The paediatric psoriasis patient: a holistic approach

Annet Oostveen
The paediatric psoriasis patient: a holistic approach
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<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
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<tr>
<td>AST</td>
<td>aspartate transaminase</td>
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<tr>
<td>BSA</td>
<td>body surface area</td>
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<tr>
<td>CAPTURE</td>
<td>continuous assessment of psoriasis treatment use registry</td>
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<tr>
<td>CDLQI</td>
<td>Children's Dermatology Life Quality Index</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>CSP</td>
<td>Children's ScalpDEX in Psoriasis</td>
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<td>DEL</td>
<td>deletion</td>
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<td>DFI</td>
<td>Dermatitis Family Impact</td>
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<tr>
<td>ERAP1</td>
<td>endoplasmic reticulum aminopeptidase 1</td>
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<tr>
<td>F</td>
<td>female</td>
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<tr>
<td>FAE</td>
<td>fumaric acid esters</td>
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<td>GGT</td>
<td>gamma-glutamyltransferase</td>
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<td>GWAS</td>
<td>genome wide association studies</td>
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<tr>
<td>HLA</td>
<td>human lymphocyte antigen</td>
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<tr>
<td>IFIH1</td>
<td>Interferon induced with helicase C domain 1</td>
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<tr>
<td>IGA</td>
<td>investigator global assessment</td>
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<td>IL</td>
<td>interleukin</td>
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<td>IQR</td>
<td>interquartile range</td>
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<td>ISIDL</td>
<td>Impact of Chronic Skin Disease on Daily Life</td>
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<tr>
<td>KvL</td>
<td>kwaliteit van leven</td>
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<tr>
<td>LCE</td>
<td>late cornified envelope</td>
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<tr>
<td>LCE3C_LCE3B-del</td>
<td>deletion of the LCE3C and LCE3B genes</td>
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<tr>
<td>M</td>
<td>male</td>
</tr>
<tr>
<td>MAF</td>
<td>minor allele frequency</td>
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<tr>
<td>MHC</td>
<td>major histocompatibility</td>
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<tr>
<td>MTX</td>
<td>methotrexate</td>
</tr>
<tr>
<td>NA</td>
<td>not applicable</td>
</tr>
<tr>
<td>NAPSI</td>
<td>nail psoriasis severity index</td>
</tr>
<tr>
<td>NBS</td>
<td>Nijmegen Biomedical Study</td>
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<tr>
<td>NEG</td>
<td>negative</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>PaGA</td>
<td>patient global assessment</td>
</tr>
<tr>
<td>PAMPS</td>
<td>pathogen-associated molecular patterns</td>
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<td>PASI</td>
<td>psoriasis area and severity index</td>
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<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
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<td>PGA</td>
<td>Physician global assessment</td>
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<tr>
<td>PhGA</td>
<td>physician global assessment</td>
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<td>POS</td>
<td>positive</td>
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<td>PsA</td>
<td>psoriatic arthritis</td>
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<td>PSSI</td>
<td>psoriasis scalp severity index</td>
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<td>PSORS</td>
<td>psoriasis susceptibility locus</td>
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<td>PUVA</td>
<td>psoralen and ultraviolet-A phototherapy</td>
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<td>QoL</td>
<td>quality of life</td>
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<td>RUMC</td>
<td>Radboud University Medical Center</td>
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<td>SD</td>
<td>standard deviation</td>
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<td>SIFS</td>
<td>Stein Impact on Family Scale</td>
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<td>SNP</td>
<td>single nucleotide polymorphisms</td>
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<tr>
<td>TE</td>
<td>treatment episode</td>
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<td>Th</td>
<td>T helper</td>
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<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
</tr>
<tr>
<td>TRAF3IP2</td>
<td>TRAF3-interacting protein 2</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal value</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
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<td>WT</td>
<td>wildtype</td>
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1
General introduction and outline of this thesis
1.1. Introduction

In this introduction some general aspects of psoriasis will be highlighted. For the readability of this thesis, a short summary of the pathogenesis of psoriasis in adults (and probably in paediatric patients) will be described below. Thereafter, this introduction will focus on the known literature of paediatric psoriasis with respect to epidemiology, clinical features, treatments and quality of life.

1.2. History of psoriasis

Psoriasis is a chronic, immune-mediated inflammatory skin disease. The history of psoriasis goes back to the ages of the bible, and up until 200 years ago people mistook this common disease for leprosy. In 1808, Robert Willan described psoriasis as an independent entity and distinguished this disorder from leprosy. The foundation for the classification of psoriasis in its current form dates back to Ferdinand van Hebra, using Robert Willan’s notes, in 1841.

1.3. Pathogenesis

Psoriasis is a multifactorial disease and has both environmental and genetic causes in its aetiology. In addition, both the innate and the adaptive immune system are thought to play an important role in the pathogenesis. Evidence for a genetic component comes from population studies, showing that the incidence of psoriasis is greater in first and second degree relatives of patients than in the general population. The risk of psoriasis is two or three times higher in monozygotic twins compared to dizygotic twins. Many genetic associations have been established in epidemiological and genetic psoriasis studies. These studies did not distinguish for age at onset of psoriasis. In the past decades studies demonstrated the strongest linkage and association for PSORS1 locus on chromosome 6p21.3, covering much of the human major histocompatibility complex. Human lymphocyte antigen/HLA-C*06 is the most likely susceptibility gene in the PSORS1 region, which probably accounts for 35% to 50% of the heritability of the disease. More recently, genome-wide association studies (GWAS) have been conducted to find susceptibility loci for psoriasis. Nowadays, 36 susceptibility loci are associated with psoriasis. For most of these loci, single nucleotide polymorphisms (SNPs) have been identified in or near candidate genes. So far, studies have shown that variants in the innate (for example; interferon induced
with helicase C domain 1 (IFIH1) and adaptive immune system (for example; HLA-C*06 and endoplasmic reticulum aminopeptidase 1 (ERAP1)), the Th17 pathway (for example; TRAF3-interacting protein 2 (TRAF3IP2), interleukin(IL)-23 receptor (IL23R) and interleukin-12B (IL12B)) and the skin barrier function (for example; deletion of late cornified envelope 3B and 3C (LCE3C_LCE3B-del)) are genetically linked with psoriasis. 

Recent studies have shown genetic (epistatic) interactions between HLA-C*06 and LCE3C_LCE3B-del, and between HLA-C*06 and ERAP1. On the basis of these genetic findings, it is a challenge to explain the observed epistasis in molecular or cellular terms.

Figure 1: Pathogenesis of psoriasis.

(adapted from: Bergboer JGM, Zeeuwen PLJM, Schalkwijk J. Genetics of Psoriasis: Evidence for epistatic interaction between skin barrier abnormalities and immune deviation.

Figure 1 demonstrates a schematic overview of the suggested pathogenesis of psoriasis. The epidermis is exposed to trauma and infections. Therefore, environmental antigens and microbial components will enter the epidermis (collectively named pathogen-associated molecular patterns (PAMPs)). These PAMPs can activate keratinocytes and immunocompetent cells via pattern recognition receptors and also activate the epidermal innate immune system and drive expression and secretion of antimicrobial proteins (such as defensins, SLPI, S100 proteins and LL-37) and chemokines/cytokines (such as IL-8, CXCL10, IL-1b, and TNF-α). Disturbances of the skin barrier will also initiate a repair response, which includes upregulation of regular skin barrier proteins (such as involucrin, transglutaminase-1) but will also induce de novo expression of structural proteins involved in repair, regeneration, and temporal barrier recovery (such as keratins 6 and 17, SPRRs, SKALP/elafin, and members of the LCE3 group). A superficial injury and exposure to PAMPs and cytokines in a genetically predisposed person could lead to inflammatory responses, increased production of β-defensins in individuals with high copy numbers, and insufficient or delayed skin barrier repair in individuals who are heterozygous or homozygous for LCE3C_LCE3B-del. This will affect the innate and adaptive immune system in several ways. Secretion of mediators such as IL-8, CXCL10, and β-defensins will attract neutrophils, T cells, and dendritic cells to the epidermal compartment. Incomplete barrier repair will allow sustained penetration of PAMPs or even larger (protein) antigens that will be taken up by Langerhans cells and dendritic cells and presented to T-cells. T-cell activation will be initiated, which could be facilitated by genetic predispositions such as HLA-C*06 or polymorphisms in genes of the IL-23 pathway. Activated T cells will secrete Th1 and Th17 cytokines (IFN-γ, TNF-α IL-17, IL-23, IL-22), which will further activate the keratinocytes. This model creates a vicious circle: activated keratinocytes produce chemokines and antimicrobial proteins that attract immunocompetent cells. Keratinocytes will continue to proliferate, and differentiate incompletely. In addition, skin barrier repair may be incomplete in individuals carrying heterozygous or homozygous deletions of the LCE3B and LCE3C genes. The incomplete barrier of lesional psoriatic skin will continuously allow PAMPs and protein antigens to enter the skin and activate immunocompetent cells. Chronicity of psoriasis could be explained because of the absence of a negative feedback in this process.

In paediatric psoriasis, up to almost 75% reported a positive family history of psoriasis, however large continental differences are reported. Most of the genetic studies did not distinguish for age at disease onset, besides a few studies on HLA-C*06 and ERAP1. HLA-C*06 was detected to be associated with early onset psoriasis. One study demonstrated an association between ERAP1 and a psoriasis onset between 10 and 20 years. In this thesis, the associations between known genetic risk factors for psoriasis and age of onset of psoriasis is investigated. In addition, associations between observed clinical parameters and known genetic risk factors of psoriasis in a well-defined cohort of paediatric psoriasis patients is described.
1.4. Epidemiology

Psoriasis is affecting between 1 – 4% of the world population.23–41 Epidemiological studies have demonstrated variable psoriasis prevalence rates across the globe.42 Psoriasis tends to occur more frequently in Caucasians than in other races and more frequently at higher latitudes than lower latitudes.31 Although it can occur at all ages, approximately a third of affected patients with psoriasis recall signs of disease before adulthood.43–45 The prevalence in children reported varied between 0% in Taiwan and 2.1% in Italy.46,47 The total prevalence of psoriasis in children aged <18 years is approximately 0.7% and the rate increases linearly with age from 0 to 18 years.50 Most studies showed that psoriasis in children occurs almost equally in males and females.29–33,53,54,56–59 However, some described a female predilection.31,51 Henseler and Christophers stated in 1985 that two clinical forms could be distinguished based on clinical grounds, namely early onset (<40 years of age; positive family history) and late onset psoriasis (>40 years of age; no positive family history).34

1.5. Clinical features

Psoriasis is clinically a heterogeneous disease with several clinical subtypes. The phenotyping of psoriasis has traditionally been based on historical morphologic descriptions.57 All of the clinical variants of psoriasis described in adults are recognized in childhood.31 The commonest type of psoriasis in children is psoriasis vulgaris (also known as plaque type psoriasis), with a reported frequency rates up to 89%.29,33,33,54,56–58 Characteristic features are lesions with sharply demarcated erythematous and scale papules which may be thick, thin, large or small. Affected areas are usually distributed symmetrically, and occur most commonly on the extensor sides of elbows and knees; scalp, lumbosacral region, and umbilicus. Scalp involvement is reported up to almost 90% of children with psoriasis.29,33,33,54,60 Around a quarter of children with psoriasis report a history of psoriatic diaper rash.31,61

Several children showed an overlap with “eczema like” lesions, excoriated, not well-circumscribed plaques without typical Auspitz’s sign or psoriatic scaling. Psoriasis in children may be confused clinically with atopic dermatitis and, the two conditions may co-exist.62 The morphology of paediatric psoriasis has previously been recorded to differ from adults and may resemble atopic dermatitis, as plaques in children are thinner, lack white scale and are less well defined.31 It has been estimated that approximately 5% of paediatric patients show an overlap of both psoriasis and eczema.31,62 Another subtype is guttate psoriasis, which often occurs after a streptococcal throat infection.63 Guttate psoriasis is a sudden dissemination of small, reddish and scaly papules on the trunk and extremities. It is described that this subtype of psoriasis can be self-limiting, resolving within a few months of onset, however some patients may develop classic plaque type psoriasis.15 Frequency rates of guttate psoriasis in children vary between approximately 5% to 30%.29,33,33,54,56–58,64 Pustular psoriasis and erythrodermic psoriasis are two rare subtypes of psoriasis in children.29,33,53,54 Four distinct patterns of pustular psoriasis have been described: generalized or von Zumbusch, annular, exanthematosus, and localized.65

Psoriatic arthritis (PsA) is an inflammatory, seronegative spondyloarthropathy that is associated with psoriasis. Paediatric PsA, a subtype of juvenile idiopathic arthritis, may be difficult to diagnose because of similarities in clinical presentation with rheumatoid arthritis. The exact incidence of PsA in children is unknown, possibly because skin disease may follow articular disease, and early cases may not be diagnosed. In cohort studies of children with psoriasis PsA is reported between 0.7% and 3.6%, an outlier is a multicenter study from the United States with 10.5% PsA.30,31,53,54,65

Koebner phenomenon, the appearance of psoriasis lesions in the uninvolved skin of psoriasis patients as a consequence of trauma, is reported in approximately a quarter of psoriasis patients.67 Seasonal influences in psoriasis are well known, mostly exacerbations of the disease are reported during the winter.32,15 Some degree of pruritus is often described in children with psoriasis.29,33,54,65 Clinical manifestations of nail involvement of psoriasis can be recognized as pitting, distal onycholysis, subungual hyperkeratosis, oil drop discoloration, leukonychia, splinter haemorrhages and red spots in the lunula.68,69 Nail involvement was detected in up to 40% of children with psoriasis.29,33,33,54,56–58,59,65 Pitting was the most common nail change seen.30,16 Patients with nail psoriasis are more often diagnosed with PsA.1,69

1.6. Treatment

Management of paediatric psoriasis is a great challenge because there is currently no cure for psoriasis. In general, treatment modalities are the same as with adults, however most of these modalities are not registered for children. In addition, there is still not much evidence on the safety and efficacy of treatments in paediatric psoriasis. Especially long-term safety is important in this vulnerable age group, in which treatments are started at an early age. The following treatments are used in (paediatric) psoriasis: topical corticosteroids, keratolytics, vitamin D analogues, calcineurin inhibitors, topical coal tar, dithranol, phototherapy, acitretin, ciclosporin, methotrexate, fumaric acid esters and biologics.
CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

Topical corticosteroids have become a mainstay in the treatment of psoriasis and are considered as a first-line therapy.⑨ They have anti-inflammatory, anti-pruritic and anti-proliferative properties. Topical corticosteroids are available in a variety of potencies (four classes) and preparations.⑩ Cutaneous complications of corticosteroids are striae, (irreversible) atrophy, perioral dermatitis and telangiectasia.⑩ Infants and younger children are at increased risk of local and systemic side effects, including growth retardation and suppression of the pituitary-adrenal axis as a result of their higher skin surface to body mass ratio.⑩ Several approaches have been utilized to minimize the side effects of topical corticosteroids, including transitioning to weaker potency agents after clinical improvement, intermittent usage, and combination with other non-steroidal agents.⑩

Keratolytics are agents that decrease intercellular cohesion and allow for desquamation of terminally differentiated keratinocytes to occur, thus reducing hyperkeratosis and scaling. Examples include salicylic acid and urea. They are often used in combination with other topical agents. There are no published studies on the specific use of these agents in children.

Calcipotriol and calcitriol are vitamin D₃ analogues that inhibit keratinocyte proliferation and DNA synthesis and promote keratinocyte differentiation.⑤ Both calcipotriol and calcitriol have not been registered for children.⑤ Calcipotriol, as single compound treatment, is not available in the Netherlands anymore. Vitamin D₃ analogues can be considered as first choice treatment for paediatric psoriasis, a combination with class II or III topical corticosteroid is recommended.⑤ A two-compound formulation ointment and gel of vitamin D₃ analogue (calcipotriol) and topical corticosteroid (betamethasone dipropionate) has been developed for the treatment of psoriasis in adults.⑤⑥ The efficacy and safety of the two compound gel for scalp psoriasis in children and adolescents is described in this thesis.

Topical tacrolimus (0.03% and 0.1% ointment) and topical pimecrolimus (1% cream) are non-steroidal anti-inflammatory agents that decrease T-cell activation and proliferation and decrease production of IL-2 via inhibition of calcineurin.⑤ They are approved only for the treatment of atopic dermatitis but are frequently used off-label to treat other inflammatory skin diseases such as psoriasis. They are useful as corticosteroid sparing agents. Tacrolimus (0.03% or 0.1%) can be considered in paediatric psoriasis for the use on areas such as the face, genitals, and flexures.⑦⑧ Irritation of the skin is the most frequently reported side effect.⑧

Topical coal tar is a complex by-product of coal distillation that has been used medicinally for over 150 years due to its anti-pruritic and anti-proliferative effects, and although the exact mechanism of its effectiveness in treating inflammatory skin diseases such as psoriasis is not completely understood, it appears to inhibit DNA synthesis and mitosis. There are no age-specific data on safety and efficacy of coal tar in paediatric psoriasis.

Dithranol (also known as anthralin or cignolin) has been available since 1916.①⑦⑨ The mechanism of action is not well understood, but it is known to induce a cascade of free radicals in the skin, resulting in anti-proliferative effects and a modulation of inflammation in psoriasis.⑤⑦ Treatment with dithranol in paediatric psoriasis can be considered if calcipotriol and topical corticosteroids treatments fail, or if psoriasis is moderate to severe.⑤⑨ In a retrospective study, it was shown to be effective and safe in 60 children treated with short contact dithranol therapy.⑥⑩ Dithranol may cause a burning sensation, irritation and staining at the application site or clothing. No serious adverse events have been reported.⑥⑩ In this thesis a prospective study about the effectiveness and safety of short-contact dithranol therapy in paediatric psoriasis is described.

Ultraviolet (UV) radiation has long been recognized as beneficial for the control of psoriatic skin lesions. Phototherapy with ultraviolet B (UVB) and photochemotherapy with ultraviolet A (UVA) following ingestion of or topical application of psoralen is used in the management of moderate to severe psoriasis in adult patients.⑥① Only in case of lack of efficacy of topical modalities, treatment with narrowband-UVB can be considered in adolescents with psoriasis, but only for a short duration.①⑨ No studies are available on the long-term safety of UVB phototherapy in paediatric psoriasis. In choosing UV therapy, consideration must be given to the potential of UV radiation to accelerate photodamage and increase the risk of cutaneous malignancy. Because of the photocarcinogenicity of PUVA, its use in the paediatric age group is contra-indicated.②②

Acitretin is a synthetic retinoid (derivatives of vitamin A). In children with psoriasis, retinoids can be considered in cases of pustular and erythrodermic psoriasis.②③②④ Common side effects include cheilitis and dryness of the mucosa (eyes, nasal or oral), these side effects are dose-dependent. Acitretin is teratogenic and should be avoided in women of childbearing age.⑥①

Ciclosporin is a calcineurin inhibitor, which prevents T-lymphocyte activation from being translated into the release of effector cytokines.⑥① Ciclosporin can induce a rapid improvement of psoriasis. Close monitoring is required since renal toxicity and hypertension are common and broad immune suppression may occur, permitting opportunistic infections.⑥① Treatment with ciclosporin in paediatric psoriasis should
only be deliberated in exceptional cases, as the evidence is controversial and only based on case series and case reports.78,80

Methotrexate (MTX) is a folic acid analogue and competitively inhibits the enzyme dihydrofolate reductase and several other folate-dependent enzymes.71 MTX seems to be an effective systemic treatment option in moderate to severe paediatric psoriasis with a reasonable safety profile.73 The most important side effects of MTX include pancytopenia and hepatotoxicity (hepatic fibrosis and cirrhosis). Subjective side effects are gastrointestinal complaints (nausea, abdominal discomfort) and malaise.73 MTX is considered as the first systemic treatment of choice in children with psoriasis.74-81

Fumaric acid esters (FAE) are small molecules that are thought to improve psoriasis by a broad range of immunomodulatory effects.82-85 FAE are not licensed in the Netherlands. FAE can be considered in children with psoriasis in case MTX is ineffective or contraindicated.80 Most frequently subjective side effects are gastrointestinal complaints (abdominal cramps, diarrhoea) and flushing of the skin.84 In this thesis, a retrospective analysis of the effectiveness and safety of FAE of 14 paediatric psoriasis patients is described.

Biologics used for psoriasis are therapeutic proteins produced by recombinant DNA technology, which selectively interfere in the pathogenesis of psoriasis. The biologic that has been licensed at this moment for the use in children with psoriasis is etanercept (Enbrel®). Etanercept is a fully human dimeric fusion protein and inhibits the activity of tumor necrosis factor (TNF)-α by competitively binding to this pro-inflammatory cytokine and preventing interactions with its cell surface receptors.83 Etanercept can be considered as a third-line drug in severe and/or recalcitrant psoriasis when the conventional systemic treatments are ineffective.78,80

In the future, other biologics will get their licence for the use in paediatric psoriasis. Case reports are published on the use of adalimumab, ustekinumab and infliximab in the treatment of paediatric psoriasis.85-89 However, the number of patients described in these studies are too low to draw firm conclusions about the efficacy and safety of these biologics in paediatric psoriasis.

1.7. Quality of life

A chronic disease in childhood can affect physical appearance and growth, resulting in reduced activity, pain, the need for regular therapy and sometimes unpleasant procedures, and possible loss of schooling.94 Health-related quality of life (QoL) is defined as the subjective perception of the impact of health status, including disease and treatment, on physical, psychological and social functioning and wellbeing.95 By measuring QoL, it is possible to ascertain the effects of disease upon individuals from the child’s perspective. In the limited data published about the QoL in paediatric psoriasis, all studies demonstrated a negative effect on the QoL of those affected.94,98-99 A cross-sectional study in 2006 showed that the QoL impairment in children with a chronic skin disease is at least as much as or even more than experienced by children with other chronic diseases, such as diabetes and epilepsy.95 In addition, in the child’s opinion, psoriasis and eczema caused the greatest impairment in the QoL of children with a chronic skin disease.94 Only a few studies described the negative impact on QoL in paediatric psoriasis.96-100 A cross-sectional study in 39 patients demonstrated a negative influence of psoriasis on the QoL in children by means of the Children’s Dermatology Life Quality Index (CDLQI) questionnaire.98 A Swedish study showed that paediatric psoriasis impairs the children’s QoL and also affects their families.95 No significant gender differences in QoL scores were reported.96-101 One longitudinal study described the influence of a treatment on QoL of children with psoriasis.97 This randomized controlled trial demonstrated an improvement in patients’ QoL after 12 weeks of treatment with etanercept. In this thesis a cross-sectional and longitudinal, observational study about the influence of paediatric (scalp) psoriasis on the QoL in a cohort of patients treated in daily clinical practice is described. In addition, a multidisciplinary training program for children and adolescents with psoriasis is developed and described.

1.8. Aims and outline of this thesis

In this thesis, the paediatric psoriasis patient will be approached from a holistic point of view. Psoriasis in a child or adolescent encompasses much more than the assessment of the psoriasis plaques, and the prescription of medication. Obviously, a safe and effective treatment of psoriasis in this age group is important and, as mentioned above, prospective data are sparse. Therefore, the prospective exploration of different treatments in a daily clinical practice setting in paediatric psoriasis is one of the main aims in this thesis. However, there is more to paediatric psoriasis. Little is known about the genetics of paediatric psoriasis, and about the association between the genotype and the phenotype in these children. Last but not least, the impact of psoriasis on the QoL of children and adolescents with psoriasis has not been studied intensively. In view of these niches in our current knowledge on these important aspects we formulated the following aims for this thesis:
CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

In Chapter 4.2 we presented the development and validation of a questionnaire to assess the influence of scalp psoriasis on QoL in children. The development and design of a multidisciplinary training program together with the medical psychologist for children and adolescents with psoriasis and their parents was described in Chapter 4.3.

The results of the subsequent chapters, together with the possible implications for future clinical research and care are summarized and discussed in Chapter 5. Finally, a summary in Dutch is provided in Chapter 6.

Genetics
1. To explore the genetic features of paediatric-onset psoriasis.
2. To detect genotype-phenotype associations in children and adolescents with psoriasis.

Treatments
3. To prospectively investigate the effects of different treatments in paediatric psoriasis in daily clinical practice.

Quality of life
4. To achieve more insight in the quality of life of children and adolescents with psoriasis.
5. To develop together with the medical psychologist a multidisciplinary training program for children and adolescents with psoriasis.

Several studies to provide answers to the aims formulated above were performed and are presented in the following chapters.

This first chapter of the thesis provides a short introduction. Most genetic studies in psoriasis did not distinguish for age at disease onset, therefore Chapter 2 focussed on the genetics of paediatric psoriasis. The role of genetic risk factors for specific paediatric onset psoriasis were examined in Chapter 2.1. In Chapter 2.2 we investigated associations between observed clinical parameters and known genetic risk factors of psoriasis in a well-defined prospective cohort of paediatric patients with plaque psoriasis. We examined a possible role of LCE3C_LCE3B-del in the Koebner phenomenon in psoriasis patients in Chapter 2.3.

Because there is still not much real clinical practice data providing evidence for treatments in paediatric psoriasis, the goal of Chapter 3 was to investigate the effects of different treatments in paediatric psoriasis in daily clinical practice. In Chapter 3.1 the effectiveness and safety of calcipotriol/betamethasone dipropionate scalp formulation was prospectively described in children with scalp psoriasis until 48 weeks of follow-up. In Chapter 3.2 we investigated prospectively the effectiveness and safety of short-contact dithranol therapy in paediatric psoriasis in daily clinical practice. In addition, the effectiveness, safety, duration of treatment and number of visits between regular day care and day care with telemedicine were compared. We retrospectively described case series in Chapter 3.3 about the effectiveness and safety of fumaric acid esters in 14 children and adolescents with psoriasis.

Chapter 4 focussed on the impact of paediatric psoriasis on the quality of life. In Chapter 4.1 we investigated the CDLQI questionnaire in paediatric psoriasis and evaluated the influence of treatments in daily clinical practice on this questionnaire.
References

GENERAL INTRODUCTION AND OUTLINE OF THIS TESIS

2
Genetics
Paediatric onset psoriasis is associated with *ERAP1* and *IL23R* loci, *HLA-C*/*06* and *LCE3C*_*_LCE3B* deletion


Published in: *British Journal Dermatology* 2012;167(4):922-5.
Abstract

**Background**
Recent genome-wide association studies have identified several genetic risk factors for psoriasis, but data on their association with age at onset are lacking.

**Objective**
To compare the association between known risk alleles and psoriasis in well-defined cohorts with paediatric- and adult onset psoriasis.

**Methods**
Based on previous studies we selected seven genes and loci associated with psoriasis. Psoriasis patients with paediatric onset (< 18 years) and adult onset psoriasis (≥ 18 years) and controls were genotyped. Genotype frequencies were compared between controls (n=450) and all cases (n=217), and between controls and cases stratified for confirmed age at onset (paediatric onset n=80, adult onset n=85).

**Results**
Paediatric onset psoriasis showed a significant association with single nucleotide polymorphism (SNP) in the ERAP1 (P = 0.042) and IL23R loci (P = 0.042), LCE3C_LCE3B deletion (P = 0.003) and HLA-C*06 (P = 1.72 x 10^-19) when compared with the control group. A significant association of these four genes was also demonstrated when all psoriasis cases were compared with controls. In adult onset psoriasis a significant association was found for HLA-C*06 (P = 5.11 x 10^-06) and for LCE3C_LCE3B deletion (P = 0.042). No associations were found for the IFIH1, IL12B and TRAF3IP2 loci.

**Conclusion**
Notwithstanding the small cohort sizes, we demonstrated an association with established and recently discovered genetic risk factors in paediatric onset psoriasis including genes involved in epidermal barrier function and adaptive immunity. Our data suggest that heritable factors may play a more important role in paediatric onset psoriasis than in adult onset psoriasis.

Introduction
Psoriasis is a common, chronic skin disorder, affecting around 2% of the population. The disease is caused by both environmental and genetic factors, like HLA-C*06. In recent years, independent genome-wide association studies (GWAS) and candidate gene approaches identified other genetic susceptibility factors for psoriasis. These were mainly single nucleotide polymorphisms (SNPs).

Previous studies have already demonstrated a strong association with HLA-C*06 in type I psoriasis, which is defined as disease onset before the age of 40 and a positive family history. Recently, Xu et al. demonstrated an association between LCE3C_LCE3B-del and type I psoriasis. These studies were based on the observed age of onset peaks in psoriasis. The occurrence of such a distribution, however, has recently been discussed. Besides two studies on HLA-C*06, limited data about the association of psoriasis risk genes and age of disease onset are available. Therefore, we investigated the possible association of known psoriasis risk genes in paediatric onset (<18 years) and adult onset (≥ 18 years) psoriasis.

We analysed seven genetic risk factors for psoriasis in well-defined cohorts of paediatric onset and adult onset psoriasis. We chose variants that play a (putative) role in the various pathways underlying the pathophysiology of psoriasis. Several studies showed that variants in the innate (IFIH1) and adaptive immune system (HLA-C*06 and ERAP1), the Th17 pathway (TRAF3/IP2, IL23R and IL12B) and the skin barrier function (LCE3C_LCE3B-del) are genetically linked with psoriasis.

Materials and methods

**Sample collection**
DNA samples from psoriasis patients (n=217) were obtained from individuals referred to the outpatient clinic of the Department of Dermatology of the Radboud University Nijmegen Medical Center. Only patients with psoriasis vulgaris were included in this study. The 450 control samples were obtained from the Nijmegen Biomedical Study (NBS). For the LCE and HLA analysis, we used another control group consisting of 386 samples, which were used in our previous studies. Only self-reported data were available for all controls, and individuals reported to have psoriasis were excluded from this study. All patients and controls were of European descent. For cohort characteristics see Table 1.
**Genotyping**

As quality control on the SNP typing 5% of the samples were analysed in duplicate: all genotypes were concordant. The SNPs were successfully genotyped in the psoriasis and control samples with genotyping success rates between 98.4% and 99.6%. Genotype cluster plots were evaluated prior to analysis to ensure satisfactory assay performance. For the LCE3C_LCE3B-del genotyping a polymerase chain reaction (PCR) using three different primers was performed as earlier described. Briefly, 10 ng DNA template was amplified with one universal forward primer and two different reverse primers, one spanning the breakpoint of the deletion and one located in the possible deleted region generating PCR products of 199 and 240 bp, respectively. These were visualized on an agarose gel. HLA-C*06:02 was determined by PCR with sequence specific primers for C*06:02. Using this method the HLA-C*06 gene itself is identified rather than a tagging SNP. This method does not allow distinction between homozygotes and heterozygotes.

**Statistical analysis**

The observed genotype frequencies were compared with the expected Hardy-Weinberg distribution by a χ² test, for none of the variants deviations from Hardy-Weinberg equilibrium were found both in the control and the psoriasis group. Power was calculated using the Genetic Power Calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/gpc2.html). Input for the power calculations, like allele frequency and genotypic relative risk per genotype, were derived from previous studies. Powers shown in Table 2 were derived from the values given for additive models, except for HLA-C*06 in which numbers derived from dominant models were used.

### Table 1 Cohort characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>All psoriasis</th>
<th>Paediatric onset psoriasis</th>
<th>Adult onset psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N, numbers</td>
<td>450</td>
<td>217</td>
<td>80</td>
<td>85</td>
</tr>
<tr>
<td>Boys, n (%)</td>
<td>176 (39.1)</td>
<td>118 (54.2)</td>
<td>29 (36.2)</td>
<td>58 (68.2)</td>
</tr>
<tr>
<td>Age, years, mean ± SD</td>
<td>49.6 ± 14.1</td>
<td>40.1 ± 24.6</td>
<td>14.9 ± 9.7</td>
<td>60.7 ± 12.2</td>
</tr>
<tr>
<td>Age of onset psoriasis, years, mean ± SD</td>
<td>-</td>
<td>21.3 ± 15.4</td>
<td>8.2 ± 3.8</td>
<td>33.5 ± 12.5</td>
</tr>
</tbody>
</table>

*Data were available for 165 subjects

### Table 2 Association analysis of a several known psoriatic risk factors in all psoriasis and stratified by age of onset adjusted for sex

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>Allele*</th>
<th>Population</th>
<th>MAF Cases</th>
<th>MAF Controls</th>
<th>P trend</th>
<th>OR 95% CI</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs11209026</td>
<td>IL23R</td>
<td>G/A</td>
<td>All psoriasis</td>
<td>0.04</td>
<td>0.08</td>
<td>0.007</td>
<td>2.19 (1.23 to 3.91)</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>Adult onset psoriasis</td>
<td>0.06</td>
<td>0.08</td>
<td>0.279</td>
<td>1.49 (0.72 to 3.10)</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paediatric onset psoriasis</td>
<td>0.03</td>
<td>0.08</td>
<td>0.042</td>
<td>2.59 (1.03 to 6.49)</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.16</td>
<td>0.17</td>
<td>0.996</td>
<td>0.051</td>
<td>0.51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs3213094</td>
<td>IL12B</td>
<td>T/C</td>
<td>All psoriasis</td>
<td>0.17</td>
<td>0.17</td>
<td>0.956</td>
<td>1.01 (0.64 to 1.60)</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>Adult onset psoriasis</td>
<td>0.14</td>
<td>0.17</td>
<td>0.207</td>
<td>0.75 (0.48 to 1.21)</td>
<td>0.27</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Paediatric onset psoriasis</td>
<td>0.14</td>
<td>0.17</td>
<td>0.31</td>
<td>1.14 (0.71 to 1.82)</td>
<td>0.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.17</td>
<td>0.17</td>
<td>0.996</td>
<td>0.19</td>
<td>0.042</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs27524</td>
<td>ERAP1</td>
<td>A/G</td>
<td>All psoriasis</td>
<td>0.40</td>
<td>0.33</td>
<td>0.726</td>
<td>1.09 (0.67 to 1.78)</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Adult onset psoriasis</td>
<td>0.13</td>
<td>0.14</td>
<td>0.887</td>
<td>0.97 (0.59 to 1.58)</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paediatric onset psoriasis</td>
<td>0.12</td>
<td>0.14</td>
<td>0.726</td>
<td>0.97 (0.59 to 1.58)</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs17716942</td>
<td>IFIH1</td>
<td>T/C</td>
<td>All psoriasis</td>
<td>0.11</td>
<td>0.14</td>
<td>0.042</td>
<td>1.09 (0.67 to 1.78)</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Adult onset psoriasis</td>
<td>0.13</td>
<td>0.14</td>
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<td>0.97 (0.59 to 1.58)</td>
<td>0.22</td>
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<td></td>
<td>Paediatric onset psoriasis</td>
<td>0.12</td>
<td>0.14</td>
<td>0.726</td>
<td>0.97 (0.59 to 1.58)</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results

In our complete psoriasis cohort, we found significant associations between the G allele of SNP rs11209026, IL23R (P\text{trend} = 0.007), the A allele of SNP rs27524, ERAP1 (P\text{trend} = 0.019), with LCE3C_LCE3B-del (P\text{trend} = 0.001) and HLA-C*06 (P\text{trend} = 3.94 \times 10^{-19}) and psoriasis (Table 2). All found associations were in the same directions as previously reported.

Next, we stratified our data into paediatric and adult onset psoriasis and performed subgroup analyses. Logistic regression models showed that in the paediatric onset psoriasis cohort all found associations in the full cohort were still present. Paediatric onset psoriasis was significantly associated with IL23R (P\text{trend} = 0.042), ERAP1 (P\text{trend} = 0.042) LCE3C_LCE3B-del (P\text{trend} = 0.003) and HLA-C*06 (P\text{trend} = 1.72 \times 10^{-19}). Adult onset psoriasis was associated only with the LCE3C_LCE3B-del (P\text{trend} = 0.042) and HLA-C*06 (P\text{trend} = 5.11 \times 10^{-6}).

Moreover, when comparing the paediatric onset psoriasis cohort with the adult onset psoriasis cohort, we found a significant difference for HLA-C*06 (P = 2.3 \times 10^{-6}), but not for the other genes.

Lastly, we confirmed the known genetic interaction between HLA-C*06 and LCE3C_LCE3B-del in our full cohort (P = 0.017). Furthermore, specifically the paediatric onset psoriasis group significantly differed from the control group when stratified for HLA-C*06 and LCE3C_LCE3B-del (\chi^2-test; P = 0.001). The logistic regression model, however, showed no significant contribution of the interaction term (P = 0.174), probably due to the large effect of the HLA-C*06-component in paediatric onset psoriasis.

Discussion

In this study, we showed in a small cohort that paediatric onset psoriasis is significantly associated with SNPs in ERAP1 (rs27524) and IL23R (rs11209026) loci and LCE3C_LCE3B-del and we confirmed the association for HLA-C*06. Previous studies have reported a genetic interaction of ERAP1 and LCE3C_LCE3B-del with HLA-C*06. Given the high HLA-C*06 allele frequency in our paediatric onset patients, it is not surprising that the associations with ERAP1 and LCE3C_LCE3B-del were detected in such a modestly sized cohort. In adult onset psoriasis significant associations were only found for LCE3C_LCE3B-del and HLA-C*06. In our study we used a relatively small number of samples compared to large GWAS. It should be noted, however, that the subgroup analysis had between 12% and 100% power to
detect an association. The power in paediatric and adult onset psoriasis groups was equal owing to similar group sizes (Table 2).

In the current study, we have chosen the cut-off point at 18 years of age, which is an accepted cut-off point for adulthood in clinical investigations of medicinal products in the paediatric population, based on developmental biology and pharmacology. 18

ERAP1 encodes an amino peptidase, which regulates the quality of peptides bound to MHC class I molecules, such as HLA-Cw6. 19 Activation of the interleukin (IL)-23 receptor (IL23R) stimulates CD4+ T cells into IL-17 producing Th17 cells instead of Th1 cells. 20 The late cornified envelope 3 (LCE3) genes have a role in skin barrier repair. 21 The deletion of LCE3C_LCE3B may lead to a compromised barrier repair response upon barrier disruption, which could lead to the penetration of exogenous agents. Against a genetic background of HLA-C*06 positivity, these could evoke a response of the adaptive immune system. It should be noted, however, that for all associated variants a nearby functional variant in linkage disequilibrium with the genotyped variant could also contribute to psoriasis. Our data suggest that at least genes involved in epidermal barrier function and adaptive immunity play a role in paediatric onset psoriasis.

We hope that this study will stimulate other centres to evaluate their psoriasis patient cohorts and define patient groups with reliable and definite age of onset, in order to replicate and extend our current study.

In conclusion, an association of known genetic risk factors with paediatric onset psoriasis, even in a relatively small cohort, was established and our data suggest that heritable factors may play a more important role in paediatric onset psoriasis than in adult onset psoriasis. Further elucidation of genetic factors and triggering environmental factors in an early stage may lead to a better understanding of the pathogenesis of psoriasis and could contribute to the development of more targeted therapies or even preventive measures for paediatric onset psoriasis.

Acknowledgements
We would like to thank all our volunteers for participating in this study and M. Nabers (Department of Human Genetics, Nijmegen) for technical assistance.

Supplemental material

Table S1 Numbers of association analysis stratified for age of onset

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>Allele</th>
<th>Population (N)</th>
<th>MAF Cases (N)</th>
<th>MAF Controls (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs11209026</td>
<td>IL23R</td>
<td>G/A</td>
<td>All psoriasis (208)</td>
<td>0.04 (17)</td>
<td>0.08 (71)</td>
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<tr>
<td></td>
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<td>Adult onset psoriasis (81)</td>
<td>0.06 (9)</td>
<td>0.08 (71)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Paediatric onset psoriasis (78)</td>
<td>0.03 (5)</td>
<td>0.08 (71)</td>
</tr>
<tr>
<td>rs3213094</td>
<td>IL12B</td>
<td>T/C</td>
<td>All psoriasis (214)</td>
<td>0.16 (67)</td>
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<td>Adult onset psoriasis (82)</td>
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<td>0.17 (155)</td>
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<td>rs27524</td>
<td>ERAP1</td>
<td>A/G</td>
<td>All psoriasis (215)</td>
<td>0.40 (172)</td>
<td>0.33 (295)</td>
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<td></td>
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<td>Adult onset psoriasis (85)</td>
<td>0.39 (67)</td>
<td>0.33 (295)</td>
</tr>
<tr>
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<td>IFIH1</td>
<td>T/C</td>
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<td>0.14 (121)</td>
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<td>Adult onset psoriasis (85)</td>
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<td>0.14 (121)</td>
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<td>Paediatric onset psoriasis (80)</td>
<td>0.12 (20)</td>
<td>0.14 (121)</td>
</tr>
<tr>
<td>rs240993</td>
<td>TRAF3P2</td>
<td>T/C</td>
<td>All psoriasis (216)</td>
<td>0.32 (139)</td>
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<td>Adult onset psoriasis (85)</td>
<td>0.32 (55)</td>
<td>0.27 (241)</td>
</tr>
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<td>Paediatric onset psoriasis (78)</td>
<td>0.33 (52)</td>
<td>0.27 (241)</td>
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<tr>
<td>direct PCR</td>
<td>LCE3C_</td>
<td>DEL/WT</td>
<td>All psoriasis (215)</td>
<td>0.30 (128)</td>
<td>0.40 (308)</td>
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<tr>
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<td>LCE3B</td>
<td></td>
<td>Adult onset psoriasis (85)</td>
<td>0.31 (53)</td>
<td>0.40 (308)</td>
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<td></td>
<td>Paediatric onset psoriasis (78)</td>
<td>0.27 (42)</td>
<td>0.40 (308)</td>
</tr>
<tr>
<td>direct PCR</td>
<td>HLA-C*06</td>
<td>POS/</td>
<td>All psoriasis (214)</td>
<td>0.54 (115)</td>
<td>0.17 (63)</td>
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<td>NEG</td>
<td>Adult onset psoriasis (85)</td>
<td>0.40 (34)</td>
<td>0.17 (63)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Paediatric onset psoriasis (77)</td>
<td>0.78 (60)</td>
<td>0.17 (63)</td>
</tr>
</tbody>
</table>

a N represents the number of successful genotypes samples. N for controls samples were 444, 444, 447, 448, 447, 383 and 367 for IL23R, IL12B, ERAP1, IFIH1, TRAF3P2, LCE3C_LCE3B-del and HLA-C06 respectively.
b Numbers in MAF represent individuals instead of allele frequencies.
References

2.2 Genotype-phenotype correlations in a prospective cohort study of paediatric plaque psoriasis: lack of correlation between HLA-C*06 and family history of psoriasis


Abstract

Background
Psoriasis is a clinically heterogeneous skin disease with a complex genetic background. Data on the association between clinical features in paediatric psoriasis and psoriasis risk factors are lacking.

Objective
This study aims to investigate the associations between observed clinical parameters and known genetic risk factors of psoriasis in a well-defined prospective cohort of paediatric psoriasis patients.

Methods
Children with psoriasis were genotyped for HLA-C*06, LCE3C_LCE3B deletion (LCE3C_LCE3B-del) and single nucleotide polymorphisms (SNPs) tagging ERAP1, IFIH1, IL12B, IL23R and TRAF3IP2. Clinical data were obtained from the Child-CAPTURE, a prospective registry of children with psoriasis.

Results
Significant associations were found for paediatric onset psoriasis (n=151) with ERAP1 (P = 0.002), IL23R (P = 0.01), LCE3C_LCE3B-del (P = 0.00049) and HLA-C*06 (P = 3.15 x 10^-30). Psoriasis severity was associated with the SNPs tagging IFIH1 and ERAP1 (P < 0.05). Age of onset before 10 years was associated with IL12B (P = 0.02). Nail psoriasis was more often seen in HLA-C*06 negative patients (P = 0.008). Although 67.6% of the cohort has a positive family history and 76.1% is HLA-C*06 positive, an association between HLA-C*06 and family history could not be found.

Conclusion
Psoriasis severity, age at onset and nail psoriasis are, in our well-defined cohort of paediatric psoriasis, associated with known genetic risk factors of psoriasis. Remarkably, family history is clearly not associated with HLA-C*06 in this specific group. The large proportion of patients with a positive family history in HLA-C*06 negative patients (and the lack of correlation between the two) indicates that other genes, either alone or in epistasis, may have significant effects on heritability.

Introduction
Psoriasis is a clinically heterogeneous skin disease with a complex genetic background. It affects around 2% of the population and in approximately 30% of these patients the disease first appears during childhood. By means of genome-wide association studies, the number of genome regions identified to be associated with psoriasis jumped recently to 36. Different pathways evidently play a role in the pathophysiology of psoriasis, as the innate and adaptive immune system, the Th17 pathway and the skin barrier function are genetically linked with psoriasis. Some studies have investigated correlations between genetic risk factors of psoriasis and clinical parameters, and these were mainly focused on major histocompatibility (MHC) gene HLA-C*06. In a cohort of adult psoriasis patients a strong association was demonstrated between psoriasis severity and single nucleotide polymorphisms (SNPs) tagging HLA-C*06 and a deletion of LCE3B and LCE3C. Several studies have shown that early age at onset may be associated with distinct genetic factors, such as ERAP1 and HLA-C*06. Previous studies detected an association between HLA-C*06 and early onset psoriasis (onset < 30 or 40 years), and a positive family history of psoriasis and early onset of psoriasis, suggesting an association between HLA-C*06 and family history of psoriasis in patients with early onset psoriasis. This association has however, never been investigated. Data about associations between clinical parameters and genetic risk factors in paediatric psoriasis are lacking. The current study aims to investigate associations between observed clinical parameters and known genetic risk factors in a well-defined cohort of paediatric patients with plaque psoriasis.

Materials and methods
Sample collection
DNA samples were obtained from children with psoriasis referred to the outpatient clinic of the Department of Dermatology of the Radboud University Medical Center. Only patients of European descent with a primary diagnosis of plaque-type psoriasis, before the age of 18 years, were included in this study. Patients with guttate psoriasis were excluded. The phenotype classification is based on phenotype at examination and not at onset of disease. We obtained clinical data from our prospective observational paediatric psoriasis registry in daily clinical practice, called Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry). In this registry, patient characteristics including age at onset, family history of psoriasis (up to the third-degree relative) and Koebner phenomenon are recorded at the first visit. Psoriasis severity and presence of observed nail psoriasis by the physician are recorded every visit.
The characteristics of the control group of European descent were previously described. Only self-reported data were available for all controls, and individuals reported to have psoriasis were excluded from this study. All participants (or parents, if patients were under 18 years) gave written informed consent.

Genotyping
Genotyping was executed as previously described. In short, SNP genotyping was performed using Taqman® SNP genotyping assays ( assay IDs C_920308_20, C_1272298_10, C_3056837_10, C_3424955_10, and C_29927086, for SNPs rs240993, rs11209026, rs27524, rs17716942, and rs3213094, respectively) according to the manufacturer’s recommendations (Applied Biosystems, Nieuwerkerk aan den IJssel, The Netherlands). LCE3C_LCE3B-del genotyping was performed using a previous described polymerase chain reaction (PCR). HLA-C*06:02 itself (rather than a tagging SNP) was determined by PCR with sequence specific primers for C*06:02 which does not allow distinction between homozygotes and heterozygotes. As quality control on the SNP typing 5% of the samples were analysed in duplicate; all genotypes were concordant. The SNPs, LCE3C_LCE3B-del and HLA-C*06:02 were successfully genotyped in the psoriasis and control samples with genotyping success rates between 97.9% and 99.7%, 99.1% and 95.8%, respectively. For SNP genotyping, genotype cluster plots were evaluated prior to analysis to ensure satisfactory assay performance.

Statistical analysis
No deviations from Hardy-Weinberg equilibrium were found in the control groups. Logistic regression analyses were performed in SPSS software 20.0 (SPSS Inc., Chicago, IL, U.S.A.) using co-dominant models. The odds ratio (OR) and 95% confidence interval (CI) were calculated using homozygosity for the non-risk variant (from previous studies) as a reference for the case-control study. Age at onset was analysed comparing two groups; before 10 years and at or after 10 years. Clinical severity of psoriasis was assessed by a clinician using three different severity scales: Psoriasis Area and Severity Index (PASI; range 0 – 72), Physician Global Assessment (PGA; range 0 - 5) and Body Surface Area (BSA; range 0 - 100). The highest reported psoriasis severity scores for each individual were used. Patients were divided in two groups based on psoriasis severity scores; mild-to-moderate and severe psoriasis. Mild-to-moderate psoriasis was defined as those patients that have never reached PASI ≥ 10, PGA ≥ 3 or BSA ≥ 10. Severe psoriasis was defined as those patients that have ever reached PASI ≥ 10, PGA ≥ 3 or BSA ≥ 10. Nail psoriasis was scored by using the Nail Psoriasis Severity Index (NAPSI; range 0 - 80). Koebner phenomenon was assessed based on a 4-point scale, how often a psoriasis plaque appeared after skin damage of their non-involved skin: never, rarely, often, or very common. The individuals who responded with “often” or “very common” were considered as Koebner-positive patients and the others as Koebner-negative patients, which is in line with our previous study. To test for the association with psoriasis clinical variables, chi-square tests were executed from the allele frequency table (2 x 2 tables). Logistic regression analyses were performed to calculate ORs and 95% CIs. The level of significance was considered to be 0.05. Power calculations were performed using the Genetic Power calculator.

Results
Cohort characteristics
The investigated cohort for the replication of the associations between paediatric-onset psoriasis and healthy controls consisted of 151 cases and 450 controls, which is a doubling of the number of cases compared to our previous study. The power to detect an association ranged between 18% and 100%. Patient cohort characteristics are reported in Table 1. A female preponderance was found (59%) in the cases, which was also present in the control group (60.9%). For a total of 139 psoriasis patients clinical data were available from our Child-CAPTURE registry (see below). We found no significant phenotype differences between patients with an age at onset < 10 years and ≥ 10 years.

<table>
<thead>
<tr>
<th>Table 1 Cohort characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort characteristics</td>
</tr>
<tr>
<td>Number of cases</td>
</tr>
<tr>
<td>Boys, n (%)</td>
</tr>
<tr>
<td>Age, years, mean ± SD&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Psoriasis characteristics&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age at onset of psoriasis, years, mean ± SD (range)</td>
</tr>
<tr>
<td>Duration of psoriasis, months, mean ± SD (range)</td>
</tr>
<tr>
<td>Time of follow-up, months, mean ± SD (range)</td>
</tr>
<tr>
<td>Family history of psoriasis first-degree relatives, n (%)</td>
</tr>
<tr>
<td>Family history of psoriasis up to the third degree relatives, n (%)</td>
</tr>
<tr>
<td>Severe psoriasis, n (%)</td>
</tr>
<tr>
<td>Nail involvement, n (%)</td>
</tr>
<tr>
<td>Koebner-positive patients, n (%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data were available for 139 subjects. SD, standard deviation.
Replication of genetic associations with paediatric-onset psoriasis

Logistic regression analysis of our extended cohort demonstrated the same associations, albeit with increased significance, with four of the seven tested loci and paediatric-onset psoriasis as in our previous study. These four genes were IL23R (OR 2.42, 95% CI 1.23 - 4.74), ERAP1 (OR 1.55, 95% CI 1.18 - 2.03), LCE3B/LCE3C-del (OR 1.67, 95% CI 1.25 - 2.22) and HLA-C*06 (OR 17.1, 95% CI 10.5 - 27.9) (Table 2).

Table 2 Association analysis of several known psoriatic risk factors in all patients and stratified by age of onset adjusted for sex

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>Allele *</th>
<th>Frequency risk allele cases</th>
<th>Frequency risk allele controls</th>
<th>P_trend</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1209026</td>
<td>IL23R</td>
<td>G/A</td>
<td>0.97</td>
<td>0.92</td>
<td>0.010</td>
<td>2.42 (1.23 to 4.74)</td>
</tr>
<tr>
<td>rs3213094</td>
<td>IL12B</td>
<td>T/C</td>
<td>0.13</td>
<td>0.18</td>
<td>0.088</td>
<td>0.72 (0.50 to 1.05)</td>
</tr>
<tr>
<td>rs27524</td>
<td>ERAP1</td>
<td>A/G</td>
<td>0.43</td>
<td>0.33</td>
<td>0.002</td>
<td>1.55 (1.18 to 2.03)</td>
</tr>
<tr>
<td>rs17716942</td>
<td>IFIH1</td>
<td>T/C</td>
<td>0.88</td>
<td>0.86</td>
<td>0.445</td>
<td>1.16 (0.79 to 1.72)</td>
</tr>
<tr>
<td>rs240993</td>
<td>TRAF3IP2</td>
<td>T/C</td>
<td>0.29</td>
<td>0.27</td>
<td>0.132</td>
<td>1.09 (0.82 to 1.45)</td>
</tr>
<tr>
<td>direct PCR</td>
<td>LCE3C/LCE3B</td>
<td>DEL/WT</td>
<td>0.72</td>
<td>0.60</td>
<td>0.00049</td>
<td>1.67 (1.25 to 2.22)</td>
</tr>
<tr>
<td>direct PCR</td>
<td>HLA-C*06</td>
<td>POS/NEG</td>
<td>0.78</td>
<td>0.17</td>
<td>3.15E-30</td>
<td>17.1 (10.5 to 27.9)</td>
</tr>
</tbody>
</table>

SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; DEL, deletion; WT, wild type; PCR, polymerase chain reaction; POS, positive; NEG, negative. *The first allele called is the allele associated with psoriasis. Significant P-values are shown in bold.

## Associations with clinical psoriasis characteristics

### Age at onset of psoriasis

The mean age ± SD at onset of psoriasis in our cohort was 8.2 ± 4.1 years. The group of children with an early onset (< 10 years; n=86) had a mean age at onset of 5.5 ± 2.2 years and the other group (≥ 10 years; n=53) had a mean age at onset of 12.7 ± 2.0 years. For IL12B, analysed using SNP rs3213094, we demonstrated a significant association between age at onset < 10 years with the risk (T) allele, with an OR of 2.59 (95% CI 1.14 - 5.88, P = 0.02); 17% of patients with an age at onset < 10 years carried this risk allele, compared to 7.5% of the patients with an age at onset ≥ 10 years (Table 3). None of the other analysed loci showed significant associations.

### Psoriasis severity

In our cohort 55.4% (n=77) of the patients were classified as having severe psoriasis. Significant associations were demonstrated between severe psoriasis and the risk (T) allele of SNP rs17716942 (IFIH1) with an OR of 2.41 (95% CI 1.14 - 5.12, P = 0.019) and the risk (A) allele of SNP rs27524 (ERAP1, OR 1.64, 95% CI 1.01 - 2.67, P = 0.047) (Table 3).

### Family history of psoriasis

In 38.1% (n=53) of the patients a first-degree relative stated to have psoriasis. Two-thirds of the patients (67.6%, n=94) reported a positive family history of psoriasis up to third degree relatives. However, we found no significant associations between family history of psoriasis (first and up to third degree relatives) and the allele frequency of the psoriasis risk factors. Remarkably, even HLA-C*06 showed no significant association with family history of psoriasis (first degree relatives P = 0.92 and up to third degree relatives P = 0.76). In patients with a positive family history up to third degree relatives 76.1% were HLA-C*06 positive and in patients with only first-degree relatives with psoriasis, 76.5% were HLA-C*06 positive. In patients with a negative family history up to third degree relatives 78.6% was HLA-C*06-positive, this was 77.2% in patients with no first degree relatives with psoriasis (Table 4).
For analysis of a possible effect of age at onset, we divided the patients into two groups with a cut-off point at 10 years of age, which is in line with data previously published by Lysell et al.\textsuperscript{23} They demonstrated, in a Swedish cohort, that \textit{ERAP1} showed an association, albeit weak, with a psoriasis onset between 10 and 20 years. Also the strongest association with HLA-C*06 was found for this age group. We did not, however, find associations between age at onset and \textit{ERAP1} and HLA-C*06 in the Dutch paediatric psoriasis patients, which may be due to ethnic variation. In our cohort, an age at onset before 10 years was demonstrated to be associated with \textit{IL12B}, which encodes the p40 subunit of interleukin (IL)-23 and IL-12 and is involved in both the IL12/Th1 pathway and IL23/Th17 pathway of psoriasis.\textsuperscript{29,30} Previous studies detected associations between HLA-C*06 and early onset psoriasis, and between a positive family history and early onset of psoriasis in groups of mainly adult patients.\textsuperscript{14,16,17,19} These findings suggest an association between HLA-C*06 and a positive family history. In our paediatric cohort, however, with 67.6% of the patients having a positive family history up to third degree relatives, including 38.1% with first degree relatives with psoriasis, and a total of 77.8% HLA-C*06 positive patients, an association between family history and HLA-C*06 was not found. This is due to the fact that similar proportions of HLA-C*06 positivity in both the group with a positive family history (first degree relatives 76.5% vs up to the third degree relatives 76.1%) and a negative family history (first degree relatives 77.2% vs up to the third degree relatives 78.6%) were found (Table 4). Although our cohort is relatively small, it is highly unlikely that increasing the number of cases would reveal such an association. Previous studies reported an association of HLA-C*06 with type 1 psoriasis (early onset, positive family history) but not with type 2 (late onset, no positive family history).\textsuperscript{14,16} There are, however, several discrepancies with regard to the age criteria. Type 1 psoriasis is variably and loosely defined, depending on the study, as having an onset before 30 or 40 years and by a positive family history. Clearly this cannot be a comprehensive classification as there are many patients with early onset and negative family history and also patients with adult onset that have a positive family history. We analysed truly paediatric patients (onset < 18 years), which is by definition not type 2 psoriasis, but neither necessarily type 1 because of the requirement of positive family history.

Although the lack of correlation between HLA-C*06 and positive family history comes somewhat as a surprise, it is clearly not unprecedented. Gudjonsson et al.,\textsuperscript{19} demonstrated in a large mixed cohort of paediatric and adult-onset psoriasis that also many of the HLA-C*06 positive patients have a negative family history. Based on our own data and those of Gudjonsson et al. we would argue that the historic classification of type 1 and 2 psoriasis is no longer meaningful. Classifications based

**Table 4** Distribution of family history of psoriasis and HLA-C*06 in our cohort of paediatric psoriasis

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>HLA-C*06\textsuperscript{a}</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Positive (n (%))</td>
<td>Negative (n (%))</td>
</tr>
<tr>
<td>Only first degree relatives with psoriasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>51 (39.2)</td>
<td>39 (76.5)</td>
<td>12 (23.5)</td>
</tr>
<tr>
<td>No</td>
<td>79 (60.8)</td>
<td>61 (77.2)</td>
<td>18 (22.8)</td>
</tr>
<tr>
<td>Up to third degree relatives with psoriasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>88 (67.7)</td>
<td>67 (76.1)</td>
<td>21 (23.9)</td>
</tr>
<tr>
<td>No</td>
<td>42 (32.3)</td>
<td>33 (78.6)</td>
<td>9 (21.4)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Data were available for 130 subjects

**Nail involvement**
In HLA-C*06 negative patients we found a significant increase of nail involvement (OR 0.32, 95% CI 0.14 - 0.76, P = 0.008, Table 3). None of the other psoriasis risk alleles showed a positive or negative association with this clinical parameter.

**Koebner-phenomenon**
Forty-three patients (30.9%) were Koebner-positive. None of the investigated risk factors showed a significant association with Koebnerization in our cohort.

**Discussion**
This is the first study to report associations between clinical parameters and genetic risk factors in a prospective paediatric psoriasis cohort. We could confirm and strengthen, in a larger patient group, our previous findings that paediatric-onset psoriasis is associated with HLA-C*06, \textit{LCE3C, LCE3B} deletion and SNPs in the \textit{ERAP1} and \textit{IL23R} loci.\textsuperscript{24} We performed additional analyses based on clinical data from these children and demonstrated that age at onset, psoriasis severity and nail psoriasis are associated with different genetic risk factors of psoriasis. Remarkably, family history of psoriasis is clearly not associated with HLA-C*06 in this specific group.
on the presence of established genetic risk factors are likely to be more helpful in future studies for personalized approaches with respect to prognosis and treatment. Even when age of onset is used as a classifier, the distinction between paediatric (< 18 years) and adult psoriasis (≥ 18 years) is probably more informative than the cut-off point of age 30 or 40 years, which is used in early and late onset psoriasis.

The most striking clinical association in our paediatric cohort with any of the genetic risk factors was the observation that nail psoriasis was found more often in HLA-C*06 negative patients (P < 0.008). This association has been previously reported for a larger cohort (unstratified for age) by Gudjonsson et al.11

Psoriasis severity in adults was previously demonstrated to be associated with HLA-C*06 and LCE3C_LCE3B deletion.17,18,20,22 In our paediatric cohort we did not find these associations. We did, however, identify an association between psoriasis severity and IFIH1 and ERAP1. IFIH1 encodes the interferon-induced with helicase C domain 1 (innate immune system), which triggers type I interferon in response to microbial infection,31 and variants are associated with type 1 diabetes.32 ERAP1 encodes an aminopeptidase, which regulates the quality of peptides bound to MHC class I molecules, such as HLA-C*06.33

A limitation of this study is the modest sample size for genetic studies. Considering that only children were included, it is, however, the largest cohort described with clinical features. In our cohort more than 50% of the patients was defined as severe psoriasis which could introduce a selection bias.

In conclusion, our findings suggest that genetic polymorphisms in both innate and adaptive immunity play a role in paediatric plaque psoriasis severity and age at onset of psoriasis. We confirm earlier associations found in adult psoriasis between HLA-C*06 with respect to nail involvement. The large proportion of patients with a positive family history in HLA-C*06 negative patients (and the lack of correlation between the two) indicates that other genes, either alone or in epistasis,34 may have significant effects on heritability.

Acknowledgements

We thank all patients and volunteers for participating in this study.

References


33 York IA, Chang SC, Saric T et al. The ER aminopeptidase ERAP1 enhances or limits antigen presentation by trimming epitopes to 8-9 residues. *Natl Immunol* 2002; 3: 1177-84.

Koebner Phenomenon in Psoriasis is not Associated with Deletion of Late Cornified Envelope Genes LCE3B and LCE3C


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The late cornified envelope (LCE) genes are a group of highly homologous genes located on chromosome 1 in the epidermal differentiation complex, which is a 1.6 Mb region on the human genome containing a large number of genes involved in epidermal differentiation. The epidermal differentiation complex contains a total of 18 LCE genes, divided over 6 groups. Two genes of the LCE3 group, LCE3B and LCE3C, are subject to copy number variation due to a commonly deleted segment of 32kb. Individuals can have copy number 0 (homozygous for the deletion), 1 (heterozygous for the deletion) or 2 (homozygous for the wild type ancestral haplotype). Deletion of LCE3B and LCE3C (LCE3C_LCE3B-del) is a strong and widely replicated risk factor for psoriasis. Recent studies indicate that LCE3C_LCE3B-del may also be a risk factor for other autoimmune diseases, but it is not associated with atopic dermatitis. LCE proteins are expressed in a limited number of epithelia and we have recently shown that the genes of the LCE3 group, including the psoriasis-associated LCE3B and LCE3C genes, show distinct expression patterns under inflammatory conditions or upon skin injury. Out of all the identified psoriasis-associated risk factors, only LCE3C_LCE3B-del and copy number variation in the beta-defensin cluster affect expression of putative skin barrier proteins. Although the observed odds ratios (ORs) in various cohorts are smaller than those published for HLA-Cw6 (current notation HLA-C*06), the strongest known psoriasis risk factor, LCE3C_LCE3B-del has a large population attributable risk (23%). Both the significant contribution to the genetic basis of psoriasis and its plausible biological function, render LCE3C_LCE3B-del an important risk factor that is amenable to mechanistic studies.

In 1877, Heinrich Koebner described the appearance of psoriatic lesions in uninvolved skin of psoriatic patients as a consequence of trauma. Now, it is known that patients with other dermatological conditions can koebnerize as well. Several causes for this phenomenon are known, like trauma, allergic or drug reactions and therapeutics, although the pathogenesis is not well understood. In previous studies it was shown that on average 25% of psoriasis patients will koebnerize on external stimulation of the skin. We hypothesized that the deletion of the LCE3B and LCE3C genes could lead to an inferior barrier function or to an impaired repair function following barrier disruption. This would make the skin more susceptible to penetration by microbial or other environmental molecules, which could trigger innate or adaptive immune responses. Based on our hypothesis that the Koebner reaction may be caused by breaching the skin barrier and/or insufficient barrier repair, we investigated a possible association of the Koebner phenomenon with LCE3C_LCE3B-del. In a Dutch cohort of psoriasis patients that were previously typed for LCE3C_LCE3B-del (by PCR) and HLA-C*06:02 status (by PCR) we assessed their propensity to koebnerize following skin injury. The “Commissie mensgebonden onderzoek Arnhem-Nijmegen” approved
for this study. Patients/parents of the patients gave their informed consent. The investigations were conducted according to the Declaration of Helsinki principles. Adult patients were approached via written questionnaires. In the case of juvenile psoriasis patients we approached the parents by telephone. Both the patients/parents and the interviewers were unaware of the LCE3C_LCE3B-del and HLA-C*06 status of the patients. We assessed, on a 4-point scale, how often a psoriasis plaque appeared after skin damage of their non-involved skin: never, rarely, often or very common. The individuals that responded with often or very common were considered as Koebner positive patients and the others as Koebner negative. We approached 259 patients of whom 192 responded (response rate 74%). Of these, 46 patients (24%) were Koebner positive. This percentage is in line with the previously reported data. We found similar figures for adults (22%, n=24) and children (27%, n=22). Table 1 shows an equal distribution over the three LCE3B/C genotypes for the Koebner positive and negative group. Logistic regression analysis demonstrates that there is no association between LCE3C_LCE3B-del and the Koebner phenomenon in psoriasis patients (P = 0.835, OR 1.06, 95% confidence interval (95% CI) 0.64 - 1.74). Also for HLA-C*06 we did not observe an association with the Koebner phenomenon (P = 0.310, OR 1.43, 95% CI: 0.72 – 2.82). This is in contrast with a previously reported association between Koebner effect and HLA-C*06 in Icelandic psoriasis patients. This discrepancy may have several causes such as the study design (family-based versus population-based), ethnic background, inaccurate reporting because of self-reported data or lower statistical power of our study (66%, input values were derived from Gudjonsson et al. significance level 0.05, OR 2.3, allele frequency 0.28, dominant model).

Our results suggest that the Koebner phenomenon in psoriasis is unlikely to be dependent on the LCE3B/C genotype. Therefore, the biological role of LCE3B and LCE3C deletion in development and/or maintenance of psoriasis remains to be explained.

Acknowledgements
We would like to thank all the patients that participated in this study.

<table>
<thead>
<tr>
<th>LCE3B/C copy number</th>
<th>Genotype</th>
<th>Koebner positive</th>
<th>Koebner negative</th>
<th>P-value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>del/del</td>
<td>20 (43%)</td>
<td>66 (45%)</td>
<td>0.835</td>
<td>1.06 (0.64 – 1.74)</td>
</tr>
<tr>
<td>1</td>
<td>del/wt</td>
<td>21 (46%)</td>
<td>65 (45%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>wt/wt</td>
<td>5 (11%)</td>
<td>15 (10%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; del, deletion; OR, odds ratio; wt, wildtype.
References

3 Treatments
Treatment of paediatric scalp psoriasis with calcipotriol/betamethasone dipropionate scalp formulation: effectiveness, safety and influence on children’s quality of life in daily practice

A.M. Oostveen, E.M.G.J. de Jong, A.R.T. Donders, P.C.M. van de Kerkhof, M.M.B. Seyger

Abstract

Background
Evidence on efficacy and safety of topical treatments for paediatric scalp psoriasis is lacking.

Objective
This study aims to evaluate the effectiveness and safety of calcipotriol/betamethasone dipropionate scalp formulation for paediatric scalp psoriasis in daily clinical practice. The influence of this formulation on the quality of life (QoL) was assessed as well.

Methods
Data of children treated with the scalp formulation were extracted from a prospective observational daily clinical practice registry of children with psoriasis, called Child-CAPTURE. Severity was expressed by Psoriasis Scalp Severity Index (PSSI) and the impact on the QoL was reflected by the validated Children’s Scalpdex in Psoriasis (CSP).

Results
Eighty-four treatment episodes were analysed. Significant improvements of PSSI score (18.7 ± 11.8 to 12.7 ± 9.4) was demonstrated in the first 12 weeks and this result was well maintained during 48 weeks of follow-up. Three patients (4.1%) developed striae of the skin (arms, trunk and legs), which are possibly related to the scalp formulation. CSP scores (79.0 to 46.3) declined significantly after three months.

Conclusion
In a daily clinical practice cohort of children with scalp psoriasis, calcipotriol/betamethasone dipropionate scalp formulation was effective with a 32.1% improvement of PSSI at week 12 and a maintenance of this effect until 48 weeks of follow-up, in combination with improvement of QoL.

Introduction
Up to almost 90% of children with psoriasis report some degree of scalp involvement. Scalp psoriasis is a challenging element of psoriasis to treat, as it is difficult to apply topical treatment at the scalp, resulting in poor compliance. A two-compound scalp formulation composed of both vitamin D analogue (calcipotriol) and corticosteroid (betamethasone dipropionate) has been developed specifically for the treatment of scalp psoriasis. This scalp formulation was effective in adults and improved the quality of life (QoL) of adults with scalp psoriasis. Literature on the effectiveness of treatment of scalp psoriasis in children is lacking. Therefore, this study aims to evaluate, in daily clinical practice, the effectiveness and safety of calcipotriol/betamethasone dipropionate scalp formulation in children with scalp psoriasis. In addition, the impact of this formulation on the QoL of these children was analysed.

Materials and methods
Patient population
Data were extracted from a prospective observational daily clinical practice registry, called Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry). All children (<18 years) with psoriasis receiving calcipotriol/betamethasone dipropionate scalp formulation between September 2008 and April 2013 were enrolled. Concomitant systemic antipsoriatic treatments were excluded, but it was allowed to use topical therapy for other parts of the body, such as topical corticosteroids, vitamin D analogues or dithranol creme. As this study was performed in daily clinical practice patients were treated according to the opinion of the treating dermatologist and visits were not planned according to a fixed schedule. At the beginning of treatment, patients were advised to use the scalp formulation once daily for the first two weeks and subsequently three times a week. Depending on the severity of scaling the scalp was pre-treated with 10% salicylic acid in unguentum cetomacrogolis for two nights. Because patients were seen in daily clinical practice, a wash-out period was not implemented. Data were analysed as separate treatment episodes, which was defined as the time between the beginning and the end of treatment. An individual patient could have more than one treatment episode. Restart of a treatment after an interruption of three months or longer was determined as a new treatment episode. At baseline, patient characteristics were recorded including: age, gender, age at onset, family history and duration of psoriasis.
CHAPTER 3

TREATMENTS

Results

Patients

In total 130 children (146 treatment episodes) were prescribed the calcipotriol/betamethasone dipropionate scalp formulation. Sixty-two treatment episodes were excluded (n=8 concomitant systemic antipsoriatic treatments, n=27 had already been prescribed the scalp formulation before the first visit and n=27 no follow-up). Thus, 84 treatment episodes (73 patients) were analysed (Table 1).

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n</td>
</tr>
<tr>
<td>Number of treatment episodes, n</td>
</tr>
<tr>
<td>Boys, n (%)</td>
</tr>
<tr>
<td>Age, years, mean ± SD (range)</td>
</tr>
<tr>
<td>Mean duration of follow-up, weeks ± SD</td>
</tr>
<tr>
<td>With prescribed treatment in the last four weeks before the beginning of the scalp formulation, n (%)</td>
</tr>
</tbody>
</table>

PASI, Psoriasis Area and Severity Index; PSSI, Psoriasis Scalp Severity Index.

Effectiveness

At the beginning of the study, a mean baseline PSSI of 18.7 ± 11.8 was found. At week 6, a 19.2% PSSI improvement (15.1 ± 11.0) was achieved and at week 12 this increased to 32.1% PSSI improvement (12.7 ± 9.4). This effect was well maintained until week 48, with PSSI rates varying between 13.8 ± 11.5 and 12.8 ± 4.8 (Figure 1). Mixed model analysis demonstrated a significant positive effect of the scalp formulation on scalp psoriasis over time (P < 0.001). Seventy-two patients had a follow-up of at least 12 weeks. The response rate of at least 50% PSSI improvement at week 12 compared to baseline was 29.2% (n=21). In 16 children clearance (PSSI = 0) was achieved after a median treatment duration of 19 weeks. Analyses of the separate items of the PSSI.

Outcome measures

Clinical and QoL data were recorded every time the patient visited our outpatient clinic. Safety data were prospectively collected based on side-effects reported by the patients and observations of the physician at each visit. Scalp psoriasis severity was expressed by the Psoriasis Scalp Severity Index (PSSI; range 0 – 72). The PSSI is calculated by a 5-point scale (0 = no symptoms, to 4 = very severe) for each individual symptom (redness, scaling, and infiltrate). These three scores are added and multiplied with a score for the percentage of the scalp involved (0 = 0% to 6 = 90 – 100%). Clinical severity of psoriasis was assessed by a clinician using Psoriasis Area and Severity Index (PASI; range 0 – 72). Since March 2011 data about the impact on the QoL of scalp psoriasis was collected by the validated Children’s Scalpdex in Psoriasis (CSP; range 0 – 100). The CSP questionnaire comprises of 22 items that consists of three major constructs: ‘symptoms’, ‘emotions’ and ‘functioning’. A lower score represents a better QoL.

Statistics

PSSI scores were analysed at baseline, every 6 weeks until week 24 and thereafter every 12 weeks until week 48. The scores were interpolated to the most nearby time point. Effectiveness was analysed using the as-treated analysis, in which the analysis is performed on the treatment that patients actually received. Subanalyses were performed for patients with and without pretreatment with salicylic acid preparations, and for patients that treated their scalp psoriasis in the last four weeks before the beginning of the scalp formulation versus those who did not. Descriptive statistics were used to represent study results as means (= standard deviation; SD). Comparisons of numeric variables were analysed with the (un)paired t-test. P < 0.05 was considered statistically significant. A linear mixed modelling approach was applied to investigate the difference in scalp psoriasis severity across multiple visits. CSP scores were analysed at baseline, 3 and 6 months after treatment, and were converted to the most nearby time point. Changes in the median scale CSP scores (interquartile range; IQR) at month 3 and month 6 compared to baseline were analysed by using the Wilcoxon rank sum test. Analyses of this questionnaire beyond 6 months were considered inappropriate, as the number of available questionnaires were too low.

The statistical analyses were performed using SPSS software 20.0 (SPSS Inc., Chicago, IL, U.S.A.). The study was approved by the research ethics committee of the Radboud University Medical Center and has been carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees and informed consent.

Patients

In total 130 children (146 treatment episodes) were prescribed the calcipotriol/betamethasone dipropionate scalp formulation. Sixty-two treatment episodes were excluded (n=8 concomitant systemic antipsoriatic treatments, n=27 had already been prescribed the scalp formulation before the first visit and n=27 no follow-up). Thus, 84 treatment episodes (73 patients) were analysed (Table 1).

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induration, desquamation and area) demonstrated for all items a significant decline in the first 12 weeks (P < 0.05), until week 48 these items remained more or less the same. The PASI demonstrated also a significant effect over time (from 5.7 ± 3.1 to 4.1 ± 2.1, P = 0.038) (Figure 1).

Twenty-eight treatment episodes were pre-treated with salicylic acid. In subanalysis, patients who pre-treated their scalp psoriasis with salicylic acid had a higher baseline PSSI than those who did not (26.7 ± 11.0 vs 14.7 ± 10.0, P < 0.001). Both groups showed a significant improvement of PSSI at week 12 (with salicylic acid, mean PSSI 15.8 ± 11.4, 40.1% PSSI improvement, P = 0.012; without salicylic acid, mean PSSI 11.0 ± 9.1, 25.2% PSSI improvement, P = 0.04). Until week 48, scalp psoriasis severity in both groups were more or less the same with PSSI rates varying between 14.6 ± 12.8 and 11.5 ± 9.1 (Figure 1). Mixed model analysis demonstrated a significant positive effect of the scalp formulation on scalp psoriasis for both groups over time (P < 0.05).

There were no differences in baseline PSSI nor in effectiveness over time of those who used a treatment in the last four weeks before start versus those who did not (P > 0.05).

Safety
Patients did not report any complaints. In three overweight patients (4.1%) the physician observed striae of the skin. The first is a 12-year-old female with striae after pubertal growth on both thighs. Another a 13-year-old female had striae on both thighs, lower back and buttocks. A 17-year-old male developed striae on his elbows and abdomen after extreme increase in bodyweight and waist circumference. There were no serious adverse events.

Quality of life of scalp psoriasis
The total score of the CSP questionnaire showed a significant improvement from baseline (median 79.0; IQR 82.9) to 3 months of follow-up (median 46.3; IQR 89.3, P < 0.001), with a median CSP score of 59.0 (IQR 69.7) after 6 months. The median baseline (n=64) scores were as follows: scale symptoms 41.7 (IQR 31.3), scale emotions 26.8 (IQR 35.7) and scale functioning 15.0 (IQR 30.0) (Figure 2). Significant improvements from baseline were observed at 3 months (n=47) for all three of the scales (scale symptoms 25.0, IQR 25.0, P = 0.009; scale emotions 17.9, IQR 30.4, P < 0.001; scale functioning 10.0, IQR 30.0, P = 0.006). The median scale scores of the CSP after 6 months (n=38) remained more or less the same compared to 3 months (scale symptoms 33.3, IQR 27.1, scale emotions 16.1, IQR 27.7, scale functioning 15.0, IQR 25.0).

The influence of calcipotriol/betamethasone dipropionate scalp formulation on the quality of life by means of the Children’s Scalpex in Psoriasis median scale scores at baseline, 3 and 6 months.

*P < 0.05.
Discussion

This prospective observational study describes in daily clinical practice the effectiveness and safety of calcipotriol/betamethasone dipropionate scalp formulation in paediatric scalp psoriasis and analysed the influence of this formulation on the QoL of these children. The scalp formulation was effective in daily clinical practice with a 32.1% PSSI improvement at week 12 and a maintenance of this effect until 48 weeks of follow-up. Patients pre-treated with salicylic acid for two nights demonstrated the highest improvement in the first 12 weeks. This might be due to a fast reduction in scaling, but is more probably due to the fact that these patients had a higher PSSI at the beginning and could therefore show a greater reduction. The efficacy and safety of the scalp formulation in adults with scalp psoriasis has been investigated in many studies. In these randomized, controlled trials, the outcome measures were the investigator global assessment and patients were only included after a pre-defined wash-out period. In 68 - 83% of the patients, an absent or very mild scalp psoriasis was found after 8 weeks of once daily treatment. In a 52-week follow-up study, 92.3% of the patients treated with the scalp formulation reported an adequately controlled scalp psoriasis. Because of the different outcome measures used, and different treatment regimes, a direct comparison of our results with prior studies is not possible. In addition, no wash-out period was applied and patients may not be nearly so motivated to use their medication compared to patients participating in clinical trials, which probably leads to poor adherence.

In our study in three overweight patients (4.1%) striae distensae were observed. These striae are possibly related to the scalp formulation, although the overweight in combination with an increase in body weight can also cause striae distensae. In addition, topical corticosteroids for other parts of the body were used as well. A long-term study in adults reported a proportion of corticosteroid-related events in 2.6% of the patients. Other 8-week randomized, controlled trials in adults reported adverse events rates between 3.4% and 7.0%. The number of patients and adverse events in our study were too small to draw firm conclusions about safety. In addition, it should be kept in mind that adverse events in this study were based on patients own experience or observations of the physician and not actively reported and collected as in randomized, controlled trials. In this study no pharmacokinetics was taken into account. This might be interesting in a future study.

A positive influence on the QoL of the scalp formulation was demonstrated. Our results confirm two former studies in adults with scalp psoriasis. However, these studies used other instruments to measure quality of life, namely Skindex-16 (16-item Short Form Health Survey) and the Scalp Life Quality Index (derived from the Dermatology Life Quality Index). Both studies only investigated short-term improvement of QoL until 8 weeks of treatment.

In conclusion, this prospective daily clinical practice study for paediatric scalp psoriasis showed that calcipotriol/betamethasone dipropionate scalp formulation was effective and seems well tolerated, with a 32.1% improvement in the first 12 weeks and a maintenance of this effect during a 48 weeks of follow-up. In addition, a positive influence on the QoL of these children was demonstrated.
References

The effectiveness and safety of short-contact dithranol therapy in paediatric psoriasis: a prospective comparison of regular day care and day care with telemedicine

A.M. Oostveen, C.A. Beulens, P.C.M. van de Kerkhof, E.M.G.J. de Jong, M.M.B. Seyger

CHAPTER 3 TREATMENTS

Abstract

Background
Evidence on the effectiveness and safety of short-contact dithranol therapy in paediatric psoriasis is sparse and only based on retrospective data. The best results are achieved in a time consuming day care setting.

Objective
To study prospectively the effectiveness and safety of short-contact dithranol therapy in paediatric psoriasis. In addition, the effectiveness, safety, duration of treatment and number of visits between regular day care and day care with telemedicine were compared.

Methods
Data were collected from the prospective observational Child-CAPTURE registry of children with psoriasis. Effectiveness was measured as the mean percentage improvement in Psoriasis Area and Severity Index (PASI). Safety was assessed by recording adverse events. The number of visits and duration of treatment were reported.

Results
For all patients a mean percentage reduction in PASI score of -69.3% was found, with no significant differences between regular day care and day care with telemedicine. The only adverse event reported was irritation of the skin. Neither the frequency of irritation during treatment nor the mean duration of treatment significantly differ between the two groups. Patients with telemedicine had significantly less number of visits.

Conclusion
This first prospective observational study demonstrated that short-contact dithranol therapy in paediatric psoriasis is effective and safe. Regular day care and day care with telemedicine are equally effective. Telemedicine can be of additional value as it is less time consuming. We hope is will therefore make dithranol treatment appropriate for a larger number of children with psoriasis.

Introduction
In one-third of patients with psoriasis, disease onset occurs during childhood. Three studies have been published on the effectiveness of dithranol in paediatric psoriasis, of which two did not use an objective severity score. Short-contact dithranol therapy involves a complex, time consuming treatment schedule, and best results are obtained when it is administered in a day care centre setting, with regular visits. Contact by means of telemedicine can reduce this burden.

This study aims to provide the first prospective observational data on the effectiveness and safety of short-contact dithranol therapy in children with psoriasis in daily clinical practice. In addition, the effectiveness, safety, duration of treatment and number of visits between two groups were compared – regular day care and day care with telemedicine.

Materials and methods
Data were extracted from the prospective observational, daily clinical practice registry of children with psoriasis, called Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use REgistry). All children (aged <18 years) with plaque psoriasis receiving short-contact dithranol therapy between September 2008 and December 2012 were analysed. Exclusion criteria are depicted in Figure 1.

Short-contact dithranol cream was started if topical corticosteroids with or without calcipotriene treatment failed, or if patients had a moderate-to-severe psoriasis (Psoriasis Area and Severity Index (PASI) score around 10 and/or a Children’s Dermatology Life Quality Index (CDLQI) score around 10). The formulation of dithranol cream, can be washed off totally and cleanly as follows: dithranol (0.05, 0.1, 0.2, 0.3, 0.4, 0.8, 1, 2, 3 or 5 gram), ascorbic acid 0.1 gram, salicylic acid 1 gram and cremor lanette I ad 100 gram.

As of March 2011 patients were given the possibility to choose between regular day care or day care with telemedicine, primarily to reduce the burden of travelling for patients living far away. Telemedicine was performed by video calls established through the Skype for Windows desktop software (Skype Communications SARL, Luxembourg City, Luxembourg).

In the first week, all patients were seen for four days at the day care centre; thereafter visits were scheduled two times a week. From the second week, the telemedicine...
Psoriasis severity was assessed by means of PASI. Safety was assessed by counting the frequency of irritation as reported in the day care centre patient status. Each interruption of dithranol treatment caused by irritation of the skin (burning sensation of the skin and erythema) was counted as one event. All other reported adverse events were noted. Quality of life was scored with a validated Dutch version of the CDLQI.

Descriptive statistics were used to provide baseline characteristics. All analyses were performed as treated. For differences within or between groups paired samples t-tests or independent t-tests were used or, if applicable, Wilcoxon signed-rank tests or Mann–Whitney U tests. A P-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software 20.0 (IBM Corp., Armonk, NY, U.S.A.). The study was approved by the research ethics committee of the Radboud University Nijmegen Medical Center and has been carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees and informed consent.

**Results**

Thirty-four patients could be analysed (Figure 1): 17 on regular day care and 17 on day care with telemedicine. At baseline, the patients overall had a median PASI of 8.9 with a mean CDLQI of 9.6 (Table 1). The PASI, CDLQI or demographic characteristics did not differ significantly between the two groups, except for a preponderance of males (82.4%) in the telemedicine group.

Overall, dithranol treatment resulted in a mean significant change in PASI score of -69.3%. Effectiveness between the groups did not significantly differ (-67.2% regular day care vs. -71.3% telemedicine P = 0.62). Overall, a significant mean ΔCDLQI score of -5.1 was found (-4.1 regular day care vs. -6.1 telemedicine; P = 0.25).

The only adverse event reported was irritation of the skin, with a mean frequency of 3.6 events and no difference in frequency between the two groups. None of the patients and parents reported unwanted staining of their furniture and bathroom.

The mean treatment duration was 11.4 weeks, without significant difference between the groups. The mean number of day care centre visits was 14.5, with patients in the telemedicine-assisted group having significantly fewer visits (mean 12.1 versus 16.8, P = 0.014). Instead, they made a mean of 7.1 video calls, and more often phone contact between the visits.

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**Figure 1** Study flow diagram.

CAPTURE, Continuous Assessment of Psoriasis Treatment Use Registry; RUMC, Radboud University Medical Center. *Within 1 month prior to the start and during treatment; † during dithranol treatment; ‡ interruption of > 1 week; ‡‡ to avoid learning bias.

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Our results are consistent with percentages reported in a randomized controlled trial involving short-contact dithranol therapy in adults, which demonstrated a PASI improvement of -63.3%.[12] With respect to quality of life, short-contact dithranol therapy resulted in a significant decline in CDLQI score, both in the regular day care and day care with telemedicine group.

The maximum biological effect of dithranol is achieved just below the level of irritation of the surrounding uninvolved skin.[13] Compared to other studies,[14] the obtained frequency of irritation in our study is relatively high. As these studies were retrospectively performed, the reported frequency might have been biased or our application time may be too long. In children with psoriasis, no studies have been performed that investigated which application time schedule of short-contact dithranol therapy is the most sufficient. Dithranol staining is a common reported limitation.

This study is the first to compare the effectiveness and safety of short-contact dithranol treatment application between regular day care and day care with telemedicine. The most important benefit of patients in telemedicine group is the reduction in travel time, which results in the possibility to attend school more often. In addition, for the convenience of the children, the telemedicine contacts were planned before or after school. Patients were given the possibility to choose between the two treatment regimes. Obviously, all patients in the telemedicine group lived far away. The preponderance of males is considered to be coincidental. We found no significant differences in effectiveness, safety and improvement in quality of life between the groups. Additional studies are needed to investigate the possibility of decreasing day care visits while preserving good results.

A limitation of the study are the relatively small treatment groups, but considering the fact that data and evidence of treatment in children with psoriasis are sparse, we think it is still an acceptable number of patients to draw conclusions. In addition, there

### Table 1 Patient and treatment characteristics of regular day care and day care with telemedicine

<table>
<thead>
<tr>
<th></th>
<th>Regular day care</th>
<th>Day care with telemedicine</th>
<th>All treatments</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>17</td>
<td>17</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Age, years, mean ± SD (range)</td>
<td>11.4 ± 3.4 (5 – 17)</td>
<td>10.2 ± 4.0 (3 – 17)</td>
<td>10.8 ± 3.7 (3.0 – 17.0)</td>
<td>0.39</td>
</tr>
<tr>
<td>Boys/girls, n (%)</td>
<td>6/11 (35.3/64.7)</td>
<td>14/3 (82.4/17.6)</td>
<td>20/14 (58.8/41.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Psoriasis history</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age at onset, years, mean ± SD (range)</td>
<td>7.8 ± 4.4 (1 – 15)</td>
<td>7.4 ± 4.0 (3 – 16)</td>
<td>7.6 ± 4.2 (1 – 16)</td>
<td>0.68</td>
</tr>
<tr>
<td>Duration of psoriasis, months, mean ± SD (range)</td>
<td>43.4 ± 39.2 (1 – 135)</td>
<td>38.7 ± 30.8 (5 – 107)</td>
<td>41.0 ± 34.8 (1 – 135)</td>
<td>0.97</td>
</tr>
<tr>
<td>Effectiveness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline PASI, median (IQR)</td>
<td>9.9 (7.6 – 12.0)</td>
<td>8.2 (6.6 – 9.6)</td>
<td>8.9 (6.6 – 11.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>End of treatment PASI, median (IQR)</td>
<td>2.7 (2.0 – 3.9)</td>
<td>2.0 (0.8 – 3.3)</td>
<td>2.4 (1.1 – 3.8)</td>
<td>0.15</td>
</tr>
<tr>
<td>Percentage change in PASI, 95% CI</td>
<td>-67.2 (-78.9 to -55.6)</td>
<td>-71.3 (-83.6 to -58.9)</td>
<td>-69.3 (-77.3 to -61.2)</td>
<td>0.62</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Frequency of irritation during treatment, mean ± SD</td>
<td>3.7 ± 1.8</td>
<td>3.5 ± 3.1</td>
<td>3.6 ± 2.5</td>
<td>0.89</td>
</tr>
<tr>
<td>Short-contact dithranol therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of treatment, weeks, mean ± SD</td>
<td>10.8 ± 3.8</td>
<td>11.9 ± 4.8</td>
<td>11.4 ± 4.3</td>
<td>0.48</td>
</tr>
<tr>
<td>Total number of visits at the day care centre, mean ± SD</td>
<td>16.8 ± 6.1</td>
<td>12.1 ± 4.3</td>
<td>14.5 ± 5.7</td>
<td>0.014</td>
</tr>
<tr>
<td>Frequency of telemedicine contacts, mean ± SD</td>
<td>-</td>
<td>7.1 ± 3.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Frequency of phone contacts, mean ± SD</td>
<td>0.5 ± 0.7</td>
<td>1.7 ± 1.7</td>
<td>1.1 ± 1.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Max concentration of dithranol cream, median (IQR)</td>
<td>0.2 (0.2 – 0.3)</td>
<td>0.3 (0.2 – 0.4)</td>
<td>0.2 (0.2 – 0.4)</td>
<td>0.16</td>
</tr>
<tr>
<td>Quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline CDLQI, mean ± SD</td>
<td>8.6 ± 3.9</td>
<td>10.8 ± 6.6</td>
<td>9.6 ± 5.4</td>
<td>0.28</td>
</tr>
<tr>
<td>End of treatment CDLQI, mean ± SD</td>
<td>4.8 ± 4.4</td>
<td>4.4 ± 4.5</td>
<td>4.4 ± 4.4</td>
<td>0.29</td>
</tr>
<tr>
<td>Absolute change in CDLQI score, mean ± SD</td>
<td>-4.1 ± 4.3</td>
<td>-6.1 ± 5.6</td>
<td>-5.1 ± 5.0</td>
<td>0.25</td>
</tr>
</tbody>
</table>

SD, standard deviation; IQR, interquartile range; PASI, Psoriasis Area and Severity Index; 95% CI, 95% confidence interval; CDLQI, Children’s Dermatology Life Quality Index. *between regular day care and day care with telemedicine. Significant P-values are shown in bold.
was an absence of a wash-out period of topical treatments, and patients were not randomized to regular day care or telemedicine, which might introduce a bias.

In conclusion, short-contact dithranol therapy is an effective and safe treatment in paediatric psoriasis, as demonstrated in this first prospective study. The introduction of telemedicine in addition to regular day care resulted in a reduction of visits, while preserving good results. Whether these results can be conserved while reducing the number of visits even more, should be investigated. By combining telemedicine with regular day care, this effective and very safe treatment option will become appropriate for a larger group of children with psoriasis.

References
Effectiveness and safety of fumaric acid esters in children with psoriasis: a retrospective analysis of 14 patients from the Netherlands


# Abstract

**Background**
Fumaric acid esters (FAE) are used as an effective and safe oral treatment for plaque psoriasis in adult patients, but little is known about their efficacy and safety in children with psoriasis.

**Objective**
To assess the effectiveness and safety of FAE in the treatment of paediatric psoriasis.

**Methods**
A retrospective analysis of 14 paediatric psoriasis patients (age < 18 years) treated with FAE between 2004 and 2012 at several Dutch university and regional clinics. Patients were identified through databases or registries.

**Results**
The median age at start of FAE treatment was 15 years (range 8 – 17 years). The median duration of FAE treatment was 10 months (range 1 – 80 months), and the median maintenance dosage per day was 360 mg dimethylfumarate (range 240 – 600 mg). Five patients (36%) achieved a complete clearance of their psoriasis, one patient (7%) had a good improvement, three patients (21%) had a partial response, and five patients (36%) were non-responders. FAE treatment was well-tolerated, but two patients (14%) discontinued FAE, one with severe diarrhoea and one with flushing of the skin. Five patients (36%) had transient, slightly abnormal laboratory values of liver-function tests or leukocytes that did not necessitate FAE dosage reduction or treatment discontinuation. No serious adverse events occurred.

**Conclusion**
In this retrospective case series FAE seemed to be an effective and safe treatment for children with psoriasis. FAE may be an attractive therapeutic alternative to the currently used systemic immunosuppressive agents for paediatric psoriasis patients. Further studies are needed to evaluate the suitability of FAE in paediatric psoriasis.

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# Introduction
Psoriasis is a common inflammatory skin disease that manifests in 30-50% of patients in the first 2 decades of life. Treatment of psoriasis in childhood is often challenging, and there is a substantial unmet need for alternative treatment options to broaden the therapeutic armamentarium for paediatric psoriasis. Fumaric acid esters (FAE) may be an alternative option for paediatric psoriasis.

FAE are small molecules that are thought to improve psoriasis by a broad range of immunomodulatory effects. FAE were licensed in Germany in 1994 for severe plaque psoriasis in adults and in 2008 for moderate plaque psoriasis. In adults the efficacy of FAE is comparable to that of methotrexate, and the long-term safety profile is favourable. Data on paediatric use of FAE is relatively scarce, with only 3 case reports published to date.

In this study, we aimed to expand the current knowledge on the use of FAE in paediatric psoriasis by assessing the effectiveness and safety of FAE in 14 children with psoriasis.

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# Patients and methods

**Study design and study population**
This is a retrospective analysis of patients with psoriasis aged < 18 years treated with oral FAE. All patients were treated by dermatologists, and were identified through databases or registries from several Dutch university and regional hospitals.

**Treatment regimen**
Treatment with FAE was administrated according to local and Dutch guidelines with one of three standardized Dutch FAE-formulations. Routine laboratory testing and urine analysis were performed before the start of treatment and at fixed intervals during treatment. FAE were given according to the progressive dosing regimen applied in adult patients, starting at dimethylfumarate 30 mg, with an incremental increase up to a maximum daily dosage of 720 mg based upon clinical response and tolerability. Patients were allowed topical psoriasis treatments in addition to FAE, including topical steroids, vitamin D analogues and dithranol.

**Data collection**
We extracted clinical data from the patient’s medical records. Effectiveness was based on the treating physician’s notes and with the psoriasis area and severity index (PASI) when available.
Results

Patient characteristics
The study population consisted of 14 children with chronic plaque psoriasis (Table 1). The median disease duration was 5 years (range 1 – 10 years). The majority of the patients (83%) had received prior phototherapy and/or systemic treatment. The median age at start of FAE treatment was 15 years (range 8 – 17 years).

Treatment duration and dosage of fumaric acid esters
The median duration of FAE treatment was 10 months (range 1 – 80 months). The median maintenance dosage per day was 360 mg dimethylfumarate (range 240 – 600 mg). Six patients were maintained on FAE at time of data closure, with a median treatment duration of 26 months (range 4 – 80 months). Five patients discontinued FAE after a median duration of 8 months (range 2 – 17 months) because of an insufficient clinical response. Two patients discontinued FAE because of subjective side-effects after having been treated for 1 and 4 months, respectively. One patient with a complete resolution of her psoriasis discontinued FAE after 20 months of treatment.

Effectiveness
Five of the 14 patients (36%) achieved a complete clearance of their psoriatic skin lesions with FAE treatment. One (7%) patient had a good improvement with an 82% reduction in PASI after 4 months of treatment. A partial response was seen in three patients (21%), one of whom had a PASI reduction of 69% following 6 months of treatment. Five patients (36%) did not sufficiently respond to FAE, or their psoriasis deteriorated. Of these, two patients had a 27% and a 31% increase in PASI, respectively.

Tolerability
The most common reported subjective adverse events were abdominal cramps (n=5), diarrhoea (n=4), and flushing of the skin (n=2), which in most cases were tolerable and transient of nature. However, one patient discontinued FAE because of

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Type of psoriasis</th>
<th>Disease duration (years)</th>
<th>Previous systemic treatments/phototherapy</th>
<th>Age at start of FAE (years)</th>
<th>Highest daily dose of FAE (mg)</th>
<th>Maintenance daily dose of FAE (mg)</th>
<th>Duration of treatment (months)</th>
<th>Response</th>
<th>Adverse events</th>
<th>Laboratory deviations</th>
<th>Reason for discontinuation</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 b</td>
<td>M</td>
<td>Plaque</td>
<td>6</td>
<td>UV-B</td>
<td>8</td>
<td>240  c</td>
<td>240  c</td>
<td>8</td>
<td>No response; PASI increase from 9.8 to 12.4 (+27%)</td>
<td>Diarrhoea</td>
<td>None</td>
<td>Insufficient clinical response</td>
<td>Treated with MTX</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Plaque and palmoplantar</td>
<td>7</td>
<td>UV-B, PUVA</td>
<td>12</td>
<td>600  c</td>
<td>480-600  c</td>
<td>33 (ongoing)</td>
<td>Complete response</td>
<td>None</td>
<td>None</td>
<td>NA</td>
<td>FAE continued</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>Plaque</td>
<td>9</td>
<td>UV-B</td>
<td>13</td>
<td>360  c</td>
<td>360  c</td>
<td>12</td>
<td>No response; PASI 10 at end of treatment</td>
<td>None</td>
<td>Reduction in neutrophils</td>
<td>Insufficient clinical response</td>
<td>Treated with MTX</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>Plaque</td>
<td>1</td>
<td>UV-B</td>
<td>13</td>
<td>240  d</td>
<td>240  d</td>
<td>6 (ongoing)</td>
<td>Partial response; PASI reduction from 16.4 to 5.1 (-69%)</td>
<td>Flushing of the skin</td>
<td>Not reported</td>
<td>NA</td>
<td>FAE continued</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>Plaque, acitretin</td>
<td>5</td>
<td>UV-B, acitretin</td>
<td>13</td>
<td>720  *</td>
<td>600  *</td>
<td>17</td>
<td>Partial response</td>
<td>Bronchitis</td>
<td>Reduction in lymphocytes, increase in neutrophils</td>
<td>Insufficient clinical response</td>
<td>Treated with MTX, etanercept</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>Plaque</td>
<td>8</td>
<td>UV-B, acitretin, MTX</td>
<td>15</td>
<td>720  *</td>
<td>NA</td>
<td>4</td>
<td>Partial response</td>
<td>Abdominal cramps</td>
<td>Increase in eosinophils, proteinuria</td>
<td>Insufficient clinical response</td>
<td>Treated with etanercept, MTX</td>
</tr>
</tbody>
</table>

Table 1 Overview of clinical characteristics, treatment course and outcome of children with psoriasis treated with fumaric acid esters (FAE)
### Table 1 Continued

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Type of psoriasis</th>
<th>Disease duration (years)</th>
<th>Previous systemic treatments/phototherapy</th>
<th>Age at start of FAE (years)</th>
<th>Highest daily dose of FAE (mg)</th>
<th>Maintenance daily dose of FAE (mg)</th>
<th>Duration of treatment (months)</th>
<th>Response(^a)</th>
<th>Adverse events</th>
<th>Laboratory deviations</th>
<th>Reason for discontinuation</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 (^{1})</td>
<td>F</td>
<td>Plaque</td>
<td>4</td>
<td>UV-B</td>
<td>15</td>
<td>480 (^{c})</td>
<td>120-240 (^{a})</td>
<td>20</td>
<td>Complete response</td>
<td>Abdominal complaints</td>
<td>None</td>
<td>Sufficient clinical response</td>
<td>Remission of psoriasis at 1-year of follow-up</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>Plaque and guttate</td>
<td>7</td>
<td>UV-B</td>
<td>15</td>
<td>360 (^{c})</td>
<td>120-360 (^{c})</td>
<td>80 (ongoing)</td>
<td>Complete response</td>
<td>None</td>
<td>None</td>
<td>NA</td>
<td>FAE continued</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>Plaque</td>
<td>3</td>
<td>UV-B</td>
<td>16</td>
<td>720 (^{c})</td>
<td>480 (^{a})</td>
<td>18 (ongoing)</td>
<td>Complete response</td>
<td>Abdominal cramps</td>
<td>Increase in ALT, increase in AST, increase in GGT, increase in serum creatinine</td>
<td>NA</td>
<td>FAE continued</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>Plaque and guttate</td>
<td>1</td>
<td>None</td>
<td>16</td>
<td>480 (^{c})</td>
<td>240 (^{c})</td>
<td>33 (ongoing)</td>
<td>Complete response</td>
<td>None</td>
<td>None</td>
<td>NA</td>
<td>FAE continued</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>Plaque</td>
<td>2</td>
<td>MTX</td>
<td>16</td>
<td>720 (^{c})</td>
<td>NA</td>
<td>2</td>
<td>No response; PASI increase from 7.5 to 9.8 (+31%)</td>
<td>Diarrhoea, flatulence</td>
<td>Increase in ALT</td>
<td>Insufficient response</td>
<td>Not reported</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>Plaque</td>
<td>3</td>
<td>UV-B</td>
<td>17</td>
<td>120 (^{c})</td>
<td>NA</td>
<td>1</td>
<td>No response; PASI increase from 3.2 to 3.3 (+22%)</td>
<td>Abdominal pain, diarrhoea, severe flushing of the skin</td>
<td>None</td>
<td>Subjective adverse events</td>
<td>Treated with topical treatment</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>Plaque</td>
<td>4</td>
<td>UV-B, MTX</td>
<td>17</td>
<td>720 (^{c})</td>
<td>NA</td>
<td>4</td>
<td>No response</td>
<td>Nausea, abdominal complaints</td>
<td>Increase in ALT</td>
<td>Subjective adverse events</td>
<td>Treated with adalimumab</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>Plaque</td>
<td>10</td>
<td>UV-B, MTX, cyclosporin</td>
<td>17</td>
<td>270 (^{c})</td>
<td>NA</td>
<td>4 (ongoing)</td>
<td>Good response; PASI reduction from 6.5 to 1.2 (-62%)</td>
<td>Diarrhoea, fatigue</td>
<td>Not reported</td>
<td>NA</td>
<td>FAE continued</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; AST, aspartate transaminase; F, female; FAE, fumaric acid esters; GGT, Gamma-glutamyltransferase; M, male; MTX, methotrexate; NA, not applicable; PUVA, psoralen and ultraviolet-A photochemotherapy; UV-B, Ultraviolet-B phototherapy.\(^{1}\) Complete response: a complete resolution of the psoriatic skin lesions; Good response: at least 75% improvement of the psoriasis; Partial response: 50-75% improvement or in case of initial improvement but later deterioration of the psoriasis; Insufficient response: in case of less than 50% improvement; No response in case of worsening of psoriasis. \(^{2}\) FAE in combination with topical treatment (1% dithranol once daily). \(^{3}\) FAE-formulation with enteric-coated tablets of 30 mg dimethylfumarate and 120 mg dimethylfumarate (De Magistrale Bereider\(^{1}\), Oud-Beijerland, the Netherlands). \(^{4}\) FAE-formulation with enteric-coated slow-release tablets of 30 mg dimethylfumarate and 120 mg dimethylfumarate (‘Merlio-Hout’, Helmond, the Netherlands). \(^{5}\) FAE-formulation with enteric-coated tablets of 105 mg (30 mg dimethylfumarate) and 215 mg (120 mg dimethylfumarate plus 95 mg calcium-monoethylfumarate) (De Magistrale Bereider\(^{1}\), Oud-Beijerland, the Netherlands). \(^{6}\) This patient was described previously by us in a Dutch journal.\(^{11}\)
abdominal complaints. Another patient discontinued FAE because of a severe episode of flushing with diffuse reddening of the skin, a burning sensation, epistaxis, and an inability to stand on her feet following 6 hours after the first intake of 120 mg FAE; however, this resolved quickly with oral steroids (prednisone) and oral histamine antagonist (fexofenadine).

Safety
Abnormal laboratory tests were observed in five patients (36%). Most of these involved slightly elevated liver-function tests (n = 3). In all patients the elevations were less than twice of the upper limit of normal value (ULN). Other changes in laboratory tests included mild, temporary shifts in leukocyte counts. One patient developed a mild increase in serum creatinine levels up to 93 µmol/L (ULN 90 µmol/L). A mild proteinuria (1+) was reported in another patient, but disappeared within 4 weeks. In all cases the abnormal laboratory values normalized without any intervention and while continuing FAE treatment. There were no serious adverse events reported.

Discussion
This is the first case series in which the effectiveness and safety of FAE are described in children with chronic plaque psoriasis. Our findings demonstrated positive effects of FAE and the treatment was well-tolerated.

Several limitations need to be considered. Our retrospective study lacked a predefined study protocol and a control group, and uniform objective disease assessment scores such as PASI were not available for all patients. Nevertheless, we classified treatment responses based on the physicians’ notes, which would for a large part reflect the changes during treatment. Furthermore, patients were treated relatively long time with FAE. The median treatment duration was 10 months and seven patients were treated continuously for at least 1 year.

The literature on FAE in children is limited. There have been three case reports on FAE in paediatric psoriasis, and one report on granulomatous cheilitis and pityriasis rubra pilaris. Compared with the very limited experience in children, the literature on FAE in adult patients is much larger. About 50 to 70% of adult psoriasis patients treated with FAE achieve a 75% improvement in PASI score following 16 weeks of treatment, while 8 to 44% do not respond. These data are in line with the results in this study, in which 43% of the children achieved a complete or almost complete clearance of their psoriasis and 36% were non-responders.

In long-term observational studies FAE was associated with a favourable side-effect profile without any indications of an increased risk of infections, malignancies or serious side-effects. It is tempting to speculate whether the favourable long-term safety profile as observed in adults also applies in children. The adverse events and changes in laboratory tests in this study are comparable with previous findings in adult patients.

The number of dermatologists treating paediatric psoriasis with FAE is limited. In the Dutch guidelines FAE are not recommended because of insufficient evidence. To improve evidence on the use of FAE in children with psoriasis, further randomized controlled trials are needed to evaluate the efficacy of FAE in children with psoriasis and to compare the efficacy of FAE with other systemic treatments such as methotrexate. Also, long-term observational studies are needed to assess the safety profile of FAE in children.

In conclusion, we report the effectiveness and safety of FAE in a retrospective series of 14 children with plaque psoriasis. FAE may be considered an alternative systemic treatment option in paediatric psoriasis.

Acknowledgements
We would like to thank all the dermatologists who have treated the patients described in this study.
References


4

Quality of life
4.1

The influence of treatments in daily clinical practice on the Children’s Dermatology Life Quality Index (CDLQI) in paediatric psoriasis: a longitudinal study from the Child-CAPTURE Patient Registry


Abstract

Background
Paediatric psoriasis has a negative effect on the quality of life (QoL). The influence of treatments on QoL of these children has never been investigated before in a prospective observational study.

Objective
To assess the Children’s Dermatology Life Quality Index (CDLQI) in a cohort of patients with paediatric psoriasis and to evaluate the influence of treatments in daily clinical practice on CDLQI.

Methods
We conducted a prospective observational study of children with psoriasis from a registry containing daily clinical practice data. Before and after treatment, QoL was assessed by the CDLQI and disease severity was documented by the Psoriasis Area and Severity Index (PASI). Three clusters of treatments were analysed: topical, dithranol and systemic therapy.

Results
In total, 125 patients were enrolled in the registry. Cross-sectionally, a mean ± SD CDLQI score of 7.5 ± 6.0 and a mean ± SD PASI score of 7.0 ± 5.8 were recorded. Itching and problems with treatment had the highest impact on the children’s QoL. Longitudinally, 85 patients were analysed with a total of 137 treatment episodes. All treatments contributed to a significant decline in total CDLQI score, with the largest decrease seen in dithranol and systemic treatments. A significant correlation was found between ΔCDLQI and ΔPASI for all treatment modalities. The highest positive impact of treatments was found in a decline of itch and sleep disturbance.

Conclusions
In this first prospective observational study on CDLQI in paediatric psoriasis, a positive influence of treatments in daily clinical practice on QoL was demonstrated.

Introduction
Psoriasis is a chronic, remitting and relapsing scaly inflammatory skin disease that affects 1 – 3% of the population. Although it can occur at all ages, approximately a third of affected patients with psoriasis recall signs of disease before adulthood. Treatment can provide temporary remission of physical symptoms but not a cure. Skin disease in children can have detrimental effects on the quality of life (QoL), disrupting family and social relationships, interfering with playing, sport and affecting normal development. In 1995 the Children’s Dermatology Life Quality Index (CDLQI) was developed to allow QoL assessment of children with skin conditions. Data about QoL in paediatric psoriasis are limited. Only a few cross-sectional studies demonstrated the negative influence of psoriasis on the QoL in children by means of the CDLQI. Longitudinally, only one randomized controlled trial described a significant positive effect of etanercept therapy on QoL in moderate to severe paediatric plaque psoriasis.

The influence of treatments in daily clinical practice on QoL of children with psoriasis is important in clinical decision-making. As this has never been investigated before, the current prospective observational study assessed the QoL in paediatric psoriasis by means of the CDLQI in a cohort of patients treated in daily clinical practice. In order to assess what aspects of QoL were mainly influenced by psoriasis treatments, the 10 items of the CDLQI questionnaire were analysed as well.

Materials and Methods

Study population
Data were obtained from a prospective observational paediatric psoriasis registry, called Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry). The Child-CAPTURE included all patients under the age of 18 years, with the diagnosis of psoriasis, who had attended the dermatology outpatient clinic at the Radboud University Nijmegen Medical Center, between September 2008 and October 2011. Patients were referred by general practitioners and dermatologists. At the initial visit patient characteristics were recorded including: age, gender, age at onset, family history and duration of psoriasis. During visits at the out-patient clinic, patients are actively asked if they have joint pain and when needed patients are referred to a paediatric rheumatologist.

Treatments
Patients were treated according to the treatment algorithm as published by de Jager et al. A rough summary of this algorithm is as follows: first, calcipotriene with or without
topical corticosteroids, followed by dithranol. Methotrexate is considered to be the first systemic treatment of choice, followed by etanercept. Based on the above-mentioned treatments a division into three clusters was made: topical (only topical treatment including topical corticosteroids, calcipotriol/betamethasone dipropionate, vitamin D analogues, calcineurin inhibitors and salicylic acids), dithranol (anthralin) and systemic therapy (including methotrexate, etanercept, acitretin and ciclosporin). Dithranol therapy was given in a day clinic setting. According to the Dutch guidelines for psoriasis, phototherapy for paediatric psoriasis is only limited recommended. A treatment episode was defined as the time between the start and the end of a treatment in one of the three clusters. The discontinuation of a treatment episode was either because of clearance or almost clearance of psoriasis, or because the treatment was not effective enough. A patient could have more than one treatment episode in different treatment clusters because of switch to another therapy.

Outcome measures
At every visit, the patient’s quality of life, disease severity and type of treatment were documented. To quantify the impact of psoriasis on the children’s QoL, a validated Dutch version of the CDLQI was used (10 items; range 0 – 30). Clinical severity of psoriasis was assessed by a clinician using Psoriasis Area and Severity Index (PASI; range 0 – 72). Higher scores indicated more impairment in QoL, and more severe psoriasis. Responders were defined as patients with a lower PASI at the end of a treatment episode compared to the start of that treatment episode. Non-responders were patients with an equal or higher PASI at the end of a treatment episode compared to the start of that treatment episode.

Analysis
At baseline descriptive statistics were provided using mean and standard deviation (SD). To demonstrate differences between the subgroups, an independent samples t-test was performed. Correlation coefficients were calculated with the Pearson correlation test. For each cluster of treatments, differences in scores of CDLQI and PASI were calculated before and after a treatment episode. These different scores were analysed using mixed models to accommodate the dependencies caused by the repeated measurements on some of the patients. To test effects of treatment on the CDLQI scores, models were fitted with and without these factors and likelihood ratio test were performed. The level of significance was considered to be 0.05. The statistical analyses were performed using SPSS software 16.0 (SPSS Inc., Chicago, IL, U.S.A.), R2.13 and the nlme package.

Results
Cohort characteristics and baseline
In total, 125 patients were enrolled in the Child-CAPTURE registry. One patient was diagnosed with psoriatic arthritis. None of the paediatric psoriasis patients were hospitalized. Patient characteristics of the study population are reported in Table 1. The mean ± SD age at baseline was 10.7 ± 3.9 years, with a female preponderance (63.2%). The mean ± SD age at onset of psoriasis was 7.4 ± 3.9 years. Before visiting our clinic the patients had a mean ± SD duration of their psoriasis of 39.2 ± 37.0 months (range 1 – 154). A large proportion of patients (70.4%) had one or more family members affected with psoriasis. At the initial visit, patients had a mean ± SD psoriasis severity score (PASI) of 7.0 ± 5.8 and documented a mean ± SD CDLQI of 7.5 ± 5.0. A significant positive correlation between PASI and CDLQI of \( r = 0.31 \) (\( P = 0.001 \)) was found. Boys and girls had a comparable mean score in total CDLQI (7.5 vs. 7.6; \( P = 0.89 \)). The mean ± SD CDLQI of patients under the age of 12 (n=68; 7.0 ± 4.5) and patients aged 12 years and above (n=57; 8.2 ± 5.6) did not significantly differ (\( P = 0.173 \)). No significant correlation was found between duration of the psoriasis and total CDLQI score (\( P = 0.48 \)).

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD (range)</td>
<td>10.7 ± 3.9 (3 – 17)</td>
</tr>
<tr>
<td>Boys/girls, n(%)</td>
<td>46/79 (36.8/63.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psoriasis history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, years, mean ± SD (range)</td>
</tr>
<tr>
<td>Duration of psoriasis, months, mean ± SD (range)</td>
</tr>
<tr>
<td>Familial history of psoriasis, n (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psoriasis baseline assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDLQI, mean ± SD (range)</td>
</tr>
<tr>
<td>PASI, mean ± SD (range)</td>
</tr>
</tbody>
</table>

SD, standard deviation; CDLQI, Children’s Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index.
Figure 1 shows the cross-sectional distribution of the 10 items of the CDLQI, reflecting that two items documented the highest mean ± SD scores: itch (1.27 ± 0.89) and problems with treatment (1.16 ± 0.89). On the other hand, friendships seem to be least affected by psoriasis (mean ± SD 0.18 ± 0.52). Analyses of the 10 separate items of the CDLQI demonstrated no significant differences between boys and girls. Adolescents (≥12 years), had significantly more problems with issues of clothes (mean ± SD 0.7 ± 0.93) and with sport (mean ± SD 0.91 ± 0.95) than patients under the age of 12 years (mean ± SD 0.28 ± 0.67, P = 0.001 and 0.38 ± 0.71, P < 0.0001 respectively). No other items of the CDLQI showed a significant difference between those two age-groups.

Influence of treatments in daily clinical practice on the quality of life

The longitudinally analysed cohort, consisting of 85 patients, had a total of 137 treatment episodes. Sixty-nine patients went through 81 treatment episodes with topical treatment. Twenty-seven patients received in total 31 treatment episodes of dithranol short-contact therapy. The systemic treatments consisted of 25 treatment episodes in 19 patients: 16 with methotrexate, seven with etanercept, one with acitretin and one with ciclosporin. In our cohort only five patients were treated with phototherapy, this number was too small to analyse the influence of this treatment on quality of life. If all treatments were taken together, a significant improvement in total CDLQI score of -2.7 (95% confidence interval (CI) -3.7 to -1.7; P < 0.005) with a mean change in PASI of -2.1 (95% CI -3.1 to -1.1; P < 0.005) was found before and after a
Analyses of the three clusters of treatments demonstrated the highest improvement in CDLQI for dithranol, with a mean change of -4.0 (95% CI -6.1 to -1.8, P < 0.005) and a mean alteration in PASI of -5.3 (95% CI -8.1 to -2.5, P < 0.005), followed by systemic treatments with a mean ΔCDLQI of -3.6 (95% CI -4.6 to -2.6, P < 0.005) and a ΔPASI of -4.4 (95% CI -6.9 to -2.0, P < 0.005). Topical treatment demonstrated a mean ΔCDLQI of -2.2 (95% CI -3.6 to -0.9, P < 0.005) with a mean ΔPASI of -0.5 (95% CI -1.4 to 0.4, P = 0.26). A comparison of ΔCDLQI for these three clusters of treatments with the likelihood ratio test was not significant in our population (P = 0.38), in contrast to ΔPASI which is very significant (P < 0.0001). The ΔCDLQI correlated significantly with ΔPASI for all treatments together, r = 0.48 (P < 0.05). Also in all the three different clusters of treatments significant correlations between ΔCDLQI and ΔPASI were found: topical r = 0.48 (P < 0.05), dithranol r = 0.46 (P < 0.05) and systemic r = 0.55 (P < 0.05). Subgroup analysis comparing patients who stopped treatment because of success (responders) with patients who stopped treatment because of ineffectiveness (non-responders) showed only a significant improvement in CDLQI in responders for all three treatment clusters (P < 0.005). This is in contrast to non-responders, in whom no significant improvement in CDLQI was found (P-values between 0.17 and 0.54).

Analyses of the influence of all treatments on the 10 items of the CDLQI showed a significant decline in eight of the 10 items (Fig. 2). The highest positive impacts were found in an improvement of itch (mean -0.4; 95% CI -0.6 to -0.2; P < 0.005) and sleep disturbance (mean -0.4; 95% CI -0.6 to -0.2; P < 0.005). The items relating to friendship and changing clothes did not decline significantly (P = 0.068 and P = 0.052). There were no significant differences in the influence of the treatments on the 10 items of the CDLQI when comparing the younger (< 12 years) and older group (≥ 12 years).

Discussion

Paediatric psoriasis causes a significant negative impact on mental health and QoL of those affected.5-8,15 This first prospective, cross-sectional and longitudinal, observational study confirmed the negative impact of paediatric psoriasis on QoL, and also demonstrated a positive influence of treatments in daily clinical practice on the CDLQI in a cohort of children with psoriasis, with the highest impact on itch and sleep disturbance.

Previous studies have reported cross-sectional mean CDLQI scores between 5.05 and 10.0 in children with psoriasis.4-8 The total mean CDLQI score in our cross-sectional analyses was 7.5, which is in line with the mean scores found in other studies. The 10 items of the CDLQI were only once reported before in paediatric psoriasis.7 Our results confirm the fact that the items itch and problems with treatment had the highest impact on the children’s QoL. In addition, we found that the adolescents (≥ 12 years) had significantly more problems with issues of clothes and sport, as compared to the younger children (< 12 years). We did not find a difference in the 10 separate items of the CDLQI when comparing boys and girls.

A cross-sectional correlation between CDLQI and PASI has been analysed in two studies before.6,7 De Jager et al. demonstrated a significant moderate correlation in 39 children with psoriasis; on the other hand a Swedish group did not show a significant correlation in 45 patients. In the present paper the cross-sectional correlation between CDLQI and PASI in 125 patients was 0.31 (P = 0.001). Strikingly, the correlation between ΔCDLQI and ΔPASI in this longitudinal study was remarkably higher (r = 0.48, P < 0.05).

Longitudinally, 85 patients were analysed with a total of 137 treatment episodes. This study is the first to describe prospective data in daily clinical practice in paediatric psoriasis. A significant decline in total CDLQI score was found for all treatments, with the highest improvement in CDLQI for dithranol, followed by systemic and other...
topical treatments. However, a conclusion about the superiority of one of these three treatment clusters with respect to influencing the CDLQI cannot be made, because the likelihood ratio test between the treatment clusters was not significant. Only one other longitudinal study described the influence of a treatment on QoL of children with psoriasis. This study, however, was designed as a randomized controlled trial and the only treatment modality was etanercept. Therefore, the results of this study can hardly be compared with the present study, in which daily clinical practice data were analysed.

In conclusion, the present study is the first prospective observational study in which the positive influence of different treatments in daily clinical practice on the CDLQI was demonstrated in a cohort of children with psoriasis. The largest influence on the CDLQI was achieved by dithranol and systemic treatments. The highest positive impact of all treatments was found in a decline of itch and sleep disturbance.

References

4.2

Reliability, responsiveness and validity of Scalpdex in children with scalp psoriasis – the Dutch study

A.M. Oostveen, E.M.G.J. de Jong, A.W.M. Evers, A.R.T. Donders, P.C.M. van de Kerkhof, M.M.B. Seyger

Abstract

This study validated the Scalpdex, a quality of life questionnaire for adults with scalp dermatitis, in children with scalp psoriasis. The reliability, responsiveness and validity of the three scales (symptoms, functioning and emotions) of this 22-item questionnaire were analysed in a cohort of children with scalp psoriasis (age range 6 – 18 years). A total of 94 children completed the questionnaire once, and 53 children a second time, after treatment of their scalp psoriasis. The Children's Scalpdex in Psoriasis (CSP) demonstrated reliability with internal consistency (Cronbach α, 0.69 – 0.91). The CPS scales proved sensitive to change in the expected direction for children whose scalp psoriasis improved. Moderate effect sizes were observed between both visits for all three the scales of the CSP (Cohen’s d, 0.44 – 0.58). In conclusion, CSP is a reliable, responsive and valid questionnaire which is the first to illustrate the specific influence of scalp psoriasis on the quality of life in children.

Introduction

In children, the scalp is a predilection site for psoriasis and a few studies demonstrated that the scalp is most often the initial site affected.1-4 Scalp involvement is reported between 47.0 – 88.9% of all children with psoriasis.5-8 Scalp involvement can be a particular burden for psoriasis patients because of the visibility of the lesions and it is difficult to apply therapy.9 Chen et al. developed and validated the Scalpdex, a quality of life (QoL) questionnaire special for adults with scalp dermatitis (psoriasis and seborrheic dermatitis).10 This instrument can be used to determine which aspect of the scalp dermatitis bothers patients the most and to evaluate the influence of therapeutic intervention on this QoL.

The impact of scalp psoriasis on QoL, especially in children with psoriasis, has not been investigated. Although a skin-specific questionnaire exists to measure QoL in children with skin diseases of the whole body (Children’s Dermatology Life Quality Index, CDLQI),11 there is no specific instrument to assess the influence of scalp psoriasis on QoL in children.

This study aims to validate the Scalpdex in children with scalp psoriasis. This Children’s Scalpdex in Psoriasis (CSP) was assessed for its reliability, responsiveness and validity. The validation of an additional QoL questionnaire for children with scalp psoriasis will make it possible to focus on the symptoms and emotional and psychological impact of scalp psoriasis in children and to assess the influence of treatments.

Materials and methods

Instrument development

The content of the questions of the CSP were based on the validated Scalpdex questionnaire.10 The Scalpdex was developed based on focus sessions with adult patients with scalp psoriasis and seborrheic dermatitis. Fourteen scalp dermatitis-specific items were formulated from these in-depth interviews and also nine items from the Skindex were included.12 This questionnaire comprised of 23 items, which were clustered and tested by factor analyses into three scales, labelled ‘symptoms’, ‘functioning’ and ‘emotions’.

For the CSP, the Scalpdex items were translated into Dutch and discussed in a steering group, comprising of two dermatologists, one paediatric dermatologist and one psychologist with a broad expertise in questionnaires for children with psoriasis. When necessary, the questions were modified slightly in order to make them more...
coefficient equal to or larger than 0.70 is considered to be acceptable. For construct validity, first the confirmatory factor analysis was performed to test whether the three constructs of the Scalpdex (symptoms, functioning and emotions) are similar in the CSP. Thereafter, the correlations between the mean scale scores of the CSP and the CDLQI and the scalp psoriasis severity scores by patient and physician were examined using Spearman’s rank correlation coefficient. It was hypothesized that CSP would be positively correlated with all the different scalp psoriasis severity scores and have higher correlations than the CDLQI with the scalp severity scores. For the discriminant validity, we hypothesized that the CDLQI, a skin-specific questionnaire for the whole body, is not sensitive enough to measure responsiveness over time for changes in the QoL specific to scalp psoriasis. Cohen’s D was calculated for responsiveness of both the CSP and CDLQI. Responsiveness of the CSP and CDLQI questionnaire was tested by calculating the change in the mean scale scores (symptoms, functioning and emotions) of the CSP and the change in total CDLQI of the patients who completed the questionnaire twice. Cohen’s D was used to calculate within-group effect sizes, to indicate the standardized differences between two means at the two occasions, before and after treatment of the scalp psoriasis, for both the CSP and CDLQI. Cohen’s D is defined as the difference between two means, divided by the standard deviation (SD). A Cohen’s D of 0.2 was considered to indicate a small effect, 0.5 to indicate a medium effect, and effects higher than 0.8 to indicate large effects. The paired t-test was applied to the baseline answers and the answers of the second time-point for three groups: those who improved according to the physician’s opinion of the physician (PhGA scalp) or their own opinion (PaGA scalp); those who showed no change of their scalp psoriasis and those whose scalp condition worsened. Statistical analyses were performed in SPSS software 18.0 (SPSS Inc., Chicago, IL, U.S.A.) and Mplus version 6.11.

Results

Study sample

Patient characteristics of the study cohort are reported in Table 1. A total of 94 children, mean age 12.4 ± 3.3 years, completed the questionnaire once. The majority of the patients were female (59.6%). Patients had a mean duration of psoriasis of 3.7 ± 3.5 years and a mean psoriasis severity (PASI) of 4.8 ± 2.6. Both patients (PaGA scalp) and physician (PhGA scalp) reported a median scalp psoriasis severity of 2 (range 1 – 5). Fifty-three patients completed the questionnaire a second time.

Sample population

The department of dermatology of the Radboud University Nijmegen Medical Center has a prospective observational paediatric psoriasis cohort (<18 years) from daily clinical practice, called the Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry). All children between 6 and 18 years who visited the department between March 2011 and May 2012 with more than 5% scalp area involvement completed in the questionnaire at baseline. Patients were treated for their scalp psoriasis according to the physician’s opinion. The following patient characteristics were recorded: age, gender, age at onset, family history and duration of psoriasis.

Outcome measures

At baseline, and if applicable at a second visit, the 22-items of the CSP were completed (range 0 – 100). In addition, patient’s QoL was evaluated with the validated Dutch version of the Children’s Dermatology Life Quality Index, CDLQI (10 items: range 0 – 100). For both questionnaires, higher scores indicate worse QoL. It is hypothesized that the CSP is better than the CDLQI questionnaire to assess explicit characteristics of scalp psoriasis on the QoL in children. Severity of scalp psoriasis was established by the Physician Global Assessment of the Scalp (PhGA scalp; range 0 – 5) and Patient Global Assessment of the Scalp (PaGA scalp; range 0 – 5). Clinical severity of psoriasis of the whole body was assessed by a clinician using the Psoriasis Area and Severity Index (PASI; range 0 – 72).

Statistical analyses

The CSP was tested for reliability, responsiveness and validity. Reliability was assessed by Cronbach’s α at scale level. This expresses the internal consistency; whether the items in the scale are correlated, and thus measuring the same concept. A Cronbach’s α comprehensive for children. The item; ‘The cost of caring for my scalp condition bothers me’, was not included, because the steering group agreed that children are not likely to be concerned about this topic. The CSP thus comprises of 22 items, which consists of three major constructs, ‘symptoms’, ‘functioning’ and ‘emotions’, which is in line with the original Scalpdex. All items enquired about the past four weeks. Responses to the questions were based on a 5-point Likert-type scale (‘never’ = 0, ‘rarely’ = 25, ‘sometimes’ = 50, ‘often’ = 75, and ‘all the time’ = 100). A lower score represents a better QoL. The responses to item 19, ‘I feel that my knowledge about caring for my scalp psoriasis is adequate’, were reverse scored. Scale scores were the average of responses to items in a given scale. If necessary, patients aged between 6 and 12 years were allowed to complete the questionnaire with the help of the child’s parent or guardian. The CSP will takes 5 – 10 minutes to complete.
functioning $r = 0.46$ ($P < 0.001$) and emotions $r = 0.46$ ($P < 0.001$). PhGA scalp also showed a significant positive correlations with the three scales; symptoms $r = 0.44$ ($P < 0.001$), functioning $r = 0.32$ ($P = 0.002$), and emotions $r = 0.27$ ($P = 0.009$). The CDLQI correlated less significant positive with both PhGA scalp ($r = 0.21$; $P = 0.05$) and PaGA scalp ($r = 0.30$; $P = 0.004$) compared with the CSP scales.

### Table 1 Patient characteristics (n=94)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD (range)</td>
<td>12.4 ± 3.3 (6 – 17)</td>
</tr>
<tr>
<td>Boys/girls, n(%)</td>
<td>38/56 (40.4/59.6)</td>
</tr>
<tr>
<td>Psoriasis history, mean ± SD (range)</td>
<td></td>
</tr>
<tr>
<td>Age at onset, years</td>
<td>8.3 ± 4.2 (0 – 17)</td>
</tr>
<tr>
<td>Duration of psoriasis, years</td>
<td>3.7 ± 3.5 (0 – 13)</td>
</tr>
<tr>
<td>Psoriasis baseline assessments</td>
<td></td>
</tr>
<tr>
<td>PASI psoriasis, mean ± SD</td>
<td>4.8 ± 2.8</td>
</tr>
<tr>
<td>PhGA Scalp, median (range)</td>
<td>2 (1 – 5)</td>
</tr>
<tr>
<td>PaGA Scalp, median (range)</td>
<td>2 (1 – 5)</td>
</tr>
</tbody>
</table>

SD, standard deviation; PASI, Psoriasis Area and Severity Index; PhGA, Physician Global Assessment; PaGA, Patient Global Assessment.

### Item Analysis

Mean ± SD item scores of the CSP demonstrated that the following three items were most affected (Table 2): ‘I am bothered by the persistence/reoccurrence of my scalp psoriasis’ ($55.3 \pm 33.4$), ‘My scalp psoriasis itches’ ($52.9 \pm 31.5$) and ‘I feel that my knowledge about caring for my scalp psoriasis is adequate’ ($51.9 \pm 34.0$). The item with the lowest mean score was the question: “My scalp psoriasis affects the colour of clothes I wear” ($9.8 \pm 20.2$). In Table 2 the mean scores of all items are listed. In 8 out of 22 CSP items (36.4%) versus 8 out of 10 CDLQI items (80%), at least 50% of the patients answered never.

### Reliability

Internal consistency reliability of the three scales was analysed with Cronbach’s $\alpha$. For all the three scales the internal consistency were relatively high (‘symptoms’ = 0.69; ‘functioning’ = 0.74, ‘emotions’ = 0.91).

### Construct validity

Confirmative factor analysis demonstrated an acceptable fit for the three-factor model. This indicates that the three scales of the Scalpdex (symptoms, functioning and emotions) can also be used in our CSP. Correlations were calculated between the scale scores of the CSP and the scores of scalp psoriasis severity, PhGA and PaGA (Table 3). The highest significant positive correlations for all scales were demonstrated between PaGA scalp and the three scales; symptoms $r = 0.51$ ($P < 0.001$),

### Table 2 Mean score of the items of the Children’s Scalpdex in Psoriasis (n=94)

<table>
<thead>
<tr>
<th>Item</th>
<th>Scale</th>
<th>Mean score ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. My scalp psoriasis hurts</td>
<td>S</td>
<td>23.9 ± 26.7</td>
</tr>
<tr>
<td>2. My scalp psoriasis makes me feel sad</td>
<td>E</td>
<td>23.1 ± 27.5</td>
</tr>
<tr>
<td>3. My scalp psoriasis itches</td>
<td>S</td>
<td>52.9 ± 31.5</td>
</tr>
<tr>
<td>4. I am ashamed of my scalp psoriasis</td>
<td>E</td>
<td>28.2 ± 31.2</td>
</tr>
<tr>
<td>5. I am embarrassed by my scalp psoriasis</td>
<td>E</td>
<td>14.9 ± 23.6</td>
</tr>
<tr>
<td>6. I am angry/frustrated by my scalp psoriasis</td>
<td>E</td>
<td>28.5 ± 29.6</td>
</tr>
<tr>
<td>7. I am humiliated by my scalp psoriasis</td>
<td>E</td>
<td>13.8 ± 23.7</td>
</tr>
<tr>
<td>8. My scalp psoriasis bleeds</td>
<td>S</td>
<td>26.1 ± 26.9</td>
</tr>
<tr>
<td>9. I am annoyed by my scalp psoriasis</td>
<td>E</td>
<td>43.1 ± 36.7</td>
</tr>
<tr>
<td>10. I am bothered by the appearance of my scalp psoriasis</td>
<td>E</td>
<td>31.4 ± 32.8</td>
</tr>
<tr>
<td>11. My scalp psoriasis makes me feel self-conscious</td>
<td>E</td>
<td>17.3 ± 24.6</td>
</tr>
<tr>
<td>12. I am bothered that my scalp psoriasis is incurable</td>
<td>E</td>
<td>41.5 ± 35.3</td>
</tr>
<tr>
<td>13. My scalp psoriasis affects how to wear my hair (hairstyle, hats)</td>
<td>F</td>
<td>20.7 ± 31.2</td>
</tr>
<tr>
<td>14. I am bothered by people’s questions about my scalp psoriasis</td>
<td>E</td>
<td>34.0 ± 30.2</td>
</tr>
<tr>
<td>15. My scalp psoriasis affects the colour of clothes I wear</td>
<td>F</td>
<td>9.8 ± 20.2</td>
</tr>
<tr>
<td>16. I am bothered by the persistence/reoccurrence of my scalp psoriasis</td>
<td>E</td>
<td>55.3 ± 33.4</td>
</tr>
<tr>
<td>17. I feel stressed about my scalp psoriasis</td>
<td>E</td>
<td>12.8 ± 21.0</td>
</tr>
<tr>
<td>18. Caring for my scalp psoriasis is inconvenient for me</td>
<td>F</td>
<td>39.9 ± 34.8</td>
</tr>
<tr>
<td>19. I feel that my knowledge about caring for my scalp psoriasis is adequate</td>
<td>E</td>
<td>51.9 ± 34.0</td>
</tr>
<tr>
<td>20. My scalp psoriasis makes my daily life difficult</td>
<td>F</td>
<td>20.5 ± 25.4</td>
</tr>
<tr>
<td>21. My scalp psoriasis makes me feel different from others</td>
<td>E</td>
<td>22.6 ± 28.4</td>
</tr>
<tr>
<td>22. My scalp condition makes it hard to go to the hairdresser</td>
<td>F</td>
<td>22.3 ± 32.7</td>
</tr>
</tbody>
</table>

*Scales: symptoms (S), emotions (E) and functioning (F). Item scores: 0 ‘never’, 25 ‘rarely’, 50 ‘sometimes’, 75 ‘often’ and 100 ‘all the time’. Three items with the highest mean scores.

4
Responsiveness and discriminant validity

A total of 53 patients completed the questionnaire a second time and were analysed for the responsiveness. Because patients were seen in daily clinical practice, the period of time between the first and second visit varied between one and seven months (mean ± SD: 4.3 ± 1.8). First, effect sizes with Cohen’s D were calculated between the two time points for both CSP and CDLQI. Cohen’s D for CSP showed moderate effect sizes (symptoms = 0.44; functioning = 0.58 and emotions = 0.51), whereas no effect size was found for the CDLQI (Cohen’s D = -0.03).

To evaluate the responsiveness of the CSP and the CDLQI with respect to changes in severity of scalp psoriasis, patients were divided into three groups. The first group consisted of patient with a worsening of their scalp psoriasis, either according to the physician (Table 4), or according to the patient’s own opinion (Table 5). The second and third group reported no change in severity or an improvement of their scalp psoriasis, respectively. Significant changes in all three scales of the CSP were found in the group with an improvement of their scalp psoriasis (P ≤ 0.001). This effect was found in improvements based on both PhGA and PaGA with a moderate size effect, Cohen’s D between 0.66 and 0.98. Patients with worsening of the scalp condition based on alterations in PhGA scalp showed a significant increase in mean score for the scale ‘symptoms’ (14.6 ± 13.8; P = 0.004), but for the other two scales. It is notable that patients with the same scalp condition at both visits based on PhGA scalp showed a significant improvement for the emotions scale (-9.3 ± 11.0). All other alterations in both PaGA and PhGA scalp and the other scales demonstrated no significant increase or decrease in mean scores.

Interestingly, for patients in whom the scalp psoriasis improved from both physician and patient’s point of view (Table 4 and 5) the skin-specific CLDQI questionnaire

### Table 3: Correlations between scalp psoriasis severity scores and Children’s Dermatology Life Quality Index and the Children’s in ScalpDEX Psoriasis scales

<table>
<thead>
<tr>
<th>Children’s ScalpDEX in Psoriasis scales</th>
<th>CDLQI</th>
<th><strong>Symptoms</strong></th>
<th><strong>Functioning</strong></th>
<th><strong>Emotions</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>PhGA</td>
<td>0.44**</td>
<td>0.32**</td>
<td>0.27**</td>
<td>0.21**</td>
</tr>
<tr>
<td>PaGA</td>
<td>0.51**</td>
<td>0.46**</td>
<td>0.46**</td>
<td>0.30**</td>
</tr>
</tbody>
</table>

CDLQI, Children’s Dermatology Life Quality Index; PhGA, Physician Global Assessment; PaGA, Patient Global Assessment. *P < 0.05; **P < 0.01.

### Table 4: Mean scale scores for Children’s ScalpDEX in Psoriasis and Children’s Dermatology Life Quality Index based on alterations in Physician Global Assessment of the scalp

<table>
<thead>
<tr>
<th>Scale</th>
<th>PhGA Score (n=12)</th>
<th>PaGA Score (n=26)</th>
<th>CDLQI Score (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>22.9 ± 25.4</td>
<td>24.6 ± 19.7</td>
<td>3.5 ± 3.4</td>
</tr>
<tr>
<td>Functioning</td>
<td>16.2 ± 22.4</td>
<td>20.4 ± 15.4</td>
<td>6.6 ± 3.9</td>
</tr>
<tr>
<td>Emotions</td>
<td>30.6 ± 26.7</td>
<td>29.5 ± 17.1</td>
<td>14.6 ± 13.8</td>
</tr>
<tr>
<td>PhGA Worse</td>
<td>23.9 ± 22.5</td>
<td>30.9 ± 20.7</td>
<td>19.6 ± 3.9</td>
</tr>
<tr>
<td>PaGA Worse</td>
<td>27.1 ± 27.4</td>
<td>20.6 ± 15.4</td>
<td>14.6 ± 13.8</td>
</tr>
<tr>
<td>PhGA Same</td>
<td>30.6 ± 26.7</td>
<td>29.5 ± 17.1</td>
<td>14.6 ± 13.8</td>
</tr>
<tr>
<td>PaGA Same</td>
<td>27.1 ± 27.4</td>
<td>20.6 ± 15.4</td>
<td>14.6 ± 13.8</td>
</tr>
<tr>
<td>PhGA Better</td>
<td>24.6 ± 19.7</td>
<td>29.5 ± 17.1</td>
<td>3.5 ± 3.4</td>
</tr>
<tr>
<td>PaGA Better</td>
<td>20.4 ± 15.4</td>
<td>14.6 ± 13.8</td>
<td>6.6 ± 3.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Children’s Dermatology Life Quality Index</th>
<th>PhGA Score (n=12)</th>
<th>PaGA Score (n=26)</th>
<th>CDLQI Score (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>-14.6 ± 13.8</td>
<td>-19.0 ± 15.5</td>
<td>-3.5 ± 3.4</td>
</tr>
<tr>
<td>Functioning</td>
<td>-9.3 ± 11.0</td>
<td>-16.0 ± 19.7</td>
<td>-6.6 ± 3.9</td>
</tr>
<tr>
<td>Emotions</td>
<td>-4.0 ± 14.6</td>
<td>-9.3 ± 11.0</td>
<td>-14.6 ± 13.8</td>
</tr>
<tr>
<td>PhGA Worse</td>
<td>-13.0 ± 13.9</td>
<td>-15.2 ± 160</td>
<td>3.5 ± 3.4</td>
</tr>
<tr>
<td>PaGA Worse</td>
<td>-9.7 ± 22.1</td>
<td>-15.2 ± 160</td>
<td>3.5 ± 3.4</td>
</tr>
<tr>
<td>PhGA Same</td>
<td>-4.0 ± 14.6</td>
<td>-9.3 ± 11.0</td>
<td>3.5 ± 3.4</td>
</tr>
<tr>
<td>PaGA Same</td>
<td>-9.7 ± 22.1</td>
<td>-15.2 ± 160</td>
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<td>PaGA Better</td>
<td>-9.7 ± 22.1</td>
<td>-15.2 ± 160</td>
<td>3.5 ± 3.4</td>
</tr>
</tbody>
</table>

SD, standard deviation. Significant P-values are shown in bold.
showed a significant increase in mean total CDLQI score (more impairment in QoL) (Table 4, n=26, PhGA scalp: ΔCDLQI 3.3 ± 5.1, P = 0.03; Table 5, n=27, PaGA scalp: ΔCDLQI 2.5 ± 5.7, P = 0.03). Because of this fact, we analysed the course of psoriasis severity on other parts of the body for the patients in whom the scalp psoriasis improved. Surprisingly, the psoriasis severity of the entire body, expressed by the PASI, increased in this group (PhGA scalp: ΔPASI 3.1 ± 4.2, P = 0.001; PaGA scalp: ΔPASI 3.2 ± 4.7, P 0.001), whilst the scalp psoriasis improved.

Discussion

The results of this study show that the CSP is a reliable, responsive and valid questionnaire. It is the first instrument to focus on scalp psoriasis in children, illustrating the specific influence of scalp psoriasis on QoL. This QoL questionnaire makes it possible to assess the symptoms and emotional and psychological impact of paediatric scalp psoriasis. For this group of children, the development of this questionnaire is important for clinical research, decision making and evaluation of therapeutic interventions. In this study the questionnaire was validated for children with scalp psoriasis. However, it is highly likely that this questionnaire can also be used for other paediatric scalp conditions.

This study is performed in a paediatric psoriasis cohort, drawn from daily clinical practice, called the Child-CAPTURE. This registry was set up in 2008 and aims to record clinical and QoL data from children with psoriasis every time they visit our outpatient clinic. For this study there was no wash-out period, and all patients were treated for their psoriasis according to the physician’s opinion. Therefore, the psoriasis severity at baseline of this study was mild.

In our cohort of children with scalp psoriasis the items ‘my scalp itches’ and ‘I am bothered by the persistence/reoccurrence of my scalp condition’ are the two items with the highest scores. This is in line with the original Scalpdex, in which Chen et al.10 also demonstrated that adults with scalp dermatitis (psoriasis and seborrhoeic dermatitis) reported most problems with these items as well. In contrast to adults, however, children report more bleeding of their scalp, and they are more troubled by people’s questions about their scalp psoriasis. On the other hand, the children are less embarrassed and frustrated by their scalp psoriasis than adults are by their scalp condition and the children feel that their knowledge about caring for the scalp psoriasis is adequate, more so than the adults. The reliability of the CSP scales were relatively high (Cronbach’s α, 0.69 – 0.91), which is slightly better than the reliability reported by Chen et al. for the Scalpdex (Cronbach’s α, 0.62 – 0.80).10
Construct validity was tested by calculating confirmative factor analyses. These analyses supported the three scales in the CSP, as used in the Scalpdex; namely, symptoms, functioning and emotions. The scores of the three scales of the CSP showed a significant positive correlation with both patient- and physician-reported scalp severity; this is in line with the hypothesis for the construct validity. Interestingly, the scales have higher correlations with patient’s perception of the severity of the scalp psoriasis than with the physician’s opinion. The correlation between both patient- and physician-reported scalp severity and the CDLQI was less strong.

Responsiveness analysis proved that the three scales of the CSP are sensitive to change in the expected direction in the children whose scalp psoriasis improved. In contrast to the improvement of CSP and scalp psoriasis of these children, the CDLQI and PASI deteriorated. This suggests that the CDLQI is not specific enough to reflect the QoL of particularly children with scalp psoriasis.

In conclusion, the Children’s Scalpdex in Psoriasis proved to be reliable, responsive and valid for the assessment of QoL of children with scalp psoriasis. The CSP can be used as a targeted questionnaire in the evaluation of outcome assessments and the effect of therapeutic interventions on QoL in children with scalp psoriasis.

References

Development and design of a multidisciplinary training program for outpatient children and adolescents with psoriasis and their parents

A.M. Oostveen, S. Spillekom-van Koulii, M. E. Otero, W. Klompmaker, A.W.M. Evers, M.M.B. Seyger

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Abstract

Objective
To describe and illustrate in a case-study design the development and design of a multidisciplinary training program for outpatient children and adolescents with psoriasis and their parents.

Methods
For the development of the program, a steering group was assembled, systematic semi-structured interviews were held and the literature was reviewed.

Results
Aim of the training program was to strengthen patients and their parents in coping with and diminishing psoriasis-related problems in an outpatient setting. The program included treatment modules of medical information and skin care, itch and scratch problems, psychological issues in coping with the psoriasis, sleep hygiene, and relapse prevention. Descriptive results in the case patient showed improvement of all outcome variables in the expected direction.

Conclusion
This is the first multidisciplinary training program for outpatient children and adolescents with psoriasis and their parents. It aims at improving coping skills and self-management and could be a promising addition to regular treatment.

Introduction
Psoriasis is a chronic, inflammatory skin disease, which affects 2% of the general population. Approximately 30% of patients with psoriasis report onset during childhood. Research in children with psoriasis demonstrated that these patients report itch, pain, and feelings of shame or stigmatization. In conjunction with standard dermatological care, several educational and training programs have been developed for adult patients with psoriasis, which have resulted in improved knowledge and coping. To our knowledge, only one study outlined an inpatient educational program for children and adolescents with psoriasis which resulted in improved disease management and self-estimated long-term skin condition and reduced psychosocial impairment.

In the present paper, we describe the development and design of the first multidisciplinary training program for outpatient children with psoriasis and their parents. In a case-study design, the program is illustrated and evaluated.

Methods
Development of the program
To design the training program a steering group was assembled, consisting of two dermatologists, two psychologists and two dermatology nurse specialists. First, systematic semi-structured interviews were held with 15 children with psoriasis and their parents. Based on content analysis the following items were found to be important for the children with psoriasis: information about psoriasis and treatments, itch, coping with psoriasis in daily life and contact with other fellow sufferers. Their parents reported to be relevant: information about psoriasis and treatment, scratch behaviour and coping with psoriasis in daily life. Next, the literature on educational and training programs for skin conditions was reviewed and parts of these evidence-based programs were used for the development of the present training program.

Procedure and Assessments
To be included in the program, the diagnosis of psoriasis had to be clinically confirmed by a dermatologist and the patient had to be under the age of 18 years. Due to different phases of cognitive and emotional development of children, the program was designed for two age-related groups: primary school children (6 – 12 years) and adolescents visiting secondary school (12-18 years). Assessments were made pre- and post-treatment, and after three months of follow up.
Outcome measures
The primary end points were differences in patient’s quality of life, intensity and duration of itch and scratch responses, illness cognitions, and impact on family life. Disease severity was a secondary end point.

The patient’s quality of life was assessed with the Children’s Dermatology Life Quality Index (CDLQI).\textsuperscript{15} Itch and scratch responses were assessed with the Impact of Chronic Skin Disease on Daily Life (ISDL).\textsuperscript{16} Illness cognitions were assessed using two chronic-disease related cognitions of the ISDL: helplessness and acceptance.\textsuperscript{16,17} Disease-related impact on family life was assessed with the Stein Impact on Family Scale (SIFS) and the Dermatitis Family Impact (DFI).\textsuperscript{18,19} 

Clinical evaluation of skin severity was performed by a dermatologist using three different parameters: Psoriasis Area and Severity Index (PASI; range 0 – 72), Physician Global Assessment (PGA; range 0 – 5) and Body Surface Area (BSA; range 0 – 100). Higher scores indicated a more severe psoriasis.

Results
Design of the program
The goal of the program was to support patients and their parents with coping and diminishing the consequences of psoriasis in daily life. All sessions were delivered by three trainers: a dermatologist, a clinical psychologist/cognitive behaviour therapist and a dermatology nurse specialist. The program consisted of three sessions, once every two weeks, plus one follow-up session four weeks after the last meeting. Duration was 2.5 h including a short break. A small group-size (four to five participants with one or both parents) was determined in order to create a confidential environment.

Children and their parents were given a booklet containing information about the program’s content and homework assignments. At the end of each session, homework was given and explained to promote the transfer of what was learned into daily life. This required approximately one hour a week. Referral addresses were offered if further counselling seemed to be indicated after the program. Table 1 provides a schematic overview of the specific topics of each session.

Medical information and skin care: session 1
In the first session the dermatologist explained basic medical information about psoriasis, including basic pathogenetic mechanisms, clinical symptoms and treatment. Furthermore, information about compositions and ingredients of skin care products and recommendation for daily skin care were offered. For homework, the children were instructed to register the frequency and kind of ointments used to improve daily skin care routines with a reward system.

Itch and scratch responses: session 2
In session 2, patients and parents learned that itching and scratching frequently lead to a vicious itch-scratch cycle. In addition, it was discussed how to deal with (triggering factors of) itching and scratching, prevention of itching and alternatives for scratching behaviour. For homework, the children were asked to register their itch and scratch behaviour and implement and evaluate alternative measures to cope with itch and scratching.

Psychological issues and sleep hygiene: session 3
During the last session psychological issues concerning coping strategies with regard to social encounters and self-esteem were discussed. The children practiced (without parents) with role plays how to cope with reactions from other children, promoting a positive self- and body-image. At the same time, the parents discussed how to deal with transfer of responsibilities for self-management during the development of the child. Furthermore, sleep hygiene was discussed and patients and parents learned to use relaxation exercises. For homework, the children completed an exercise on long-term goals and relapse prevention.

Follow-up session: session 4
In the follow-up session, all previous issues were passed in review. Patients and parents discussed the most important items they learned during the program. Finally, relapse prevention exercise and future goals were discussed.

<table>
<thead>
<tr>
<th>Session</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Medical information about psoriasis Daily skin care</td>
</tr>
<tr>
<td>2</td>
<td>Triggering factors for itch and scratching Dealing with itching and scratching</td>
</tr>
<tr>
<td>3</td>
<td>Coping with psoriasis, including social encounters and self-esteem Sleep hygiene and relaxation exercises</td>
</tr>
<tr>
<td>4</td>
<td>Long-term goals and relapse prevention</td>
</tr>
</tbody>
</table>

Table 1 Structure and content of training program for children and adolescents with psoriasis
Case presentation
We present a representative case of a 6-year-old girl who was diagnosed with psoriasis since she was five years old. At the start of the program, the severity of her psoriasis was moderate (PASI 11.3). Treatment existed of topical corticosteroids alternating with a vitamin D analogue, which was not adjusted during the program and follow-up. The following treatment goals were set: more frequent use of topical ointments, learn how to deal with itch and scratching, learn how to cope with the psoriasis in general for both the patient and parents.

At the end of the training, the patient and her mother reported that it was especially important to keep using the reward system to maintain the use of topical treatment and reduce conflicts. Furthermore, both declared that the itch-scratching problems were diminished and also the psoriasis was improved (PASI 6.6). The assessment of the outcome variables with questionnaires supported these descriptive results (Table 2). All outcome variables improved in the expected direction, more specifically:

| Table 2 Results of the case study patient for the outcome measures pre- and post-treatment and at 3-months follow-up |
|---|---|---|---|
| Quality of life Children | | | |
| CDLQI | 11 | 7 | 0 |
| Itch and Scratching | | | |
| ISDL – Itch | 12.4 | 6.2 | 3.0 |
| ISDL – Scratch | 8 | 5 | 3 |
| Illness cognitions | | | |
| Helplessness | 8 | 6 | 6 |
| Acceptance | 12 | 15 | 19 |
| Family impact | | | |
| DFI | 7 | 0 | 0 |
| SIFS | 4 | 2 | 0 |
| Disease severity | | | |
| PASI | 11.3 | 6.6 | 0.4 |
| PGA | 3 | 2 | 1 |
| BSA | 10.0 | 6.0 | 0.5 |

BSA = body surface area; CDLQI: Children’s Dermatology Life Quality Index; DFI = Dermatitis Family Impact; ISDL: Impact of Chronic Skin Disease on Daily Life; PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment; SIFS = Stein Impact on Family Scale.

improved patient’s quality of life, reduced itching and scratching, enhanced illness cognitions, decreased impact on family life and improved disease severity. At 3 months of follow-up, these results improved even further.

Discussion
In this paper, the development and design of the first multidisciplinary training program for outpatient children and adolescents with psoriasis and their parents was described. The goal of this program was to support patients and their parents with coping and diminishing the consequences of psoriasis in daily life.

Other programs for children with skin conditions have shown to be successful in improving coping and catastrophizing. However, only one study had so far investigated the efficacy of an inpatient intervention in paediatric psoriasis. In contrast to the aforementioned program, we choose an outpatient setting in order to make the program more feasible and improve the transfer to daily practice. Furthermore, itch and scratch behaviour were introduced since this is a complaint that is often reported by children with psoriasis.

In addition, in order to aspire the most optimal effect and the lowest burden for the patient and their parents, the number of meetings in our program was kept as low as possible. Therefore, our program comprised of three sessions and one follow-up session with a duration of 2.5 h per meeting. This is in contrast to other programs for children in which the number and duration of the sessions varied between a single 2-h workshop, and 10 lessons of 45 minutes in a 4- to 6-week period of rehabilitation. The results of the case patient – who represents the average problems of children or adolescents with psoriasis attending the training program – showed that this intervention is promising. However, although the results of the case study suggest that the program can be promising, it does not prove the efficacy of this training program. Therefore, the efficacy of this program had to be evaluated in the future when more patient are included.

In summary, this is the first multidisciplinary training program for outpatient children and adolescents with psoriasis and their parents. The program could be a promising addition to regular treatment.
References

5
Summary and general discussion
5.1 Summary and general discussion

The aim of this thesis was to achieve more insight in genetic, therapeutic and psychological aspects of paediatric psoriasis. Therefore, five aims were formulated in Chapter 1 divided into three parts; genetics, treatments and quality of life. In this concluding chapter a summary of the major conclusions of the current thesis will be given and discussed in the light of a holistic understanding of paediatric psoriasis. Thereafter, clinical implications and directions for future research will be outlined.

The majority of the data was extracted from the Child-CAPTURE registry, a prospective observational daily clinical practice registry containing data of children with psoriasis (aged < 18 years) seen at the outpatient clinic of the department of Dermatology of the Radboud University Medical Center in Nijmegen.

Genetics

Aim 1: To explore the genetic features of paediatric onset psoriasis

A lot of genetic studies have been performed within the field of psoriasis. However, limited data about the association of psoriasis risk genes and age at onset of psoriasis (specifically onset < 18 years) are available. Therefore, the possible associations of seven known psoriasis risk genes (Human Leukocyte Antigen (HLA)-C*06, deletion of Late Cornified Envelope 3B and 3C genes (LCE3C_LCE3B-del) and psoriasis-associated single nucleotide polymorphisms (SNPs) in interleukin(IL)-23 receptor (IL23R), interleukin-12B (IL12B), endoplasmic reticulum aminopeptidase 1 (ERAP1), interferon induced with helicase C domain 1 (IFIH1) and TRAF3-interacting protein 2 (TRAF3IP2) loci) in paediatric onset psoriasis (< 18 years) and adult onset (≥ 18 years) were investigated and described in Chapter 2.1 and 2.2. In our relatively small cohort (151 patients) we demonstrated that paediatric onset psoriasis compared to controls without psoriasis was associated with genes involved in epidermal barrier function (LCE3C_LCE3B-del) and adaptive immunity (HLA-C*06 and SNPs in the IL23R and ERAP1 loci). We showed in our cohort of 85 adult onset psoriasis patients compared to healthy controls associations with LCE3C_LCE3B-del and HLA-C*06. When comparing paediatric onset psoriasis with adult onset psoriasis we found an association for only HLA-C*06 in the paediatric onset cohort. Based on our data shown in Chapter 2.1 and 2.2, we think that in paediatric onset psoriasis heritable factors may play an even more important role than in adult onset psoriasis. However, a limitation of our studies presented in Chapter 2.1 and 2.2 is the relatively small number of patients. Although our genetic study in a cohort of 151 paediatric onset psoriasis patients was one of the first to describe these associations in children with psoriasis, the number of patients is limited compared to the large genome wide
SUMMARY AND GENERAL DISCUSSION

and family history of psoriasis in our cohort. Based on our results and the

CHAPTER 5 SUMMARY AND GENERAL DISCUSSION

Several studies previously showed an association between HLA-C*06 and an early age at onset of psoriasis. A Swedish cohort demonstrated that ERAP1 was associated with a psoriasis onset between 10 and 20 years. They also demonstrated the strongest association with HLA-C*06 for these pubertal children. In our cohort we could not replicate these associations in this specific age group (between 10 and 20 years), but found an association between age at onset before 10 years and the SNP in the IL12B locus (Chapter 2.2). Recently, Nikamo et al. published that regulatory elements in the IL22 promoter are associated with onset of psoriasis before puberty (< 10 years).

In conclusion, in our cohort associations were found for paediatric onset psoriasis with ERAP1, IL23R, LCE3C_LCE3B-del and HLA-C*06. Based on our results and the reported associations in the literature, it seems that that in paediatric onset psoriasis heritable factors may play an even more important role than in adult onset psoriasis. For the future, we hope that our published data will motivate other centers to carefully register patient characteristics (age at onset) in order to replicate and extend our data. Further clarification of genetic factors at an early stage may lead to a better long term management of paediatric psoriasis and could contribute to the development of more targeted therapies for paediatric onset psoriasis.

Aim 2: To detect genotype-phenotype associations in children with psoriasis.

Psoriasis is a complex and heterogeneous disease, which varies in clinical presentation (phenotype) and genomic predisposition (genotype). In fact, heterogeneity is an outstanding feature of a variety of subtypes. To better understand paediatric psoriasis we investigated in Chapter 2.2 and 2.3 associations between known genetic risk factors for psoriasis (HLA-C*06, ERAP1, LCE3C_LCE3B-del, TRAF3IP2, IL23R, IL12B and IFIH1) and different parameters such as family history of psoriasis, age at onset and phenotype traits (psoriasis severity, nail psoriasis and Koebner phenomenon).

In Chapter 2.2 we demonstrated that severe psoriasis (defined: patients that ever reached Psoriasis Area and Severity Index (PASI) ≥ 10, Physician Global Assessment (PGA) ≥ 3 or Body Surface Area (BSA) ≥ 10) was associated with the SNPs tagging IIFIH1 and ERAP1. We are the first to describe these genetic associations with psoriasis severity (in this specific group) in a genetically relatively small cohort and this finding requires replication in larger cohorts. IFIH1 encodes for the interferon-induced with helicase C domain 1 (innate immune system), which triggers type I interferon in response to microbial infection, and variants are associated with type 1 diabetes mellitus. ERAP1 encodes an amino peptidase, with regulates the quality of peptides bound to major histocompatibility class I molecules, such as HLA-C*06. Previous studies in mainly adults with psoriasis demonstrated the psoriasis risk factors HLA-C*06 and LCE3C_LCE3B-del to be associated with severe psoriasis. Recently Lysell et al. showed that HLA-C*06 positive patients had more often facial lesions and guttate phenotype and were mostly pubertal children.

In our cohort, nail psoriasis was more often seen in HLA-C*06-negative patients. This association was previously reported in larger studies, however unstratified for age at onset. Why HLA-C*06 negative patients tend to have nail psoriasis more often, is still unclear.

We assumed an association between HLA-C*06 and family history of psoriasis in patients with early onset psoriasis based on data of previous studies which demonstrated an association between a positive family history of psoriasis and early onset of psoriasis (onset < 30 or 40 years), and HLA-C*06 and early onset psoriasis. Remarkably, we found that family history (first and up to third degree relatives) was clearly not associated with HLA-C*06 in our specific group of early onset psoriasis (< 18 years). The large proportion of patients with a positive family history in HLA-C*06 negative patients (and the lack of correlation between the two) indicates that other genes, either alone or in epistasis, may have significant effects on heritability.

Previous genetic studies suggest a role for the LCE3 genes in skin barrier function. We hypothesized that a compromised skin barrier function plays a role in psoriasis susceptibility. Therefore, we investigated in Chapter 2.2 and 2.3 the possible association between the Koebner phenomenon in psoriasis patients and LCE3C_LCE3B-del. Koebner phenomenon is the appearance of psoriasis lesions after damage of the uninvolved skin, which is seen in approximately 25% of all psoriasis patients. We could not confirm our hypothesis that there is an association between LCE3C_LCE3B-del and Koebner phenomenon in (paediatric) psoriasis patients. The biological role of LCE3B and LCE3C deletion in development and/or maintenance of psoriasis remains to be explained.

In conclusion, in our cohort severe psoriasis was associated with the SNPs tagging IFIH1 and ERAP1. Remarkably, we found no significant associations between family history of psoriasis and the allele frequency of the psoriasis, even HLA-C*06 showed...
no significant association. Further research is needed to elucidate the relationships between psoriasis susceptibility genes and clinical phenotypes. An intriguing question is to what extent the above mentioned genetic parameters represent a prognostic marker for the march of psoriasis from childhood to adulthood. The advances in the understanding of genotype-phenotype associations are the possibilities of stratification of psoriasis, targeted patient management and predict clinical outcomes.

Treatments

Aim 3: To investigate the effectiveness and safety of different treatments in children with psoriasis in daily clinical practice.

In this thesis we have prospectively investigated the effectiveness and safety of calcipotriol/betamethasone dipropionate scalp formulation for children with scalp psoriasis in Chapter 3.1. In addition in Chapter 3.2, the effectiveness and safety of short-contact dithranol therapy for chronic paediatric plaque psoriasis was prospectively studied. A retrospective analysis in which the effectiveness and safety of fumaric acid esters (FAE) in paediatric patients with psoriasis was performed in Chapter 3.3.

Evidence on efficacy and safety of (topical) treatments for paediatric psoriasis is lacking. In Chapter 3.1 the effectiveness and safety of calcipotriol/betamethasone dipropionate scalp formulation in daily clinical practice was prospectively described in children with scalp psoriasis. This scalp formulation (applied in the first two weeks daily and subsequently three times a week) proved to be effective with a 32.1% improvement of Psoriasis Scalp Severity Index (PSSI) at week 12 and a maintenance of this effect until 48 weeks of follow-up. Subanalysis of patients pre-treated with salicylic acid for two nights (prescribed depending on the severity of scaling in the opinion of the physician) showed to have an additive effect in the first 12 weeks in this subgroup. A response rate of at least 50% PSSI improvement at week 12 compared to baseline was found in 29.9% of the patients (n=21). In 22.2% of the children (n=16) clearance (PSSI=0) was achieved after a median treatment duration of 19 weeks. Three overweight patients (4.1%) developed striae of the skin (arms, trunk and legs), which were possibly related to the scalp formulation. However, the overweight in combination with an increase in bodyweight may also in its own right cause striae distensae.

In our study, no serious adverse events were reported. Apart from our study, only one recent publication (Gooderham et al.) addressed the use of calcipotriol/betamethasone dipropionate scalp formulation in adolescents with scalp psoriasis (12 – 17 years). This study mainly focussed on safety and in addition effectiveness of this scalp formulation once daily up to 8 weeks. Treatment success in this study was defined as an assessment of the investigator global assessment (IGA) and patient global assessment (PaGA) of clear or almost clear. In 65% (IGA) and 87% (PaGA) of patients treatment success was achieved at the end of the treatment. They reported that calcipotriol/betamethasone dipropionate scalp formulation was well tolerated in adolescents with at least moderate scalp psoriasis with few adverse events (6%) and no serious adverse events reported. The reported adverse drug reactions were: application-site pruritus, headache, acne, dermatitis acniform, blood calcium decrease, blood parathyroid hormone increase and urine calcium decrease. In randomized controlled trials in adults in 68 - 83% of the patients a complete clearance or very mild residual lesions of scalp psoriasis were found after 8 weeks of once daily treatment, with a comparable low number of adverse events (up to 7.0%).

A direct comparison of our results with prior studies is not possible because of different outcome measures and different treatment regimes. In the study of Gooderham et al. no striae were observed, probably because of the short period of follow-up. It should be kept in mind that adverse events in our study were based on patients’ own experience or observations of the physician and, not actively reported and collected as in randomized, controlled trials. In addition, patients had no wash-out period in our study and may be less motivated to use their scalp formulation compared to patients participating in clinical trials, which probably leads to poor adherence. We did not collected laboratory data about systemic absorption of the formulation. The number of patients in our study was too small to draw firm conclusions about safety.

Dithranol is one of the oldest topical therapeutics for psoriasis which is unjustifiably on the verge of falling into oblivion. Based on the available literature about the effectiveness and safety of dithranol in paediatric psoriasis, it can be considered in case first line topicalis such as calcipotriol and topical corticosteroids failed. In addition, our group previously demonstrated in a retrospective study that dithranol can be regarded as an efficacious and safe treatment option for paediatric psoriasis.

In Chapter 3.2 we prospectively investigated the effectiveness and safety of short-contact dithranol therapy in paediatric psoriasis in daily clinical practice and besides we compared the addition of telemedicine to regular day care. Dithranol short-contact therapy demonstrated to be effective with a mean reduction in PASI score of -69.3%. Previous studies with this treatment in children with psoriasis did not report objective severity scores to evaluate outcome effects. In adults, a PASI improvement of -63.3% was demonstrated in a randomized controlled trial. As treatment with dithranol short-contact therapy involves a complex treatment schedule, best results were obtained when it is administered in a day care centre setting, with regular visits. Contact by means of telemedicine may reduce the burden of travelling to the hospital. We demonstrated that the addition of telemecine (instead of a visit
to the day care centre) can be of additional value as it is less time consuming. Effectiveness did not significantly differ between patients with only regular day care and patients with day care in combination with telemedicine (PASI reduction: -67.2% regular day care vs. -71.3% day care with telemedicine). Patients in the telemedicine-assisted group had obviously a lower number of visits to the day care centre. The only adverse event reported in our study was irritation of the skin (mean number of irritation events during treatment 3.6), with no differences in frequency between the group of patients with only regular day care and the group of patients with day care with telemedicine. The maximum biological effect of dithranol is achieved just below the level of irritation of the surrounding uninvolved skin.36 Compared with other retrospective studies, we found a relatively high frequency of irritation.31,33 The reported frequency in other studies might have been biased due to their retrospective design, or our application time may be too long, because no studies investigated which application schedule of short-contact dithranol therapy is the most sufficient. For the future it might be interesting to investigate the intensity of the irritation. None of the patients or parents reported unwanted staining of their bathroom or furniture. From this study we can conclude that short-contact dithranol therapy is a very effective and safe treatment option in paediatric psoriasis and well beyond the efficacy of currently available first line topicals. The introduction of telemedicine in addition to regular day care resulted in a reduction of visits, while preserving good results. It is interesting to investigate whether these results can be preserved when decreasing the number of day care visits even further. Dithranol short-contact therapy can be popularized to larger populations of children with psoriasis by combining telemedicine with regular day care.

FAE is a systemic treatment that has been used in adult patients with psoriasis for more than 25 years, mainly in German speaking countries.36 FAE is not licensed in the Netherlands. The literature on FAE in paediatric psoriasis is sparse, with only a few case reports suggesting effectiveness in children.37,38 In Chapter 3.3 we retrospectively described the first published case series regarding the effectiveness and safety of FAE in 14 children with psoriasis. We reported a median duration of FAE treatment of 10 months with a median age at start of 15 years. In 36% of the patients a complete response of their psoriasis was achieved. 7% of the patients had a good improvement, 21% of the patients had a partial response and 36% of the patients were non-responders. Literature in adults with psoriasis treated with FAE demonstrated a 75% improvement in PASI score in about 50-70% of the patients.40 A limitation in our retrospective study is the fact there were no PASI scores available for all patients. Gastrointestinal complaints (abdominal complaints, diarrhoea and nausea) and flushing of the skin are the most frequent reported adverse drug reactions during treatment with FAE in our study. We reported in 36% of the patients transient, slightly abnormal laboratory values of liver-function test or mild, temporary shifts in leukocyte counts. In all patients the abnormal laboratory values normalized without any intervention or treatment discontinuation. No serious adverse events have been reported in our case series. The adverse events and changes in laboratory test in our study are in line with adult patients with psoriasis treated with FAE.40 Further prospective studies are needed to evaluate the efficacy and safety of FAE in children with psoriasis and to compare the efficacy of FAE with other systemic treatments such as methotrexate. At this moment, a prospective multicenter study is being performed in Germany addressing the efficacy and safety of FAE in paediatric psoriasis.41 In addition, we are still collecting long-term prospective data about effectiveness and safety of FAE in the Child-CAPTURE registry.

In conclusion, the present studies suggested that in real clinical practice calcipotriol/betamethasone dipropionate scalp formulation seems to be effective and safe. Dithranol short-contact treatment has a so far underestimated value as the vast majority of patients improved substantially. Dithranol should, therefore, be offered as a treatment to children with psoriasis that do not respond to first line topical treatments. The use of telemedicine in addition to regular day care dithranol treatment created the opportunity to treat patients who live far away from the hospital, and therefore made it available for larger groups of patients. Our study on FAE challenged methotrexate as first line systemic treatment in paediatric psoriasis. Due to the low number of patients studied, further, preferably comparative studies are required.

Quality of life

Aim 4: To achieve more insight in the quality of life of children with psoriasis.

Skin disease in children can have detrimental effects on the quality of life (QoL).42 Data about the QoL in children with psoriasis are limited.43-44 In Chapter 4.1 we investigated in a cross-sectional and longitudinal study the influence of psoriasis on the QoL of children. Cross-sectionally, we demonstrated in 125 patients with psoriasis a mean Children’s Dermatology Life Quality Index (CDLQI) score of 7.5. Previous studies have reported cross-sectional mean CDLQI scores between 5.05 and 10.0 in children with psoriasis.42-44,47 Our results demonstrated that the items itch and problems with treatment had the highest impact on the children’s QoL. In addition, we found that the adolescents (≥12 years) had significantly more problems with issues of clothes and sport, as compared to younger children (<12 years). We showed that all treatment clusters (topical, dithranol and systemic treatment) induce a decline in CDLQI score. Treatment of paediatric psoriasis thus improved QoL. Subanalysis for different treatment clusters demonstrated that a conclusion about the superiority of one of these three treatment clusters with respect to influencing the CDLQI could not
be made. Analyses of the influence of all treatments together on the 10 items of the CDLQI showed that the highest positive impacts were found in an improvement of itch and sleep disturbance. Only one previous study investigated the influence of treatment in children with psoriasis on the QoL.48 Because this study was a randomized controlled trial with etanercept, results of this study can hardly be compared with our daily clinical practice study. Our study demonstrated that children and adolescents with psoriasis still experience a negative impact on their QoL despite (successful) treatment. Therefore, it is important to focus on psychological aspects in conjunction to the standard dermatological care. Educational programs can support children and adolescents to cope with psoriasis. This important subject is highlighted and discussed in aim 5.

In conclusion, paediatric psoriasis has a negative influence on the QoL of those affected. Especially itch and problems with the treatment itself bothered the children most. Treatments did influence the quality of life in a positive way, especially with a reduction of itch and an improvement in sleep. However, even after successful treatments, QoL is still impaired.

In Chapter 4.2 we described the development and validation of a specific instrument to assess the influence of scalp psoriasis on QoL in children, the Children’s Scalpdex in Psoriasis (CSP). The content of the CSP questions was based on the validated Scalpdex questionnaire.49 In our cohort of children with scalp psoriasis the items “my scalp itches” and “I am bothered by the persistence/reoccurrence of my scalp condition” were the two items with the highest scores, which is in line with the original Scalpdex in adults with scalp dermatitis (psoriasis and seborrhoeic dermatitis).46 The reliability of the CSP scales (symptoms, emotions, functioning) was relatively high (Cronbach’s $\alpha$ 0.69–0.91), and slightly better than the reliability reported by the original Scalpdex (Cronbach’s $\alpha$ 0.62–0.80).50 The scores of the three scales of the CSP showed a significant positive correlation with both patient- and physician-reported scalp severity. Responsiveness analysis proved that the three scales of the CSP are sensitive to change in the expected direction in the children whose scalp psoriasis improved.

In conclusion, the results of this study showed that the CSP is a reliable, responsive and valid questionnaire. It is the first instrument to focus on scalp psoriasis in children, illustrating the specific influence of scalp psoriasis on QoL, with itch and reoccurrence of the condition being the most important issues in scalp psoriasis. In this study the questionnaire was validated for children with scalp psoriasis. However, it is highly likely that this questionnaire can also be used for other paediatric scalp conditions. The CSP can be used as a targeted questionnaire in the evaluation of outcome assessments and the effect of therapeutic interventions on QoL in children with scalp psoriasis. In Chapter 3.1 we demonstrated that calcipotriol/betamethasone dipropionate scalp formulation had a positive influence on the QoL measured by the CSP questionnaire after three months of treatment.

Aim 5: To develop together with the medical psychologist a multidisciplinary training program for children with psoriasis.

Patient education programs focussing on psychological interventions in adult psoriasis patients have been developed and resulted in improved knowledge and coping.49,50 In Chapter 4.3 we described the development and design of the first multidisciplinary training program for outpatient children with psoriasis and their parents. This program was developed in collaboration with two medical psychologists specialised in the field of dermatology. For the development of the program, literature was reviewed, a steering group was assembled and systematic semi-structured interviews were held. The aim of the training program was to strengthen patients and their parents in coping with and diminishing psoriasis related problems in an outpatient setting. The program included treatment modules of medical information and skin care, itch and scratch problems, psychological issues in coping with psoriasis, sleep hygiene and relapse prevention. To our knowledge, only one study described an educational program for children and adolescents with psoriasis, however this is in an inpatient setting.54 In contrast to this inpatient program, our program is in an outpatient setting in order to make the program more feasible and improve the transfer to daily practice. Based on the systematic semi-structured interviews and in agreement with the steering group, the subjects itch and scratch behaviour were introduced in our program since these subjects were often reported by children with psoriasis.43 The number of meetings in our program was kept as low as possible, in order to achieve the most optimal effect and the lowest burden for the patient and their parents. Therefore, our program consists of three sessions and one follow-up session with a duration of 2 ½ h per meeting. This is in contrast to other programs for children in which the number and duration of the sessions varied between a single 2-h workshop, and 10 lessons of 45 minutes in a 4- to 6-week period of rehabilitation.56-59

Till now, 23 patients participated in the program. It is already known that the program is highly appreciated by both the children and their parents. The efficacy of this training program will be evaluated soon in a pilot study. It could be a promising addition to the standard dermatological care for paediatric psoriasis patients.
5.2 Main conclusions of this thesis

The present thesis comprises genetics, treatment responsiveness, and quality of life in paediatric psoriasis. The main conclusions are listed below:

**Genetics (Chapter 2)**
- Our complete psoriasis cohort (paediatric and adult onset) compared to controls without psoriasis demonstrated significant associations with HLA-C*06, LCE3C_LCE3B-del and SNPs in the ERAP1 and IL23R loci.
- In the complete psoriasis cohort we showed an interaction between HLA-C*06 and LCE3C_LCE3B-del.
- Paediatric onset psoriasis compared to controls without psoriasis was associated with genes involved in epidermal barrier function (LCE3C_LCE3B-del) and adaptive immunity (HLA-C*06 and SNPs in the ERAP1 and IL23R loci).
- In paediatric onset psoriasis heritable factors might play an even more important role than in adult onset psoriasis.
- An onset of psoriasis < 10 years of age was significant associated with the psoriasis risk allele of SNP in the IL12B locus.
- No significant associations were found between family history of psoriasis and the allele frequency of the psoriasis risk factors. Even HLA-C*06 showed no significant associations.
- In our cohort severe psoriasis was associated with the SNPs tagging IFIH1 and ERAP1.
- In HLA-C*06 negative patients a significant increase of nail involvement was found.
- None of the investigated risk factors showed a significant association with Koebnerization in our cohort.

**Treatments (Chapter 3)**
- Calcipotriol/betamethasone dipropionate scalp formulation in paediatric scalp psoriasis in daily clinical practice demonstrated to be effective with a 32.1% improvement of PSSI at week 12 and a maintenance of this effect until 48 weeks of follow-up.
- Subanalysis of patients pre-treated with salicylic acid for two nights demonstrated the highest improvements in the first 12 weeks.
- At week 12, the response rate of at least 50% PSSI improvement compared to baseline was found in 29.9% (n=21) of the patients.
- Clearance (PSSI = 0) was achieved in 22.2% of the patients (n=16) after a median treatment duration of 19 weeks.
- In 4.1% of the patients (n=3) striae of the skin (arms, trunk and legs) were observed, which were possibly related to the scalp formulation.

**Quality of life (Chapter 4)**
- Paediatric psoriasis caused a significant negative impact on QoL of those affected.
- A positive influence of psoriasis treatments in daily clinical practice on the QoL in a cohort of children with psoriasis was demonstrated, with most improvement found in a reduction of itch and a reduction of sleep disturbance.
- The CSP questionnaire showed to be a reliable, responsive and valid questionnaire. It is the first instrument to focus on the influence of scalp psoriasis on the QoL of children with psoriasis.
- The development and design of a multidisciplinary training program for outpatient children and adolescents with psoriasis and their parents was described and illustrated.

5.3 Implications for current clinical practices and future perspectives

This thesis approaches the paediatric psoriasis patient in a holistic manner including genetic, therapeutic and psychological aspects.

As has been demonstrated in this thesis, paediatric psoriasis might be a genetically different subgroup from adult psoriasis but also the therapeutic and psychological aspects of this vulnerable subgroup differ from adult psoriasis. By knowing the genetic and phenotypic profile of a paediatric patient the course of psoriasis might be better predicted. Future studies might focus on the genetic profile in combination with the effect of a treatment, to identify a predictor of treatment response paediatric...
and thus develop an individualized tailored approach. Recently Talamonti et al. demonstrated HLA-C*06 as a pharmacogenetic marker of response to ustekinumab in adults with psoriasis.50 The collection of the genetic profile and treatment effectiveness data by means of patient registries in daily clinical practice can be of additional value in the field of pharmacogenetics.

The treatment of a paediatric psoriasis patient is complicated by a gap of evidence in safety and efficacy data. Many potential psoriasis treatments do not have an official label for paediatric use, forcing dermatologist to use them off-label. Registries can provide safety and effectiveness data and represent daily clinical practice. In contrast to randomized controlled trials, daily clinical practice registries include non-ideal and high-risk patients and it is possible to collect long term follow-up data. In addition to regular treatment, it is important to focus on the impact of psoriasis on the QoL of a child. An educational program can be of additional value to strengthen children and their parents in coping with and diminishing psoriasis related problems.

In order to collect more evidence on the genetics, efficacy and safety of treatments and psychological aspects of paediatric psoriasis, larger numbers of patients are necessary. By means of a large, prospective international registry, efficacy and safety data could be collected, as well as DNA samples, other biologic markers and QoL measurements. In this thesis, a first step in the holistic approach of the paediatric psoriasis patient has been made. The publications in this thesis will be helpful in the daily clinical practice of physicians treating paediatric psoriasis. In addition, these articles hopefully encourage other research groups to collaborate, and construct a prospective, international registry for paediatric psoriasis.

References

SUMMARY AND GENERAL DISCUSSION

Long-Term Efficacy of an Inpatient Rehabilitation with Systemic Treatments in Paediatric Psoriasis: A Systematic Review


5
Nederlandse Samenvatting
6.1 Samenvatting en discussie

Het doel van dit proefschrift was om meer inzicht te krijgen in genetische, therapeutische en psychologische aspecten van kinderen met psoriasis. In Hoofdstuk 1 werden vijf doelen geformuleerd, verdeeld over drie onderwerpen; genetica, behandelingen en kwaliteit van leven. In dit hoofdstuk worden de belangrijkste conclusies van dit proefschrift samengevat en bediscussieerd. Tot slot worden toepassingen voor de dagelijkse klinische praktijk beschreven en suggesties voor toekomstig onderzoek gedaan.

In dit proefschrift werd het grootste gedeelte van de gegevens verkregen uit de Child-CAPTURE database. Dit is een prospectieve observationele database die gegevens bevat van kinderen met psoriasis (ontstaan < 18 jaar) die verwezen werden naar de polikliniek dermatologie van het Radboudumc in Nijmegen. De data zijn een weergave van behandelingen uit de dagelijkse praktijk.

Genetica

Doel 1: Onderzoeken naar genetische kenmerken van kinderen met psoriasis.

Op het gebied van psoriasis zijn veel genetische onderzoeken verricht. Er zijn echter weinig gegevens beschikbaar over de associatie van genetische risicofactoren voor psoriasis en de leeftijd waarop psoriasis zich voor het eerst presenteert. Vooral naar een associatie tussen genetische risicofactoren en leeftijd van ontstaan voor het 18e levensjaar werd nauwelijks onderzoek gedaan. Daarom werden in Hoofdstuk 2.1 en 2.2 de mogelijke associaties onderzocht tussen zeven bekende genetische risicofactoren voor psoriasis (HLA*C06, LCE3C_LCE3B-del, IL23R, IL12B, ERAP1, IFIH1 en TRAF3-IP2) en het ontstaan van psoriasis op de kinderleeftijd (< 18 jaar) en volwassen leeftijd (≥ 18 jaar). We hebben laten zien, (in ons relatief kleine cohort van 151 patiënten), dat psoriasis ontstaan op de kinderleeftijd is geassocieerd met genetische risicofactoren voor psoriasis die betrokken zijn in epidermale barrière functie (LCE3C_LCE3B-del) en het verworven afweersysteem (HLA*C06, IL23R en ERAP1) vergeleken met een controle groep zonder psoriasis Als de groep van patiënten met psoriasis ontstaan op de kinderleeftijd wordt vergeleken met een groep patiënten waarbij de psoriasis op volwassen leeftijd is ontstaan, wordt in de kinderleeftijd groep een duidelijke associatie met HLA*C06 gevonden ten opzichte van de volwassen groep. Worden patiënten met psoriasis vanaf volwassen leeftijd vergelijken met een controle groep zonder psoriasis, dan worden associaties met LCE3C_LCE3B-del en HLA*C06 gevonden. We bevestigden een eerder beschreven interactie tussen de psoriasis risicogenen HLA*C06 en LCE3C_LCE3B-del in de totale groep van psoriasis patiënten.1-3

Een beperking van onze studies is het relatieve kleine aantal onderzochte patiënten. Onze genetische studie van 151 patiënten met psoriasis vanaf de kinderleeftijd is de
een van de eerste studies die deze associaties heeft onderzocht en beschreven in deze specifieke leeftijdsgroep. Zoals gezegd is het aantal geïncludeerde patiënten beperkt, zeker in vergelijking met grote genoom wijde associatie studies, waarin vaak duizenden patiënten worden geïncludeerd.

De associatie tussen HLA-C*06 en jonge leeftijd van ontstaan van psoriasis was al wel eerder in de literatuur beschreven.9,10 Een Zweeds cohort toonde aan dat ERAP1 is geassocieerd met psoriasis ontstaan tussen 10 en 20 jaar.9,10 Zij vonden in deze groep van pubers de sterkste associatie met HLA-C*06.9,10 In ons cohort konden deze associaties in deze specifieke leeftijdsgroep (tussen 10 en 20 jaar) niet geregistreerd worden, maar wij vonden wel een associatie met leeftijd van ontstaan voor 10e levensjaar en genetische variatie in het IL12B gen (Hofdstuk 2.2).

Concluderend kunnen we stellen dat in ons cohort associaties werden gevonden tussen kinderpsoriasis en de psoriasis risicogenen ERAP1, IL23R, LCE3C, LCE3B-del en HLA-C*06. Gebaseerd op onze resultaten beschreven in Hofdstuk 2.1 en 2.2 en eerdere publicaties lijken erfelijke factoren mogelijk een belangrijkere rol te spelen bij psoriasis ontstaan op kinderleeftijd dan psoriasis die op latere leeftijd is ontstaan. Voor de toekomst hopen we dat onze bevindingen andere centra motiveren om patiëntekarakteristieken te registreren en DNA te verzamelen om op die manier onze bevindingen te repliceren en hopelijk nieuwe associaties te vinden. Opheffing van de genetisch factoren in een vroege fase zou kunnen leiden tot een beter lange termijn management van kinderpsoriasis en zou kunnen bijdragen aan de ontwikkeling van meer gerichte behandeling voor kinderpsoriasis.

Doel 2: Detecteren van genotype-fenotype associaties in kinderen met psoriasis.

Psoriasis is een complexe heterogene ziekte, met een variatie in klinische presentatie (fenotype) en genoom predispositie (genotype). Om psoriasis beter te kunnen begrijpen hebben we in Hofdstuk 2.2 en 2.3 associaties onderzocht tussen bekende genetische risicofactoren voor psoriasis (zoals beschreven bij doel 1) en verschillende parameters zoals familie anamnese voor psoriasis, leeftijd van ontstaan en klinische kenmerken (ernst van psoriasis, nagelpsoriasis en Koebner fenomeen).

In Hofdstuk 2.2 hebben we laten zien dat een ernstige psoriasis was geassocieerd met de genetische risicofactoren voor psoriasis IFIH1 en ERAP1. Onze studie is de eerste die deze genetische associaties met ernstige psoriasis heeft beschreven in deze specifieke groep van kinderpsoriasis patiënten. Deze studie vond echter plaats in een klein cohort, zeker voor genetica begrippen. Het zou daarom goed zijn dat deze bevindingen worden geregistreerd in een groter cohort. Eerdere studies die voornamelijk bij patiënten met psoriasis vanaf volwassen leeftijd werden uitgevoerd, hebben een associatie aangetoond tussen een ernstige psoriasis en de genetische risicofactoren HLA-C*06 en LCE3C_LCE3B-del.11,12 Recent heeft een Zweedse groep aangetoond dat voornamelijk kinderen in de puberleeftijd HLA-C*06 positieve patiënten zijn die vaker plekken in het gezicht hebben en een guttata fenotype.9

In ons cohort werd nagelpsoriasis vaker gezien in HLA-C*06 negatieve patiënten. Deze associatie is eerder beschreven in grotere studies, echter niet gespecificeerd voor leeftijd van ontstaan van psoriasis.10,13 Het is niet duidelijk waarom HLA-C*06 negatieve patiënten vaker nagelpsoriasis hebben.

Eerdere studies hebben een associatie beschreven tussen een positieve familie anamnese voor psoriasis en psoriasis vanaf jonge leeftijd (ontstaan voor 30e of 40e levensjaar), en tevens de associatie tussen HLA-C*06 positiviteit en psoriasis vanaf jonge leeftijd.9,10 Op basis van deze studies veronderstelden we een sterke associatie te kunnen vinden, bij patiënten met psoriasis vanaf kinderleeftijd, tussen HLA-C*06 en een positieve familie anamnese voor psoriasis. Wij vonden dat een positieve familie anamnese (eerste tot en met derdegraads familieleden) niet geassocieerd was met HLA-C*06 in onze specifieke groep van kinderpsoriasis (ontstaan voor 18e jaar). Ook de andere onderzochte genetische risicofactoren voor psoriasis waren niet geassocieerd met familie anamnese voor psoriasis. Mogelijk spelen andere genen een belangrijke rol bij de erfelijkheid van psoriasis.

Eerdere studies suggereren een rol voor de LCE3 genen in de huid barrièrefunctie.14 Op deze studies baseerden wij onze hypothese dat een verminderde barrièrefunctie (LCE3C_LCE3B-del) van de huid mogelijk een oorzaak zou kunnen zijn voor het ontstaan van psoriasis.15 Koebner fenomeen is het ontstaan van psoriasis plekken na beschadiging van de niet aangedane huid. Dit komt voor bij ongeveer een kwart van de psoriasis patiënten.15 In Hofdstuk 2.2 hebben we de relatie tussen LCE3C_LCE3B-del en het optreden van Koebner fenomeen in psoriasis patiënten onderzocht. Uit dit onderzoek bleek dat LCE3C_LCE3B-del het optreden van Koebner fenomeen in ons patiënten cohort niet verklaart.

Concluderend kunnen we stellen dat in ons cohort met kinderpsoriasis een ernstigere psoriasis was geassocieerd met de genetische risicofactoren voor psoriasis IFIH1 en ERAP1. We konden geen associatie aantonen tussen familie anamnese voor psoriasis en genetische risicofactoren voor psoriasis (zelfs niet voor HLA-C*06) en niet tussen LCE3C_LCE3B-del en het optreden van Koebner fenomeen. Verder onderzoek is nodig om de relatie tussen genetische risicofactoren voor...
psoriasis en de verschillende klinische fenotypen beter te verklaren. Door meer duidelijkheid te krijgen over de associatie tussen genotype en fenotype ontstaat de mogelijkheid om psoriasis te kunnen stratificeren, doelgerichte behandelingen te geven en mogelijk klinische resultaten te voorspellen.

Behandelingen

Doel 3: Het onderzoeken van de effectiviteit en veiligheid van verschillende behandelingen van kinderpsoriasis in de dagelijkse klinische praktijk.

Er is weinig bewijs over de effectiviteit en veiligheid van (lokale) behandelingen voor kinderpsoriasis. In dit proefschrift hebben we prospectief de effectiviteit en veiligheid van calcipotriol/betamethason hoofdgel bij kinderen met psoriasis op het behaarde hoofd onderzocht in Hoofdstuk 3.1. Deze hoofdgel bleek effectief te zijn, met op week 12 een 32,1% verbetering van de ernst score van psoriasis op de behaarde hoofdhuid (Psoriasis Scalp Severity Index (PSSI)). Dit effect bleef behouden tot een follow-up duur van 48 weken. Twee nachten voorbehandeling met salicyzuur ter ontschilfering van de behaarde hoofdhuid (voorgeschreven op basis van de mening van de behandelend arts) toonde een positief additioneel effect op de PSSI in de eerste 12 weken. Op week 12 werd er in 29,9% van de patiënten (n=21) een 50% verbetering in de PSSI gevonden ten opzichte van start van de behandeling. Bij 22,2% van de patiënten (n=16) werd er een PSSI score van 0 bereikt na een gemiddelde behandelduur van 19 weken. Drie patiënten (met overgewicht) (4,1%) ontwikkelden strieën van de huid (armen, romp en benen), dit was mogelijk gerelateerd aan het gebruik van de hoofdgel. In onze studie werden er geen ernstige bijwerkingen geraapporteerd. Een vergelijking van onze studie met andere studies is niet mogelijk omdat er verschillende uitkomstmaten zijn gebruikt en verschillende behandelregimes zijn toegepast. In onze studie is het bijwerkingenprofiel gebaseerd op zelf geraapporteerde bijwerkingen van de patiënten, en observaties door de arts. Er is niet actief naar geïnformeerd, zoals dat in gerandomiseerd onderzoek met een controlegroep vaak wordt gedaan. Verder kregen de patiënten in onze studie geen wash-out periode voor aanvang van de behandeling. Bovendien waren onze patiënten in de dagelijkse praktijk mogelijk minder gemotiveerd om de behandeling te gebruiken en opzichte van patiënten die deelnamen aan gerandomiseerd onderzoek.13,14 Gezien het beperkte aantal patiënten in onze studie, is het niet mogelijk om harde conclusies te trekken met betrekking tot de veiligheid van calcipotriol/betamethason hoofdgel bij kinderen met psoriasis op het behaarde hoofd.

Ditrano is een van de oudste lokale behandelingen voor psoriasis. Deze behandeling kan worden overwogen indien behandeling met calcipotriol en lokale corticosteroiden onvoldoende effectief zijn.17 In een eerdere retrospecitieve studie werd door onze groep aangetoond dat ditranol korte contact therapie kan worden gezien als een effectieve en veilige behandeling bij kinderen met psoriasis.18 We hebben in Hoofdstuk 3.2 prospectief onderzoek gedaan naar de effectiviteit en veiligheid van ditranol korte contact therapie bij kinderen met psoriasis. Daarbij hebben we ook onderzocht of er een verschil is in effectiviteit en veiligheid tussen patiënten die alleen via dagbehandeling behandeld werden, en patiënten waarbij de dagbehandeling deels vervangen werd door telezorg. Wij hebben aangetoond dat ditranol korte contact therapie bij kinderen met psoriasis effectief is, met 69,3% verbetering van de ernst score van de psoriasis (gemeten met behulp van de PASI score). Er werd geen verschil gevonden in effectiviteit tussen patiënten met alleen dagbehandeling en patiënten met dagbehandeling in combinatie met telezorg. Eerdere studies naar de behandeling van ditranol bij kinderen met psoriasis beschreven geen objectieve bare scores als uitkomstmaat.19,20 In het verleden is aangetoond dat de beste resultaten met ditranol korte contact therapien worden bereikt wanneer het wordt toegepast in een dagbehandeling setting met regelmatige bezoeken.21 Contacten met behulp van telezorg kan de belasting van regelmatige bezoeken aan het ziekenhuis verminderen. Wij hebben aangetoond dat toevoeging van telezorg (ter vervanging van een bezoek aan de dagbehandeling) van toegevoegde waarde kan zijn, aangezien het minder tijdsintensief is. De groep patiënten met telezorg had logischerwijs minder bezoeken aan de dagbehandeling. De enige bijwirkende in deze studie werd geraapporteerd was irritatie van de huid. Er werd geen verschil gevonden in de frequentie van irritatie tussen beide patiëntgroepen. Vergeleken met eerdere retrospecitieve studies vonden wij een relatief hoge frequentie van irritatie van de huid.18,19 De frequentie van irritatie in andere studies zou mogelijk niet correct kunnen zijn vanwege het retrospectieve karakter of, onze aanpak zou te lang kunnen zijn. Er zijn echter nog geen studies geweest die hebben onderzocht welk applicatie schema van ditranol korte contact therapie het meest effectief is. Uit onze gegevens concluderen we dat ditranol korte contact therapie een zeer effectieve en veilige behandeling is. De introductie van telezorg als gedeeltelijke vervanging van bezoeken aan de dagbehandeling zorgt voor een vermindering van het aantal bezoeken met behoud van goed resultaat. Het is interessant om te onderzoeken of het aantal bezoeken aan de dagbehandeling nog verder omlaag zou kunnen. Door de toevoeging van telezorg aan de reguliere dagbehandeling kan ditranol korte contact therapie beschikbaar worden voor een grotere groep kinderen met psoriasis.
Kwaliteit van leven

Doel 4: Meer inzicht verkrijgen in de kwaliteit van leven van kinderen met psoriasis.

Huidziekten kunnen een negatieve impact hebben op de kwaliteit van leven (KvL) bij kinderen. Gegevens over de impact van psoriasis op de KvL bij kinderen zijn beperkt. In *Hoofdstuk 4.1* onderzoeken we cross-sectioneel en longitudinaal de invloed van psoriasis op de KvL van kinderen met behulp van de ‘Children’s Dermatology Life Quality Index’ (CDLQI) vragenlijst (score 0 tot 30; hogere score betekent een slechtere KvL). In een groep van 125 kinderen met psoriasis vonden we cross-sectioneel een gemiddelde CDLQI score van 7,5. Eerdere cross-sectionele studies bij kinderen met psoriasis beschreven een gemiddelde CDLQI score tussen de 5 en 10. De resultaten toonden dat de items ‘jeuk’ en ‘problemen met de behandeling’ de meeste impact op de KvL van de kinderen hadden. Verder zagen we dat de adolescenten (≥ 12 jaar) significant meer problemen hadden met kleding en sporten in vergelijking met jongere kinderen (< 12 jaar). Behandelingen (lokaal, ditranol en systemische) zorgen voor een daling in de CDLQI score (verbetering van KvL). De grootste positieve impact werd gevonden in een verbetering van de jeukklachten en verminderde slaapproblemen. Slechts één eerdere studie had (tot onze publicatie) de invloed van een behandeling op de kwaliteit van leven van kinderen met psoriasis onderzocht. Omdat dit een gerandomiseerde gecontroleerde studie betrof, konden deze resultaten niet worden vergeleken met onze resultaten uit de dagelijkse klinische praktijk. Onze studie toonde dat kinderen en adolescenten met psoriasis een negatieve impact op de kwaliteit van leven ervaren ondanks (succesvolle) behandeling. Het is daarom belangrijk om ook op psychologische aspecten te focussen naast de standaard dermatologische zorg. Educatie programma’s kunnen kinderen en adolescenten ondersteunen bij het leren omgaan met psoriasis. Dit belangrijke onderwerp wordt besproken in doel 5.

Concluderend kan gezegd worden dat kinderpsoriasis een negatieve impact op de KvL heeft. De kinderen irriteren zich het meest aan de jeuk en problemen met de voorgeschreven behandeling. Behandeling heeft een positieve invloed op de KvL, voornamelijk door een verbetering van jeukklachten en een verbetering van de slaapproblemen. Echter ondanks een succesvolle behandeling blijven deze kinderen een verminderde KvL hebben.

In *Hoofdstuk 4.2* beschrijven we de ontwikkeling en validatie van een specifieke vragenlijst om de invloed van psoriasis op het behaarde hoofd op de KvL van kinderen te meten, de ‘Children’s Scalpex in Psoriasis’ (CSP). In de inhoud van de
De betrouwbaarheid van de drie CSP schalen (symptomen, emoties en functioneren) was relatief hoog, en iets beter dan de betrouwbaarheid gerapporteerd bij de oorspronkelijke Scalpdex. De scores van de drie schalen van de CSP toonden een significant positieve correlatie met patiënt en arts gerapporteerde ernst van psoriasis op behaarde hoofd. Analyses toonden dat de drie schalen van de CSP vragenlijst gevoelig zijn om te veranderen in de te verwachten richting bij de kinderen waarbij de psoriasis op het behaarde hoofd verbetert.

Concluderend kunnen we stellen dat onze studie toonde dat de CSP een betrouwbare, responsieve en valide vragenlijst is. Het is de eerste vragenlijst die zich richt op de invloed van psoriasis op het behaarde hoofd bij kinderen. In ons studie was de vragenlijst gevalideerd voor kinderen met psoriasis op het behaarde hoofd. Deze vragenlijst zou mogelijk ook gebruikt kunnen worden voor andere aandoeningen op het behaarde hoofd bij kinderen. De CSP kan gebruikt worden als een specifieke vragenlijst voor de evaluatie van resultaten en effect van therapeutische interventie op de KvL bij kinderen met psoriasis op het behaarde hoofd. In Hoofdstuk 3.1 toonden we dat calcipotriol/betamethason hoofdgel een positieve invloed heeft op de KvL na drie maanden behandelingen, gemeten met de CSP vragenlijst.

**Doel 5: Het ontwikkelen van een multidisciplinair trainingsprogramma voor kinderen met psoriasis samen met de medisch psycholoog.**

Er zijn diverse patiënt educatie programma’s ontwikkeld voor volwassen patiënten met psoriasis gericht op psychologische interventie. Deze programma’s resulteerden in een verbetering van kennis en coping. In Hoofdstuk 4.3 beschreven we de ontwikkeling en het ontwerp van het eerste politklinische multidisciplinaire trainingssproogramma voor kinderen met psoriasis en hun ouders. Dit programma is ontwikkeld samen met twee medisch psychologen gespecialiseerd op het gebied van de dermatologie. Voor de ontwikkeling van dit programma werd literatuur onderzoek gedaan, een stuurgroep samengesteld en werden systematische semi-gestructureerde interviews gehouden. Het trainingsprogramma is gericht op het zo goed mogelijk leren omgaan met de huidaandoening. Onderwerpen die tijdens de training aan bod komen zijn informatie over de huidaandoening en mogelijke behandelvormen, regelmatige huidverzorging, het leren omgaan met jeuk en krabgedrag en leren omgaan met de gevolgen van de huidaandoening in het dagelijks leven. Voor zo ver bekend is er één andere studie die een educatie programma beschrijft voor kinderen en adolescenten met psoriasis, echter is dit in een klinische setting. Ons programma is daarentegen in een politklinische setting opgesteld, om het programma beter uitvoerbaar te maken. De onderwerpen die tijdens de training aan bod komen zijn informatie over de huidaandoening en mogelijke behandelvormen, regelmatige huidverzorging, het leren omgaan met jeuk en krabbedrag en leren omgaan met de gevolgen van de huidaandoening in het dagelijks leven. Het aantal bijeenkomsten in ons programma is zo laag mogelijk gehouden om het meest optimale effect te bereiken bij de laagste belasting voor de patiënt en ouders. Het programma bestaat uit drie sessies en een follow-up sessie met een duur van 2.5 uur per bijeenkomst. Tot nu toe hebben er 23 patiënten deelgenomen aan het programma. Kinderen en ouders stellen het programma zeer op prijs. Het effect van het programma wordt binnenkort geëvalueerd in een pilot studie. Het programma kan veel belovend zijn in aanvulling op standaard dermatologische zorg voor kinderen met psoriasis.

**6.2 De belangrijkste conclusies van dit proefschrift**

**Genetica (Hoofdstuk 2)**

- In ons cohort van psoriasis (kinder- en volwassen leeftijd) vergeleken met controle groep zonder psoriasis werden significante associaties gevonden met HLA-C*06, LCE3C_LCE3B-del, ERAP1 en IL23R.
- Psoriasis ontstaan op kinderleeftijd vergeleken met controle groep zonder psoriasis was geassocieerd met genetische risicofactoren voor psoriasis LCE3C_LCE3B-del, HLA-C*06, ERAP1 en IL23R.
- Erfelijke factoren zouden mogelijk een belangrijkere rol spelen bij psoriasis ontstaan op de kinderleeftijd dan psoriasis die op latere leeftijd is ontstaan.
- Psoriasis ontstaan voor het 10e levensjaar was in ons cohort geassocieerd met de genetische risicofactor voor psoriasis IL12B.
- Er konden geen associaties worden aangetoond tussen een positieve familie anamnese voor psoriasis en genetische risicofactoren voor psoriasis.
- In ons cohort was een ernstigere psoriasis geassocieerd met de genetische risicofactoren IFI1H en ERAP1.
- Er werd vaker nagelpsoriasis gezien bij patiënten die HLA-C*06 negatief waren.
- Geen van de onderzochte genetische risicofactoren voor psoriasis toonde een significante associatie met het Koebner fenomeen.

**Behandelingen (Hoofdstuk 3)**

- Calcipotriol/betamethason hoofdgel in de dagelijkse praktijk was effectief met een 32,1% verbetering in PSSI score op week 12; dit effect werd gehandhaafd tot 48 weken follow-up.
6.3 Implicaties voor de huidige klinische praktijk en toekomst perspectieven

Dit proefschrift heeft de kinderen en adolescenten met psoriasis benaderd vanuit een holistische visie, waarbij zowel naar genetische aspecten als behandelingen en psychologische aspecten werd gekeken.

In dit proefschrift is aangetoond, dat psoriasis ontstaan vanaf kinderleeftijd mogelijk een genetische subgroep is ten opzichte van psoriasis ontstaan vanaf volwassen leeftijd. Maar ook de behandelingen en psychologische aspecten van deze kwetsbare groep verschillen van volwassen patiënten met psoriasis. Door het genetische en fenotypische profiel van kinderpsoriasis in kaart te brengen, zou het beloop mogelijk beter voorspeld kunnen worden. Toekomstige studies zullen zich meer richten op het genetische profiel in combinatie met het effect van een behandeling, om een therapeutisch respons te kunnen voorspellen en daarmee een meer geïndividualiseerde aanpak op maat te kunnen ontwikkelen. De verzameling van het genetische profiel en effectiviteit data van behandelingen met behulp van patiënt registries in de dagelijkse klinische praktijk kan van toegevoegde waarde zijn op het gebied van farmacogenetica.

De behandeling van psoriasis bij kinderen is complex door een gebrek aan data over veiligheid en effectiviteit van behandelingen. Veel psoriasis behandelingen hebben geen officiële registratie voor gebruik bij kinderen, waardoor dermatologen gedwongen worden tot off-label gebruik. Registries kunnen zorgen voor representatieve veiligheids- en effectiviteits- gegevens uit de dagelijkse praktijk. In tegenstelling tot gerandomiseerde gecontroleerde studies bevatten dagelijkse klinische praktijk registries de niet-ideale patiënten met comorbiditeiten en is het mogelijk om lange termijn data te verzamelen. Naast de standaard behandeling van psoriasis, is het belangrijk om ons te richten op de impact van de psoriasis op de KVL van een kind. Een educatie programma kan van toegevoegde waarde zijn om kinderen en hun ouder(s) sterker te maken in het leren omgaan met, en verminderen van psoriasis gerelateerde problemen.

Om meer bewijs te verzamelen over de genetische aspecten effectiviteit en veiligheid van behandelingen, en psychologische aspecten van kinderpsoriasis zijn grote groepen van patiënten nodig. Met behulp van een grote prospectieve internationale registry, kunnen effectiviteits- en veiligheidsdata worden verzameld, net als DNA, andere biologische markers en KvL metingen. In dit proefschrift is een eerste stap gemaakt in de holistische benadering van het kind en de adolescent met psoriasis. Hopelijk moedigt dit proefschrift andere onderzoeksgroepen aan om samen te werken in het opbouwen van een prospectieve, internationale registry voor kinderen met psoriasis.
List of publications
Curriculum Vitae
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7.1 List of publications

Publications related to this thesis:

Koebner Phenomenon in Psoriasis is not Associated with Deletion of Late Cornified Envelope Genes LCE3B and LCE3C.

Development and design of a multidisciplinary training program for outpatient children and adolescents with psoriasis and their parents.
Oostveen A.M., Spillekom-van Kouill S., Otero M. E., Klompmaker W., Evers A.W.M., Seyger M.M.B.

Paediatric onset psoriasis is associated with ERAP1 and IL23R loci, HLA-C*06 and LCE3C_LCE3B deletion.

The influence of treatments in daily clinical practice on the Children’s Dermatology Life Quality Index (CDLQI) in paediatric psoriasis: a longitudinal study from the Child-CAPTURE Patient Registry.

Effectiveness and safety of fumaric acid esters in children with psoriasis: a retrospective analysis of 14 patients from the Netherlands.
Balak D.M.W., Oostveen A.M., Bousema M.T., Venema A.W., Arnold W.P., Seyger M.M.B., Thio H.B.

The effectiveness and safety of short-contact dithranol therapy in paediatric psoriasis: a prospective comparison of regular day care and day care with telemedicine.


Genotype-phenotype correlations in a prospective cohort study of paediatric plaque psoriasis: lack of correlation between HLA-C*06 and family history of psoriasis.


Publications not related to this thesis:

Association of pediatric psoriasis severity with excess and central adiposity: an international cross-sectional study.


Psoriasis bij kinderen.


Methotrexate in pediatric plaque-type psoriasis: Long-term daily clinical practice results from the Child-CApTure registry.

7.2 Curriculum Vitae


7.3 Dankwoord

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