheless, the request for biological therapy is evidently made for merely a small percentage of patients with psoriasis.

Only 5.5% of all initial applications were rejected by LABAG. This validates the conclusion that dermatologists are familiar with the demanded criteria for reimbursement of biological therapies.7 Three times more applications were received for etanercept than efalizumab. Apparently, dermatologists have a preference for etanercept as first-choice biological
therapy. The fact that etanercept is approved for the treatment of psoriatic arthritis as well, whereas efalizumab is not, might account for this.\(^8\) Furthermore, according to the presented data, the efficacy of etanercept is superior to efalizumab. However, the presented data are unsuitable for objective comparison between etanercept and efalizumab. For this purpose, a randomized controlled trial is needed.

Epidemiologic literature states that psoriasis is equally common in males and females.\(^9\) In the current analysis, however, 60.9\% of all patients was male and 37.8\% was female. This gender difference could be explained by the fact that women of childbearing potential will less frequently be treated with systemic medication of which data about the influence on pregnancy are limited. On the other hand, male patients may suffer from a more severe psoriasis than women, as studies show that plaque thickness is associated with male gender.\(^10,11\) Mean baseline PASI was slightly higher than baseline data of randomized clinical trials.\(^12\)

According to the application data concerning medication history, phototherapy was used by most patients, followed by ciclosporin and methotrexate. The relatively infrequent use of ciclosporin and methotrexate may have resulted from the fact that many patients actually did receive these therapies, but did not completely fulfil the required criteria for dosage and treatment duration. Remarkably, methotrexate was only used by fewer than half of the patients. This may be due the fact that patients did not reach the required dosage of 22.5 mg per week because of side effects at lower dosage. Another explanation may be that many patients with psoriasis requiring systemic treatment are successfully treated with methotrexate, and consequently do not need biological therapy. The latter explanation may also clarify why the request for biological therapy is made for merely a small percentage of patients with moderate to severe psoriasis.

As expected, response on phototherapy was insufficient in most cases, whereas reasons for failure of ciclosporin and methotrexate were mostly side effects or contraindications. However, questions about medication history seemed to be misinterpreted many times. Data, therefore, were less suitable for analysing the medication history exactly, although the documentation was sufficient for decision-making by LABAG. Furthermore, distinguishing contraindications and side effects was difficult.

A PASI 50 response was achieved by 69.0\% of all patients with an approved initial treatment application for etanercept, and by 50.0\% of all patients with an approved initial treatment application for efalizumab. These results are slightly lower than randomized controlled trial data (etanercept 76\%, efalizumab 55\%)\(^12\), but comparable to the results of a daily practice cohort studies, in which the efficacy, safety and adverse events of etanercept and efalizumab treatment in daily practice were evaluated.\(^13,14\)
Overall, the mean reduction in PASI relative to baseline at week 12 was 53.1% for etanercept and 35.5% for efalizumab. However, in this analysis treatment efficacy is underestimated, as the baseline PASI was carried forward to week 12 in case of missing follow-up PASI. The analysis of only responding patients leads to an overestimation of treatment efficacy (etanercept 75.0%, efalizumab 68.3%), so the real values should be somewhere in between the results of both analyses.

The present analysis demonstrates that, as a consequence of strict adherence to reimbursement criteria, only 0.4% of Dutch patients with psoriasis are treated with etanercept or efalizumab. The question arises whether it is indicated to broaden these criteria, in particular considering the long-term and presumably safe control of psoriasis by biologics.
References

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CHAPTER 13

Analysis of four-year Dutch reimbursement application data of biological therapies for psoriatic arthritis

Abstract

Objectives: To get the approval for reimbursement of biological therapies for psoriatic arthritis (PsA), patients need to fulfil specific criteria in many countries. Aim of this study was to evaluate the four-year Dutch reimbursement application data, including diagnostic, disease activity and response criteria, which were applied for treatment of PsA with biologics.

Methods: All initial and follow-up applications for approval of treatment with biologics were included for investigation. Data were analysed descriptively with regard to application characteristics, patient characteristics and response to therapy.

Results: In the period studied, 3723 application forms of 1991 patients were received. This concerned 2118 initial treatment applications and 1605 follow-up applications. Of all initial treatment applications, 2003 (94.6%) were approved. The major part of all applications concerned requests for etanercept (59.1%), followed by adalimumab (38.2%). Patients were suffering from polyarthritis in most cases (63.1%). Methotrexate was used by nearly all patients, but only 55.8% had used the required dosage of 25 mg/week. Approximately 79.4% of all patients had met the response criteria after three months of treatment. The mean number of affected joints declined from 7.7 at first application to 1.4 at follow-up. The initial visual analogue scale (VAS) score indicated by patients decreased from 71.2 to 24.1 at follow-up. The VAS score indicated by physicians decreased from 66.0 to 18.4.

Conclusions: Biologics are expensive, but highly effective in the treatment of PsA. Careful compilation of treatment and reimbursement criteria is important for patients as well as for physicians and health insurance companies.

Introduction
Psoriatic arthritis (PsA) is a seronegative inflammatory joint disease associated with psoriasis. Mild PsA can be successfully treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or intra-articular corticosteroid injections. In case of severe PsA, synthetic or biological disease-modifying antirheumatic drugs (DMARDs), or combinations of these therapies are needed to alleviate signs and symptoms, and to inhibit structural joint damage.1

Currently, three anti-tumor necrosis factor α (TNF-α) agents are registered for the treatment of PsA, including adalimumab, etanercept and infliximab. Biologics are expensive and therefore in many countries criteria are developed that patients need to fulfill to get approved for reimbursement of these therapies. Nevertheless, a recent pharmacoeconomic study on PsA showed that anti-TNF-α therapy is cost-effective in short-term clinical practice.2

In The Netherlands, the reimbursement criteria for biological treatment for PsA as well as for other rheumatological indications are formulated by the Dutch Society for Rheumatology (Nederlandse Vereniging voor Reumatologie), and subsequently authorized by the Health Care Insurance Board (College Voor Zorgverzekeringen). Which criteria are applicable is dependent on the type of PsA. At joint count, at least two inflamed joints should be found. Patients are eligible for reimbursement of biological treatment if they are not responsive to methotrexate in a dosage of at least 25 milligram (mg)/week, or if they have a contraindication or intolerance for this therapy. Secondly, the global assessment of disease activity, measured on the basis of a visual analogue scale (VAS) of 0-10, should be at least 4 according to the physician as well as the patient. Thirdly, the arthritis should be persistent despite local (intra-articular) therapy. In case of polyarticular PsA (5 or more joints affected), there should be at least 5 tender and 5 swollen joints, or a mutilating arthritis should be present. After three months of therapy, patients should have met the response criteria, implying a diminution of number of painful or swollen joints, in at least one affected joint in case of an oligoarticular PsA, or in at least 20% of the affected joints in case of a polyarticular PsA. Disease activity measures on psoriasis are left out of consideration.

From February 2004 to March 2008, evaluation of these diagnostic, disease activity and response criteria in The Netherlands occurred centrally by a subcommittee of an independent foundation (LANdelijke Beoordeling Aanvragen Geneesmiddelen [LABAG], National Evaluation of Applications of Drugs). This committee was appointed by health insurance companies and comprises representatives of rheumatologists, dermatologists, paediatricians, health insurance companies and the government. Applications for biological therapies for PsA could only be submitted by physicians with experience in
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treating patients with PsA.
Aim of this study was to evaluate the four-year Dutch reimbursement application data, including diagnostic, disease activity and response criteria, which were applied for treatment of PsA with biological therapies.

Patients and methods
Requests for reimbursement of biologics were made by rheumatologists filling out an application form, which was submitted to the national committee (LABAG). This application form contained the patient’s demographic data, questions about the number of affected joints, specific questions about methotrexate use and dosage in history, type of PsA and VAS scores on global disease activity of patients and physicians. After three months of therapy, a second, identical form was filled out and submitted for evaluation of the response criteria.
All initial and follow-up applications for approval of treatment with biologics submitted to LABAG between February 2004 and March 2008 were included for investigation. Data were analysed descriptively with regard to application characteristics, patient characteristics and response to therapy. Patient characteristics were analysed from the patient perspective. Response to therapy was analysed from the treatment perspective.

Application characteristics
The number of received application forms and the number of patients concerned were calculated. The percentage of approved initial and follow-up treatment applications was computed.

Patient characteristics
Patient characteristics included gender, age at very first application, type of PsA, baseline VAS scores and medication history with regard to methotrexate use.

Response to therapy
The assumption was made that rheumatologists did not submit a follow-up application when there was insufficient response or side effects to biological therapy. Therefore, the percentage of patients meeting the response criteria after three months of therapy was calculated by dividing the number of approved follow-up applications by the number of approved initial applications. Furthermore, the response to therapy was represented by the decline in the number of affected joints and the reduction in VAS scores of patients and physicians.
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Results

Application characteristics
In the period studied, 3723 application forms were received by LABAG. This concerned 2118 initial treatment applications and 1605 follow-up applications. Of all initial treatment applications, 2003 (94.6%) were approved, 51 (2.4%) were rejected because reimbursement criteria were not fulfilled, 47 (2.2%) could not be taken into consideration due to insufficient data, 10 (0.5%) were withdrawn by physicians before approval, three (0.1%) were considered as reflecting no reason to treat, two (0.1%) had no decision status, one (0.0%) received no follow-up advice and one (0.0%) received a neutral advice, meaning that direct consultation of the health insurance company by the prescribing physician was required. Of the 1605 follow-up applications, 1591 (99.1%) met the response criteria and were approved, 7 (0.4%) did not meet the response criteria and thus were rejected, 5 (0.3%) were withdrawn, one (0.1%) was considered as reflecting no reason to treat and one (0.1%) could not be taken into consideration due to insufficient data.

Of the 2118 initial treatment application forms, 1251 (59.1%) concerned an application for etanercept, 810 (38.2%) for adalimumab, 7 (0.3%) for infliximab, one (0.0%) for anakinra and in 49 (2.3%) forms the medication requested for was not discernible. The number of applications for infliximab was low, as this biologic, in contrast to etanercept and adalimumab, was not fully reimbursed by health insurance companies in The Netherlands.

Patient characteristics
Initial and follow-up application forms comprised 1991 patients. Of all patients, 1075 (54.0%) were males, 868 (43.6%) were females, and for 48 (2.4%) the gender was not mentioned. Mean age at first application was 47.9 (range 8.7-85.1; standard error of the mean (SEM) 0.3) years. According to the application forms, patients had different types of PsA, including polyarthritis (n = 1256, 63.1%), oligoarthritis (n = 641, 32.2%), mutilating arthritis (n = 57, 2.9%), polyarthritis as well as mutilating arthritis (n = 19, 1.0%), oligoarthritis as well as mutilating arthritis (n = 5, 0.2%) or the type of PsA was unclear (n = 13, 0.7%). At first application, the mean number of affected joints was 7.7 (range 0.0-62.0; SEM 0.1). Mean VAS score indicated by patients was 71.2 (range 9.0-100.0; SEM 0.3); mean VAS score indicated by physicians was 66.0 (range 8.0-100.0; SEM 0.3). Of all 1991 patients, 1945 (97.7%) used methotrexate in history, of whom 1085 had used the required dosage of methotrexate of 25 mg/week. In the other 860 patients, this dosage was not reached as a consequence of side effects at lower dosages of methotrexate. The mean maximum dosage of methotrexate used was 20.9 (range 5.0-50.0; SEM 0.1) mg/week.
Response to therapy

A total of 2003 of all initial treatment applications and 1591 of all follow-up applications were approved by LABAG, indicating that approximately 79.4% (1591 out of 2003) of all patients had met the response criteria after three months of treatment. From the data it is unclear whether biological treatment was withdrawn because of unresponsiveness to the treatment, side effects or other reasons. Categorized for different biological therapies, the percentage of patients meeting the response criteria came down to approximately 80.1% (966 out of 1206) for patients treated with etanercept and approximately 83.3% (622 out of 747) of patients treated with adalimumab.

The mean number of affected joints declined from 7.7 (range 0.0-62.0; SEM 0.1) at first application to 1.4 (range 0.0-28.0; SEM 0.1) at follow-up, corresponding with an 81.8% decline in the number of affected joints in three months. The initial VAS score indicated by patients decreased from 71.2 (range 9.0-100.0; SEM 0.3) to 24.1 (range 0.0-95.0; SEM 0.4) at follow-up, i.e. a reduction of 66.2%. Likewise, the VAS score indicated by physicians decreased from 66.0 (range 8.0-100.0; SEM 0.3) to 18.4 (range 0.0-90.0; SEM 0.3; 72.1% reduction).

Discussion

This report represents the four-year Dutch national diagnostic, disease activity and response criteria data, which were applied for reimbursement of treatment of PsA with biologics. Analysed application forms comprised data of 1991 patients, who were potentially eligible for biological therapy. A previous analysis of three-year Dutch reimbursement application data, which were applied for treatment of psoriasis with etanercept or efalizumab, concerned 1197 patients.3 Thus, relatively more requests for biological treatment are made for PsA than for moderate to severe psoriasis. Several explanations for this can be given. First of all, PsA may be more prevalent than moderate to severe psoriasis, although the exact prevalence of PsA is unknown. Data about the prevalence of inflammatory arthritis in patients with psoriasis vary from 6 to 42%.4 Secondly, rheumatologist may be more inclined than dermatologist to prescribe systemic therapies, including biologics. Thirdly, the criteria for (initial) reimbursement of biologics may be easier to meet for PsA than for moderate to severe psoriasis, as only one systemic drug that must have been used in history (i.e. methotrexate) is specified. The criteria only encompass disease activity measures specific for PsA and do not include severity measures on psoriasis. Besides, the reimbursement criteria do not incorporate frequently used measures such as C-reactive protein (CRP) or Disease Activity Score in 28 joints (DAS-28).5 Finally, PsA may be more disabling than psoriasis, necessitating intensive systemic therapy.
A high percentage of all initial and follow-up applications (94.6% and 99.1%, respectively) were approved, indicating that rheumatologists are familiar with the demanded criteria for reimbursement of biological therapies. The major part of all applications concerned requests for etanercept, followed by adalimumab. This is very likely related to the different moments of approval of reimbursement by health insurance companies of etanercept and adalimumab in The Netherlands, as etanercept has been reimbursed since December 2003 and adalimumab since October 2005. Likewise, as infliximab was not fully reimbursed, the number of applications for this pharmaceutical was low.

The patients considered were predominantly male (54.0%) and were suffering from polyarthritis in most cases (63.1%). The latter is in agreement with literature, which says that polyarthritis is the most common type of PsA in patient with established disease. In the current study, the mean number of affected joints was 7.7. Methotrexate was used by nearly all patients, but only 55.8% had used the required dosage of 25 mg/week.

Global disease activity, indicated on a VAS, was assessed higher by patients than by physicians at both moments of evaluation. In a publication by Nicolau et al. on discrepancy in the perception of rheumatoid arthritis disease activity between patient and physician, the same difference was established in the majority of patients. Interestingly, approximately 80% of all patients had met the response criteria after three months of treatment. This is much higher than the response percentages calculated by using the application data on biological therapies for psoriasis. Like the initial criteria for reimbursement of biologics, the response criteria may also be easier to meet for PsA than for psoriasis. Nevertheless, in randomized controlled trials on biological therapies for PsA, the American College of Rheumatology 20% improvement criteria (ACR20) response after 12 weeks, which roughly resembles the Dutch response criteria, was far below 80%. Data from large registries may be valuable to establish the efficacy of biological therapies for PsA in daily practice.

In conclusion, biologics are expensive but highly effective therapies for different immune-mediated diseases, including PsA. Currently, biological therapies are indicated exclusively for severely affected patients. Careful compilation of treatment and reimbursement criteria is of importance for patients as well as for physicians and health insurance companies. The Dutch protocol for reimbursement of biologics for PsA, with diagnostic, disease activity and response criteria, has facilitated that every rheumatologist could prescribe biologics for PsA. Moreover, it has increased the confidence between rheumatologists and health insurance authorities. Hence, the central evaluation of the criteria for reimbursement of treatment with biologics in The Netherlands by LABAG could be ceased in April 2008.
PART IV

References


CHAPTER 14

Appropriate infliximab infusion dosage and monitoring:
results of a panel meeting of rheumatologists, dermatologists and gastroenterologists

Abstract

Background: Infliximab, an anti-tumor necrosis factor biological agent, is currently indicated and reimbursed for rheumatoid arthritis, ankylosing spondylitis, Crohn's disease (both adult and paediatric), ulcerative colitis, psoriatic arthritis and plaque psoriasis. Development of national and international guidelines for rheumatology, gastroenterology and dermatology was mostly based on clinical studies and expert opinion.

Objective: To compare available guidelines and local protocols for rheumatology, dermatology and gastroenterology regarding dosage of infliximab, synergy of infliximab with concomitant medication and monitoring of vital signs during infliximab administration.

Methods: Current international, national and local guidelines on the use of infliximab were reviewed and compared, differences and shortcomings were identified, and optimal treatment schedules were discussed during an expert panel meeting (July 2008) of clinical experts and researchers from the three departments of a Dutch university hospital.

Results: Recommended dosages of infliximab are not equal for different indications. Loss of response to infliximab is a common problem encountered within the three medical specialties, but indicators for adjustments in treatment schedules are lacking in all guidelines. Monitoring of vital signs (blood pressure, pulse, temperature) during infusion with infliximab is common practice and recommended by some guidelines. In our experience and confirmed by literature on inflammatory bowel disease, routine measurement of vital signs is not of any value in predicting or recognizing acute infusion reactions.

Conclusion: Different indications encompass different dosing schedules for infliximab. National and internal guidelines do not provide advices regarding loss of response. Routine measurement of vital signs during infusion is not valuable in detecting acute infusion reactions and should only be performed in case of an acute infusion reaction. These topics need to be studied in future studies and covered in future guidelines.

Adapted from: De Vries HS, van Oijen MG, Driessen RJ, de Jong EM, Creemers MC, Kievit W, de Jong DJ. Appropriate infliximab infusion dosage and monitoring: results of a panel meeting of rheumatologists, dermatologists and gastroenterologists. Accepted for publication, Br. J. Clin. Pharmacol.
Introduction
Rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriatic arthritis, ankylosing spondylitis, and psoriasis are chronic inflammatory diseases. Although the exact causes of these diseases remain unknown, over the past two decades major advances have been made in understanding the inflammatory processes. It is likely that in each of these diseases the innate and adaptive immune system are activated, with subsequent production of pro-inflammatory cytokines like tumor necrosis factor α (TNF-α). Antibodies against TNF-α have been developed for the treatment of several chronic inflammatory diseases, including the monoclonal antibodies infliximab and adalimumab. Infliximab, a chimeric (partly human, partly murine) monoclonal antibody, is the only intravenously administered anti-TNF antibody indicated and reimbursed for all of the following diseases: rheumatoid arthritis, ankylosing spondylitis, Crohn's disease (both adult and paediatric), ulcerative colitis, psoriatic arthritis and plaque psoriasis.

National and international guidelines and consensus statements on the use of infliximab have been developed for each of the three medical specialties involved in the treatment with infliximab (i.e. gastroenterology, rheumatology and dermatology) and reflect the current use in clinical practice.

In many centres like ours, the care for patients receiving infliximab is combined for patients with autoinflammatory disorders. This emphasizes the need for a combination of guidelines for the treatment with infliximab for patients with these disorders within the involved medical specialities.

Methods
This paper is the product of an expert panel meeting, held by the authors in July 2008. The purposes of this meeting were as follows:

- To identify similarities and differences within international, national and local guidelines and additional consensus statements from the medical specialties currently using infliximab as anti-TNF therapy, with regards to:
  - Indications for infliximab
  - Dosage for initial and maintenance therapy
  - Monitoring of vital signs during infusion with infliximab
  - Synergetic effects with concomitant medication use

- To discuss the following topics: optimal dosage of infliximab, monitoring of vital signs and use of concomitant medication.

- To discuss the optimal strategy in patients who lost response to infliximab.

Members of the panel were selected, based on each member’s clinical and/or
research experience on the use of infliximab, from the Departments of Rheumatology, Gastroenterology and Dermatology from our university hospital. Members from each medical field performed a literature search in their own discipline by searching the MEDLINE database until July 2008, using the keyword “infliximab”, limiting their search to practical guidelines and consensus statements. Additionally, the National Guideline Clearinghouse, a public resource for evidence-based clinical practice guidelines of the Agency for Healthcare Research and Quality in the United States (http://www.guideline.gov) was searched on guidelines related to infliximab. Furthermore, (local) Dutch guidelines from the medical specialties not accessible by MEDLINE but used in clinical practice were reviewed. Regarding these guidelines and consensus statements, we limited ourselves to the previous identified topics, namely indication, dosage, monitoring, synergy and loss of response (i.e. secondary inefficacy). Results were presented and discussed during the panel meeting. Additionally, hiatuses within guidelines and consensus statements were discussed.

Results

Indication
Infliximab was first approved for patients with Crohn’s disease in 1998. Approval for other indications followed in the subsequent years (Figure 1). In general, patients not responding to conventional therapy and having a moderate to high level of disease activity are eligible for treatment with a biologic like infliximab.

Gastroenterology
Both the international consensus statements of the American Gastroenterological Association (AGA) and the European Crohn’s and Colitis Organisation (ECCO) as well as national guidelines agree that treatment with infliximab is appropriate for patients with inflammatory bowel disease experiencing corticosteroid dependency, glucocorticoid and/or immunomodulative treatment refractoriness or active fistula associated with Crohn’s disease. Especially patients with Crohn’s disease with extraintestinal manifestations and fistulising disease are eligible for treatment with infliximab.

Rheumatology
The international consensus statement on biologics for the treatment of rheumatoid arthritis, which is updated nearly every year, does not provide criteria on which patients should be treated with antibodies against TNF-α, like infliximab. National guidelines,
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however, do provide such criteria. Patients should have failed on at least one (Swedish, French and Japanese guidelines) or two (British and Dutch guidelines) disease-modifying antirheumatic drugs (DMARDs), including methotrexate in an adequate dosage, and should have a disease activity measured by the Disease Activity Score using 28 joint counts (DAS28) of > 5.1 (British guidelines). However, according to the Swedish guidelines no specific disease activity is required for starting with biologics. The consensus statement of the American College of Rheumatology (ACR) recommends starting with anti-TNF therapy like infliximab in case of 1) high disease activity (DAS28 > 5.1) for 3 to 6 months; or 2) high disease activity for less than three months in combination with features of a poor prognosis (e.g. functional limitation, extra-articular disease, rheumatoid factor positivity, bony erosions by radiography); 3) moderate disease activity (DAS28 > 3.2 and < 5.1) for > 6 months and inadequate response to monotherapy with methotrexate in combination with features of poor prognosis.

Figure 1. International approval of infliximab for autoinflammatory disorders.

Dermatology

Few guidelines and consensus statements on the use of infliximab exist for patients with plaque psoriasis. According to the international consensus statement by Reich et al. patients with psoriatic arthritis in association with skin symptoms or moderate to severe
psoriasis who have failed two or more systemic therapies are eligible for treatment with biologics. Furthermore, patients with a Psoriasis Area and Severity Index (PASI) of at least 20 or patients with an improvement of less than 50% on this scale with previous (non-)biological treatment, were eligible for treatment with infliximab.\textsuperscript{17} The guideline of the British Association of Dermatologists state that patients should have severe disease, defined as a PASI of 10 or more (or a body surface area of 10% or greater where PASI is not applicable) and a Dermatology Life Quality Index > 10. Secondly, patients should be unresponsive or intolerant to standard therapy.\textsuperscript{18} In The Netherlands, patients are eligible for biological therapies if they have a PASI of at least 10, and have failed to respond to phototherapy, methotrexate and ciclosporin in the past, or have a contraindication to, or are intolerant of these treatments.\textsuperscript{19}

**Dosage**
The first randomized clinical trial with infliximab (by that time called cA2) in patients with rheumatoid arthritis randomized patients over a single dose of 1 milligram/kilogram (mg/kg) bodyweight, 10 mg/kg bodyweight and placebo.\textsuperscript{20} In this study, a dosage dependent response was observed. A subsequent study comparing the effect of multiple infusions with infliximab in patients with rheumatoid arthritis compared 1 mg to 3 mg and 10 mg per kilogram bodyweight, showing the best results with the latter two.\textsuperscript{21} Furthermore it was shown that the median duration of response to the lowest dosage (i.e. 1 mg/kg bodyweight) lasted three weeks, compared to 5 and 8 weeks with dosages of 3 and 10 mg/kg bodyweight, respectively.\textsuperscript{22} Additional studies, performed in patients with Crohn’s disease, compared a single dose of 5 mg, 10 mg, or 20 mg per kilogram bodyweight, administered over a two-hour period. In this trial, patients receiving 5 mg/kg had the best response to infliximab.\textsuperscript{23} An open-label trial in patients with Crohn’s disease, which was performed earlier, compared doses of 1 mg, 5 mg, 10 mg, and 20 mg per kilogram. The group receiving 1 mg/kg had a more transient response than the groups given the higher doses.\textsuperscript{24} One of the first case reports of patients with psoriasis treated with infliximab reported a significant response with 5 mg/kg bodyweight, and the first randomized trial in patients with psoriasis showed significant responses to 5 mg/kg and 10 mg/kg bodyweight.

**Gastroenterology**
With regard to dosing of infliximab in inflammatory bowel disease, international and national consensus statements/guidelines recommend a dosage of 5 mg/kg body weight, given in a 0-2-6- weeks induction regimen and followed by maintenance dosing every 8 weeks.\textsuperscript{4,5}
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The ECCO statement provides the same dosage schedule, since 5 mg/kg body weight has been shown effective in large placebo controlled trials.\textsuperscript{7,25} Primary non-response can be determined after two doses.\textsuperscript{4} However, the Dutch guidelines recommend to determine the treatment effect 8 weeks after the third infusion since optimal effect will then be obtained.\textsuperscript{5} When patients attenuate response, dosage can be increased to 10 mg/kg body weight or the interval between infusions can be shortened up to 4 weeks.\textsuperscript{5,7}

Rheumatology

In case of patients with rheumatoid arthritis, the standard dosage of infliximab administered recommended by most guidelines is 3 mg/kg body weight in an induction regiment at weeks 0, 2, and 6, and every 8 weeks thereafter.\textsuperscript{10,13,14} Some of the national and international guidelines do not explicitly state that infliximab should be administered at 3 mg/kg body weight, but rather assume that clinicians will administer this ‘standard dosage’.\textsuperscript{9,11,16} As it is for patients with inflammatory bowel disease, attenuation of response should be treated with increasing the dosage or shortening the dosing intervals, together with the addition or substitution of another DMARD, according to the international consensus statement.\textsuperscript{9} The Japanese guideline, however, does not allow any increment of dosage or shortening of the interval, and quite a few guidelines do not give recommendations regarding this topic.\textsuperscript{11,14,16} The NICE guideline is most explicit in its recommendation, recommending increasing the dose of infliximab stepwise by approximately 1.5 mg/kg, up to a maximum of 7.5 mg/kg every 8 weeks, or alternatively administration of 3 mg/kg as often as every 4 weeks.\textsuperscript{10}

Dermatology

The guidelines on the treatment of psoriasis with biologics from the American Academy of Dermatology, The British Association of Dermatologists and the international consensus panel of dermatology experts advises to dose infliximab in a 5 mg/kg infusion schedule at weeks 0, 2, and 6, followed by maintenance treatment every 6 to 8 weeks.\textsuperscript{17,18,26} The British guidelines, however, state that no studies have been performed to establish the optimal dose or frequency of repeated infusions required in order to achieve disease control.\textsuperscript{18} The dermatology guidelines give no recommendation regarding how to manage attenuated response to infliximab.

Synergy

Repeated administration of infliximab has been associated with immunogenicity, i.e. the formation of antibodies to infliximab (ATI, also known as HACA; human anti-chimeric
antibodies). The concomitant use of immunosuppressants may increase the efficacy of infliximab, partially because it prevents the development of ATI, and partially by other mechanisms currently unknown.27-29

Gastroenterology
The international ECCO guideline has been very clear and advocates that every patient receiving infliximab should receive an immunomodulator (i.e. azathioprine, methotrexate or 6-mercaptopurine) in order to prevent development of ATI that in turn may reduce efficacy and increase the risk for side effects.7 The consensus statement of the AGA strongly recommends co-administration with immunosuppressive therapy as well.4 The Canadian guidelines are most clear by recommending that all patients should receive concomitant immunosuppressants, even if they failed to respond to immunomodulators in the past.6 The Dutch national guideline recommends initiation of immunosuppressants prior to infliximab in order to reduce the formation of antibodies.5

Rheumatology
Nearly all efficacy studies with infliximab in patients with rheumatoid arthritis have been performed in patients receiving concomitant methotrexate.21 Therefore, all international, national and local guidelines recommend concomitant treatment with methotrexate in case of starting treatment with any anti-TNF-α agent, including infliximab.13,16

Dermatology
The American Academy of Dermatology does not recommend concomitant prescription of low-dose methotrexate, although some dermatologists do so to decrease the formation of antibodies.28 The international consensus statement on the treatment of psoriasis with infliximab does not provide guidelines on the use of concomitant medication during treatment with infliximab.17 According to the British guidelines, concomitant systemic therapies may be indicated for some patients with very severe or unstable psoriasis, although doses should be minimized.18

Monitoring of vital signs
As a foreign protein-derived agent administered intravenously over a two-hour infusion period, infliximab can cause infusion reactions. Formation of ATI may increase the risk of infusion reactions.27,28 These infusion reactions can be categorized as acute or delayed. An acute infusion reaction is defined as any adverse event occurring during infusion or within a period of 24 hours after infusion.27,30 Severity can vary from mild to severe life
threatening, and symptoms may include nausea, flushing, dizziness, dyspnea, chest pain and hypotension or hypertension. Delayed infusion reactions are defined as reactions occurring from 24 hours to 14 days after treatment with infliximab and symptoms may include arthralgia, rash, myalgia and fatigue.\textsuperscript{27,30}

In randomized controlled trials with infliximab, vital signs (blood pressure, body temperature and pulse) were monitored vigorously. Monitoring body temperature at baseline is performed to rule out fever possibly based on infection and monitoring during infusion is performed while concerns exist about developing fever during an acute infusion reaction. The monitoring of blood pressure and pulse is based on the concern that during infusion with infliximab an anaphylactic shock could develop with typical hypotension.

\textit{Gastroenterology}

Study protocols with infliximab in patients with inflammatory bowel disease and some experts state that 30 minutes prior to infusion, every 30 minutes during infusion, and up till two hours after infusion, vital signs (blood pressure, body temperature and pulse) should be monitored.\textsuperscript{31} Randomized controlled trials in patients with inflammatory bowel disease reported incidences of acute infusion reactions ranging from 9 to 17\%.\textsuperscript{25,32} In clinical practice the overall incidence of acute infusion reactions with infliximab is approximately 4 to 10\%.\textsuperscript{30,33} None of the international or national guidelines state that during infusion vital signs should be monitored. However, it is common practice to monitor vital signs during infusion with infliximab.

\textit{Rheumatology & Dermatology}

As it is the case for gastroenterology, current practice in rheumatology and dermatology is to monitor vital signs of patients during infusion with infliximab. However, none of the guidelines give specific recommendations regarding monitoring of vital signs.

\textit{Interpretation}

With the exception of patients treated for rheumatoid arthritis who are treated with a dosage of 3 mg/kg bodyweight, all patients who are treated with infliximab receive a dosage of 5 mg/kg bodyweight (Table 1). To our knowledge, however, studies comparing response rates between dosing schedules of 3 mg/kg and 5 mg/kg in patients with inflammatory bowel disease, rheumatoid arthritis or psoriasis have not been performed. The optimal concentration of infliximab may still need to be established. In view of this, several recent studies in patients with rheumatoid arthritis, Crohn’s disease, ulcerative colitis, ankylosing spondylitis and psoriasis have shown that trough serum concentrations of infliximab
correlate with the clinical response to infliximab\textsuperscript{34-38}. The implication of this might be that in the near future, dosage of infliximab will be individualized based on the trough serum concentration, thereby optimizing clinical response and cost effectiveness.

Table 1. Dosage regimen of infliximab for different autoinflammatory disorders.

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>AS</th>
<th>PsA</th>
<th>CD</th>
<th>UC</th>
<th>PCD</th>
<th>Ps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>3 mg/kg</td>
<td>5 mg/kg</td>
<td>5 mg/kg</td>
<td>5 mg/kg</td>
<td>5 mg/kg</td>
<td>5 mg/kg</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td>Induction therapy (weeks)</td>
<td>0, 2, 6</td>
<td>0, 2, 6</td>
<td>0, 2, 6</td>
<td>0, 2, 6</td>
<td>0, 2, 6</td>
<td>0, 2, 6</td>
<td>0, 2, 6</td>
</tr>
<tr>
<td>Maintenance therapy (weeks)</td>
<td>8</td>
<td>6</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

RA, Rheumatoid Arthritis; AS, Ankylosing Spondylitis; PsA, Psoriatic Arthritis; CD, Crohn’s Disease; UC, Ulcerative Colitis; PCD, Pediatric Crohn’s Disease; Ps, Psoriasis.

Regarding attenuation of response, the guidelines of each specialty recommend dosage increase or interval shortening or changing to another biological therapy. However, there is no clear recommendation which option should be chosen in which subset of patients. Pharmacokinetic modelling of infliximab in patients with rheumatoid arthritis showed that interval reduction might be more effective in raising serum infliximab concentrations than dosage increase\textsuperscript{38}. Flendrie et al. observed in an open-label study a more pronounced efficacy in patients with rheumatoid arthritis receiving interval reduction, compared to patients receiving a dosage increase\textsuperscript{39}. These observations need to be studied in large randomized trials.

With the exception of ankylosing spondylitis, the need of concomitant administration of immunosuppressants during treatment with infliximab has been stressed by most of the guidelines throughout the different specialties, since it appears to prevent the development of ATI\textsuperscript{27-29}. However, benefits and risks of combined strategies should be balanced carefully as the evidence for increased risks of combined therapies is growing. In patients with inflammatory bowel disease treated with infliximab an increased risk for serious infections was observed\textsuperscript{40,41}.

Monitoring of vital signs during infusion with infliximab is based on strict regulations during clinical trials and is still advocated in some treatment algorithms and guidelines\textsuperscript{6,30,31}. We recently showed that scheduled monitoring of vital signs during infusion did neither indicate nor predict development of acute infusion reactions. When baseline vital signs from patients with and without acute infusion reactions were compared, no significant differences were observed. Furthermore, during an acute infusion reaction, vital signs did not show a significant change compared to baseline\textsuperscript{42}.
Conclusions and recommendations

Different indications encompass different dosing schedules. Several studies have shown a correlation between trough serum concentration of infliximab and clinical response. Future studies are needed to study the concentration-effect relationship of infliximab as a necessary step before therapeutic drug monitoring can be recommended in guidelines. National and internal guidelines do not provide advices regarding loss of response. Although some evidence exists that interval reduction might be more effective in raising serum infliximab concentrations than dosage increase, large randomized trials are needed to observe whether or not interval reduction is superior to dosage increase and in which subset of patients, in order to be able to give guidance regarding loss of response in clinical guidelines. With regard to concomitant medication, efforts should be made to establish a reasonable time interval in which concomitant medication should be decreased.

Routine scheduled measurements of vital signs during infusion is not valuable in detecting acute infusion reactions and should only be performed in case of an acute infusion reaction. We recommend administering infliximab at an infusion unit under supervision of trained personnel. This approach enables direct interventions immediately after a patient reports symptoms. Baseline assessment of patients, including vital signs, should still be performed as normal clinical practice to rule out possible infections or other contraindications for infusion with infliximab. As stressed out by a recent quality appraisal of clinical practice guidelines and consensus statements on the use of biological agents in rheumatoid arthritis, guidelines should be explicit in their guidance, which has implications for the development of future guidelines.
References


PART IV


COMORBIDITIES IN PATIENTS WITH PSORIASIS
PART V

COMORBIDITIES
PART V

COMORBIDITIES
CHAPTER 15

Cardiovascular risk factors in high-need psoriasis patients and its implications for biological therapies

Abstract

Background: The associations between psoriasis and cardiovascular risk factors are reported to be stronger as psoriasis severity increases. This makes studying cardiovascular risk factors in patients with high-need psoriasis, eligible for biological therapy, interesting.

Objective: To survey the prevalence of cardiovascular risk factors in patients with high-need psoriasis and to compare these data to patients with other dermatological diseases. Furthermore, the implications of these findings for treatment with biologics were outlined.

Methods: The prevalence of cardiovascular risk factors was investigated in a high-need psoriatic patient cohort and compared with patients with other skin diseases who filled out a questionnaire about the presence of cardiovascular risk factors.

Results: A significantly higher prevalence of obesity, smoking, and hypertension was found for the cohort of patients with high-need psoriasis compared with non-psoriatic controls. Striking differences were found with respect to body mass index and obesity, as 35.5% of all patients with high-need psoriasis were obese.

Conclusions: Patients with high-need psoriasis show a high prevalence of cardiovascular risk factors, and may consequently be predisposed to cardiovascular diseases. As this is relevant for therapy management in daily clinical practice, especially biologics, cardiovascular risk should be evaluated for each patient with high-need psoriasis before and during systemic treatment.

PART V

Introduction

High-need psoriasis is defined as psoriasis in patients for whom at least two systemic treatments are unsuitable due to lack of efficacy, intolerance or contraindication. These patients are generally severely affected by psoriasis, and many are treated with tertiary care pharmaceuticals in the course of the disease. Examples of such pharmaceuticals are biologics, such as etanercept, efalizumab, adalimumab and infliximab. Most guidelines state that patients with psoriasis are eligible for a biologic if they have a Psoriasis Area and Severity Index (PASI) of at least 10, and have failed to respond to phototherapy, methotrexate, and ciclosporin in the past, or have a contraindication to or intolerance for these treatments. Therefore, all patients with psoriasis eligible for biological therapies may be termed ‘high need’.

For patients with psoriasis who are treated with biologics, safety monitoring is extremely important. On the one hand, these patients are exposed to innovative antipsoriatic agents of which long-term safety data are lacking. On the other hand, hypotheses exist that this category of patients is characterized by an exceptional profile of comorbidity.

For many years, the association of psoriasis with other diseases has been investigated. An increased incidence of occlusive vascular diseases in patients with psoriasis had already been described in 1973 by McDonald and Calabresi. In 1986, Lindegard was the first to find a concomitance of psoriasis and cardiovascular risk factors, such as alcoholism, hypertension, diabetes, and obesity. Now that concerns about lifestyle issues influencing public health in western countries are growing, general health in psoriasis is studied more and more as well.

Currently, the evidence of associations between psoriasis and cardiovascular risk factors and cardiovascular comorbidity is convincing. The associations are reported to be stronger as psoriasis severity increases. For this reason, studying cardiovascular risk factors in severely affected patients with psoriasis who are eligible for biological therapy is necessary.

Patients with high-need psoriasis may hypothetically exhibit a highly unfavourable cardiovascular risk profile compared with non-psoriatic dermatological patients.

The objective of this study was to survey the prevalence of cardiovascular risk factors and comorbidity in a high-need psoriasis cohort, and to compare these data with a group of patients with other dermatological diseases referred to the same centre. Furthermore, the implications of these findings for patients treated with biological therapies were outlined. Results of this study are important considering safety management during biological therapy, and may influence treatment strategies.
Patients and methods

The prevalence of cardiovascular risk factors was investigated in patients with high-need psoriasis, and compared with patients with skin diseases other than psoriasis. Data about psoriasis patients were extracted from an existing database. This database contains the prospective, daily practice demographic, efficacy and safety data of all patients who were treated with biologics at the Radboud University Nijmegen Medical Centre Department of Dermatology from February 2005. For all patients included in this cohort, medication history was characterized by failure to respond to phototherapy, methotrexate, and ciclosporin in the past due to lack of efficacy, intolerance or contraindication. For this reason, patients in this cohort are designated as ‘high-need’. Furthermore, all registered patients had a PASI of at least 10 before initiation of therapy.

A control group was composed of other patients from the same hospital with a dermatological disease other than psoriasis, who filled out a questionnaire about the presence of cardiovascular risk factors during their outpatient clinic visit. Patients were questioned about age, sex, height, weight, reason for dermatology outpatient clinic visit, smoking habits, and alcohol consumption. In addition, the existence of a diagnosis of diabetes, hypertension, hyperlipidemia, myocardial infarction, and cerebrovascular disease was registered. Only completely filled out questionnaires were used. If possible, data were verified using the hospital's electronic patient file. Patients younger than 18 years of age or with a diagnosis of psoriasis were excluded.

For each group, the mean age and body mass index (BMI) were calculated. BMI was calculated as weight in kilograms (kg) divided by height in meters (m) squared. The number of obese patients was registered. Obesity was defined as a BMI > 30 kg/m². The number of patients who had ever smoked and who were currently smoking was counted. Current smokers included those who were smoking at the moment of analysis as well as those who had stopped smoking for less than 1 year. The mean number of pack years, calculated as duration of smoking (years) multiplied by the number of cigarette packs (number of cigarettes divided by 20) a day, was computed for each group. Also, the number of patients who had ever used alcohol was analysed, including the current mean number of units of alcohol per month. Furthermore, the number of patients with a diagnosis of diabetes, hypertension, hyperlipidemia, myocardial infarction or cerebrovascular disease was registered. For the high-need psoriasis group, all systemic therapies used for psoriasis in the past were recorded.

The two groups were compared using SPSS 14.0.2 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to reproduce study results as numbers, percentages, and means. Continuous variables were analysed using the independent
PART V

samples t-test. Dichotomous variables were analysed using Mantel-Haenszel common
odds ratio estimates, after stratifying data by age and sex. Backward stepwise multiple
logistic regression analysis was performed to identify independent risk factors associated
with the high-need psoriasis. All tests are two-tailed. $P < 0.05$ was considered statistically
significant.

Results

The high-need psoriasis cohort consisted of 107 patients. The control group was
composed of 396 patients with dermatological diseases other than psoriasis. This group
was representative of the dermatological outpatient clinic population, as all patients
from different dermatological subspecialisms were included. In total, 533 completed
questionnaires were received. Fifty-one of these were unusable or filled out incompletely. Of
the remaining questionnaires, 38 patients were under 18, and 48 patients had a diagnosis
of psoriasis. These patients were excluded from analysis. Finally, 396 questionnaires were
suitable for analysis.

In contrast with the control group, there was a female predominance in the high-need
psoriasis cohort ($p < 0.001$). Mean age was slightly lower in the high-need psoriasis
cohort than in the control group ($p = 0.05$). Mean BMI was significantly different ($p <
0.001$) between both groups (i.e. 28.5 kg/m$^2$ for patients with high-need psoriasis and 24.9
kg/m$^2$ for controls). Remarkably, 35.5% of all high-need psoriatic patients were obese,
compared with 10.4% of the controls (OR 5.49, $p < 0.001$). Of the individuals in the high­
need psoriasis group, 75.7% had ever smoked, compared with 58.8% of the control group
(OR 1.92, $p = 0.01$). Also, the mean number of pack years was significantly higher in the
high-need psoriasis group ($p = 0.02$). Respectively, 46.7% and 28.8% of patients with
high-need psoriasis and controls were currently smoking (OR 1.73, $p = 0.02$). Compared
with the control group, a significantly lower percentage of patients in the psoriasis cohort
had ever used alcohol (70.1% versus 83.8%, $p < 0.001$), but the mean monthly amount of
alcohol consumption was higher for the patients with high-need psoriasis. A diagnosis of
diabetes, hypertension, and hyperlipidemia was more common in the patients with high­
need psoriasis than in controls. However, only data for hypertension were significantly
different (high-need psoriasis 34.6%, controls 24.2%, $p = 0.01$). Slightly more patients in
the control group had a history of myocardial infarction and cerebrovascular diseases, but
low numbers were found (Table 1).

Backward stepwise multiple logistic regression analysis showed an independent
association of high-need psoriasis with age, sex, obesity, smoking, alcohol use, and
hypertension.
Table 1. Patient characteristics.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>High-need psoriasis (n = 107)</th>
<th>Controls (n = 396)</th>
<th>Odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>37 (34.6)</td>
<td>226 (57.1)</td>
<td>2.62 (1.68-4.11)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>48.5</td>
<td>51.2</td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Stature</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean BMI (kg/m^2)</td>
<td>28.5</td>
<td>24.9</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30 kg/m^2), no. (%)</td>
<td>38 (35.5)</td>
<td>41 (10.4)</td>
<td>5.49 (3.09-9.74)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever smoking, no. (%)</td>
<td>81 (75.7)</td>
<td>233 (58.8)</td>
<td>1.92 (1.14-3.22)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean number of pack years</td>
<td>19.8</td>
<td>14.9</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Current smoking, no. (%)</td>
<td>50 (46.7)</td>
<td>114 (28.8)</td>
<td>1.73 (1.08-2.75)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever used alcohol, no. (%)</td>
<td>75 (70.1)</td>
<td>332 (83.8)</td>
<td>0.36 (0.20-0.63)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean alcohol consumption (number of units/month)</td>
<td>28.2</td>
<td>20.9</td>
<td></td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Comorbidity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>14 (13.1)</td>
<td>35 (8.8)</td>
<td>1.91 (0.91-4.04)</td>
<td>0.09</td>
</tr>
<tr>
<td>Hypertension, no. (%)</td>
<td>37 (34.6)</td>
<td>96 (24.2)</td>
<td>1.93 (1.16-3.23)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hyperlipidemia, no. (%)</td>
<td>22 (20.6)</td>
<td>68 (17.2)</td>
<td>1.17 (0.66-2.09)</td>
<td>0.59</td>
</tr>
<tr>
<td>Myocardial infarction, no. (%)</td>
<td>4 (3.7)</td>
<td>19 (4.8)</td>
<td>1.59 (0.46-5.49)</td>
<td>0.47</td>
</tr>
<tr>
<td>Cerebrovascular disease, no. (%)</td>
<td>4 (3.7)</td>
<td>17 (4.3)</td>
<td>1.14 (0.33-3.99)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

*Continuous variables were analysed by the independent samples t-test. CI, Confidence Interval; BMI, Body Mass Index.

**Previous treatments**

More than 76% of all patients with psoriasis had used methotrexate, UVB or ciclosporin previously. Other previously used therapies were PUVA, retinoids, fumaric acid, etanercept, alefacept, onercept, efalizumab, adalimumab, and infliximab (Table 2). Compared with patients who had never used ciclosporin, fewer patients who had ever used ciclosporin previously were affected by hypertension. These data probably comprehend cases in which ciclosporin was contraindicated because of hypertension. Analysis of the influence of other previous treatments on cardiovascular risk factors was not reasonable due to the unequal distribution of percentages.

**Discussion**

In the current study, a significantly higher prevalence of obesity, smoking, and hypertension was found for patients with high-need psoriasis compared with non-psoriatic controls.
Furthermore, the mean monthly amount of alcohol consumption was higher in the patients with high-need psoriasis than in controls. Striking differences between the high-need psoriasis cohort and the control group were found with respect to BMI and obesity. The mean BMI was 28.5 kg/m² for patients with high-need psoriasis and 24.9 kg/m² for controls. The prevalence of obesity was more than three times higher in the high-need psoriasis group than in the control group. In The Netherlands, Bos et al. performed a study in which the prevalence of the metabolic syndrome in two general, non-psoriatic populations in the age category 28-59 years was estimated. In this study, the mean BMI was 25.2 kg/m² for women in both populations, and 25.9 kg/m² and 25.7 kg/m² for men. A recent European cohort study by Gisondi et al. showed a mean BMI of 27.6 kg/m² in patients with psoriasis eligible for etanercept treatment. In the United States, a study was performed to investigate the impact of obesity and smoking on psoriasis. The mean BMI in that study was 29.1 kg/m² for the psoriasis cohort compared with 26.2 kg/m² for controls. In contrast, the mean BMI of the control group in our study was slightly lower than the data represented in the Dutch study, but the BMI values of the patients with high-need psoriasis come close to the data from the United States.

The results of our study are consistent with the results of studies in which the prevalence of cardiovascular risk factors was determined for patients with psoriasis who did not fulfil the criteria for high-need psoriasis. In these studies, obesity, metabolic syndrome, and cardiovascular diseases were significantly more common in patients with psoriasis than in non-psoriatic controls. Also, a higher prevalence of smoking and alcohol consumption was found in patients with psoriasis compared with controls.

Furthermore, the literature shows that cardiovascular risk factors are more strongly associated with severe psoriasis than with mild psoriasis. Severely affected psoriasis patients are more overweight, tend to smoke more and longer, consume more alcohol, show more signs of insulin resistance and diabetes, are more frequently affected by hypertension and hyperlipidemia, and have a heightened risk of myocardial infarction and cerebrovascular accident compared with less severely affected patients. Also, severe psoriasis is associated with an increased mortality, even

<table>
<thead>
<tr>
<th>Previous treatments</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>104 (97.2)</td>
</tr>
<tr>
<td>UVB</td>
<td>92 (86.0)</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>82 (76.6)</td>
</tr>
<tr>
<td>PUVA</td>
<td>76 (71.0)</td>
</tr>
<tr>
<td>Retinoids</td>
<td>76 (71.0)</td>
</tr>
<tr>
<td>Fumaric acid</td>
<td>50 (46.7)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>14 (13.1)</td>
</tr>
<tr>
<td>Alefacept</td>
<td>13 (12.1)</td>
</tr>
<tr>
<td>ONecpont</td>
<td>6 (5.6)</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>1 (0.9)</td>
</tr>
</tbody>
</table>

UVB, Ultraviolet B; PUVA, Psoralen-Ultraviolet A.
after adjustment for risk factors for death. In contrast with the studies cited here, in our study, specifically patients with high-need psoriasis were investigated. These patients not only had severe psoriasis, but had also failed to respond to at least three systemic therapies. In this special population, the occurrence of cardiovascular risk factors may be even higher than in patients with severe psoriasis. This makes extensive, multidisciplinary medical monitoring of patients with high-need psoriasis essential.

Results from our study may be biased by the fact that prevalence of cardiovascular risk factors and diseases was measured in different ways for patients with high-need psoriasis and controls. Moreover, estimating the prevalence of these issues by means of questionnaires could have led to overreporting or underreporting. We believe, nevertheless, the accuracy of this method to be sufficient to constitute a solid control group. Besides, received data were verified using the hospital’s electronic patient file. Differences in the baseline characteristics of both groups could have influenced study outcomes. Mean age was slightly lower in the high-need psoriasis group than in the control group. Also, the percentage of males was lower. As increasing age and male sex are associated with higher cardiovascular risk, the difference in prevalence of cardiovascular risk factors in the examined groups may in fact be larger.

Whether psoriasis promotes the development of cardiovascular diseases or vice versa, is still unclear. Recently, two large prospective cohort studies were accomplished, examining the relationship between obesity, smoking, and incident psoriasis in more than 75,000 women. Results showed that obesity and smoking are strong risk factors for the development of psoriasis. Conversely, psoriasis itself may lead to an increased risk of cardiovascular diseases as a consequence of chronic systemic inflammation, unhealthy lifestyle of patients with psoriasis, and arousal of cardiovascular risk factors induced by antipsoriatic medication, such as ciclosporin and retinoids.

The current data were unsuitable for a sensible analysis on the influence of previous treatments on cardiovascular risk factors. For each individual pharmaceutical, potential cardiovascular side effects are known. However, whether a patient’s risk profile is affected by successive or concomitant systemic treatments during life needs further research.

To what extent biological therapies influence the risk of cardiovascular diseases is currently under investigation. As TNF-α is involved in lipid metabolism and adipose tissue regulation, anti-TNF-α therapy may influence body weight, insulin resistance, lipid profile, and vascular function. However, studies investigating these items for rheumatoid arthritis patients show controversial results. For psoriasis, no comparable data are available yet. A highly interesting question is whether early intervention with biological treatment reduces the long-term risk for cardiovascular diseases. If so, this may be an additional argument to
introduce biologics early in the course of disease, and to use drugs with potentially severe side effects, such as ciclosporin, only if acute intervention is needed. Contrarily, obesity may lead to a suboptimal response of fixed-dose biologics such as etanercept.32

In conclusion, patients with high-need psoriasis show a significantly higher prevalence of cardiovascular risk factors compared with non-psoriatic dermatological patients, and may consequently be predisposed to cardiovascular diseases. Furthermore, the extensive systemic medication history makes these high-need psoriasis patients particularly vulnerable. As a consequence, cardiovascular risk should be evaluated for each high-need psoriasis patient both before and during systemic treatment, especially biologics. Caution should be exercised when prescribing retinoids or ciclosporin in these patients. Furthermore, patients should be encouraged to display healthy behaviour, to stop smoking, to moderate alcohol consumption, and to lose weight.
References


29. Setty AR, Curhan G, Choi HK. Obesity, waist circumference, weight change, and


PART V

CHAPTER 16

Prevalence of self-reported joint complaints in patients with psoriasis

Abstract

Background: Psoriatic arthritis (PsA) is a rheumatic joint disease associated with psoriasis of the skin and the nails. Estimates of the prevalence of arthritis among patients with psoriasis range widely from 6 to 42%.

Objective: To investigate the prevalence of self-reported joint complaints in patients with psoriasis in The Netherlands.

Methods: A total of 6000 questionnaires was sent to members of the Dutch psoriasis society. The forms contained questions about skin disease and joint complaints. Psoriasis severity was assessed using the Self-Administered Psoriasis Area and Severity Index (SAPASI). Formal joint counts and skin assessment were performed in a subsample of the responders, stratified according to self-reported joint complaints.

Results: Of the 6000 questionnaires, 1562 (26%) were returned to the study centre. Twenty-four responders were under 18 years of age and were excluded. From the 1538 remaining patients, 503 (33%) patients reported no joint complaints, and 98 (6%), 309 (20%), and 628 (41%) patients had mono-, oligo-, and polyarticular complaints, respectively. After correction using the physical examination of the subsample, it was estimated that the prevalence of polyarticular complaints attributable to synovitis was 27%. Twenty percent of the patients had an Amor score of at least 6, indicating an increased risk for the presence of spondylitis.

Conclusions: The prevalence of self-reported joint complaints in patients with psoriasis is high, but the prevalence of synovitis is considerably lower. Polyarticular involvement is the most prevalent complaint in these patients. The prevalence of polyarticular complaints increased with disease duration.

Introduction
The relationship between psoriasis and psoriatic arthritis (PsA) has been well established clinically and genetically. The typical clinical picture of PsA consists of peripheral joint inflammation with an asymmetric pattern of involvement. With longer disease duration, there is a propensity to develop a (symmetric) polyarthritis out of an initial (asymmetric) mono- or oligoarthritis. Other manifestations, such as spondylitis, sacroiliitis, enthesitis, dactylitis, and nail lesions do also appear in PsA. Within two years after onset of the disease, a substantial percentage of PsA patients develops irreversible damage of the involved joints. Consequently, PsA may not be seen as a benign disease. Nowadays, PsA can be treated using disease modifying anti-rheumatic drugs and biological response modifiers. However, it appears that the presence of arthritis in patients with psoriasis is often missed, as dermatologists generally do not actively search for articular involvement. Screening for arthritis in patients with psoriasis may improve timely diagnosis and treatment of PsA. It has repeatedly been found that the prevalence of inflammatory arthritis is raised in populations with psoriasis, and that the prevalence of psoriasis is raised in populations with inflammatory arthritis. There have only been a few studies estimating the prevalence of psoriatic arthritis (PsA) in the general population, providing rates between 0.04 and 0.1%. These studies likely underestimate the “true” prevalence of psoriatic arthritis, because the dermatological and rheumatological criteria applied will often lead to exclusion of cases with mild or early disease. In patients with severe psoriasis, the estimates of the prevalence of PsA among patients with psoriasis range widely from 6 to 42%. The aim of this study is to estimate the prevalence of self-reported joint complaints in patients with psoriasis in The Netherlands.

Materials and methods

Design
The study has a two-stage design. In the first stage, a survey by questionnaire was performed in 6000 patients with psoriasis who were members of the Dutch Psoriasis Society (Psoriasis Vereniging Nederland). The questionnaire assessed the presence of joint complaints in general, peripheral arthritis, undifferentiated spondylitis and the extent of psoriatic lesions of the skin and the nails. The questionnaires were enclosed in an issue of the Dutch Psoriasis Society journal, which is regularly distributed among all members (patients with psoriasis) in The Netherlands. Patients were invited to complete the questionnaire and send it to the data collection centre of the Department of Rheumatology of the Radboud University Nijmegen Medical Centre. In the second stage, a subsample
PART V

of 98 patients stratified according to the amount of self-reported joint complaints (none, 1-4 joints and ≥ 5 joints) has been investigated. These patients were invited to visit the Department of Dermatology for physical examination. The study was approved by the responsible medical ethics committee.

Survey
The questionnaire items included the modified Amor criteria for the diagnosis of ankylosing spondylitis\textsuperscript{1-3} and also included a mannequin to evaluate the tender joints (self-administered joint form)\textsuperscript{14}. The extent and severity of psoriasis was assessed by means of the Self-Administered Psoriasis Area and Severity Index (SAPASI).\textsuperscript{15} To estimate the body surface area covered with psoriatic lesions, patients were instructed to shade a line-drawing silhouette of a body in the areas currently affected by psoriasis. In addition, information regarding family history, demography, dates of onset of joint complaints and psoriasis and treatment were recorded.

Physical examination
It was aimed to recruit a subsample of 100 patients from the survey, stratified in three equally sized strata by the amount of self-reported joint complaints (none, 1-4 joints and ≥ 5 joints). The patients from the subsample were clinically examined for the presence of arthritis by skilled assessors who performed a 68 tender- and a 66 swollen joint count. The joints assessed for tenderness included the distal interphalangeal, proximal interphalangeal and metacarpophalangeal joints of the hands and the metatarsophalangeal joints of the feet, the carpometacarpal and wrist joints (counted separately), the elbows, the shoulders, the acromioclavicular and sternoclavicular joints, the hip, the knee and the talo-tibial and mid-tarsal joints. All of these except for the hips were also assessed for swelling.\textsuperscript{16} The extent of psoriasis was assessed by the Psoriasis Area and Severity Index (PASI).\textsuperscript{17} Finger- and toenails were examined for pitting, ridging, subungual hyperkeratosis, onycholysis, dystrophy, discoloration, leukonychia and elevation. The Nail Psoriasis Severity Index (NAPSI) was calculated to assess the severity of nail involvement.\textsuperscript{18}

Statistical analysis
Statistical analyses were conducted using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). The prevalence of self-reported joint complaints in the complete sample was obtained from the mannequin using descriptive statistics. The occurrence of synovitis in the subsample was assessed using the swollen joint count. The prevalence of joint complaints attributable to synovitis ('corrected prevalence') in the complete sample was
estimated using the information of the synovitis assessment in the subsample by multiple imputation techniques. Patterns of joint involvement were described using the Moll and Wright criteria. The relation between disease duration and joint complaints was analysed using logistic regression, with joint complaints as the dependent variable, and gender and duration of complaints as the independent variables. The Chi-square test was used to analyse the distribution of mono-, oligo- and polyarticular involvement according to gender. A p-value of less than 0.05 was used to indicate statistical significance.

Results

Patients
Of the 6000 questionnaires, 1562 (26%) were returned to the study centre. Twenty-four responders were under 18 years of age and were excluded. From the 1538 remaining patients, 49% was female. The mean age of the patients was 55 years (SD 14.0), ranging from 18 to 90 years. The mean duration of skin psoriasis was 27 years (SD 15.8) and the mean duration of joint complaints was 15 years (SD 10.3), indicating that in most patients psoriasis preceded joint complaints. Of the total group of responding patients, 1077 (70%) were treated by a dermatologist, 275 (18%) were treated by a rheumatologist, and 186 (12%) were treated by both specialists. Ninety-eight patients in the subsample underwent a physical exam for this study. Their mean age was 51 years (SD 14.5). Forty-four patients (45%) were female. The mean duration of skin complaints was 26 years (SD 15.2) and the mean duration of joint complaints was 15 years (SD 12.5).

Severity of psoriasis
The median (interquartile range, IQR) SAPASI in the complete sample was 4.8 (2.8-7.0). Of all patients, 733 (48%) had a mild psoriasis (SAPASI < 5), 537 (35%) had a moderate psoriasis (SAPASI ≥ 5 and < 10), and 150 (10%) had a severe psoriasis (SAPASI ≥ 10). For 118 (8%) patients the SAPASI was not available.
In the subsample, nearly all patients had active psoriasis with a median (IQR) PASI of 3.7 (2.2-5.1) and a median (IQR) NAPSI of 16.0 (3.7-40.5). Of these patients, 73 (74%) had a mild psoriasis (PASI < 5), 19 (19%) had a moderate psoriasis (PASI ≥ 5 and < 10), and 6 (6%) had a severe psoriasis. Most patients (89%) had nail involvement (NAPSI > 0) whereas only 11% had no nail involvement (NAPSI = 0).

Prevalence of joint complaints
Among the 1538 patients, 67% had self-reported complaints in one or more peripheral
joints. The median (IQR) number of painful joints was 3.0 (0.0-9.0). Of all patients, 503 (33%) reported to have no joint complaints, and 98 (6%), 309 (20%), and 628 (41%) patients reported complaints in one joint, 2 to 4 joints, or 5 or more joints, respectively (Table 1). According to the swollen joint count in the patients of the subsample who underwent physical examination, it appeared that in 45% of these patients there was no synovitis present, 28% of the patients had synovitis in 1 to 4 joints, and 27% of the patients had synovitis in at least 5 joints (Table 1). The correction by using the information of observed synovitis in the strata of the subsample led to lower estimations of joint involvement in the sample. Consequently, the percentage of patients without joint involvement increased, the percentage of patients with 1 to 4 involved joints also increased, and the percentage of patients with 5 or more joints involved decreased (Table 1). The prevalence of polyarticular synovitis in patients with psoriasis may be estimated at 27%. In 315 (20%) of the returned questionnaires an Amor score of at least 6 was calculated, indicating an increased risk for the presence of spondylitis

Table 1. Prevalence of joint involvement.

<table>
<thead>
<tr>
<th>Joint Involvement</th>
<th>Sample n = 1538</th>
<th>Subsample n = 98</th>
<th>Corrected</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No involvement</td>
<td>0.33</td>
<td>0.45</td>
<td>0.40</td>
<td>0.30-0.50</td>
</tr>
<tr>
<td>Mono/oligoarticular involvement</td>
<td>0.26</td>
<td>0.28</td>
<td>0.32</td>
<td>0.22-0.41</td>
</tr>
<tr>
<td>Polyarticular involvement</td>
<td>0.41</td>
<td>0.27</td>
<td>0.27</td>
<td>0.22-0.32</td>
</tr>
</tbody>
</table>

95% CI, 95% confidence interval.

Patterns and course of joint involvement
In the complete sample and according to the self-assessment, the most frequently affected large joint was the knee, followed by the shoulder and the hip (Table 2). The small joints of the hands and feet, as well as the wrists, were frequently involved. According to the patterns as described by the Moll & Wright criteria, 2.2% of the patients had predominant distal interphalangeal joint complaints, 30.0% had symmetric polyarticular complaints, 9.6% had asymmetric polyarticular complaints, 25.2% had oligoarticular complaints and 33.0% of patients had no joint complaints at

Table 2. Distribution of self-assessed joint involvement.

<table>
<thead>
<tr>
<th>Joint involvement</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Distal interphalangeal</td>
<td>20.6</td>
</tr>
<tr>
<td>Proximal interphalangeal</td>
<td>36.4</td>
</tr>
<tr>
<td>Metacarpophalangeal</td>
<td>31.3</td>
</tr>
<tr>
<td>Wrist</td>
<td>21.7</td>
</tr>
<tr>
<td>Elbow</td>
<td>15.3</td>
</tr>
<tr>
<td>Shoulder</td>
<td>24.8</td>
</tr>
<tr>
<td>Hip</td>
<td>20.3</td>
</tr>
<tr>
<td>Knee</td>
<td>29.1</td>
</tr>
<tr>
<td>Ankle</td>
<td>17.1</td>
</tr>
<tr>
<td>Metatarsophalangeal</td>
<td>28.6</td>
</tr>
</tbody>
</table>
all. Twenty percent of the patients had a relatively high number of signs and symptoms of spondylitis (Amor score ≥ 6), while 1.6% of the patients had spondylitis as their only joint complaint. Joint involvement was more common in female patients (43%) than in males ($p < 0.05$). Also polyarticular involvement was more frequently reported by women (58%) than by men ($p < 0.05$).

In Figure 1 it is shown that with increase of complaint duration and age, the prevalence of patients with mono/oligoarticular complaints decreases (Figure 1A), while the prevalence of patients with polyarticular complaints increases (Figure 1B). The prevalence of spondylitis complaints also increases with time (Figure 1C).

Among patients with polyarticular complaints, 210 (33%) were regularly seen by a rheumatologist.

Figure 1. Probabilities of mono/oligoarticular, polyarticular and spondylitis complaints according to gender.
Discussion

In the present study we used a survey to estimate the prevalence of self-reported joint complaints in patients with psoriasis. Secondly, a physical examination in a subsample of patients was performed to estimate the prevalence of joint complaints that could be attributed to synovitis. According to the results of this study, a high prevalence (67%) of self-reported joint complaints in the sample of patients with psoriasis was found. The prevalence of polyarticular complaints was higher in women and increased with disease duration. The proportion of patients visiting a rheumatologist was 30%. Using the physical examination results in the subsample as a correction factor, it was estimated that the prevalence of joint complaints attributable to synovitis was 27%. Most patients of the subsample (74%) had a mild psoriasis and 89% of the patients showed psoriasis of the nails. Given the large prevalence of joint complaints in these patients, the relevant question is who and how many of these patients do have arthritis, notably PsA or rheumatoid arthritis.

Diagnosing PsA is a difficult task for a clinician because this is hampered by the absence of a “gold standard”. Persistent arthritis or spondylitis, probably enthesitis, in patients with manifestations of psoriasis who are Rheumatoid Factor negative may be the best description of what characterizes the clinical picture of PsA. The ClASsification criteria for Psoriatic Arthritis (CASPAR criteria) are a means to formally classify patients as having PsA. However, there is still a lack of universal agreement on the diagnosis of PsA. The lack of proper case definitions may also contribute to the difficulty in estimating the prevalence of PsA in the population. Estimates of the prevalence of PsA among patients with psoriasis range widely from 6 to 42%, which may also be caused by differences in populations and study design.

It has been shown that in most of the patients with PsA the skin lesions develop before the arthritis (70%), whereas in 15% both types of manifestations start at the same time, leaving 15% of patients with PsA who firstly develop arthritis. That prompted us in the present study to use the self-assessment method in a large population of patients with psoriasis for reasons of efficiency. It was not possible to invite all participants for physical examination. Therefore, we used a two-stage sampling method in order to ‘correct’ the self-reported estimations by using the information of a stratified subsample of patients who underwent a physical exam. As a result, the estimated prevalence decreased, but remained high. As suggested by the high prevalence of complaints in the large load bearing joints, osteoarthritis is one of the underlying disorders. Nevertheless, polyarticular involvement and involvement of the small joints of the hand and feet also are suggestive for a high prevalence of arthritis. There are some other studies that report the pattern of joint complaints in patients with PsA. Inconclusively, polyarthritis was predominant in
some PsA groups\textsuperscript{26,27}, while oligoarthritis was predominant in others\textsuperscript{28,29}. Until now, the highest prevalence of self-reported joint complaints in patients with psoriasis was found by Van Romunde et al., who found a prevalence of self-reported joint complaints of 49\% in a Dutch population-based cohort regarding patients with psoriasis. The small group (41 versus 1538 patients) and perhaps a lower mean age (44 versus 55 years) may contribute to the difference with our study. Of note, after physical and radiological examination of the group of patients with psoriasis, the authors found a prevalence of arthritis of 20\%.\textsuperscript{30}

In the current study, major spinal complaints were present in 20\% of the patients, with a tendency to increase with time. Spinal involvement in clinically diagnosed PsA (axial PsA) has a prevalence between 40\% and 78\%, depending on the criteria utilized for classification.\textsuperscript{31} For assessment purposes, axial PsA was considered similar as ankylosing spondylitis.\textsuperscript{32,33} Although there are studies that underscore the need for a clinical evaluation of axial involvement in psoriatic arthritis, in clinical practice there is currently no established way for classifying and evaluating spinal involvement in PsA. Therefore, spinal disease may not be properly recognized and the incidence of spinal involvement in patients with PsA may be underestimated.\textsuperscript{34}

This study has limitations. The two-stage sampling procedure relies on joint count assessments in a subsample of the patients instead of a complete ascertainment. The response rate of the survey was 26\%, which is quite low in comparison with population based surveys that may have response rates of 40\%. The low response rate makes the survey more liable to selection bias, presumably in direction of overestimation of the prevalence of joint complaints. For reasons of privacy, it was not possible to achieve data of non-responders for comparison with responders to the survey. However, even in the unlikely scenario that all non-responders do not have joint complaints, the prevalence of joint complaints would be 15\%.

In conclusion, we found a high prevalence of articular complaints in Dutch patients with psoriasis, who showed polyarticular complaints and complaints indicative of spondylitis. A considerable portion of these patients may have PsA. Therefore, to detect patients with PsA in a population of patients with psoriasis, a screening procedure may be fruitful. PsA can be treated well nowadays.\textsuperscript{35} Early screening, proper diagnosis and early effective treatment are the keys for an optimal treatment strategy for PsA.
CHAPTER 16

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CHAPTER 17

Daily practice assessment of liver injury in patients with psoriasis on methotrexate

The antimetabolite methotrexate is one of the most widely used systemic therapies for psoriasis. However, its use is limited by potential side effects such as bone marrow toxicity and hepatic fibrosis. The use of liver biopsy has been advocated for monitoring patients with psoriasis who are receiving methotrexate. This recommendation is controversial, as evidence points out that liver biopsies are not routinely necessary in patients with rheumatoid arthritis who are undergoing treatment with methotrexate.

Recently, several biochemical parameters have been investigated as a marker of liver toxicity with the main aim to predict the development of liver fibrosis in order to avoid liver biopsies. The amino-terminal propeptide of type III procollagen (PIIINP) is an extension peptide of the type III procollagen, which is cleaved off during conversion from type III procollagen to type III collagen and released into serum. Elevated serum PIIINP reflects enhanced collagen turnover, including synthesis and deposition as well as alteration in degradation and elimination. One of the earliest studies in psoriasis showed that patients with liver fibrosis had significantly higher PIIINP levels.

Despite the optimism that PIIINP measurement might be used as a biomarker for liver fibrosis in methotrexate-treated patients with psoriasis, there are still a few unresolved questions. The diagnostic value of a single measurement is unclear as a single serum PIIINP level does not discriminate between individuals with and without significant liver pathology. Moreover, a relatively high frequency of abnormal results has been reported in patients with normal or nonspecific liver histology. This may be partially explained by the fact that PIIINP levels can be raised in patients with psoriatic arthritis, which is a common comorbidity in patients with psoriasis.

In each patient treated with methotrexate at the Radboud University Nijmegen Medical Centre Department of Dermatology, a liver biopsy is performed after a cumulative dose of 1.5 g methotrexate according to the guidelines of the Dutch Society of Dermatology and Venereology. Since April 2006, patients with psoriasis treated with methotrexate are additionally monitored for liver injury by assessment of PIIINP (UniQ PIIINP RIA, Orion Diagnostica Oy, Espoo, Finland), preferably each 3 months.

At the end of 2008, PIIINP serum levels were assessed in 211 patients with psoriasis, including 113 males and 98 females with a mean age of 49.4 years. In this group, PIIINP levels were determined 686 times. The number of PIIINP values assessed per patient ranged from 1 to 11. For 110 patients, three or more consecutive PIIINP values were available.

In the same group, a liver biopsy was performed 164 times in 75 patients since 1986. The number of liver biopsies performed per patient ranged from 1 to 9. Of all 164 liver biopsies, 124 were classified as Roenigk grade I, 25 as Roenigk grade II, and 11 as Roenigk grade
III A. For 4 liver biopsies no histological classification was provided. No cases of moderate to severe liver fibrosis (Roenigk grade IIIB) or cirrhosis (Roenigk grade IV) were found. According to the Manchester protocol, indications for considering liver biopsy are elevation of pretreatment PIIINP above 8.0 microgram/litre (µg/l), elevation of PIIINP above the normal range (1.7-4.2 µg/l) in at least three samples over a 12-month period, or elevation of PIIINP above 8.0 µg/l in two consecutive samples. Withdrawal of methotrexate is indicated after elevation of PIIINP above 10.0 µg/l in at least three samples in one 12-month period. In our cohort, 72 patients showed at least one PIIINP value of more than 4.2 µg/l. Nineteen patients had an indication for considering liver biopsy according to the Manchester protocol. In two of these patients a single serum PIIINP level of more than 10.0 µg/l was found. In 5 of the 19 patients with increased PIIINP series, a liver biopsy was actually performed during or after the PIIINP measurements. These liver biopsies did not reveal any sign of significant liver damage as 4 biopsies were classified as Roenigk grade I and one biopsy was classified as Roenigk grade IIIA (in a patient with a history of hepatitis A and type II diabetes). Ten of the 19 patients with increased PIIINP levels had a history of psoriatic arthritis.

The present study shows that hepatotoxicity is limited in a cohort of patients with psoriasis treated with methotrexate according to the guidelines of the Dutch Society of Dermatology and Venereology. Since 1986 no case of serious liver fibrosis or cirrhosis was discerned in this group. As investigated previously, liver injury in long-term methotrexate treatment in psoriasis is relatively infrequent. Likewise, only 19 out of 211 patients had increased PIIINP series, of whom 10 had psoriatic arthritis, which may have influenced PIIINP levels. Furthermore, in 5 of the 19 patients with increased PIIINP levels (including one patient with psoriatic arthritis), a liver biopsy did not reveal any significant liver damage. These data reconfirm that routine liver biopsies may be abolished as serious liver injury is uncommon. Monitoring liver damage only by PIIINP has been shown to reduce the number of liver biopsies considerably and provides an acceptable tool to monitor for liver damage.
References


SUMMARY AND DISCUSSION
PART IV

SUMMARY AND DISCUSSION
SUMMARY AND DISCUSSION
Summary and discussion

Introduction
In the present thesis, the outcomes of observational studies on biological treatment for severe psoriasis in daily practice have been described. Most study data were obtained from a patient registry, in which efficacy and safety data on biological therapies for psoriasis were prospectively collected. Additional studies concentrated on the economic impact of psoriasis and psoriasis treatment, procedures on prescription and application of biological therapies in daily practice and comorbidities in patients with (severe) psoriasis. In this chapter, the main conclusions of the current thesis will be outlined and discussed in accordance with the objectives as formulated in Chapter 5.
Prospective investigation of the effects and side effects of biological treatment in patients with severe psoriasis in daily practice.

Effects

In the current thesis, the results of different studies on the effects and side effects of biological therapies for patients with severe psoriasis in daily practice have been outlined. This type of investigation is part of 'outcomes research', which is the science of defining the patient experience and measuring the end result or consequence of medical care. In most studies the term 'efficacy' was used to describe the effects of biological therapies. However, as these studies were conducted in a real life setting, the term 'effectiveness' would have been more appropriate. Outcomes research has the potential to further define the effectiveness and generalization of randomized controlled trials (RCTs). To keep consistency with the content of this thesis, the term efficacy will be used all the same in the following paragraphs.

Chapter 6, 7 and 8 of this thesis include the outcomes of the analyses after one, two and three years of investigation, respectively. Efficacy of biologics can be obtained from these studies, as well as from the reimbursement application data analysis (Chapter 12) and antibody analysis (Chapter 10). Most study data concern etanercept, followed by efalizumab and adalimumab.

In general, biologics proved effective and safe treatments of psoriasis in daily clinical practice, even in a high-need population. In contrast to etanercept, efalizumab was beneficial only in small percentage of patients. The dropout rate in the efalizumab-treated group was substantial, i.e. 29% after 12 weeks, 47% after 24 weeks, 62% after approximately two years, and 71% after approximately three years of treatment (data not presented). Moreover, antibodies against adalimumab were associated with lower serum adalimumab concentrations and non-response or loss of response to treatment with adalimumab (Chapter 10).

In Table 1 an overview of efficacy of biological treatment in patients with severe psoriasis in daily practice compared with RCTs is given. Initially, the efficacy data of etanercept and efalizumab seemed roughly comparable to the results of RCTs, although no head-to-head comparison could be made. However, as the study population grew, critical comparison with RCT data revealed that the efficacy of biological treatment in daily clinical practice was actually lower than the efficacy of biologics in RCTs. This is the matter not only when observing the registry data, but also with respect to the efficacy data presented in the reimbursement application study and the study on antibodies against adalimumab. As expected, the efficacy percentages obtained from per protocol (PP) analyses appear to be
slightly higher than the percentages obtained from intention to treat (ITT) analyses. The reason for the lower efficacy of biologics for psoriasis in daily clinical practice compared with RCTs could not exactly be discerned in the studies performed. Multiple factors related to the patient, the physician (or investigator) and the pharmaceutical may play a role. First of all, the study population in RCTs may be different from the population observed in daily practice with respect to baseline Psoriasis Area and Severity Index (PASI), weight, medication history, comorbidities and interfering medication. As outlined in Chapter 8, the influence of patient characteristics (including baseline PASI, body mass index, number of previous systemic treatments and duration of psoriasis) on the response of biological treatment was limited. The study population in this analysis, however, was small, but trends were observable. To establish the actual contribution of patient factors to the outcomes of biological treatment in daily practice, a multivariate analysis should be executed in a much larger cohort.

Secondly, the course of biological treatment in RCTs may be different from daily practice, as a result of differences in the usage of biologics by patients or differences in intervention by the physician (defined as ‘clinical strategies’ in Chapter 7). Compared with treatment and follow-up schedules in daily practice, protocols for RCTs are generally more extensive and stricter. Such strictness may increase compliance and adequate use of medication by patients, known as the ‘Hawthorne effect’. Furthermore, as outlined in Chapter 7, frequently applied clinical strategies such as treatment interruptions, dosage adjustments and combinations of treatment influence treatment outcome of biological therapies for psoriasis in routine practice. However, to what extent these interventions influence the outcomes is difficult to measure, as most interventions are done reactively, and not proactively. With regard to combination of systemic therapies, Chapter 9 shows that combining etanercept with methotrexate is beneficial and apparently safe when efficacy of etanercept monotherapy is insufficient.

Thirdly, outcomes may be influenced as a result of industry sponsorship, conflicts of interest, competitive inclusion of patients and specific treatment targets, which may play a role in RCTs and observational studies to a different extent. In an article by Perlis et al., studies with potential conflicts of interest were associated with greater methodological quality scores, greater number of study participants and greater likelihood of reporting a result favourable to the study intervention compared with studies without conflicts of interest. Another study found that systematic bias favoured products which were made by the company funding the research. Explanations included the selection of an inappropriate comparator to the product being investigated and publication bias. From a purely scientific point of view, all factors that may have influenced the treatment
### Table 1. Overview of efficacy of biological treatment in patients with severe psoriasis in daily practice compared to randomized controlled trials.

<table>
<thead>
<tr>
<th></th>
<th>Week 12</th>
<th>Week 24</th>
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<td></td>
<td>PASI 50</td>
<td>PASI 75</td>
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<td></td>
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<tr>
<td>Etanercept 2 x 50 mg group</td>
<td>82</td>
<td>39</td>
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<td>Etanercept 2 x 25 mg group</td>
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<td>Efalizumab</td>
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<td>Adalimumab</td>
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Presented numbers indicate the percentage of patients achieving a specific PASI response. PASI, Psoriasis Area and Severity Index; PASI 50, 50% reduction in PASI relative to baseline; PASI 75, 75% reduction in PASI relative to baseline; PASI 90, 90% reduction in PASI relative to baseline; ITT, Intention To Treat; PP, Per Protocol; BAD, British Association of Dermatologists. *Week 12 data were obtained by ITT analysis. **Week 24 data were obtained by PP analysis.

Outcomes would have been labelled ‘confounders’. However, the primary aim of the observational studies in this thesis was to prospectively investigate the effects and side
effects of biological treatment in patients with severe psoriasis in a real life setting, and not under ideal circumstances. The analyses performed did therefore not measure the internal validity of biological therapies. Additionally, within the framework of the current thesis, treatment efficacy data on RCTs were adapted from systematic reviews. Relevant RCTs not included in the review may therefore be missing. Moreover, data analysis was performed differently in the studies performed. Missing values may cause both systematic and unpredictable bias, leading to a discordance between reported ITT and PP analyses. In most publications on RCTs, only results for a treatment-optimised subpopulation (per protocol analysis) are presented, whereas for daily routine therapy the ITT data appear to be more relevant. In a study on differences in efficacy between ITT and PP analyses for patients with psoriasis and atopic dermatitis, striking differences in the therapeutic effect between both groups were found using relative PASI and SCORAD (SCORing Atopic Dermatitis) score improvement. All data from the publications included in the reviews presented in Table 1, however, were obtained through ITT analyses, mostly in combination with methods of non-responder imputation or last observation carried forward in case of missing data. In spite of that, the efficacy data presented in this review are still higher than the observational study data obtained through ITT analyses.

**Side effects**

In all studies performed, biological therapies were apparently safe as serious adverse events were infrequent. After two years of treatment, 93% of all patients reported at least one adverse event that was mild in most cases (Chapter 7). After three years of treatment, serious adverse events included exacerbations of psoriasis requiring hospitalization, muscle and joint complaints, basal cell carcinomas, squamous cell carcinomas, one cerebrovascular accident, one pneumonia, one infusion reaction, one case of breast cancer and one oesophageal carcinoma. Moreover, two female patients died of a sudden cardiac arrest during etanercept treatment (Chapter 8).

Whether adverse events were related to the use of biologics was usually difficult to establish. Besides, comparison of frequencies of adverse events with other studies is problematic due to differences in interpretation and classification of such events. In the studies performed, adverse events were of the same nature as those observed in RCTs. It would be sensible, though, to have a control group, either composed of healthy individuals, patients with psoriasis using systemic therapies other than biologics, or patients with diseases other than psoriasis who are treated with biologics. Confounding factors, as mentioned earlier, may not only affect outcomes on treatment efficacy, but also outcomes on safety of treatment.
PART VI

Although biological therapies were apparently safe for the treatment of severe psoriasis in the short term, long-term safety data on biologics are sparse, and long-term safety data on these therapies for psoriasis in daily practice are lacking. That pharmacovigilance is extremely important for relatively new drugs such as biologics was illustrated recently by the efalizumab case. In February 2009, efalizumab was withdrawn from the market, because there was a risk of serious side effects in patients receiving the medicine. These included three confirmed cases of progressive multifocal leukoencephalopathy (PML) reported between September 2008 and January 2009 in patients who had been receiving efalizumab for more than three years. Remarkably, in May 2008 an article on efalizumab was published, which enclosed the longest continuous study data (up to 36 months) using a biologic therapy for psoriasis at that moment. In that study, the safety profile of efalizumab was stable, with no new or no increase in common events over 36 months of treatment. So, besides RCTs and observational studies, spontaneous reports of adverse events are essential to preserve safety when using biological therapies.

Investigation of the economic impact of psoriasis and psoriasis treatment, including biological therapies.

Part III, Chapter 11 of the current thesis concerned a study on the economic impact of high-need psoriasis in daily clinical practice before and after the introduction of biologics. In this study, direct costs, related to the treatment of high-need psoriasis in daily clinical practice, appeared significantly higher during the biological treatment period than during the period before. In the biological treatment period, direct costs increased by €7,566.- per patient per year. For 6 patients in the cohort, introduction of biologics led to a reduction of direct costs, as these patients did not need long hospitalizations. Introduction of biological therapies for psoriasis may therefore have cost-neutral or cost-saving effects, especially for patients who otherwise require long hospitalizations. Besides, biological therapy was accompanied by a high patient satisfaction, indicated by a mean Treatment Satisfaction Questionnaire for Medication (TSQM) score of 77.8.

The results of this study and other studies on health economics with reference to psoriasis therapies are essential for policy makers. Although cost estimations for different therapies can be made during RCTs, the actual cost of illness may best be measured using real life practice data. The current study did not reflect the cost of illness on psoriasis in total, as only patients with high-need psoriasis were analysed, costs on comorbidities were not measured and indirect costs were not included.

Considering the fact that only 0.4% of all patients with psoriasis appeared to be treated with biologics (Chapter 12), the effect of the increase in direct costs due to introduction
CHAPTER 18

of biological therapies on the cost of illness for psoriasis as a whole may be limited. However, as for other indications, the number of prescriptions of biologics for psoriasis may increase as experience with these pharmaceuticals is growing. Without intervention of the government, the expenditures for different drugs in The Netherlands will rise 9 to 10% per year, particularly as a result of the use of expensive medication. In 2008, the sales of these expensive drugs increased with 158 million Euro to 852 million Euro. 2

Investigation of procedures on prescription and application of biological therapies in daily practice.

Chapter 12, 13 and 14 focused on procedures on prescription and application of biological therapies in daily practice. Chapter 12 and 13 concerned analyses of national reimbursement application data on biologics, indicated for psoriasis and psoriatic arthritis, respectively. Outcomes of both analyses demonstrated that dermatologists and rheumatologists are familiar with the demanded criteria for reimbursement of biological therapies. Of all initial treatment applications, 94.5% and 94.6% were approved by LABAG (LAndelijke Beoordeling Aanvragen Geneesmiddelen, National Evaluation of Applications of Drugs) for psoriasis and psoriatic arthritis, respectively. In the meantime, biologics were prescribed for only a small percentage of patients. In January 2008, only 0.4% of Dutch patients with psoriasis were treated with etanercept or efalizumab.

As long as long-term efficacy and safety data on biologics are lacking, careful compilation of treatment and reimbursement criteria is important for patients as well as for health care providers. These criteria enable correct treatment indication and prevent needless continuation of ineffective therapy. Furthermore, such criteria enable regulation of costs for medical care.

On the contrary, as a consequence of treatment and reimbursement criteria, physicians may not always be able to choose freely between different therapeutic options. Patients may therefore not always be treated with the most appropriate therapy available. According to the new psoriasis treatment guideline formulated by the Dutch Society of Dermatology and Venereology (Nederlandse Vereniging voor Dermatologie en Venereologie, NVDV), biologics may be prescribed for the treatment of psoriasis if patients are unresponsive, intolerant or have contraindications to UVB or PUVA, and methotrexate or ciclosporin. 14 As these treatment criteria are slightly less strict compared with the criteria in the former guideline, more patients will currently be eligible for biological therapy.

Chapter 14 concerned the outcomes of a panel meeting on the use of infliximab amongst dermatologists, gastroenterologists and rheumatologists. Taken the guidelines from dermatology, gastroenterology and rheumatology together, it becomes obvious that
differences exist between the recommended dosage of infliximab for each indication (e.g. 3 mg/kg for rheumatoid arthritis and 5 mg/kg for Crohn’s disease). Besides, none of the guidelines from each specialty gives indicators how and when to choose for dosage adjustment or frequency intensification in case of loss of response. The need of concomitant administration of immunosuppressants during treatment with infliximab has been stressed by most, but not all, of the guidelines throughout the different specialties. In the opinion of the panel, routine measurement of vital signs during infusion is not valuable in detecting acute infusion reactions.

Not only the high prevalence of comorbidities in patients with immune-mediated disorders, but also the shared knowledge of different medical specialists on the use of immunomodulative therapies including biologics advocates a multidisciplinary approach for chronic inflammatory diseases such as psoriasis.

Investigation of the occurrence of comorbidities in patients with (severe) psoriasis.

In Chapter 15, 16 and 17, the prevalence and relevance of comorbidities in patients with psoriasis was studied. Special attention was paid to cardiovascular risk factors and cardiovascular diseases, joint complaints including psoriatic arthritis, and liver injury in patients using methotrexate.

Regarding cardiovascular risk factors, a significantly higher prevalence of obesity, smoking, and hypertension was found for patients with high-need psoriasis compared with non-psoriatic controls. Furthermore, the mean monthly amount of alcohol consumption was higher in the patients with high-need psoriasis. Most striking was the high prevalence of obesity in the high-need psoriasis cohort. This was observed not only in the study on cardiovascular risk factors, but also in the three-year analysis (Chapter 8). Likewise, in the antibody analysis (Chapter 10) mean body mass index was 29 kg/m².

As in the general population, monitoring weight in patients with psoriasis is essential to assess the risk for development of cardiovascular disease. Moreover, measurement of patients’ weight may be necessary for adequate selection and dosing of systemic therapies, especially biologics. For ustekinumab, which is a fixed-dosed therapy in principle, the prescribed dosage should ideally depend on whether a patients has a body weight below or above 100 kg. Dosage modifications like these may be needed for other fixed-dosed biologics as well. In the cohort investigated currently, the used etanercept dosage was considerably higher than in RCTs, as depicted in the economic analysis in Chapter 11.

In Chapter 16, the outcomes of a survey on joint complaints in patients with psoriasis were described. As deduced from the survey, the prevalence of self-reported joint complaints in patients with psoriasis is high (67%). The prevalence of synovitis, however, is considerably
lower. Osteoarthritis is probably one of the underlying disorders, since the prevalence of complaints in the large load bearing joints was substantial. Nevertheless, the frequent polyarticular involvement and involvement of the small joints of the hand and feet are suggestive for a high prevalence of arthritis. Making the right diagnosis in patients with psoriasis who report joint complaints is crucial for prognostication and therapeutic decision making. A solid rheumatologic examination in these patients is therefore essential.

Chapter 17 focussed on liver injury in patients with psoriasis using methotrexate. The study showed that hepatotoxicity was limited in a cohort of Dutch patients with psoriasis treated with methotrexate. Since 1986 no case of serious liver fibrosis or cirrhosis was discerned in this group. This is remarkable, especially as non-alcoholic fatty liver disease seems to be frequent in patients with severe chronic plaque psoriasis.\textsuperscript{19} Routine liver biopsies may consequently be abolished or substituted by amino-terminal propeptide of type III procollagen (PIIINP) measurement.

Even in the era of biological therapies, methotrexate is still a convenient therapeutic option in the treatment of psoriasis. As shown in Chapter 9, combining etanercept with methotrexate is reasonable when efficacy of etanercept monotherapy is insufficient, or when rapid deterioration of psoriasis after abrupt discontinuation of methotrexate is expected. Furthermore, addition of methotrexate to biological therapy may prevent development of anti-biologic antibodies, and may relieve symptoms related to psoriatic arthritis.
References


CHAPTER 19

Samenvatting en discussie

Introductie
In dit proefschrift worden de uitkomsten van observationele onderzoeken naar de behandeling van patiënten met ernstige psoriasis met biologicals in de dagelijkse praktijk beschreven. De meeste onderzoeksgegevens kwamen voort uit een patiëntenregistry waarin effectiviteits- en veiligheidsdata ten aanzien van behandeling van psoriasispatiënten met biologicals prospectief verzameld werden. Daarnaast werden er studies verricht naar de economische impact van psoriasis en behandelingen van psoriasis, naar procedures rondom het voorschrijven en aanvragen van biologicals in de dagelijkse praktijk, en naar comorbiditeiten bij patiënten met (ernstige) psoriasis. In dit hoofdstuk zullen de belangrijkste conclusies van dit proefschrift worden uiteengezet en bediscussieerd aan de hand van de doelstellingen zoals geformuleerd in hoofdstuk 5.
Prospectief onderzoek naar de effecten en neveneffecten van behandeling met biologicals bij patiënten met ernstige psoriasis in de dagelijkse praktijk.

Effecten

In dit proefschrift worden de resultaten van verschillende studies met betrekking tot de effecten en neveneffecten van behandeling met biologicals van patiënten met ernstige psoriasis in de dagelijkse praktijk uiteengezet. Dit type onderzoek maakt deel uit van ‘outcomes research’, wat is gedefinieerd als de wetenschap waarin de ervaring van de patiënt met medische zorg wordt nagegaan, en waarin het eindresultaat of consequenties van medische zorg wordt gemeten.1 In de meeste studies werd de Engelse term ‘efficacy’ gebruikt om de effectiviteit van biologicals te beschrijven. Echter, aangezien vrijwel alle onderzoeken werden uitgevoerd in de dagelijkse praktijk zou de term ‘effectiveness’ wellicht geschikter zijn geweest.2 Met behulp van outcomes research kan de effectiviteit en de generaliseerbaarheid van gerandomiseerde gecontroleerde onderzoeken (randomized controlled trials, RCTs) verder bepaald worden.1 Hoofdstuk 6, 7 en 8 van dit proefschrift bevatten de uitkomsten van de analyses na respectievelijk één, twee en drie jaar onderzoek. De effectiviteit van biologicals kan herleid worden uit deze onderzoeken, evenals uit de analyse van de gegevens over de aanvragen voor vergoeding van biologicals (Hoofdstuk 12) en de antistoffenanalyse (Hoofdstuk 10). De meeste onderzoeksgegevens betreffen etanercept, gevolgd door efalizumab en adalimumab.

Over het algemeen waren biologicals aantoonbaar effectief en veilig bij de behandeling van patiënten met ernstige psoriasis in de dagelijkse praktijk. In tegenstelling tot etanercept was efalizumab slechts effectief bij een klein percentage van alle patiënten. Het percentage uitvallers in de met efalizumab behandelde groep was substantieel, i.e. 29% na 12 weken, 47% na 24 weken, 62% na ongeveer twee jaar en 71% na ongeveer drie jaar behandeling (data niet getoond). Daarnaast waren antilichamen tegen adalimumab geassocieerd met lagere concentraties van adalimumab in het serum, en verminderde effectiviteit of verlies van effectiviteit van het middel (Hoofdstuk 10).

In Tabel 1 wordt een overzicht gegeven van de effectiviteit van biologicals bij de behandeling van patiënten met ernstige psoriasis in de dagelijkse praktijk in vergelijking met de resultaten zoals weergegeven in RCTs.34 In eerste instantie leken de effectiviteitsdata ten aanzien van etanercept en efalizumab grofweg vergelijkbaar met de resultaten van RCTs, hoewel er geen directe vergelijking gemaakt kon worden. Echter, naarmate de studiepopulatie in omvang toeneemde werd duidelijk dat de effectiviteit van biologicals in de dagelijkse praktijk feitelijk lager uitviel dan de effectiviteit van deze middelen in RCTs. Dit is niet
alleen het geval wanneer de registrydata worden bekeken, maar ook ten aanzien van de
effectiviteitsdata zoals weergegeven in het onderzoek naar de aanvragen voor vergoeding
van biologicals en de studie naar antistoffen tegen adalimumab. Zoals verwacht lijken de
effectiviteitspercentages verkregen via ‘per protocol’ (PP) analyses enigszins hoger uit te
vallen dan de percentages verkregen door middel van ‘intention to treat’ (ITT) analyses.
De reden voor de lagere effectiviteit van biologicals in de dagelijkse praktijk vergeleken
met RCTs kon in de studies die gedaan werden in het kader van dit onderzoeksproject
niets worden vastgesteld. Multipele factoren, gerelateerd aan de patiënt, de arts (of
onderzoeker) en het geneesmiddel, spelen mogelijk een rol hierbij.

Ten eerste is er mogelijk een verschil tussen de onderzoekspopulatie in RCTs en
de populatie die werd gevolgd in de dagelijkse praktijk op het gebied van baseline
Psoriasis Area and Severity Index (PASI), gewicht, medicatiehistorie, comorbiditeiten
en interfererende medicatie. Zoals weergegeven in hoofdstuk 8 bleek de invloed van
patiëntkarakteristieken (zoals baseline PASI, body mass index, het aantal systemische
behandelingen in het verleden en de duur van de psoriasis) op de respons op behandeling
met biologicals beperkt. De studiepopulatie van dit onderzoek was klein, maar desondanks
waren er trends waarneembaar. Om de werkelijke bijdrage van patiëntfactoren aan de
outcomes van behandeling met biologicals in de dagelijkse praktijk vast te stellen zou een
multivariate analyse uitgevoerd moeten worden in een veel groter cohort.

Ten tweede is er mogelijk een verschil tussen het beloop van de behandeling met
biologicals in RCTs en de dagelijkse praktijk als het gevolg van verschillen in het
gebruik van medicatie door de patiënt, of verschillen in interventies verricht door de arts
(gedefinieerd als ‘clinical strategies’ in hoofdstuk 7). Vergeleken met behandelings- en
follow-upschema’s in de dagelijkse praktijk zijn protocollen voor RCTs in het algemeen
uitgebreider en strikter. Mogelijk leidt een dergelijke striktheid tot een grotere compliance
van patiënten en een meer adequaat gebruik van medicatie, iets wat bekend staat als
het ‘Hawthorne effect’.5 Daarnaast beïnvloeden frequent toegepaste klinische strategieën,
zoals onderbreking van de behandeling, dosisaanpassingen en combinatiebehandelingen
de uitkomsten van behandeling van psoriasispatiënten met biologicals in de dagelijkse
praktijk, zoals weergegeven in hoofdstuk 7. In welke mate dergelijke interventies de
uitkomsten beïnvloeden is echter lastig vast te stellen, aangezien de meeste interventies
reactief, en niet proactief, worden verricht. Met betrekking tot combinaties van systemische
behandelingen laat hoofdstuk 9 zien dat de combinatie van etanercept met methotrexaat
zinvol en ogenschijnlijk veilig is indien de effectiviteit van etanercept monotherapie
onvoldoende blijkt.

Ten derde worden uitkomsten van onderzoeken mogelijk beïnvloed door sponsoring door
Tabel 1. Overzicht van de effectiviteit van biologicals bij de behandeling van patiënten met ernstige psoriasis in de dagelijkse praktijk in vergelijking met gerandomiseerde gecontroleerde onderzoeken.

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De getoonde getallen geven het percentage patiënten weer dat een specifieke PASI respons bereikt. PASI, Psoriasis Area and Severity Index; PASI 50, 50% reductie in PASI ten opzichte van baseline; PASI 75, 75% reductie in PASI ten opzichte van baseline; PASI 90, 90% reductie in PASI ten opzichte van baseline; ITT, Intention To Treat; PP, Per Protocol; BAD, British Association of Dermatologists. ³Week 12 data werden verkregen door middel van ITT analyse. ⁴Week 24 data werden verkregen door middel van PP analyse.

industrieën, belangenverstrengeling, competitieve inclusie van patiënten en specifieke behandelingstargets. De mate waarin deze factoren een onderzoek beïnvloeden verschilt
mogelijk tussen RCTs en observationele onderzoeken. In een artikel van Perlis et al. werd aangetoond dat studies met potentiële belangenconflicten geassocieerd waren met grotere methodologische kwaliteitsscores, een groter aantal studieparticipanten en een grotere kans op publicatie van onderzoeksresultaten in het voordeel van de interventie vergeleken met studies waarin belangenconflicten geen rol speelden. Een ander onderzoek toonde dat systematische bias het product wat afkomstig is van de firma die de studie bekostigd vaak ten goede komt. Verklaringen hiervoor omvatten de selectie van een verkeerd controleproduct ter vergelijking van het onderzoeksproduct, evenals publicatiebias. Uit puur wetenschappelijk oogpunt zouden alle factoren die de behandelingsuitkomsten mogelijk beïnvloed hebben ‘confounders’ genoemd worden. Het primaire doel van de observationele onderzoeken in dit proefschrift was echter juist het prospectief onderzoeken van effecten en neveneffecten van behandeling met biologicals van patiënten met ernstige psoriasis in een dagelijkse praktijk setting, en niet onder ideale omstandigheden. De uitgevoerde analyses zeggen dientengevolge niets over de interne validiteit van biologicals. Daarnaast werden, ten behoeve van dit proefschrift, de effectiviteitscijfers van RCTs afgeleid uit systematic reviews. Relevante RCTs die niet zijn opgenomen in deze reviews ontbreken dus mogelijk. Bovendien werden data-analyses in de studies op verschillende manieren verricht. Het ontbreken van gegevens veroorzaakt mogelijk een systematische en onvoorspelbare bias, wat leidt tot verschillen tussen gerapporteerde ITT en PP analyses. In de meeste publicaties omtrent RCTs worden enkel de resultaten van een subpopulatie met een geoptimaliseerd behandelingsbeloop gepresenteerd (PP analyse), terwijl voor behandelingen in de dagelijkse praktijk de ITT gegevens relevanter blijken te zijn. In een onderzoek over de verschillen in effectiviteit tussen ITT en PP analyses bij patiënten met psoriasis en atopisch eczeem werden opvallende verschillen gevonden in het therapeutisch effect tussen de twee groepen wanneer gebruik werd gemaakt van de relatieve verbetering van de PASI en SCORAD (SCORing Atopic Dermatitis) score. Echter, alle gegevens uit de publicaties die geïncludeerd werden voor de reviews zoals weergegeven in Tabel 1 werden verkregen door middel van ITT analyses, meestal in combinatie met methodes als ‘non-responder imputation’ of ‘last observation carried forward’ in het geval van ontbrekende gegevens. Desondanks zijn de effectiviteitscijfers van deze reviews nog steeds hoger dan de data van de observationele onderzoeken die door ITT analyses verkregen werden.

Neveneffecten
In alle onderzoeken die verricht werden in het kader van dit proefschrift leek behandeling met biologicals veilig te zijn. Ernstige bijwerkingen kwamen weinig voor. Na twee jaar
behandeling rapporteerde 93% van alle patiënten ten minste één bijwerking, die meestal mild van aard was (Hoofdstuk 7). Na drie jaar behandeling werden er enkele ernstige bijwerkingen gemeld, namelijk exacerbaties van psoriasis leidend tot ziekenhuisopname, spier- en gewrichtspijnen, basaalcelcarcinomen, plaveiselcelcarcinomen, een cerebrovasculair accident, een pneumonie, een infusiereactie, een mammacarcinoom en een oesofaguscarcinoom. Tevens overleden er twee vrouwelijke patiënten aan een acute hartstilstand tijdens behandeling met etanercept (Hoofdstuk 8).

Of bijwerkingen gerelateerd waren aan het gebruik van biologicals was over het algemeen moeilijk vast te stellen. Daarnaast is de vergelijking van bijwerkingenfrequenties met andere studies problematisch vanwege verschillen in interpretatie en classificatie van dergelijke events. In de verrichte studies waren bijwerkingen van dezelfde aard als de bijwerkingen die gezien werden in RCTs. Het zou desondanks zinvol zijn om een controlegroep te hebben, samengesteld uit gezonde individuen, psoriasispatiënten met systemische therapieën anders dan biologicals, of patiënten met ziektes anders dan psoriasis die behandeld worden met een biological. Confounders, zoals eerder genoemd, beïnvloeden mogelijk niet alleen de effectiviteitscijfers, maar ook de uitkomsten ten aanzien van de veiligheid van de behandeling.

Hoewel de behandeling met biologicals van patiënten met ernstige psoriasis veilig leek te zijn op de korte termijn zijn lange termijn veiligheidsgegevens over biologicals schaars, en zijn lange termijn veiligheidsgegevens over deze behandelingen voor psoriasis in de dagelijkse praktijk überhaupt niet beschikbaar. Dat geneesmiddelenbewaking buitengewoon belangrijk is voor relatief nieuwe geneesmiddelen zoals biologicals werd recent geïllustreerd door de efalizumab casus. In februari 2009 werd efalizumab van de markt gehaald, omdat er een risico was op ernstige bijwerkingen bij patiënten die dit medicament gebruikten. Dit omvatte drie bevestigde gevallen van progressieve multifocale leuko-encefalopathie (PML) gerapporteerd tussen september 2008 en januari 2009 bij patiënten die langer dan drie jaar met efalizumab werden behandeld. Opmerkelijk genoeg verscheen er in mei van 2008 een artikel over efalizumab, waarin de op dat moment langste continue studiedata (tot 36 maanden) ten aanzien van het gebruik van een biological voor psoriasis werd weergegeven. In dat onderzoek was het veiligheidsprofiel van efalizumab stabiel, zonder nieuwe of toename van veelvoorkomende bijwerkingen gedurende 36 maanden behandeling. Naast RCTs en observationele studies is spontane rapportage van bijwerkingen daarom noodzakelijk om veiligheid te kunnen handhaven tijdens behandeling met biologicals.
PART VI

Onderzoek naar de economische gevolgen van psoriasis en de behandeling van psoriasis waaronder biologicals.

Deel III, hoofdstuk 11 van dit proefschrift betrof een onderzoek naar de economische gevolgen van ernstige psoriasis in de dagelijkse praktijk, voor en na de introductie van biologicals. In dit onderzoek bleken de directe kosten, gerelateerd aan de behandeling van ernstige psoriasis in de dagelijkse praktijk, significant hoger in de periode waarin behandeld werd met biologicals dan in de periode daarvoor. In de periode waarin behandeld werd met biologicals stegen de directe kosten met €7.566,- per patiënt per jaar ten opzichte van de periode eerder. Voor zes patiënten uit het cohort resulteerde de behandeling met biologicals in een afname van de directe kosten, aangezien langdurige ziekenhuisopnames hiermee werden voorkomen. De behandeling van psoriasis met biologicals kan dus mogelijk een kostenneutraal of kostenbesparend effect hebben, in het bijzonder voor patiënten bij wie langdurige ziekenhuisopnames anders noodzakelijk zijn. Daarnaast ging de behandeling met biologicals gepaard met een grote tevredenheid van patiënten, wat blijkt uit een gemiddelde Treatment Satisfaction Questionnaire for Medication (TSQM) score van 77.8.

De resultaten van deze en andere onderzoeken op het gebied van ‘health economics’ ten aanzien van behandelingen van psoriasis zijn essentieel voor beleidsmakers. Hoewel er ook bij RCTs een inschatting gemaakt kan worden van de kosten voor verschillende therapiën, kunnen de daadwerkelijke ziektegerelateerde kosten (‘cost of illness’) het beste worden berekend met behulp van gegevens uit de dagelijkse praktijk. De huidige studie geeft niet de totale cost of illness voor psoriasis weer, aangezien alleen patiënten met een ernstige psoriasis werden geanalyseerd, en indirect kosten en kosten met betrekking tot comorbiditeiten buiten beschouwing waren gelaten.

Gezien het feit dat slechts 0,4% van alle psoriasispatiënten behandeld bleek te worden met biologicals (Hoofdstuk 12), is het effect van de toename van directe kosten door de komst van biologicals op de totale cost of illness voor psoriasis in zijn geheel waarschijnlijk beperkt. Echter, zoals ook voor andere indicaties zal het aantal voorschriften van biologicals voor psoriasis wellicht stijgen naarmate de ervaring van artsen met deze middelen toeneemt.

Zonder ingrijpen van de overheid stijgen de geneesmiddelenuitgaven op dit moment jaarlijks met 9 tot 10%, in het bijzonder ten gevolge van het gebruik van dure geneesmiddelen. In 2008 nam de omzet van deze dure geneesmiddelen met € 158 miljoen toe tot € 852 miljoen.
Onderzoek naar procedures omtrent het voorschrijven en aanvragen van biologicals in de dagelijkse praktijk.

Hoofdstuk 12, 13 en 14 van dit proefschrift gaan over procedures omtrent het voorschrijven en aanvragen van biologicals in de dagelijkse praktijk. Hoofdstuk 12 en 13 betreffen analyses van data van nationale vergoedingsaanvragen voor biologicals, respectievelijk met als indicatie psoriasis en artritis psoriatica. De uitkomsten van beide analyses laten zien dermatologen en reumatologen bekend zijn met de vereiste criteria voor vergoeding van biologicals. Van alle eerste behandelingsaanvragen voor psoriasis en artritis psoriatica werd respectievelijk 94,5% en 94,6% goedgekeurd door de stichting LABAG (LANdelijke Beoordeling Aanvragen Geneesmiddelen). Ondertussen werden biologicals slechts voor een klein percentage van alle patiënten voorgeschreven. In januari van 2008 werd slechts 0,4% van de Nederlandse patiënten met psoriasis behandeld met etanercept of efalizumab.

Zolang er geen gegevens zijn over de effectiviteit en veiligheid van biologicals op de lange termijn is het zorgvuldig formuleren van behandelings- en vergoedingscriteria in het belang van zowel patiënten als zorgverleners. Dergelijke criteria maken een correctie indicatiestelling voor een behandeling mogelijk en voorkomen dat ineffectieve behandelingen te lang worden gecontinueerd. Daarnaast kunnen met behulp van zulke criteria de kosten voor de gezondheidszorg beter gereguleerd worden.

Aan de andere kant beperken behandelings- en vergoedingscriteria de vrijheid van artsen om uit verschillende behandelingsopties te kunnen kiezen. Patiënten worden daarom mogelijk niet altijd behandeld met de op dat moment meest geschikte therapie. Volgens de nieuwe behandelingsrichtlijn voor psoriasis, die is opgesteld door de Nederlandse Vereniging voor Dermatologie en Venereologie (NVDV), mogen biologicals voorgeschreven worden bij falen van, of contra-indicaties of intoleranties voor UVB of PUVA, en methotrexaat of ciclosporine. Aangezien deze behandelingscriteria minder strikt zijn dan de criteria zoals geformuleerd in de oude richtlijn zullen er momenteel meer patiënten in aanmerking komen voor behandeling met biologicals.

Hoofdstuk 14 beschrijft de uitkomsten van een panelmeeting tussen dermatologen, gastro-enterologen en reumatologen over het gebruik van infliximab. Wanneer de richtlijnen van dermatologie, gastro-enterologie en reumatologie worden samengevat, wordt duidelijk dat er verschillen bestaan tussen de aanbevolen dosering van infliximab voor verschillende indicaties (e.g. 3 mg/kg voor reumatoïde artritis en 5 mg/kg voor de ziekte van Crohn). Daarnaast geeft geen van de richtlijnen een indicatie over hoe en wanneer er gekozen dient te worden voor dosisaanpassing of intensivering van de toedieningsfrequentie in het geval van verlies van effectiviteit. De noodzaak van het gelijktijdige gebruik van
immunosuppressiva tijdens behandeling met infliximab wordt door de meeste, maar niet door alle, richtlijnen voor de verschillende specialismen benadrukt. Het panel is verder van mening dat het routinematig meten van vitale tekenen tijdens infliximab infusie om daarmee acute infusiereacties te detecteren niet zinvol is.

Niet alleen de hoge prevalentie van comorbiditeiten bij patiënten met immuungemedieerde aandoeningen, maar ook de gemeenschappelijke kennis van de verschillende medisch specialisten ten aanzien van het gebruik van immunomodulerende therapieën waaronder biologicals, bepleiten een multidisciplinaire aanpak van chronische inflammatoire aandoeningen zoals psoriasis.

**Onderzoek naar het vóórkomen van comorbiditeiten bij patiënten met (ernstige) psoriasis.**

In hoofdstuk 15, 16 en 17 van dit proefschrift werd de prevalentie en de relevantie van comorbiditeiten bij patiënten met psoriasis onderzocht. In het bijzonder werd er aandacht besteed aan cardiovasculaire risicofactoren en cardiovasculaire ziektes, gewrichtsklachten, inclusief artritis psoriatica, en leverschade bij patiënten die methotrexaat gebruiken. Ten aanzien van cardiovasculaire risicofactoren werd er in de groep van zeer ernstige ('high-need') psoriasispatiënten een significant hogere prevalentie gevonden van obesitas, roken en hypertensie vergeleken met dermatologische patiënten zonder psoriasis. Verder was ook de hoeveelheid alcoholgebruik per maand hoger in de groep van high-need psoriasispatiënten. Het meest opvallend was de hoge prevalentie van obesitas in het high-need psoriasiscohort. Dit werd niet alleen gezien in het onderzoek naar cardiovasculaire risicofactoren, maar eveneens in de drie-jaars analyse (Hoofdstuk 8). Bovendien was de gemiddelde body mass index ook in de antistoffenanalyse hoog, namelijk 29 kg/m². Net zoals in de normale bevolking is het ook bij patiënten met psoriasis essentieel om gewicht te monitoren, om zo een inschatting te kunnen maken van het risico op cardiovasculaire ziektes. Daarnaast is het meten van gewicht vaak noodzakelijk voor adequate selectie en dosering van systemische therapieën, in het bijzonder biologicals. Voor ustekinumab, in principe een therapie met een vastgestelde dosering, dient de voorgeschreven dosering af te hangen van of een patiënt meer of minder dan 100 kg weegt. Dosisaanpassingen zoals deze zijn mogelijk ook voor andere biologicals met een vastgestelde dosering nodig. In het cohort dat onderzocht werd ten behoeve van dit onderzoek was de gebruikte dosis etanercept aanmerkelijk hoger dan in RCTs, zoals weergegeven in de economische analyse in hoofdstuk 11.

In hoofdstuk 16 werden de uitkomsten van een enquête over gewrichtsklachten bij patiënten met psoriasis uiteengezet. Uit de enquête bleek dat de prevalentie van
zelfgerapporteerde gewrichtsklachten bij patiënten met psoriasis hoog was (67%). De prevalentie van synovitis was echter beduidend lager. Mogelijk is artrose één van de onderliggende aandoeningen, gezien de hoge prevalentie van klachten van de grote, zwaar belaste gewrichten. Desalniettemin zijn de frequente polyarticulaire betrokkenheid en betrokkenheid van de kleine gewrichten van de handen en voeten suggestief voor een hoge prevalentie van artritis. Het stellen van de juiste diagnose bij patiënten met psoriasis die aangeven gewrichtsklachten te hebben is cruciaal voor het vaststellen van de prognose en maken van de juiste keuzes ten aanzien van de behandeling. Een solide reumatologisch onderzoek is bij dergelijke patiënten daarom essentieel.

Hoofdstuk 17 richt zich op leverschade bij patiënten die methotrexaat gebruiken. Het onderzoek toont aan dat hepatotoxiciteit beperkt is in een cohort van Nederlandse psoriasispatiënten die behandeld worden met methotrexaat. Sinds 1986 werd er in deze groep geen enkel geval van ernstige leverfibrose of levercirrose gezien. Dit is opmerkelijk, vooral omdat non-alcoholische leververvetting vaak lijkt voor te komen bij patiënten met ernstige chronische plaque psoriasis. Het routinematig uitvoeren van leverbiopsieën kan dus mogelijk afgeschaft worden of worden vervangen door meting van het procollageen III aminoterminaal peptide (PIIINP).

Zelfs in het tijdperk van biologicals is methotrexaat nog steeds een waardevolle therapeutische optie voor de behandeling van psoriasis. Zoals weergegeven in hoofdstuk 9 is het combineren van etanercept met methotrexaat zinvol als de effectiviteit van etanercept monotherapie ontoereikend is, of wanneer een snelle uitbraak van psoriasis na het abrupt staken van methotrexaat verwacht wordt. Tevens voorkomt het toevoegen van methotrexaat aan een behandeling met biologicals waarschijnlijk de ontwikkeling van antistoffen tegen deze biologicals, en geeft het verlichting van symptomen van artritis psoriatica.
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Referenties


PART VII

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Vele handen maken licht werk. Zonder de hulp van onderstaande mensen, evenals vele anderen, was dit proefschrift er niet geweest. Mijn dank is daarom groot!

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Etanercept and efalizumab treatment for high-need psoriasis. Effects and side effects in a prospective cohort study in outpatient clinical practice.

‘Biologicals’ in de praktijk: prospectieve cohortmonitoring van ‘high need’ psoriasispatienten.

Psoriasis treatment with etanercept and efalizumab: clinical strategies influencing treatment outcome.

Etanercept combined with methotrexate for high-need psoriasis.

Analysis of 3-year national reimbursement application data on etanercept and efalizumab for psoriasis.

Cardiovascular risk factors in high-need psoriasis patients and its implications for biological therapies.

Three-year registry data on biological treatment for psoriasis: the influence of patient characteristics on treatment outcome.
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Persistent expression of CD26/DPPIV after treatment with infliximab in psoriasis despite clinical improvement.


Analysis of 4-year Dutch reimbursement application data of biological therapies for psoriatic arthritis.

Extent and clinical consequences of antibody formation against adalimumab in patients with plaque psoriasis.

The economic impact of high-need psoriasis in daily clinical practice before and after the introduction of biologics.

Appropriate infliximab infusion dosage and monitoring: results of a panel meeting of rheumatologists, dermatologists and gastroenterologists.

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