View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Radboud Repository

Radboud Repository

Radboud University Nijmegen

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/83268

Please be advised that this information was generated on 2017-12-06 and may be subject to change.

Childhood psoriasis

Michelle de Jager

Cover and layout by: In Zicht Grafisch Ontwerp, Arnhem
Cover concept: Michelle de Jager
Printed by: Ipskamp Drukkers, Enschede

ISBN: 978-90-9025931-4

© Michelle de Jager 2010

All rights reserved. No parts of this publication may be reproduced, stored in a retrieval system of any nature, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without prior permission of the publisher.

The financial support of this thesis was kindly provided by:
ABBOTT Immunology, Actavis B.V., Actelion Pharmaceuticals B.V., Astellas B.V., Bauerfeind Benelux B.V., Beiersdorf N.V., Cara C'air B.V., Fagron B.V., Galderma S.A., GlaxoSmithKline B.V., Tibotec, La Roche-Posay, LEO Pharma B.V., medi Nederland B.V., Nederlands Bijwerkingen Fonds, Novartis Pharma B.V., Pfizer B.V., Pierre Fabre Dermo-Cosmétique, Radboud University Nijmegen Medical Centre, Schering-Plough B.V.

Childhood psoriasis

Een wetenschappelijke proeve op het gebied van de
Medische Wetenschappen

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. mr. S.C.J.J. Kortmann,
volgens besluit van het college van decanen
in het openbaar te verdedigen op
vrijdag 11 februari 2011
om **11.00 uur** precies

door

Michelle Elisabeth Anne de Jager
geboren op 1 mei 1982
te Nijmegen

Promotor

Prof. dr. dr. P.C.M. van de Kerkhof

Copromotores

Mevr. dr. M.M.B. Seyger

Mevr. dr. E.M.G.J. de Jong

Manuscriptcommissie

Prof. dr. P.L.C.M. van Riel

Prof. dr. P.M. Steijlen (Academisch Ziekenhuis Maastricht)

Dr. J.M.T. Draaisma

Paranimfen

Mr. drs. M.P.A. de Jager

Mw. dr. R.J.B. Driessen

Contents

Chapter 1

General introduction

1.1 History

The actual condition of psoriasis was first described by the Greek physician Hippocrates, who lived between 460 and 377 BC. He described a skin condition resembling psoriasis, but this was clubbed together with diseases like leprosy, eczema and tubercular lupus.
Psoriasis was again mentioned in the first century by Cornelius Celsus (25 BC - 50 AD), a Roman author. Celsus described it as the fourth variant of impetigo. Joseph Jacob Plenck (Vienna, 1776) wrote of psoriasis as being amongst the group of scaly diseases. He also did not study in-depth to differentiate the condition from other skin diseases.
Finally, the English dermatologist Robert Willan (1757 - 1812) recognized psoriasis as an independent entity and for almost a century, psoriasis was known as Willan's lepra.
He identified two categories: Leprosa Graecorum was the term he used to describe the condition when the skin had scales. Psora Leprosa described the condition when it became eruptive. In 1841, Ferdinand Hebra, a Viennese dermatologist who was working on Willan's notes, ascribed the name "psoriasis" (from the Greek word "psora" which means "to itch") in the English dictionary. He described the clinical picture of psoriasis that is used today.[1-3]

1.2 Epidemiology

Psoriasis is a chronic relapsing non-infectious inflammatory skin disorder, which affects approximately 1.5 - 3% of the adult Caucasian population.[4-6] The occurrence is most frequent in Europeans and Scandinavians, uncommon in Chinese and non-existent in Samoans or Latin American Indians.[5;7]
Prevalence rates of childhood psoriasis have been published in two reports. In 2007, a prevalence rate of 0.55% was found in the first age decade and 1.37% in the second age decade.[4] Two years later, another study was published reporting comparable figures of 0.37% in the first age decade and 1.01% in the second age decade. The total prevalence of psoriasis in children up to 18 years was 0.71%.[8]

Data about the age of onset of psoriasis vary among investigators. Age of onset before the age of 20 years is reported in 27 - 50% of all psoriatic patients.[9-15] In 10 - 15% of patients with psoriasis, the disease started before the age of 10 years.[11;14;16]

In 1985, two peak ages of onset were found by Henseler and Christophers[17]: one at 16 - 22 years and one at 60 years. These peaks have been confirmed in one other study[18], but several other authors claim that there are no peaks[10;19] and that prevalence increases in an approximately linear matter[8]. Henseler and Christophers also stated that two clinical forms of psoriasis could be distinguished, one with an early age of onset (≤ 40 years of age) and one with a late age of onset (> 40 years of age).[17] According to the authors, psoriasis of early onset was found to follow an irregular course with frequent relapses. More patients had extensive body involvement and nail involvement, and genetic factors seemed to play a prominent role. On the other hand, late onset psoriasis followed a more stable clinical course, and extensive body and nail involvement were less frequently observed. Henseler and Christophers also postulated that in this form, genetic factors seem to be more secondary. The above described differences between the two groups were also seen by Ferrandiz et al.[20] Nevertheless, the separation of the two groups has been questioned by many others who promote that early onset and late onset psoriasis cannot be distinguished on clinical grounds.[15,21-23]

Most authors agree on the fact that the male to female ratio in juvenile psoriasis is equal.[19;24-29] On the other side, some cohorts consist of more women than men with juvenile psoriasis, with ratios up to 2.3 : 1.[30-34] In adult psoriasis, the male to female ratio is equal.[5;6]

In 4.5 - 71% of children with psoriasis a positive family history of psoriasis is noted.[20;24-35] The highest rates are found in European and Australian populations[25;33], the lowest in Indian and Chinese communities[24;29]. The same wide variation in familial distribution is found in adults with psoriasis.[10;20;36-38]

1.3 Clinical features

Classic lesions of psoriasis consist of round, erythematous, well-marginated plaques covered by a characteristic greyish or silvery-white (mica-like or "micaceous") scale. Typical signs of psoriasis are the "signe de tache de bougie", which refers to the candle wax-like appearance of a plaque when its scales are being scratched, and the "Auspitz' sign", which refers to pinpoint bleedings that become visible after removing the silvery scales.[3;39] Lesions most invariably begin as small, reddish, pinpoint to pinhead-sized papules surmounted by fine scales.

These papules coalesce and form patches or plaques that measure one centimeter or more in diameter.

All of the clinical variants of psoriasis described in adults are recognized in childhood.[25]
Plaque psoriasis is the most common variant in the juvenile population, with frequencies varying from 54.1 to 89.2%.[19;24;26-32;34;35;40] In children, plaques are often smaller and thinner, and the scale is finer and softer than in adults. In 1975, a cohort of juvenile psoriasis patients was analyzed in which only 18% had plaque psoriasis[33], but this is out of line with all other recent and larger studies.
Guttate psoriasis is the second most frequently seen subtype in childhood psoriasis. It often develops suddenly, often in response to a streptococcal throat infection. It is characterized by the eruption of multiple papules of 0.5 - 1 centimeter in diameter over the face, trunk and limbs. There is a tendency for this variety of psoriasis to resolve spontaneously, although a substantial proportion of patients will go on to develop chronic plaque disease.[41-43] Reported frequencies of guttate psoriasis lie between 6.4 - 44%.[19;24-29;31-35;40]
Pustular psoriasis is rare in children. Four clinical patterns of pustular psoriasis have been described in children: generalized pustular psoriasis (also known as von Zumbusch pattern), annular pustular psoriasis, exanthematic pustular psoriasis and localized pustular psoriasis.[44-47] Several studies have reported that annular pustular psoriasis is the most common form of juvenile pustular psoriasis.[46;47] Frequencies of juvenile pustular psoriasis vary widely between studies. Most authors report a frequency of approximately 1 - 2%[19;24;26;27;31-35], but others report a frequency around 10%[29;30].
Erythrodermic psoriasis in children is a very rare form of psoriasis that presents as erythema covering most of the body surface. Scaling is less prominent than with plaque psoriasis. Frequencies are reported from 0.7 - 5.1%.[24;26;27;29-32]

The most frequently involved sites in childhood psoriasis are the extremities, although also the scalp and trunk are frequently involved.[19;26;28;30;32-35] In children, the face is more frequently affected than in adults, with numbers ranging from 17 - 56.7%.[19;25-28;30;33-35] Nail changes are observed in up to 40% of children with psoriasis. Fingernails are more commonly involved than toenails. Most common is pitting of the nails, but all other types of nail involvement such as onycholysis, subungual hyperkeratosis, discoloration, longitudinal striae and ridging can be observed.[19;24;26-33;35;40] Pruritis is seen in up to 87% of all juvenile psoriasis patients.[24;26;28;29;32;33;35]

Psoriatic arthropathy is seen in 0.7 - 2.9% of juvenile psoriatis patients.[24;26;27;29;35] The exact incidence of juvenile psoriatic arthritis is unknown, but estimates extrapolated from population studies suggest a prevalence of 10 to 15 per 100 000 children.[48-50] In a substantial proportion of juvenile patients (23 - 58%) arthritis precedes psoriasis.[51-54] In contrast, adult psoriatic arthritis usually presents with many years of psoriasis before the onset of arthritis.[55-57] The onset of psoriatic arthritis in children is often between the ages of 7 and 13 years. Distal interphalangeal joints of hands and feet, knees and ankles may be involved during the early stages. Over time, polyarthritis may develop to include wrist, metacarpophalangeal, elbow and metatarsophalangeal joints.[55]

Predisposing factors for childhood psoriasis include a genetic background[58], a positive family history[58], group A β-haemolytic streptococcal infections[30;44], trauma[59], drugs (e.g. anti-malarials)[60] and stress[30;61]. Also, seasonal influences are seen, mostly with lesions worsening during the winter.[24;26;29;31;33]
In one study, juvenile psoriasis has been associated with increased rates of hyperlipidaemia, obesity, hypertension, diabetes mellitus, rheumatoid arthritis and Crohn's disease.[8] Up to now, there is no consensus if obesity is a risk factor for the onset of juvenile psoriasis.[62;63]

1.4 Histopathology

The superficial layers of the epidermis are characterized by absence of the granular layer and presence of remnants of nuclei within the horny layer (confluent parakeratosis). The accumulation of polymorphonuclear leukocytes in the stratum spinosum (spongiform micro-pustules of Kogoj) and the formation of infiltrates of polymorphonuclear leukocytes in the stratum corneum (micro-abscesses of Munro), are considered to be psoriasis specific.
The epidermis is thickened (acanthosis) with a thinned suprapapillary plate. Rete ridges are elongated, slim and approximately the same length. The abnormalities in the dermis consist of vasodilatation and tortuousity of the capillaries together with a mixed inflammatory infiltrate consisting of T-lymphocytes and polymorphonuclear leukocytes.[64]

1.5 Aetiology

Childhood psoriasis is a multifactorial disease. Both genetic and environmental factors participate in the risk of psoriasis. Up to 70% of paediatric patients have a family history of psoriasis and affected twins have been described. The life-time risk of developing psoriasis is thought to be 4% if no parent is affected, 28% if one parent is affected and 65% if both parents are affected.[65] Genetic susceptibility has been linked to class I and class II major histocompatibility complexes on chromosome 6. Two disease subsets have been proposed, differing in both age of onset and the human leukocyte antigen (HLA) present. Type I represents early onset psoriasis (onset ≤ 40 years of age) and has been linked to HLA-Cw6, B57 and DR7. Type II represents late onset psoriasis (onset > 40 years of age) and has been linked to HLA-Cw2.[36] Nine genetic susceptibility loci (PSORS1 - 9) have been detected by linkage analysis, but the genetic determinants at these loci have not all been identified yet. The susceptibility locus with the greatest genetic effect (PSORS1) lies on chromosome 6p21.3 in the region of the major histocompatibility complex.[66]

Laboratory studies, clinical observations and use of targeted therapy gathered evidence that psoriasis is an immune-mediated disorder. The majority of T-cells in psoriatic plaques are CD45RO+ memory-effector T-cells that migrate into skin exposed to an antigenic trigger. Th1 cytokines, particularly interferon-γ and IL-2, predominate, in contrast to the largely Th2 cytokine response of the acute lesions of atopic dermatitis.[67] Furthermore, Th17 is a T-cell subset to be of major importance in the pathogenesis of psoriasis. Th17-cells are activated by IL-23, which is a cytokine produced by dendritic cells upon activation. Anti-IL12/23p40 antibodies have been shown to have an outstanding therapeutic activity in adult psoriasis.[68;69] Recently, it has been demonstrated that not only T-cells have a role in the pathogenesis of psoriasis. The absence of two members of the late cornified envelope (LCE) gene cluster (LCE3B and LCE3C) is significantly associated with risk of psoriasis. Even more, LCE is strongly expressed in psoriatic lesions, suggesting that compromised skin barrier function has a role in psoriasis.[70]

1.6 Treatment

In the treatment of adult patients with psoriasis, a spectrum of topical treatments, photo(chemo)therapy, conventional systemic treatments and biologics is available.

For children with psoriasis most of these treatments are not registered. Only a few clinical trials in children with psoriasis have been performed.[71,72] As children are not just small adults, results of trials in adults cannot simply be extrapolated to children.

Since 26 January 2007, the Paediatric Regulation is effective in the European Union.[73] This has changed the procedure for obtaining marketing authorisation of medicines in Europe so that new medications can be adapted safely for the use in children. Additional provisions have been made for the use of authorised and generic medications in children. Research is being stimulated through grants and the extension of exclusive distribution rights for manufacturers. Other initiatives are aimed at making existing data on the use of medications in children accessible. Many of these tasks are the responsibility of a special European paediatric committee, which also assesses proposals for research on medication use in children.[74]

Successful management of childhood psoriasis requires education of the child and parents about the nature of the disease and the treatment options. Patients and their parents must understand the chronicity of the disease and have to learn to accept that there is no permanent cure for psoriasis.

It is important to tailor treatment to the patient's needs, considering their age and the extent, severity and location of the condition. The approach to medication should be made as simple as possible, since therapy is time-consuming, burdensome and easily rejected.[67] Especially in young children, compliance is dependent almost entirely on the parents.

Treatment of childhood psoriasis should intend to control the disease, rather than to achieve complete clearance. Of course, it is also important to consider short- and long-term safety profiles and the risk-to-benefit ratio for any treatment.

Regrettably, guidelines on the treatment of juvenile psoriasis are lacking. The American Academy of Dermatologists briefly mentions the paediatric use of anti-psoriatic medication in their guideline concerning the treatment of psoriasis. Unfortunately, no treatment algorithm is suggested. A Dutch guideline is currently in preparation and will soon arrive. Treatment options for children with psoriasis are mostly based on expert opinions rather than evidence. The evidence on efficacy and safety of separate treatment options in children with psoriasis will be discussed in Chapter 3 of this thesis.

The following treatments are currently used for the treatment of childhood psoriasis (although most of them are not registered for this indication): emollients,

keratolytics, topical corticosteroids, vitamin D_3 analogues, calcineurin inhibitors, dithranol, phototherapy, retinoids, ciclosporin, methotrexate and biologics.
Emollients moisturize and soften the skin and can be used to reduce redness, itching and pain of psoriatic lesions.
Keratolytics (e.g. salicylic acid) are used to descale thick hyperkeratotic plaques and can therefore improve penetration of other topical treatments. Especially in children, it should be used with caution because it may induce salicylic acid intoxication.[75]
Topical corticosteroids are probably the most frequently prescribed first-line treatment for psoriasis and have an anti-inflammatory, immunosuppressive and anti-mitotic effect.[76] Topical corticosteroids can be divided into four potency classes: class I (low potent) to class IV (ultra potent). The side effects of topical corticosteroids include epidermal atrophy (usually irreversible), dermal atrophy with the development of striae (especially in intertriginous zones), perioral dermatitis and steroid rosacea. Systemic absorption of corticosteroids can lead to suppression of the pituitary-adrenal axis, especially with class IV corticosteroids.[77]
Topical vitamin D_3 analogues are frequently used as the therapy of choice for mild to moderate psoriasis. In The Netherlands two synthetic vitamin D_3 analogues are available: calcipotriol (Daivonex®) and calcitriol (Silkis®). Vitamin D_3 analogues are usually well tolerated, but irritation of the skin may occur. To prevent effects on the calcium metabolism, a maximal dose of 100 gram calcipotriol per week is recommended for adults. For adults, the body surface has an average of 2 m^2. Consequently, the recommended maximum dose per m^2 per week is 50 gram. For children, the recommended maximum dose per week can be found by calculating the body surface of the child (body surface (m^2) = $\sqrt{}$((length(cm)*-weight(kg))/3600)) and multiplying it by 50 gram. This calculation was performed in a randomized controlled trial in children and no effects on the calcium metabolism were found.[71]
Topical calcineurin inhibitors can be used especially in facial and intertriginous psoriasis. Available formulations are tacrolimus ointment 0.03% or 0.1% (Protopic®) and pimecrolimus 1% cream (Elidel®). In contrast to corticosteroids, they do not cause atrophy and tachyphylaxis. The most frequently seen side effects are irritation and stinging after application. Although there is a theoretical concern that topical immunomodulatory therapy with tacrolimus and pimecrolimus may increase the risk of cancer, there is no evidence to date to suggest an increased risk of cutaneous or visceral cancer.[78] Nevertheless, the European Medicines

Agency (EMA) advises to use topical calcineurin inhibitors with great caution in order to reduce potential risks of skin cancer and lymphoma as far as possible.

Dithranol is one of the oldest topical therapeutics for psoriasis. The exact mechanism of action is still unknown, but it is known to induce a cascade of free radicals in the skin, resulting in antiproliferative effects and a modulation of inflammation in psoriasis.[79] No serious side effects of dithranol have been reported.[80] It may cause a burning sensation, irritation and staining at the application site or clothing.

Phototherapy with ultraviolet B (UVB) and photochemotherapy with ultraviolet A (UVA) following ingestion or topical treatment with psoralen are two classical therapies for adult patients with moderate to severe psoriasis that does not respond to topical therapies alone. In children it is less frequently used than in adults. Although there are no studies documenting the long-term safety of UVB phototherapy in childhood psoriasis, judicious use of this therapy is advised for appropriately selected patients (e.g. adolescents whose disease fails to respond to topical therapy).[81]

The term "retinoids" is used for a family of substances of natural and synthetic analogues of vitamin A. Acitretin is the only systemic retinoid that is available for the treatment of (adult) psoriasis in The Netherlands. Common side effects are mucocutaneous problems, e.g. cheilitis, dryness of the eyes, nasal and oral mucosa, epistaxis, xerosis, brittle nails, hair loss and burning or sticky skin. Increases of serum triglycerides are frequently observed. Attention should also be given to the teratogenicity of acitretin.[77]

Ciclosporin is a calcineurin inhibitor which inhibits T-cell function and thus the production of various cytokines. It is mainly used as a short period intervention in very severe psoriasis. Dose-dependent renal impairment is the most common cause of withdrawal of treatment. As well as renal side effects, hypertension, malignancies and infections may occur during treatment with ciclosporin.[77]

Methotrexate is a folic acid antagonist, which is often used in severe psoriasis unresponsive to topical therapeutics. The most common side effects are nausea, malaise, abdominal discomfort, leucopenia and hepatotoxicity. If methotrexate-related abdominal discomfort occurs, subcutaneous treatment can be endeavoured instead of oral ingestion.[77]

Biologics are the newest agents used for the treatment of psoriasis. Etanercept (Enbrel®) is the only biologic that is registered by the EMA for the use in children older than eight years with psoriasis. Etanercept is a soluble tumor necrosis factor alpha (TNFα) receptor fusion protein that antagonizes the effects of endogenous

TNFα, which is a protein that promotes an inflammatory response in psoriasis. Etanercept is usually well tolerated in paediatric patients with moderate to severe plaque psoriasis.[82] Injection site reactions can occur, as well as infections, common colds, fever and headache. The long-term side effects are not completely known, because of the limited experience with this agent. Malignancies (e.g. lymphomas) have been reported in children with polyarthritis, juvenile idiopathic arthritis, ankylosing spondylitis, vasculitis and psoriatic arthritis that were treated with etanercept. It should be noted that most of these patients were also receiving previous and concomitant immunosuppressants.[83;84] Registries will have to provide additional information on this subject.

1.7 Quality of life

The diagnosis of childhood psoriasis raises the question among parents as to the extent to which this diagnosis can influence the quality of life of their child now and in the future. It is known that having a chronic disease in childhood can diminish a child's health-related quality of life.[85] Negative life experiences, such as a chronic disease in childhood, may also have an impact on childhood development and adult life.[86] In dermatological research, quality of life studies in children mainly focus on atopic dermatitis, demonstrating the burden atopic dermatitis has on children.[85;87-89] In view of the comparable impact of atopic dermatitis and psoriasis in adult patients[90], it could be assumed that childhood psoriasis also has a comparable impairing influence on the quality of life for children with these skin conditions.

Two previous studies have reported quality of life scores of children with psoriasis.[85;91] To evaluate the disease-related quality of life the only valid questionnaire available for this purpose was used: the Children's Dermatology Life Quality Index (CDLQI) questionnaire.[92] In the validation study of the CDLQI questionnaire, 25 patients with psoriasis were questioned.[91] The mean CDLQI score was 5.4 (SD 5.0), ranging from 0 to 18 points. In another study, 29 juvenile psoriatic patients filled out the CDLQI questionnaire.[85] Their mean score was 9.2 (SD 7.8; range 0 - 27). In this study, it was also demonstrated that the quality of life of children with psoriasis is even worse than in diabetes and epilepsy in childhood.[85]

Therefore, a child-tailored treatment should not only be optimized to limit disease activity, but attention should also be paid to improving the quality of life of children with psoriasis.

1.8 Aims of this thesis

The studies carried out in this thesis were set up in order to achieve more insight in the epidemiology, treatments and quality of life of childhood psoriasis.

The following aims were formulated:
Ia)
to further explore the epidemiology and clinical features of childhood psoriasis in The Netherlands
Ib)
to compare differences and similarities between childhood onset psoriasis and adult onset psoriasis
IIa)
to obtain an overview of efficacy and safety of treatment options in childhood psoriasis
IIb)
to create an evidence-based algorithm for the treatment of childhood psoriasis
IIIa)
to get more insight in the psychological burden of psoriasis in children
IIIb)
to compare the burden of psoriasis as experienced in childhood to the burden in adulthood

1.9 Clinical approach

CAPTURE registry

In 2005, a patient registry was set up by investigators of the Department of Dermatology of the Radboud University Nijmegen Medical Centre to collect data on efficacy and safety of biological therapies for the treatment of adult patients with psoriasis in daily clinical practice.[93]
In September 2008, this registry was expanded to also register prospective data (on efficacy and safety of treatments and quality of life) of all juvenile psoriasis patients (i.e. < 18 years old) who visit the Department of Dermatology of the Radboud University Nijmegen Medical Centre. This expanded prospective registry was named "CAPTURE", an acronym for Continuous Assessment of Psoriasis Treatment Use Registry (CAPTURE). Child-CAPTURE is used for the

childhood psoriasis part of the registry, whereas Bio-CAPTURE is used for the part in which patients with biological therapies are being followed.

Methods to score psoriasis disease severity

The Psoriasis Area and Severity Index (PASI) score is the most frequently used measure to characterize the clinical severity of psoriasis. The first description of this instrument was published in 1978 by Fredriksson and Petterson[94] and it has been considered as the golden standard since.[95] The PASI scoring system assesses four body regions: the head (h), the upper limbs (u), the trunk (t) and the lower extremities (l). The extent of psoriatic involvement in these four main body areas (Ah, At, Au and Al) is assessed using numbers according to the following scale: 0, no involvement; 1, < 10%; 2, 10 - 30%; 3, 31 - 50%; 4, 51 - 70%; 5, 71 - 90% and 6, 91 - 100%. For each region, erythema (E), induration (I) and desquamation (D) were rated according to a five-point scale: 0, no involvement; 1, slight; 2, moderate; 3, marked and 4, very marked involvement. Subsequently, the PASI score is calculated from the following formula: PASI = 0.1Ah (Eh + Ih + Dh) + 0.2Au (Eu + Iu + Du) + 0.3At (Et + It + Dt) + 0.4Al (El + Il + Dl). The PASI score can vary in increments of 0.1 units from 0 to 72 with a higher score representing a greater severity of psoriasis. Although the PASI score ranges from 0 to 72, most patients have scores ranging between 0 and 15. PASI scores of 40 and higher are sporadically seen.

The severity of psoriasis is also rated with the second most often employed score to measure psoriasis severity: the Physician's Global Assessment (PGA). This assessment is easier to perform and less time-consuming than the PASI score. The investigator has to assign a single estimate of the patient's overall severity of disease on an ordinal scale. For all research performed in this thesis, a six-point Likert scale is used (0, clear; 1, minimal; 2, mild; 3, moderate; 4, severe; 5, very severe). The PGA ranges from 0 to 5.

For questionnaires in adults, the Self-Administered PASI (SAPASI) is used. This is a valid and reliable instrument that allows adult patients to assess the severity of their psoriasis. The redness, induration and scaliness of an average psoriatic lesion are rated with three visual analogue scales (VAS). The involved area of the skin is marked on an anatomical sketch and is weighted by an investigator according to the original PASI score.[96] The range of the SAPASI score is 0 - 72, with increasing severity of psoriasis with increasing SAPASI scores. Ranges to explain the severity of psoriasis were previously described as: 0, complete remission; > 0 - 3, mild; > 3 - 15, moderate; > 15, severe.[97]

The Body Surface Area (BSA) affected is also measured, with a minimum of 0% and a maximum of 100%.
Physical symptoms of itch, pain and fatigue are measured on separate VAS, measuring the mean level of itch, pain and fatigue over the past four weeks (0, no itch / pain / fatigue; 10, worst itch / pain / fatigue ever experienced).[90]

Methods to score quality of life

Disease-related quality of life is assessed with the Children's Dermatology Life Quality Index (CDLQI) questionnaire (http://www.dermatology.org.uk/quality/quality-cdlqi.html).[91] The CDLQI consists of 10 questions, each with four possible replies, scored 0 to 3. The total score is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more the quality of life is impaired. Question-categories are symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment.
For assessment of stigmatization a six-item subscale adapted from the Impact of Chronic Skin Disease on Daily Life (ISDL) questionnaire is used. Gauged is to what extent the respondent feels stigmatized by others as a result of his / her skin condition, with response categories on a four-point Likert scale (1, not; 2, a little; 3, strongly; 4, totally) (item examples: Others are staring; Others avoid contact). The stigmatization score thus ranges from 6 to 24.

Reference List

1. Fry L. Psoriasis. *Br.J.Dermatol.* 1988; 119: 445-61.
2. Giickman FS. Lepra, psora, psoriasis. *J.Am. Acad.Dermatol.* 1986; 14: 863-6.
3. van de Kerkhof PCM. Clinical features. in: *Textbook of psoriasis* (van de Kerkhof,PCM, ed), 2nd edn. Oxford: Blackwell Publishing Ltd., 2003: 3-29.
4. Gelfand JM, Weinstein R, Porter SB *et al.* Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. *Arch.Dermatol.* 2005; 141: 1537-41.
5. Gudjonsson JE, Elder JT. Psoriasis: epidemiology. *Clin.Dermatol.* 2007; 25: 535-46.
6. Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003-2004. *J.Am.Acad.Dermatol.* 2009; 60: 218-24.
7. Griffiths CEM, Camp RDR, Barker JNWN. Psoriasis. in: *Rook's Textbook of Dermatology* (Burns,T, Breathnach,S, Cox,N et al, eds), 7th edn. Oxford: Blackwell Publishing Ltd., 2004: 1-69.
8. Augustin M, Glaeske G, Radtke MA *et al.* Epidemiology and comorbidity of psoriasis in children. *Br.J.Dermatol.* 2010; 162: 633-6.
9. Braun-Falco O, Burg G, Farber EM. [Psoriasis. A questionnaire study of 536 patients]. *Munch.Med.Wochenschr.* 1972; 114: 1105-10.
10. Rigopoulos D, Gregoriou S, Katrinaki A *et al.* Characteristics of psoriasis in Greece: an epidemiological study of a population in a sunnyMediterraneanclimate.*Eur.J.Dermatol.* 2010; 20: 189-95.
11. Farber EM, Nall ML. The natural history of psoriasis in 5,600 patients. *Dermatologica* 1974; 148: 1-18.
12. Verbov J. Psoriasis in childhood. *Arch.Dis. Child* 1992; 67: 75-6.
13. Farber EM, Carlsen RA. Psoriasis in childhood. *Calif.Med.* 1966; 105: 415-20.
14. Watson W, Cann HM, Farber EM *et al.* The genetics of psoriasis. *Arch.Dermatol.* 1972; 105: 197-207.
15. Swanbeck G, inerot A, Martinsson T *et al.* Age at onset and different types of psoriasis. *Br.J.Dermatol.* 1995; 133: 768-73.
16. Beylot C, Puissant A, Bioulac P *et al.* Particular clinical features of psoriasis in infants and children. *Acta Derm.Venereol.Suppl (Stockh)* 1979; 87: 95-7.
17. Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. *J.Am.Acad.Dermatol.* 1985; 13: 450-6.
18. Smith AE, Kassab JY, Rowland Payne CM *et al.* Bimodality in age of onset of psoriasis, in both patients and their relatives. *Dermatology* 1993; 186: 181-6.
19. Tollefson MM, Crowson CS, McEvoy MT *et al.* incidence of psoriasis in children: a population-based study. *J.Am.Acad.Dermatol.* 2010; 62: 979-87.
20. Ferrandiz C, Pujol RM, Garcia-Patos V *et al.* Psoriasis of early and late onset: a clinical and epidemiologic study from Spain. *J.Am. Acad.Dermatol.* 2002; 46: 867-73.
21. Shaw FL, Cumberbatch M, Kleyn CE *et al.* Langerhans cell mobilization distinguishes between early-onset and late-onset psoriasis. *J.Invest Dermatol.* 2010; 130: 1940-2.
22. Ejaz A, Raza N, iftikhar N *et al.* Presentation of early onset psoriasis in comparison with late onset psoriasis: a clinical study from Pakistan. *Indian J.Dermatol.Venereol.Leprol.* 2009; 75: 36-40.
23. Allen MH, Ameen H, Veal C *et al.* The major psoriasis susceptibility locus PSORS1 is not a risk factor for late-onset psoriasis. *J.Invest Dermatol.* 2005; 124: 103-6.
24. Kumar B, Jain R, Sandhu K *et al.* Epidemiology of childhood psoriasis: a study of 419 patients from northern india. *Int.J.Dermatol.* 2004; 43: 654-8.
25. Morris A, Rogers M, Fischer G *et al.* Childhood psoriasis: a clinical review of 1262 cases. *Pediatr.Dermatol.* 2001; 18: 188-98.
26. Nanda A, Kaur S, Kaur i *et al.* Childhood psoriasis: an epidemiologic survey of 112 patients. *Pediatr.Dermatol.* 1990; 7: 19-21.
27. Fan X, Xiao FL, Yang S *et al.* Childhood psoriasis: a study of 277 patients from China. *J.Eur.Acad.Dermatol.Venereol.* 2007; 21: 762-5.
28. Burgers SA, van Vloten WA. [Findings in children with psoriasis]. *Ned.Tijdschr. Geneeskd.* 1999; 143: 148-51.

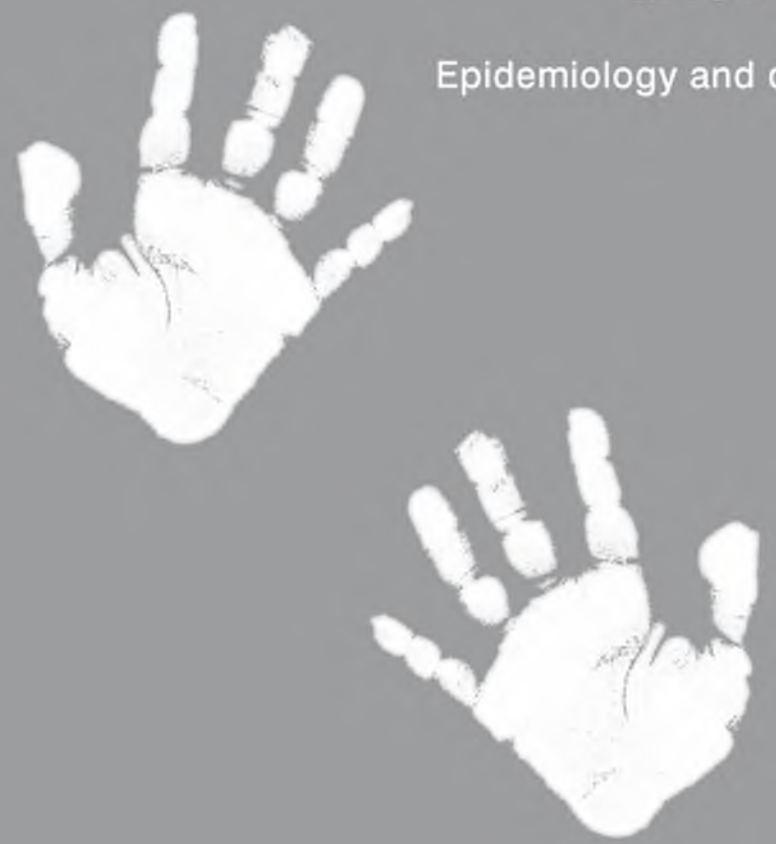
29. Wu Y, Lin Y, Liu HJ *et al.* Childhood psoriasis: a study of 137 cases from central China. *World J.Pediatr.* 2010; 6: 260-4.
30. Seyhan M, Coskun BK, Saglam H *et al.* Psoriasis in childhood and adolescence: evaluation of demographic and clinical features. *Pediatr.Int.* 2006; 48: 525-30.
31. Sigure S. Study on children psoriasis in Latvia. *Acta Dermatovenerol Alp Panonica Adriat* 2002; 11: 45-9.
32. Al-Fouzan AS, Nanda A. A survey of childhood psoriasis in Kuwait. *Pediatr.Dermatol.* 1994; 11: 116-9.
33. Nyfors A, Lemholt K. Psoriasis in children. A short review and a survey of 245 cases. *Br.J.Dermatol.* 1975; 92: 437-42.
34. Kim SK, Kang HY, Kim YC *et al.* Clinical comparison of psoriasis in Korean adults and children: correlation with serum anti-streptolysin O titers. *Arch.Dermatol.Res.* 2010; 302: 295-9.
35. Nanda A, Al-Fouzan AS, El-Kashlan M *et al.* Salient features and HLA markers of childhood psoriasis in Kuwait. *Clin.Exp.Dermatol.* 2000; 25: 147-51.
36. Henseler T. The genetics of psoriasis. *J.Am. Acad.Dermatol.* 1997; 37: S1-11.
37. Raychaudhuri SP, Gross J. A comparative study of pediatric onset psoriasis with adult onset psoriasis. *Pediatr.Dermatol.* 2000; 17: 174-8.
38. Lomholt G. *Psoriasis: Prevalence, Spontaneous Course and Genetics.* GEC GAD, Copenhagen, Denmark, 1963.
39. Bernhard JD. Clinical pearl: Auspitz sign in psoriasis scale. *J.Am.Acad.Dermatol.* 1997; 36: 621.
40. Al-Mutairi N, Manchanda Y, Nour-Eldin O. Nail changes in childhood psoriasis: a study from Kuwait. *Pediatr.Dermatol.* 2007; 24: 7-10.
41. Martin BA, Chalmers RJ, Telfer NR. How great is the risk of further psoriasis following a single episode of acute guttate psoriasis? *Arch.Dermatol.* 1996; 132: 717-8.
42. Leman JA. Recognition and treatment of psoriasis in children. *Curr Paediatr* 2003; 13: 418-22.
43. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet* 2007; 370: 263-71.
44. Cassandra M, Conte E, Cortez B. Childhood pustular psoriasis elicited by the streptococcal antigen: a case report and review of the literature. *Pediatr.Dermatol.* 2003; 20: 506-10.
45. Chao PH, Cheng YW, Chung MY. Generalized pustular psoriasis in a 6-week-old infant. *Pediatr.Dermatol.* 2009; 26: 352-4.
46. Zelickson BD, Muller SA. Generalized pustular psoriasis in childhood. Report of thirteen cases. *J.Am.Acad.Dermatol.* 1991; 24: 186-94.
47. Liao PB, Rubinson R, Howard R *et al.* Annular pustular psoriasis--most common form of pustular psoriasis in children: report of three cases and review of the literature. *Pediatr.Dermatol.* 2002; 19: 19-25.
48. Southwood TR, Petty RE, Malleson PN *et al.* Psoriatic arthritis in children. *Arthritis Rheum.* 1989; 32: 1007-13.
49. Gare BA, Fasth A. Epidemiology of juvenile chronic arthritis in southwestern Sweden: a 5-year prospective population study. *Pediatrics* 1992; 90: 950-8.
50. Cuellar ML, Espinoza LR. Psoriatic arthritis. Current developments. *J.Fla.Med.Assoc.* 1995; 82: 338-42.
51. Hamilton ML, Gladman DD, Shore A *et al.* Juvenile psoriatic arthritis and HLA antigens. *Ann.Rheum.Dis.* 1990; 49: 694-7.
52. Shore A, Ansell BM. Juvenile psoriatic arthritis--an analysis of 60 cases. *J.Pediatr.* 1982; 100: 529-35.
53. Sills EM. Psoriatic arthritis in childhood. *Johns.Hopkins.Med.J.* 1980; 146: 49-53.
54. Truckenbrodt H, Hafner R. [Psoriatic arthritis in childhood. A comparison with subgroups of chronic juvenile arthritis]. *Z.Rheumatol.* 1990; 49: 88-94.
55. Lewkowicz D, Gottlieb AB. Pediatric psoriasis and psoriatic arthritis. *Dermatol.Ther.* 2004; 17: 364-75.
56. Gladman DD, Shuckett R, Russell ML *et al.* Psoriatic arthritis (PSA)-an analysis of 220 patients. *Q.J.Med.* 1987; 62: 127-41.
57. Martel W, Stuck KJ, Dworin AM *et al.* Erosive osteoarthritis and psoriatic arthritis: a radiologic comparison in the hand, wrist, and foot. *Am.J.Roentgenol.* 1980; 134: 125-35.
58. Farber EM, Mullen RH, Jacobs AH *et al.* infantile psoriasis: a follow-up study. *Pediatr. Dermatol.* 1986; 3: 237-43.

59. Meiski JW, Bernhard JD, Stern RS. The Koebner (isomorphic) response in psoriasis. Associations with early age at onset and multiple previous therapies. *Arch.Dermatol.* 1983; 119: 655-9.
60. Tsankov N, Angelova I, Kazandjieva J. Drug-induced psoriasis. Recognition and management. *Am.J.Clin.Dermatol.* 2000; 1: 159-65.
61. Picardi A, Mazzotti E, Gaetano P *et al.* Stress, social support, emotional regulation, and exacerbation of diffuse plaque psoriasis. *Psychosomatics* 2005; 46: 556-64.
62. Boccardi D, Menni S, La VC *et al.* Overweight and childhood psoriasis. *Br.J.Dermatol.* 2009; 161: 484-6.
63. Herron MD, Hinckley M, Hoffman MS *et al.* Impact of obesity and smoking on psoriasis presentation and management. *Arch.Dermatol.* 2005; 141: 1527-34.
64. The psoriasiform reaction pattern. In: *Skin Pathology* (Weedon,D, ed), 2nd edn. Oxford: Elsevier Health Sciences, 2002: 76-81.
65. Swanbeck G, Inerot A, Martinsson T *et al.* Genetic counselling in psoriasis: empirical data on psoriasis among first-degree relatives of 3095 psoriatic probands. *Br.J. Dermatol.* 1997; 137: 939-42.
66. Veal CD, Capon F, Allen MH *et al.* Family-based analysis using a dense single-nucleotide polymorphism-based map defines genetic variation at PSORS1, the major psoriasis-susceptibility locus. *Am.J.Hum.Genet.* 2002; 71: 554-64.
67. Griffiths CE, Barker JN. Pathogenisis and clinical features of psoriasis. *Lancet* 2007; 370: 263-71.
68. Leonardi CL, Kimball AB, Papp KA *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008; 371: 1665-74.
69. Papp KA, Langley RG, Lebwohl M *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008; 371: 1675-84.
70. de Cid R, Riveira-Munoz E, Zeeuwen PL *et al.* Deletion of the late cornified envelope LCE3B and LCE3C genes as a susceptibility factor for psoriasis. *Nat.Genet.* 2009; 41: 211-5.
71. Oranje AP, Marcoux D, Svensson A *et al.* Topical calcipotriol in childhood psoriasis. *J.Am.Acad.Dermatol.* 1997; 36: 203-8.
72. Palier AS, Siegfried EC, Langley RG *et al.* Etanercept treatment for children and adolescents with plaque psoriasis. *N.Engl.J. Med.* 2008; 358: 241-51.
73. Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use. URL http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf (last accessed 28 October 2010).
74. van den Berg H., Taminiau JA. [Better medicines for children: European measures]. *Ned.Tijdschr.Geneeskd.* 2008; 152: 1537-40.
75. Lebwohl M. The role of salicylic acid in the treatment of psoriasis. *Int.J.Dermatol.* 1999; 38: 16-24.
76. Hughes J, Rustin M. Corticosteroids. *Clin. Dermatol.* 1997; 15: 715-21.
77. van de Kerkhof PCM. Psoriasis. In: *Dermatology* (Bolognia,JL, Jorritzo,JL, Rapini,RP, eds), 2nd edn. Oxford: Elsevier Health Sciences, 2008: 115-37.
78. Ormerod AD. Topical tacrolimus and pimecrolimus and the risk of cancer: how much cause for concern? *Br.J.Dermatol.* 2005; 153: 701-5.
79. van de Kerkhof PC, Barker J, Griffiths CE *et al.* Psoriasis: consensus on topical therapies. *J.Eur.Acad.Dermatol.Venereol.* 2008; 22: 859-70.
80. van de Kerkhof PC. Dithranol treatment in psoriasis: after 75 years, still going strong. *Eur.J.Dermatol.* 1991; 1: 79-88.
81. Menter A, Korman NJ, Elmets CA *et al.* Guidelines of care for the management of psoriasis and psoriatic arthritis Section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy. *J.Am.Acad.Dermatol.* 2010; 62: 114-35.
82. Palier AS, Siegfried EC, Eichenfield LF *et al.* Long-term etanercept in pediatric patients with plaque psoriasis. *J.Am.Acad.Dermatol.* 2010; 63: 762-8.

83. McCroskery P, Wallace CA, Lovell DJ *et al.* Summary of worldwide pediatric malignancies reported after exposure to etanercept. *Pediatr.Rheumatol.Online.J.* 2010; 8: 18.
84. Information for health care professionals. URL http://www.enbrel.com (last accessed 23 August 2010).
85. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br.J.Dermatol.* 2006; 155: 145-51.
86. Haavet OR, Straand J, Saugstad OD *et al.* Illness and exposure to negative life experiences in adolescence: two sides of the same coin? A study of 15-year-olds in Oslo, Norway. *Acta Paediatr.* 2004; 93: 405-11.
87. Ganemo A, Svensson A, Lindberg M *et al.* Quality of life in Swedish children with eczema. *Acta Derm.Venereol.* 2007; 87: 345-9.
88. Ben-Gashir MA, Seed PT, Hay RJ. Are quality of family life and disease severity related in childhood atopic dermatitis? *J.Eur.Acad. Dermatol.Venereol.* 2002; 16: 455-62.
89. Warschburger P, Buchholz HT, Petermann F. Psychological adjustment in parents of young children with atopic dermatitis: which factors predict parental quality of life? *Br.J.Dermatol.* 2004; 150: 304-11.
90. Evers AW, Lu Y, Duller P *et al.* Common burden of chronic skin diseases? Contributors to psychological distress in adults with psoriasis and atopic dermatitis. *Br.J.Dermatol.* 2005; 152: 1275-81.
91. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *Br.J. Dermatol.* 1995; 132: 942-9.
92. Holme SA, Man I, Sharpe JL *et al.* The Children's Dermatology Life Quality Index: validation of the cartoon version. *Br.J.Dermatol.* 2003; 148: 285-90.
93. Driessen RJ, Boezeman JB, van de Kerkhof PC *et al.* Three-year registry data on biological treatment for psoriasis: the influence of patient characteristics on treatment outcome. *Br.J.Dermatol.* 2009; 160: 670-5.
94. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. *Dermatologica* 1978; 157: 238-44.
95. van de Kerkhof PC. The Psoriasis Area and Severity Index and alternative approaches for the assessment of severity: persisting areas of confusion. *Br.J.Dermatol.* 1997; 137: 661-2.
96. Feldman SR, Fleischer AB, Jr., Reboussin DM *et al.* The self-administered psoriasis area and severity index is valid and reliable. *J.Invest Dermatol.* 1996; 106: 183-6.
97. Fleischer AB, Jr., Feldman SR, Rapp SR *et al.* Disease severity measures in a population of psoriasis patients: the symptoms of psoriasis correlate with self-administered psoriasis area severity index scores. *J.Invest Dermatol.* 1996; 107: 26-9.

Chapter 2

Epidemiology and clinical features



Chapter 2.1

No evidence found that childhood onset of psoriasis influences disease severity, future body mass index or type of treatments used

M.E.A. de Jager, E.M.G.J. de Jong, K.A.P. Meeuwis,
P.C.M. van de Kerkhof, M.M.B. Seyger

Journal of the European Academy of Dermatology and Venereology
(2010) 24: 1333 - 1339

Abstract

Background

In more than one-third of the psoriatic population, the first manifestations occur in childhood. Whether the age of onset of psoriasis influences the march of psoriasis is not known.

Objective

To describe the epidemiology and clinical features as well as prescribed treatments and familial distribution in psoriasis depending on the age of onset of the disease.

Methods

A structured questionnaire was sent to 5300 adult psoriatic patients. Respondents were divided into two groups: patients who experienced an onset of disease before the age of 18 years (childhood onset psoriasis (COP)) and patients with an onset of disease from the age of 18 years (adult onset psoriasis (AOP)).

Results

Questionnaires of 1926 patients (36.3%) were suitable for analysis. In 37.1% of patients, first signs of the disease occurred before the age of 18 years. COP occurs predominantly in females, has a longer delay in diagnosis and a higher frequency of familial distribution. The development of guttate and erythrodermic psoriasis in adulthood is more frequently seen in COP. In contrast to common believe, the type of psoriasis in COP often remains the same from childhood to adulthood. There was no evidence found that getting psoriasis before the age of 18 years influences the development of high body mass index in adulthood, disease severity in later life or type of treatments used.

Conclusions

The age of onset of psoriasis essentially does not influence the subsequent course of the disease in adulthood.

Introduction

Onset of psoriasis in childhood is not uncommon. In more than one-third of the psoriatic population, the first manifestations occur in childhood.[1-4] This points out the significance of knowledge about childhood onset psoriasis (COP). Studies have been conducted to assess the differences between early onset and late onset of psoriasis. Following the definition proposed by Henseler and Christophers,[5] most studies examined the differences in groups with an onset before or after the age of 30 years[6,7]. Only one study has been carried out to demonstrate differences between childhood onset (≤ 16 years) and adult onset of psoriasis.[4]
The purpose of the present study was to describe the epidemiology and clinical features of psoriasis of childhood and adult onset. Also, prescribed treatments as well as familial distribution in both groups were investigated.

Methods

A structured questionnaire was drawn up to assess epidemiology and clinical aspects of psoriasis. Patients were asked for age, gender, length, weight, marital status, age of onset of psoriasis, age of diagnosis of psoriasis, family history, severity of disease, joint/nail involvement and treatment history. A pilot study in 10 patients was conducted to assess the wording and the order of the questions as well as the time needed to complete the questionnaire. In the second phase, the questionnaire was sent to all 5300 members of the Dutch Psoriasis Society and responses were gathered from 14 February 2009 until 1 June 2009.
Patients were subdivided into two groups depending on the age of onset of disease. The first group consisted of patients who experienced an onset before the age of 18 years (childhood onset psoriasis (COP)); the second group comprised patients with an onset of disease from the age of 18 years (adult onset psoriasis (AOP)).
Body Mass Index (BMI) was calculated from current height and weight (BMI = weight / height^2). Severity of psoriasis was assessed by a Patient Global Assessment (PGA) and the Self-Administered Psoriasis Area and Severity Index (SAPASI).[8] The PGA was rated on a scale from clear to very severe. The SAPASI ranges from a minimum of 0 to a maximum of 72. Treatments used were stratified in six different groups: no treatment, emollients, topical 1st line therapy (cortico-steroids, vitamin D analogues, coal tar and calcipotriol/betamethasone), topical

2nd line therapy (dithranol and UV-therapy), systemic therapy (methotrexate, ciclosporin, retinoids and fumaric acid) and biologics.

Statistical analysis

Descriptive statistics were provided using mean (± SD) and range for numeric variables; frequencies and percentages were calculated for categorical variables. Missing values were not included to determine percentages. Correlation coefficients were calculated for associations between variables. Comparisons of numeric variables were analyzed with the (un)paired *t*-test; the χ^2 test was used to compare categorical variables. *P*-values < 0.002 were considered as statistically significant due to Bonferroni's correction for multiple testing. Statistical analysis was performed using SPSS16 (SPSS Inc., Chicago, IL, USA).

Results

Sample characteristics

Of the 5300 questionnaires sent, 1963 (37.0%) were returned. Due to missing values in age of onset, questionnaires of 1926 (36.3%) patients were suitable for analysis. The mean age of the respondents was 55.8 years (range 18 - 90 years; SD ± 13.4). Among the respondents, 929 (48.2%) were men and 997 (51.8%) were women. Mean duration of psoriasis was 30.4 years, ranging from 0 years to 82 years (SD ± 16). Mean age of onset of psoriasis was 25.5 years; mean age at diagnosis of psoriasis was 27.6 years of age. Mean age of onset was 26.8 years in men and 24.3 in women (unpaired *t*-test; $p < 0.001$). In 37.1% of patients, first signs of the disease occurred before the age of 18 years. Adolescent onset (13 - 18 years) was reported by 18.9% of patients and onset of the disease below the age of 13 years by 18.2%.

The total group of 1926 respondents was divided into two groups according to the age of onset of psoriasis: the COP-group (onset of psoriasis < 18 years) consisted of 715 patients (37.1%) and the AOP-group (onset of psoriasis ≥ 18 years) comprised 1211 patients (62.9%). Women represented 62.9% of the COP-group whereas in the AOP-group 45.2% were women (χ^2; $p < 0.001$). Most common skin types were types II (37.6%) and III (42.8%). Of the total group of respondents, 77.3% were married or cohabiting, whereas 13.2%, 5.9% and 3.6% was unmarried, widowed or divorced, respectively. A majority of both groups (> 75%) were married or cohabiting when filling out the questionnaire. There was no

difference between distribution in classes of marital status for COP or AOP (χ^2; p = 0.051). Mean BMI was 26.6 kg/m^2 (range 16.3 - 61.7; SD ± 4.6), which is regarded as overweight by the World Health Organization (WHO).[9] In the study population, 39.2% had a normal weight (BMI 18 - 25) and 59.6% were overweight (BMI ≥ 25). There was a weak correlation between age of onset and BMI (r = 0.074; p = 0.001). Moreover, mean BMI was significantly lower in COP than in AOP (26.2 (SD ± 4.8) vs. 26.8 (SD ± 4.5); unpaired t-test; p = 0.015).

Type of psoriasis

Plaque psoriasis was the most frequent current clinical type of psoriasis seen in 1302 (68.1%) of patients, followed by guttate psoriasis in 727 (38.0%) of patients. Erythrodermic psoriasis and pustular psoriasis were only seen in 7.3% and 5.0% of respondents, respectively.

Joint complaints were present in 818 (42.8%) patients. In addition, nail involvement was reported by 984 (51.5%) patients. Genital psoriasis was seen in 45.3% of respondents, whereas perianal psoriasis was seen in 30.0%. As displayed in Table 1, guttate and erythrodermic psoriasis are more frequently seen in adult life if the psoriasis started in childhood (χ^2; p <0.001). The occurrence of plaque psoriasis in adulthood was not statistically different for COP and AOP (χ^2; p = 0.213). Joint and nail involvement were seen in equal percentages in both groups. There were no significant differences in the prevalence of genital and perianal psoriasis in COP and AOP (χ^2; p = 0.564 and 0.152 respectively). In childhood, only 3.5% reported genital psoriasis and 1.4% reported perianal psoriasis. Patients with COP had plaque psoriasis approximately twice as much (69.9%) as guttate psoriasis (44.2%) in their adult ages. In a majority of patients with COP, the type of psoriasis at onset remains the same when the patient grows up. Precise percentages are displayed in Table 2.

Severity of psoriasis

Patient Global Assessment (PGA) of lesions in the past year was indicated as clear, minimal, mild, moderate, severe and very severe by 2.7%, 16.7%, 35.0%, 33.3%, 9.6% and 2.7% of the respondents, respectively (Table 3). Mean current SAPASI score was 6.6 (range 0 - 39.4; SD ± 4.4). SAPASI scores of COP and AOP were equal (6.9 vs. 6.4; unpaired t-test; p = 0.017). A weak correlation was found between age of onset and SAPASI (r = -0.086; p < 0.001). PGA of lesions in the past year was not significantly different between both groups (χ^2; p = 0.089). PGA of severity as experienced in childhood was usually mild to moderate.

Table 1 Clinical type of psoriasis

	Total		Childhood onset (COP)		Adult onset (AOP)		χ^2 test *p* - value
	n	%	n	%	n	%	
Clinical type as adult							
Plaque psoriasis	1302	68.1	496	69.9	806	67.1	0.213
Guttate psoriasis	727	38.0	314	44.2	413	34.4	< 0.001*
Pustular psoriasis	95	5.0	28	3.9	67	5.6	0.112
Erythrodermic psoriasis	140	7.3	74	10.4	66	5.5	< 0.001*
Joint involvement	818	42.8	500	42.3	318	43.1	0.708
Nail involvement	984	51.5	376	53.0	608	50.6	0.324
Clinical type as child							
Plaque psoriasis			462	67.4			
Guttate psoriasis			232	33.9			
Pustular psoriasis			16	2.3			
Erythrodermic psoriasis			40	5.8			
Joint involvement			41	6.0			
Nail involvement			96	14.2			
Unknown			50	7.3			

* Significant value

Table 2 Transition of type of psoriasis from childhood to adulthood in childhood onset psoriasis*

		Childhood (%)		
		PP	GP	PP & GP
Adulthood (%)	**PP**	57.1	15.7	16.7
	GP	6.3	48.5	21.8
	PP & GP	19.7	26.9	53.8
	Other	9.8	5.2	5.1
	Unknown	7.1	3.7	2.6

* Numbers presented as percentages of patients
PP plaque psoriasis
GP guttate psoriasis

Table 3 Severity of psoriasis

	Total (%)	Childhood onset (COP) (%)	Adult onset (AOP) (%)	χ^2 test p - value
	n = 1918	n = 712	n = 1206	
Current severity				0.089
Clear	2.7	3.1	2.5	
Minimal	16.7	16.0	17.1	
Mild	35.0	38.6	32.8	
Moderate	33.3	29.9	35.3	
Severe	9.6	9.4	9.8	
Very severe	2.7	2.9	2.5	
Severity in childhood		n = 695		
Clear		0.6		
Minimal		12.5		
Mild		26.0		
Moderate		31.9		
Severe		16.8		
Very severe		10.4		
Unknown		1.7		

Transition of severity according to the PGA was examined for COP (Table 4). Generally, the severity of psoriasis diminishes if compared between childhood and adulthood (paired t-test; $p < 0.001$). Transition from a moderate to mild form of psoriasis was reported by 13.8% of patients. On the other hand, 9.8% of the patients reported an increase in severity from mild to moderate. Severe psoriasis developed into mild psoriasis in 7.1% of patients. In 8.0% and 7.8% of patients who reported a mild or moderate disease, respectively, disease activity stayed in the same category when they reached their adult life.

Treatment

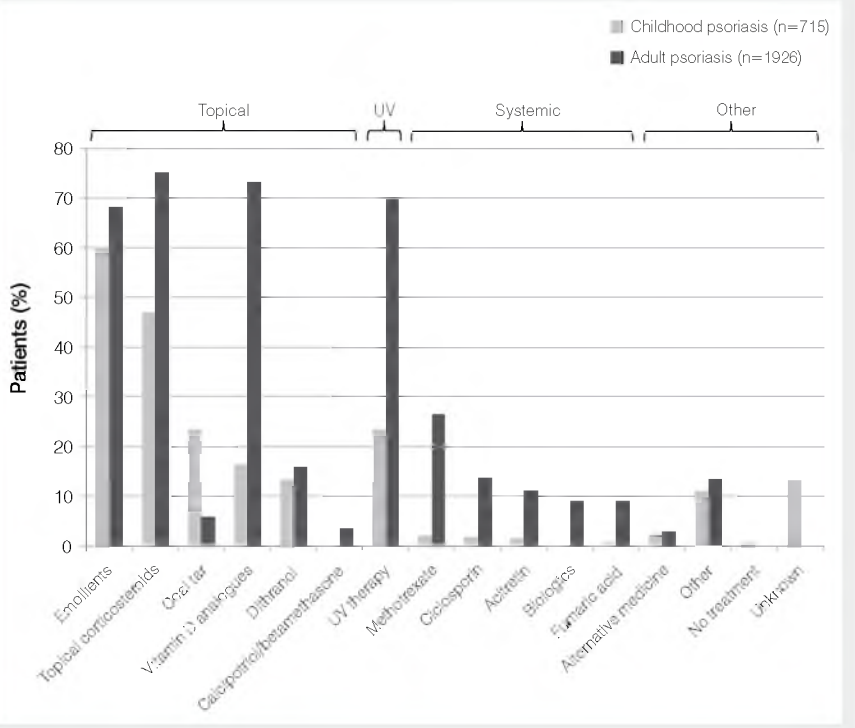
Prescribed treatments in adult psoriasis were mainly topical corticosteroids, vitamin D analogues, UV-therapy and emollients. In childhood psoriasis, mainly emollients, topical corticosteroids, UV-therapy and coal tar were prescribed (Fig. 1). After stratification of the treatments into groups according to potency, the most potent treatment used in adult life was determined. The most potent treatment

Table 4 Transition of severity of psoriasis from childhood to adulthood in childhood onset psoriasis (n= 681)*

		Severity in childhood (%)					
		Clear	Minimal	Mild	Moderate	Severe	Very severe
Severity in adulthood (%)	Clear	0.1	0.3	0.7	0.8	0.8	0.3
	Minimal	0	1.8	3.4	5.2	3.2	1.8
	Mild	0.1	4.8	8.0	13.8	7.1	3.4
	Moderate	0.3	4.1	9.8	7.8	3.5	2.8
	Severe	0	0.8	3.1	2.5	1.3	1.0
	Very severe	0	0.4	0.4	0.7	0.4	0.7

* Numbers presented as percentages of patients

Figure 1 Treatments prescribed in adult and childhood psoriasis



UV ultraviolet

used was not different between COP and AOP (χ^2; $p = 0.868$) (Table 5). Of patients with COP, 43.3% was prescribed the same potency of treatment in childhood as in adulthood, whereas 51.7% was prescribed a more potent treatment in adulthood compared to childhood. Only 5.0% of COP patients received a less potent treatment in adulthood than in childhood. Overall, treatments used in adulthood were more potent than in childhood in COP (paired *t*-test; $p < 0.001$). A majority of patients (i.e. 50.9%) indicated that they were currently treated by a dermatologist. On the other hand, 570 (29.8%) respondents were not currently treated by any medical professional for their skin disease. These percentages were not different between COP and AOP (χ^2; $p = 0.065$). If patients had severe psoriasis (SAPASI ≥ 10), they were more often under the care of a dermatologist for their skin disease than patients with a less severe form (χ^2; $p < 0.001$).

Table 5 Strongest treatment prescribed in adulthood

	Total (%) (n = 1909)	Childhood onset (COP) (%) (n = 711)	Adult onset (AOP) (%) (n = 1198)	χ^2 test *p* - value
				0.868
No treatment	0.4	0.6	0.3	
Emollients	2.0	2.0	2.1	
Topical 1st line therapy	51.3	51.2	51.4	
Topical 2nd line therapy	17.7	18.4	17.2	
Systemic treatment	19.1	18.4	19.4	
Biologics	9.5	9.4	9.6	

Delay in diagnosis

The period between the first skin lesions and the final diagnosis was designated as the delay in diagnosis. In the study population questioned, the mean delay in diagnosis was 2.1 years (range 0 - 59 years). In COP, delay in diagnosis was longer (3.1 years) compared with AOP (1.5 years) (unpaired *t*-test; $p < 0.001$).

Familial distribution

A family history of psoriasis was noted in 1268 patients (67.3%). Affected first-degree family members were seen in 33.3%, affected second-degree family members in 41.0% and affected third-degree family members in 22.9%. In 61.0% of patients in AOP, a positive family history of psoriasis was noted. In COP, this percentage was significantly higher (78.0%; χ^2; $p < 0.001$). See Table 6 for a subdivision in 1st, 2nd and 3rd degree family members affected.

Table 6 Familial distribution

	Total (%) (n = 1883)	Childhood onset (COP) (%) (n = 703)	Adult onset (AOP) (%) (n = 1180)	χ^2 test p - value
Family affected	67.3	78.0	61.0	< 0.001*
≥ one 1st degree member	33.3	39.9	29.5	< 0.001*
≥ one 2nd degree member	41.0	49.5	35.9	< 0.001*
≥ one 3rd degree member	22.9	30.3	18.6	< 0.001*

* Significant value

Precipitating factors

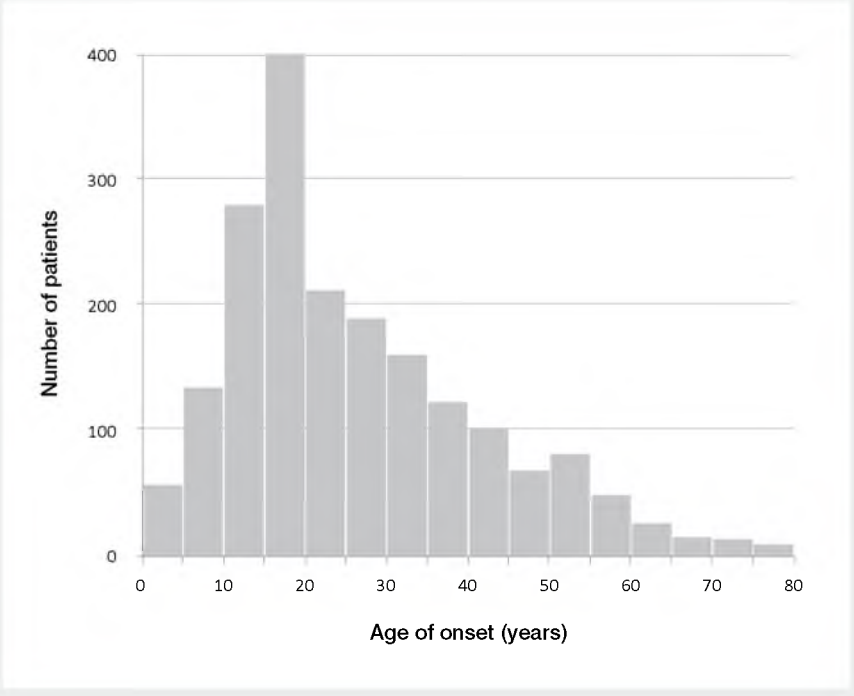
Psychological stress was regarded as the precipitating factor in 30.8% of cases, whereas an infection was only mentioned by 9.4% of patients. Injury to the skin and medication use as a precipitating factor were referred to by 6.4% and 4.6% of patients, respectively. Fifty-four percent could not recall a precipitating factor. No significant differences between COP and AOP were found for infections and injury to the skin as a precipitating factor (χ^2; $p = 0.002$ and $p = 0.457$, respectively). On the other hand, medication use and psychological stress were more often regarded as a precipitating factor in AOP (χ^2; $p < 0.001$ and $p < 0.001$).

Discussion

Studies have been conducted to examine the frequency of onset of psoriasis in childhood. Our study shows that in 37.1% of respondents, the first signs of the skin disease occurred before the age of 18 years. This accords with earlier observations,[1-4] which showed that 35 - 50% of all adult psoriasis patients already had psoriasis before the age of 20 years.

The two peaks in age of onset as found by Henseler and Christophers[5] could not be found in our study. Our results show only one peak around the age of 15 - 19 years (Fig. 2). This could be attributed to the fact that the mean age of respondents was 55.8 years, which, according to Henseler[5], is the age of the second expected peak in age of onset.

Figure 2 Age of onset of psoriasis



Several studies indicate that in children with psoriasis, BMI is often too high as compared with WHO standards.[9-11] Our study shows that COP does not seem to be an additional risk factor for a higher BMI in adult life.

In concordance with other studies[12-16], plaque psoriasis was the most frequent type of psoriasis seen in our study in both adults and children. Guttate psoriasis also often occurs in children; frequencies vary from 6.4% to 44%.[12;13;17] In the current study, 33.9% of patients are reported to have had guttate psoriasis in their childhood. This study also confirms that guttate psoriasis in adults occurs more often in COP than in AOP. Additionally, the type of psoriasis seen in childhood often remains the same in adulthood. This counts for plaque psoriasis as well as guttate psoriasis (57.1% and 48.5%). This is in contrast with the assumption in literature that guttate psoriasis resolves spontaneously or turns into plaque psoriasis in later life.[18-20] In the area of flexural, genital and perianal psoriasis not much research has been performed. Involvement of these areas was reported in 2 - 44% of adult psoriatic patients.[2,21] In the present study, perianal involvement was seen in 30% of patients, whereas genital areas were affected in 45.3%. In childhood, only a mere 1.4% and 3.5% of COP patients reported perianal or genital involvement, respectively.

After diagnosing a child with psoriasis, the course of severity is a frequently addressed subject by parents. There is no consensus in published literature whether onset of psoriasis in childhood predicts a milder or more severe form of psoriasis.[22-24] Our study indicates that the course of severity will generally not get worse from childhood to adulthood. In addition, there is no indication that the course of COP is worse than that of AOP.

Severity of psoriasis can also be determined by assessing the most potent treatment prescribed. In adulthood, there is no significant difference in potency of treatments between COP and AOP. On average, the most potent treatment prescribed increases with age in COP. This probably reflects the fact that physicians are more inclined to treat children with less potent therapies.

Diagnosis delay was significantly longer in COP than in AOP. As juvenile psoriasis sometimes has a different clinical appearance (nummular eczema-like), often itches and has a relatively low prevalence, general practitioners might miss the correct diagnosis.

In several studies, a higher percentage of familial distribution in COP has been reported.[6;17;25] Others found no statistical correlation between positive or negative family history and age of onset.[4] In the latter study, more COP patients had an affected 1st degree family member than the AOP patients. In the present study, a

positive correlation between COP and a positive family history was found, as well as a correlation between COP and affected 1st degree family members.
The present findings on gender distribution are consistent with other research, which found that in childhood more women are affected with psoriasis than men.[4;16;17;25]
A limitation of this study is that several data were obtained retrospectively. Therefore, a recall bias may be present. Also, there could be a selection bias because the questionnaires were sent to members of the Dutch Psoriasis Society. Patients in whom psoriasis only occurred in childhood are possibly missed, because they might not be members of the Dutch Psoriasis Society in adulthood. Confounding due to a shorter follow-up duration in AOP could have occurred. Despite of these possible biases, this study has uncovered several important factors of childhood and adult onset psoriasis in a large group of patients.
The present study indicates that the diagnosis of psoriasis in childhood is delayed as compared with diagnosis in adulthood. Therefore, educational programs for general practitioners and paediatricians should address the difficulties in diagnosing childhood onset psoriasis.
The main conclusions can be summarized as follows: (i) a positive family history of psoriasis is more often seen in patients with childhood onset psoriasis; (ii) the development of guttate psoriasis and erythrodermic psoriasis in adulthood is more frequent in childhood onset psoriasis; (iii) there are no differences in adult psoriatic patients with regard to severity of disease and frequency in the use of systemic treatments between childhood onset psoriasis and adult onset psoriasis; (iv) getting psoriasis in childhood does not seem to influence marital status as compared to adult onset psoriasis; (v) a strong correlation between childhood onset psoriasis and a higher BMI at adult age could not be found; (vi) type of psoriasis in childhood onset psoriasis remains the same from childhood to adulthood in a majority of patients. These conclusions can be helpful in daily practice when informing children with psoriasis and their parents.

Reference List

1. Swanbeck G, inerot A, Martinsson T *et al.* Age at onset and different types of psoriasis. *Br.J.Dermatol.* 1995; 133: 768-73.
2. Farber EM, Nall ML. The natural history of psoriasis in 5,600 patients. *Dermatologica* 1974; 148: 1-18.
3. Braun-Falco O, Burg G, Farber EM. [Psoriasis. A questionnaire study of 536 patients]. *Munch.Med.Wochenschr.* 1972; 114: 1105-10.
4. Raychaudhuri SP, Gross J. A comparative study of pediatric onset psoriasis with adult onset psoriasis. *Pediatr.Dermatol.* 2000; 17: 174-8.
5. Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. *J.Am.Acad.Dermatol.* 1985; 13: 450-6.
6. Ferrandiz C, Pujol RM, Garcia-Patos V *et al.* Psoriasis of early and late onset: a clinical and epidemiologic study from Spain. *J. Am.Acad.Dermatol.* 2002; 46: 867-73.
7. Ejaz A, Raza N, iftikhar N *et al.* Presentation of early onset psoriasis in comparison with late onset psoriasis: a clinical study from Pakistan. *Indian J.Dermatol.Venereol.Leprol.* 2009; 75: 36-40.
8. Feldman SR, Fleischer AB, Jr., Reboussin DM *et al.* The self-administered psoriasis area and severity index is valid and reliable. *J.Invest Dermatol.* 1996; 106: 183-6.
9. World Health Organization.*Website World Health Organization BMI classification* URL: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html (last accessed 20 August 2009).
10. Palier AS, Siegfried EC, Langley RG *et al.* Etanercept treatment for children and adolescents with plaque psoriasis. *N. Engl.J.Med.* 2008; 358: 241-51.
11. Boccardi D, Menni S, La VC *et al.* Overweight and childhood psoriasis. *Br.J.Dermatol.* 2009; 161: 484-6.
12. Morris A, Rogers M, Fischer G *et al.* Childhood psoriasis: a clinical review of 1262 cases. *Pediatr.Dermatol.* 2001; 18: 188-98.
13. Kumar B, Jain R, Sandhu K *et al.* Epidemiology of childhood psoriasis: a study of 419 patients from northern india. *Int.J.Dermatol.* 2004; 43: 654-8.
14. Nanda A, Kaur S, Kaur i *et al.* Childhood psoriasis: an epidemiologic survey of 112 patients. *Pediatr.Dermatol.* 1990; 7: 19-21.
15. al-Fouzan AS, Nanda A. A survey of childhood psoriasis in Kuwait. *Pediatr.Dermatol.* 1994; 11: 116-9.
16. Seyhan M, Coskun BK, Saglam H *et al.* Psoriasis in childhood and adolescence: evaluation of demographic and clinical features. *Pediatr.Int.* 2006; 48: 525-30.
17. Nyfors A, Lemholt K. Psoriasis in children. A short review and a survey of 245 cases. *Br.J.Dermatol.* 1975; 92: 437-42.
18. Leman JA. Recognition and treatment of psoriasis in children. *Current Paediatrics* 2003; 13: 418-22.
19. Martin BA, Chalmers RJ, Telfer NR. How great is the risk of further psoriasis following a single episode of acute guttate psoriasis? *Arch.Dermatol.* 1996; 132: 717-8.
20. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. *Lancet* 2007; 370: 263-71.
21. van de Kerkhof PC. Clinical features. in: *Textbook of psoriasis* (van de Kerkhof PC, ed), 2nd edn. Oxford: Blackwell, 2003: 3-29.
22. Rasmussen JE. Psoriasis in children. *Dermatol.Clin.* 1986; 4: 99-106.
23. Meiski JW, Stern RS. The separation of susceptibility to psoriasis from age at onset. *J. Invest Dermatol.* 1981; 77: 474-7.
24. Lomholt G. *Psoriasis: Prevalence, Spontaneous Course and Genetics.* GEC GAD, Copenhagen, Denmark, 1963.
25. Farber EM, Carlsen RA. Psoriasis in childhood. *Calif.Med.* 1966; 105: 415-20.

Chapter 2.2

Epidemiology and prescribed treatments in childhood psoriasis

a survey among medical professionals

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

Journal of Dermatological Treatment (2009) 20: 254 - 258

Abstract

Introduction

A study was conducted to explore epidemiology of childhood psoriasis in general practitioners (GPs) and dermatological practice in the region of our academic medical centre. The treatments used by GPs and dermatologists in juvenile psoriasis were investigated.

Methods

A questionnaire was sent to 229 GPs and 73 dermatologists. Questions were addressed about the prevalence of childhood psoriasis and treatments used in this disease.

Results

Seventy-three questionnaires were completed. The response rate was 17.0% for GPs and 46.6% for dermatologists. Almost one-third of all GPs have seen one or more patients with juvenile psoriasis under the age of 11 years in their own patient population, in contrast to more than 80% of the dermatologists. Extrapolating the results implied an estimated prevalence of childhood psoriasis of 0.17% in the overall Dutch population. Topical corticosteroids were used by 46.2% of GPs and by 91.2% of dermatologists. Vitamin D analogues were prescribed by GPs and dermatologists in 15.4% and 73.5%, respectively. Systemic medication for juvenile psoriasis was only used by 20.6% of dermatologists.

Conclusions

Calculated for the Dutch population, there should be approximately 27 500 children with psoriasis in The Netherlands are expected. Topical corticosteroids were the first-choice treatment in both GPs and dermatologists, whereas vitamin D analogues were used as a second-choice topical therapy. Systemic medication was only sparsely prescribed by dermatologists.

Introduction

Psoriasis is a chronic, inflammatory skin condition that affects about 2% of world's population. Onset in childhood is relatively common. Psoriasis accounts for 4% of dermatoses in children under 16 years of age in North America and Europe,[1] but prevalence in various parts of the world may differ[2]. According to the literature, 35 - 50% of all adult psoriasis patients already had psoriasis before the age of 20 years (Table 1).[3-6] In contrast to these facts, however, the impression of the authors is that children with psoriasis are rarely seen in out-patient dermatology clinics in The Netherlands. According to the Continuous Morbidity Registration Nijmegen (CMR-N),[7] in which, among other diseases, the prevalence of childhood psoriasis in a number of general practitioner practices is registered, the prevalence is still lower than can be expected based on published literature. These discrepancies raised the question as to what is the current situation in The Netherlands on prevalence of childhood psoriasis in general practitioners (GPs) and dermatological practices. In addition, we wanted to investigate the actual daily practice of treating childhood psoriasis in GP and dermatologist practice.

Table 1 Onset of psoriasis under the age of 20

		Onset < 20 years; % of adults with psoriasis
Swanbeck[3]	1995	50%
Farber[4]	1974	35%
Braun-Falco[5]	1972	38.5%
Raychaudhuri[6]	1995	46.3%

The two major aims of the present pilot study were to explore epidemiology of childhood psoriasis in GP and dermatological practice and to obtain an overview of treatments used by GPs and dermatologists in children with psoriasis.

Methods

A questionnaire was developed and sent to 229 GPs and 73 dermatologists in the region of our academic medical centre. The questionnaire was accompanied by an invitational letter explaining the purpose of the study. The first part of the questionnaire concerned the estimated prevalence of childhood psoriasis in the practice of GPs and dermatologists. In the second part, the treatments used in children with psoriasis were investigated. Questions were addressed about the number of children with psoriasis, age of children at diagnosis, exacerbating factors, familial components and treatments prescribed. Responses were gathered and data were analyzed. In the questionnaires, the number of affected children was requested by an estimation of number of patients according to four categories: no patients, one to five patients, six to 10 patients and more than 10 patients.

Results

A total of 73 questionnaires were returned; 39 by GPs (response rate 17.0%) and 34 by dermatologists (response rate 46.6%).
Of the 39 GPs, 30.8% (n = 12) has seen one or more patients with juvenile psoriasis under the age of 11 years in their own patient population. In the dermatologist practice, 82.4% (n = 28) of the dermatologists has one or more patients under the age of 11 years in their patient population. The number of patients seen in this age group is between one to five patients in the majority of dermatologist practices (i.e. 73.5%; n = 25). Further characteristics are depicted in Table 2.
From the results found in this study, the prevalence in the Dutch population can be calculated. After analyzing the results, this comes down to 0.92 children per GP under the age of 11 years with psoriasis and 2.26 children per GP from the age of 11 years with psoriasis. This results in a prevalence of 0.17% of childhood psoriasis in the overall Dutch population (8673 registered GPs [according to National Institute for Public Health and the Environment] and 16.4 million inhabitants in 2007 [according to Statistics Netherlands]). If the results are extrapolated across the Dutch population from the questionnaire presented, this implies a calculated prevalence of 0.37% and 1.09% for the age group of 0 - 10 years (2 166 000 children) and 11 - 19 years (1 793 000 children), respectively.

Table 2 Juvenile psoriasis divided per age category

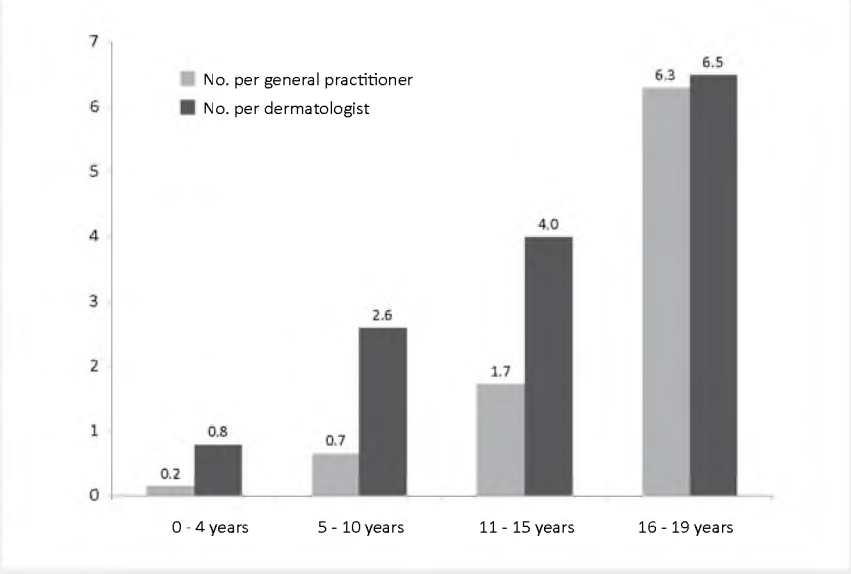
	GPs		Dermatologists	
No. of patients	**< 11 years**	**≥ 11 years**	**< 11 years**	**≥ 11 years**
0	27	13	6	1
1 - 5	12	24	25	16
6 - 10	0	2	3	9
> 10	0	0	0	23

GPs General practitioners

Age of onset was calculated per respondent (Figure 1). Most children were 16 - 19 years old when their psoriasis was diagnosed. This was the same for both populations (GP practice and dermatologist practice).

According to GPs, psoriasis was more often diagnosed in boys than in girls (61.9% versus 38.1%). By way of contrast, dermatologists reported a slightly higher percentage in girls (i.e. 57.3% versus 42.7%).

Figure 1 Age of onset of juvenile psoriasis



GPs and dermatologists reported virtually the same frequency of familial distribution among children with psoriasis: 48.4 and 52.1%, respectively.
Questions were asked about the correlation between infections and the onset of psoriasis. Eighty-one percent of GPs never found a correlation between the first appearance of skin lesions and an infection compared with 29.4% of dermatologists. Of dermatologists, 50% stated that in approximately 30% of their patients with juvenile psoriasis an infection played a role in the onset of the disease.
Nail deformities were only seen in 5.3 to 7.4% of patients. There was no difference in frequency between the groups seen by dermatologists or GPs.
The frequency of joint pain was also assessed. Almost 12% and 12.8% of GPs and dermatologists, respectively, have seen joint pain in one or more of their patients. Of the GPs who recorded joint pain, it was seen in 7.2% of patients. Only 1.2% of the children in the dermatologists' population mentioned joint pain.
Prescribed treatments for psoriasis are shown in Table 3. A large number (i.e. 46.2%) of GPs prescribed topical corticosteroids for juvenile psoriasis. Bland emollients were also used by 33.3% of GPs. Vitamin D analogues were only used by 15.4% of GPs. Dithranol (n = 1), coal tar shampoo (n = 1) and homeopathy (n = 3) were occasionally mentioned by GPs as a treatment option for childhood psoriasis.

Table 3 Treatments used for childhood psoriasis

Treatment	% of dermatologists	% of GPs
Corticosteroids	91.2	46.2
Vitamin D analogues	73.5	15.4
Phototherapy	64.7	0
Dithranol	20.6	2.6
Neotigason	8.8	0
Methotrexate	8.8	0
Excimer laser	2.9	0
Coal tar ointment at night	11.8	0
Fumaric acid	2.9	0
Homeopathy	0	7.7
Emollients	8.8	33.3

GPs General practitioners

The first-choice treatment among dermatologists was topical corticosteroids, applied by 91.2% of dermatologists, followed by vitamin D analogues (73.5%). A relatively high percentage (64.7%) of dermatologists also prescribed phototherapy for their patients. In contrast, systemic medication was only prescribed by 20.6% of the dermatologists.

Discussion

Reports on the age of onset of psoriasis vary among studies (Table 1). A large cohort study among 11 366 patients in Sweden showed that 30% of patients was younger than 15 years at the onset of their psoriasis and 20% had an onset between the age of 15 and 19 years.[3] Farber and Nall found that 10% of their whole examined population had an onset before the age of 10 years and 35% before the age of 20 years.[4] Others demonstrate an onset before the age of 16 years in 45% of patients.[8] Braun-Falco et al[5] and Raychaudhuri and Goss[6] have shown an onset before the age of 20 years in 38.5% and 46.3% of patients, respectively. Based on these articles and the assumption that 2% of the Dutch adult population has psoriasis, there should be approximately 140 000 children in The Netherlands with juvenile psoriasis. Our study shows a prevalence of 0.37% in the age group from 0 to 10 years old and a prevalence of 1.09% in the age group from 11 to 19 years old. When this is calculated for the Dutch population, there are approximately 27 500 children with psoriasis, which is substantially lower than numbers from the literature. One possibility is that literature published in the past overestimates the onset of psoriasis in childhood. However, it is also possible that our study underestimates the actual prevalence of children with psoriasis because this number only reflects the patients who are currently under the control of a GP. On the other hand, in a more recent study in the United Kingdom a prevalence of 0.55% was found of juvenile psoriasis in the age group 0 - 9 years.[9] In the same way, a prevalence of 1.37% was found in the age group 10 - 19 years old (Table 4), which is consistent with our findings.
As Table 2 indicates, young children with psoriasis (i.e. < 11 years) are more often seen by a dermatologist than a GP. In our own experience, younger children are more frequently referred to our academic centre for diagnosis, whereas older children are more often referred for the treatment of their already-diagnosed psoriasis. This could be caused by the sometimes different appearance of juvenile psoriasis. Also, because this disease has a low prevalence, GPs often do not consider or are uncertain about this diagnosis.

Table 4 Prevalence of childhood psoriasis by age group

	0 - 9 years	10 - 19 years
Gelfand[9]	0.55%	1.37%
RUNMC	0.37%	1.09%

RUNMC Radboud University Nijmegen Medical Centre

As in adults, genetic predisposition is also found in children. In the present study, a familial distribution with an average of 50.3% was described. Sigure and Rubins found evidence of psoriasis in family members in 26% of 252 children with psoriasis.[10] Others report higher percentages up to 71%.[6;11;12]

Several trigger factors in the development of psoriasis have been identified. Most important are stress, medication (e.g. antimalarials and withdrawal of oral corticosteroids) and trauma.[13;14] Beta haemolytic streptococcal pharyngitis or, less frequently, perianal streptococcal dermatitis can provoke guttate psoriasis.[15-17] Our study demonstrates that only a few GPs have linked the occurrence of psoriasis with a concurrent infection. Amongst dermatologists this share is bigger, possibly because dermatologists more often refer to this topic in their anamnesis.

As our study shows, nail psoriasis is mentioned by GPs and dermatologists in 5.3 - 7.4% of children with psoriasis. Accordingly, this has also been observed in other studies, in which 7 - 40% of patients under the age of 18 years had nail involvement. In these studies, the most frequently seen abnormality was pitting.[8;12;18-22]

Approximately 12% of GPs and dermatologists report that they have seen one or more juvenile patients with psoriasis and joint pain. The estimate of the prevalence of psoriatic arthritis among patients with psoriasis has varied from 6 to 39%.[23] Estimates of prevalence of psoriatic arthritis in children with psoriasis were not found in the literature published.

As expected, the most common treatments used were corticosteroids and vitamin D analogues. Of both treatments, topical corticosteroids are prescribed more often, even though vitamin D analogues are equally efficient and have fewer side effects than topical corticosteroids.[24-35] Another noteworthy fact is that systemic medication is sparsely prescribed, even by dermatologists. One can speculate whether this is due to milder disease in children, or maybe dermatologists have

reservations about treating children with systemic antipsoriatic medication. Further research is needed to clarify this matter.

Despite the limitations of this retrospective analysis (e.g. error in recall of information), the results found in this pilot study point out that there is a compelling need for more research on childhood psoriasis. In addition, guidelines for treatment are needed. It should also be taken into account that children will have to live longer with their disease than adults. Because of this, cumulative toxicity of treatments given is a major concern and long-term safety is an important issue.

Reference List

1. Beylot C, Puissant A, Biouiac P *et al.* Particular clinical features of psoriasis in infants and children. *Acta Derm.Venereol.Suppl (Stockh)* 1979; 87: 95-7.
2. Farber EM, Nall L. Childhood psoriasis. *Cutis* 1999; 64: 309-14.
3. Swanbeck G, inerot A, Martinsson T *et al.* Age at onset and different types of psoriasis. *Br.J.Dermatol.* 1995; 133: 768-73.
4. Farber EM, Nall ML. The natural history of psoriasis in 5,600 patients. *Dermatologica* 1974; 148: 1-18.
5. Braun-Falco O, Burg G, Farber EM. [Psoriasis. A questionnaire study of 536 patients]. *Munch.Med.Wochenschr.* 1972; 114: 1105-10.
6. Raychaudhurl SP, Gross J. A comparative study of pediatric onset psoriasis with adult onset psoriasis. *Pediatr.Dermatol.* 2000; 17: 174-8.
7. van Weel C. The Continuous Morbidity Registration Nijmegen: background and history of a Dutch general practice database. *Eur.J.Gen.Pract.* 2008; 14 Suppl 1: 5-12.
8. Nyfors A, Lemholt K. Psoriasis in children. A short review and a survey of 245 cases. *Br.J.Dermatol.* 1975; 92: 437-42.
9. Gelfand JM, Weinstein R, Porter SB *et al.* Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. *Arch.Dermatol.* 2005; 141: 1537-41.
10. Slgure S. Study on children psoriasis in Latvia. *Acta Dermatovenerol Alp Panonica Adriat.* 2002; 11: 45-9.
11. Morris A, Rogers M, Fischer G *et al.* Childhood psoriasis: a clinical review of 1262 cases. *Pediatr.Dermatol.* 2001; 18: 188-98.
12. Burgers SA, van Vloten WA. [Findings in children with psoriasis]. *Ned.Tijdschr.Geneeskd.* 1999; 143: 148-51.
13. Benoit S, Hamm H. Childhood psoriasis. *Clin.Dermatol.* 2007; 25: 555-62.
14. Burden AD. Management of psoriasis in childhood. *Clin.Exp.Dermatol.* 1999; 24: 341-5.
15. Honig PJ. Guttate psoriasis associated with perianal streptococcal disease. *J Pediatr.* 1988; 113: 1037-9.
16. Rasmussen JE. Psoriasis in children. *Dermatol.Clin.* 1986; 4: 99-106.
17. Patrizi A, Costa AM, Fiorillo L *et al.* Perianal streptococcal dermatitis associated with guttate psoriasis and/or balanoposthitls: a study of five cases. *Pediatr.Dermatol.* 1994; 11: 168-71.
18. Duperrat B, Puissant A, Oddoze L *et al.* [100 cases of psoriasis in children under 10 years old]. *Presse Therm.Clim.* 1969; 106: 129-34.
19. Farber EM, Nall L. Nall psoriasis. *Cutis* 1992; 50: 174-8.
20. Al-Fouzan AS, Nanda A. A survey of childhood psoriasis in Kuwait. *Pediatr.Dermatol.* 1994; 11: 116-9.
21. Nanda A, Kaur S, Kaur i *et al.* Childhood psoriasis: an epidemiologic survey of 112 patients. *Pediatr.Dermatol.* 1990; 7: 19-21.
22. Kumar B, Jain R, Sandhu K *et al.* Epidemiology of childhood psoriasis: a study of 419 patients from northern india. *Int.J.Dermatol.* 2004; 43: 654-8.
23. Gelfand JM, Gladman DD, Mease PJ *et al.* Epidemiology of psoriatic arthritis in the population of the United States. *J.Am.Acad.Dermatol.* 2005; 53: 573.
24. Kimball AB, Gold MH, Zib B *et al.* Clobetasol propionate emulsion formulation foam 0.05%: review of phase ii open-label and phase iii randomized controlled trials in steroid-responslve dermatoses in adults and adolescents. *J.Am.Acad.Dermatol.* 2008; 59: 448-54, 454.
25. Herz G, Blum G, Yawalkar S. Halobetasol propionate cream by day and halobetasol propionate ointment at night for the treatment of pediatric patients with chronic, localized plaque psoriasis and atopic dermatitis. *J.Am.Acad.Dermatol.* 1991; 25: 1166-9.
26. Felcht G. Psoriasis pustulosa in children. *Z Hautkr.* 1982; 57: 1694-6.
27. Oranje AP, Marcoux D, Svensson A *et al.* Topical calcipotriol in childhood psoriasis. *J.Am.Acad.Dermatol.* 1997; 36: 203-8.
28. Saggese G, Federico G, Battlni R. Topical application of 1,25-dlhydroxyvitamln D3 (calcltriol) is an effective and reliable therapy to cure skin lesions in psoriatic children. *Eur.J.Pediatr.* 1993; 152: 389-92.

29. Perez A, Chen TC, Turner A *et al.* Pilot study of topical calcitriol (1,25-dihydroxyvitamin D3) for treating psoriasis in children. *Arch. Dermatol.* 1995; 131: 961-2.
30. Darley CR, Cunliffe WJ, Green CM *et al.* Safety and efficacy of calcipotriol ointment (Dovonex) in treating children with psoriasis vulgaris. *Br.J.Dermatol.* 1996; 135: 390-3.
31. Fabrizi G. Calcipotriol and psoriasis in children. *J Dermatolog Treat.* 1997; 8: 221-3.
32. Park SB, Suh DH, Youn JI. A pilot study to assess the safety and efficacy of topical calcipotriol treatment in childhood psoriasis. *Pediatr.Dermatol.* 1999; 16: 321-5.
33. Travis LB, Silverberg NB. Psoriasis in infancy: therapy with calcipotriene ointment. *Cutis* 2001; 68: 341-4.
34. Patrizi A, Neri i, Rizzoli L *et al.* Topical calcipotriol in childhood psoriasis. *Acta Derm. Venereol.* 1999; 79: 477.
35. Choi YJ, Hann SK, Chang SN *et al.* infantile psoriasis: successful treatment with topical calcipotriol. *Pediatr.Dermatol.* 2000; 17: 242-4.

Chapter 2.3

Juvenile psoriasis in European and Asian children - similarities and differences

L.Y.T. Chiam, M.E.A. de Jager, Y.C. Giam, E.M.G.J. de Jong,
P.C.M. van de Kerkhof, M.M.B. Seyger

British Journal of Dermatology (2010) In press

Abstract

Background

The first manifestations of psoriasis begin in childhood in more than one-third of patients. However, epidemiological data of juvenile psoriasis are lacking.

Objective

To compare Dutch (NL group) and Singaporean (SG group) children with psoriasis with the aim to study the characteristics of juvenile psoriasis and to highlight similarities and differences between these different ethnic groups.

Methods

Data were collected from 207 patients younger than 18 years of age diagnosed with psoriasis from the Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands and the National Skin Centre, Singapore.

Results

A striking difference in familial distribution was found, with more Dutch children having an affected family member (73.3% vs. 13.6%). Presence of itch and triggering factors were more common among Dutch children (80% vs. 14.2% and 33.3% vs. 7.4%, respectively). However, both groups shared similar triggering factors like stress and infections. The mean age at presentation was 11.3 years in the NL group and 14.1 years in the SG group. The gender ratios in both groups were almost similar (NL group, men : women; 1 : 1.1; SG group, men : women; 1 : 1.4). Plaque psoriasis was the most common type in both cohorts while guttate and pustular psoriasis were rare. In both groups, the head, followed by the limbs, was the most common site involved. Similar proportion of children had nail involvement and psoriatic arthritis was rare in both countries.

Conclusion

The disparity in familial distribution may point to genetic differences between the two groups. Further studies to evaluate this difference in familial distribution may contribute to the understanding of the pathogenesis of psoriasis.

Introduction

Psoriasis is quite common in childhood with 31 - 45% of all adult psoriasis patients manifesting signs before the age of 20 years.[1,2] We present a comparative study between Dutch and Singaporean children with psoriasis. Our aim was to study the characteristics and epidemiology of juvenile psoriasis and to highlight the similarities and differences between European and Asian patients.

Materials and methods

Data were collected from patients younger than 18 years of age diagnosed with psoriasis in the two countries. In The Netherlands (NL group), all juvenile psoriasis patients presenting at the dermatology outpatient clinic at the Radboud University Nijmegen Medical Centre between 1 August 2008 and 31 December 2009, were included. Data were obtained directly from the patients for the purpose of this study. For Singaporean children with psoriasis (SG group), data were obtained from the electronic case files at the National Skin Centre from 1 January 2008 to 31 May 2009. The following characteristics were looked into: age at presentation, gender, age of onset, ethnicity, family history, triggering factors, presence of itch, type of psoriasis, sites of involvement, comorbidities and treatment modalities.

Results

A total of 207 patients were included in this study (NL group 45; SG group 162). The mean age at presentation for Dutch and Singaporean children was 11.3 years (range 4.3 - 17.9) and 14.1 years respectively (range 1.3 - 17.9). The male to female ratio was 1 : 1.1 (NL group) and 1 : 1.4 (SG group). The mean age of onset for Dutch patients was 7.6 years (range 0.5 - 14.8) and 10.3 years (range 0.4 - 17.1) for Singaporeans. The SG group consisted of Han Chinese (43.2%), Malays (30.9%), Indians (19.1%) and other ancestries (6.8%) (Table 1). The NL group mainly consisted of Caucasians (82.2%) (other ancestries 17.7%). Eighty-two percent of Dutch patients exhibited skin types II and III, while all Singaporean patients had skin type III to V.

Table 1 Comparison between Dutch patients and Singaporean patients

Characteristics	NL group	SG group
Number of patients	45	162
Men : Women	1 : 1.1	1 : 1.4
Mean age at presentation (range)	11.3 years (4.3 - 17.9)	14.1 years (1.3 - 17.9)
Mean age of onset (range)	7.6 years (0.5 - 14.8)	10.3 years (0.4 - 17.1)
Ancestry (%)		
Caucasian	82.2	0
Han Chinese	0	43.2
Malay	0	30.9
Indian	0	19.1
Other	17.8	6.8
Positive family history (%)		
Total group	73.3	13.6
Caucasian	83.8	-
Han Chinese	-	13.4
Malay	-	14
Indian	-	19.4
Other ancestries	25	-
Triggering factors (%)		
Total group	33.3	7.4
Caucasian	37.8	-
Han Chinese	-	4.5
Malay	-	10.0
Indian	-	12.9
Other ancestries	12.5	-
Presence of itch (%)		
Total group	80.0	14.2
Caucasian	83.8	-
Han Chinese	-	16.4
Malay	-	14
Indian	-	12.9
Other ancestries	62.5	-

Table 1 Continued

Characteristics	NL group	SG group
Type of psoriasis (%)		
Plaque	88.9	88.3
Guttate	2.2	4.3
Pustular	6.7	2.5
Sites involved (%)		
Head	88.9	75.9
Limbs	86.7	47.5
Intertriginous sites	24.4	5.6
Facial	24.4	27.3
Nail involvement (%)	22.2	35.8
Arthritis (%)	2.2	1.2

NL group Dutch patients
SG group Singaporean patients

A striking difference between the two populations was that only 13.6% of Singaporeans had a first- or second-degree relative affected by psoriasis compared to 73.3% of Dutch children (Caucasians 83.8% and other ancestries 25%). Within the Singaporean cohort, 13.4% of Han Chinese, 14% of Malays and 19.4% of Indians had a positive family history. Among patients who reported triggering factors, stress was the most common cause in both groups (NL group 66.7%; SG group 50%), followed by infections (NL group 20%; SG group 25%). However, a greater proportion (33.3%) of Dutch patients (Caucasians 37.8%; Other ancestries 12.5%) reported triggering factors compared to Singaporean patients (total group of Singaporean patients: 7.4%; Han Chinese 4.5%; Malays 10%; Indians 12.9%). Itch was experienced by 80% of Dutch children (Caucasians 83.8%; other ancestries 62.5%), but only by 14.2% of Singaporean children (Han Chinese 16.4%; Malays 14%; Indians 12.9%). In both groups, plaque psoriasis was the most common type of psoriasis (NL group 88.9%, SG group 88.3%), while few children presented with guttate psoriasis (NL group 2.2%; SG group 4.3%). Pustular psoriasis accounted for 6.7% of all cases among Dutch children and 2.5% among Singaporean children. The head was the most common site involved

in both groups (NL group 88.9%; SG group 75.9%), followed by the limbs (NL group 86.7%; SG group 47.5%). Intertriginous sites were involved in 24.4% of Dutch children compared to 5.6% of Singaporean children. Similar proportions of children had facial (NL group 24.4%; SG group 27.3%) and nail involvement (NL group 22.2%; SG group 35.8%), with pitting being the most common nail sign. Arthritis was rare in both groups (NL group 2.2%; SG group 1.2%) (Table 1).

Discussion

The most outstanding result of this study was the disparity in familial distribution between the two groups. It is known that 4.5% - 91% of psoriatic children have a family history of psoriasis.[3 9] The numbers found in the Dutch cohort (73.3%) compared favourably with data from Australia[3] (71%) and Faroe Islands[7] (91%), which have a predominantly Caucasian population. In contrast, data from the SG group (13.6%) are similar to data from Korea[8] (13.3%) and India[6;9] (4.5% to 9.8%). A Chinese survey revealed a positive family history of 34.4%.[5] The disparity in familial distribution between Caucasian and predominantly Han Chinese patients could be due to genetic differences. It has been demonstrated that IL23R polymorphisms could not be identified in the Han Chinese population with ankylosing spondylitis (AS), whereas IL23R polymorphisms were present in the Caucasian population.[10] As IL23R polymorphisms have also been identified in psoriasis as a common susceptibility factor, this same mechanism could explain the difference in familial distribution between our two populations.[11]

The mean age of onset of our patients was similar to recent published reports.[4;5] Marginally more women were found in both groups, which was also noted in other studies.[3;5;12] Although more Dutch patients recalled triggering factors, both our European and Asian children shared similar triggers of stress and infections. In India and Kuwait, itch was a frequent symptom, reported by 87.1% and 72% of patients, respectively.[6;13] The vast majority of our Dutch patients experienced itch, unlike Singaporean children.

In concordance with published reports,[3;5;6;13] plaque psoriasis was the most common type of psoriasis in both cohorts. A marked difference between our series and others was the number of cases of guttate psoriasis (NL group 2.2%; SG group 4.3%). This is lower than figures from previous reports, which ranged from 6.4% to 44%.[3;14] Pustular psoriasis is considered to be rare in children,[3;5] a finding noted in both groups. In contrast to studies from China and India[5,6], where

the most frequent site of involvement was the extremities, the head was most commonly involved in both our cohorts, followed by the limbs. Facial psoriasis was common in both groups, agreeing with earlier observations that facial involvement in juvenile psoriasis is prominent.[3;15] Intertriginous areas and genitals are commonly affected in children.[16;17] A quarter of Dutch patients had involvement of their intertriginous areas, unlike Singaporean children (5.6%). The proportion of children with nail involvement was similar to that reported by Nanda et al.[9] Our series also confirms that psoriatic arthritis is very rare in children.[4;16;17]

There were more Singaporeans in this study as the National Skin Centre is the main dermatology referral centre in Singapore, which has a population of 4.8 million. The Department of Dermatology of the Radboud University Nijmegen Medical Centre is an academic centre, serving a population of approximately 2 million. Recall bias due to the different types of data sources between the two groups may lead to differences in the more subjective and patient reported outcomes like itch and affected family members. In contrast, the more objective and clinically standardized outcomes like type and location of psoriasis were similar.

In summary, plaque psoriasis was the most common type in both European and Asian children while guttate psoriasis was rare. The groups shared similar gender ratios, sites of involvement and proportions with facial and nail involvement. Arthritis was rare in both groups. More European children reported positive family history, triggering factors and itch. The most noteworthy finding is the disparity in familial distribution between European and Asian children, which may to be due to genetic differences. Further genetic studies may contribute to the understanding of the pathogenesis of psoriasis.

Reference List

1. Farber EM, Carlsen RA. Psoriasis in childhood. *Calif.Med.* 1966; 105: 415-20.
2. Verbov J. Psoriasis in childhood. *Arch.Dis. Child* 1992; 67: 75-6.
3. Morris A, Rogers M, Fischer G *et al.* Childhood psoriasis: a clinical review of 1262 cases. *Pediatr.Dermatol.* 2001; 18: 188-98.
4. Seyhan M, Coskun BK, Saglam H *et al.* Psoriasis in childhood and adolescence: evaluation of demographic and clinical features. *Pediatr.Int.* 2006; 48: 525-30.
5. Fan X, Xiao FL, Yang S *et al.* Childhood psoriasis: a study of 277 patients from China. *J. Eur.Acad.Dermatol.Venereol.* 2007; 21: 762-5.
6. Kumar B, Jain R, Sandhu K *et al.* Epidemiology of childhood psoriasis: a study of 419 patients from northern india. *Int.J.Dermatol.* 2004; 43: 654-8.
7. Lomholt G. *Psoriasis: Prevalence, Spontaneous Course and Genetics.* GEC GAD, Copenhagen, Denmark, 1963.
8. Kim SK, Kang HY, Kim YC *et al.* Clinical comparison of psoriasis in Korean adults and children: correlation with serum anti-streptolysin O titers. *Arch.Dermatol.Res.* 2010; 302: 295-9.
9. Nanda A, Kaur S, Kaur i *et al.* Childhood psoriasis: an epidemiologic survey of 112 patients. *Pediatr.Dermatol.* 1990; 7: 19-21.
10. Davidson Si, Wu X, Liu Y *et al.* Association of ERAP1, but not iL23R, with ankylosing spondylitis in a Han Chinese population. *Arthritis Rheum.* 2009; 60: 3263-8.
11. Cargill M, Schrodi SJ, Chang M *et al.* A large-scale genetic association study confirms iL12B and leads to the identification of iL23R as psoriasis-risk genes. *Am.J.Hum.Genet.* 2007; 80: 273-90.
12. Raychaudhuri SP, Gross J. A comparative study of pediatric onset psoriasis with adult onset psoriasis. *Pediatr.Dermatol.* 2000; 17: 174-8.
13. Nanda A, Al-Fouzan AS, El-Kashlan M *et al.* Salient features and HLA markers of childhood psoriasis in Kuwait. *Clin.Exp.Dermatol.* 2000; 25: 147-51.
14. Nyfors A, Lemholt K. Psoriasis in children. A short review and a survey of 245 cases. *Br.J.Dermatol.* 1975; 92: 437-42.
15. Bernhard JD. Clinical differences in juvenile vs adult-onset psoriasis. *Br.J.Dermatol.* 1996; 135: 501-2.
16. Rogers M. Childhood psoriasis. *Curr.Opin. Pediatr.* 2002; 14: 404-9.
17. Burden AD. Management of psoriasis in childhood. *Clin.Exp.Dermatol.* 1999; 24: 341-5.

Chapter 3

Treatments

Chapter 3.1

Efficacy and safety of treatments in childhood psoriasis

a systematic literature review

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

Journal of the American Academy of Dermatology
(2010) 62: 1013 - 1030

Abstract

Background

Evidence-based recommendations for therapeutic decision making in childhood psoriasis are lacking.

Objectives

We sought to systematically review all available literature concerning treatment efficacy and safety in childhood psoriasis and to propose a recommendation for topical and systemic treatment of childhood psoriasis.

Methods

Databases searched were Pubmed, EMBASE and the Cochrane Controlled Clinical Trial Register. All studies reporting on efficacy and safety of all treatment options in childhood psoriasis were obtained and a level of evidence was determined.

Results

Literature search revealed 2649 studies, of which 64 studies met the inclusion criteria. The majority of topical and systemic therapies given in childhood psoriasis are efficacious. Short-term side effects were usually mild; long-term side effects were not described.

Limitations

Most conclusions formulated are not based on randomized controlled trials.

Conclusions

A rough summary of the proposed algorithm is as follows: first, calcipotriol with or without topical corticosteroids, followed by dithranol. Methotrexate is considered to be the systemic treatment of choice.

Introduction

Psoriasis is a chronic, inflammatory condition of the skin that affects about 2% of the general population. Onset in childhood is relatively common. Therefore, knowledge about therapeutic options in childhood psoriasis is important. Psoriasis accounts for 4% of dermatoses in children younger than 16 years in North America and Europe[1], but prevalence in various parts of the world may differ[2].

For treatment of patients with psoriasis, a spectrum of topical treatments, photo-(chemo)therapy, conventional systemic treatments and biologics is available. Treatment of childhood psoriasis has been described in a few reviews.[3-5] In these publications, the literature was not systematically reviewed and recommendations were not based on the principles of evidence-based medicine. To our knowledge, evidence-based guidelines describing the preferential order of treatments used for childhood psoriasis are not available.

The aim of this paper was to systematically review all available literature concerning efficacy and safety of all treatment options for childhood psoriasis. On this basis, a recommendation for the topical and systemic treatment of childhood psoriasis is made.

Methods

Three bibliographic databases were searched from January 1980 to September 2008: Pubmed, EMBASE and the Cochrane Controlled Clinical Trial Register. "Psoriasis", "child", and "treatment" were used as main key words, including all possible synonyms and antipsoriatic treatments (generic names and brand names). Languages were limited to English, German and Dutch. Full details on the search strategy are available from the corresponding author on request. Because the available literature about childhood psoriasis is limited, all available literature was reviewed, including case reports, case series, retrospective studies, open-label trials and randomized controlled trials (RCTs) concerning all different types of childhood psoriasis (e.g. plaque, guttate, pustular). Studies reporting on efficacy of all different treatment options for childhood psoriasis (age < 18 years) were included. Description of an outcome measure was mandatory. Outcome measures included Psoriasis Area and Severity Index (PASI); Physician Global Assessment (PGA); total severity score for erythema, scaling and thickness; and more subjective parameters such as percentage of clearance. Excluded were

studies describing antipsoriatic combination therapies (except for a combination with low- to moderate-potency topical corticosteroids) and studies concerning psoriatic arthritis. If the treatment regimen was unclear, the study was not included. Articles on both children and adults were only included if their data were reported separately. Studies on treatment modalities that were only described once as a monotherapy in the literature were also excluded. The bibliographies of all articles identified were checked for additional relevant articles that were not identified in the database search. After the initial search was performed, abstracts were screened for inclusion and exclusion independently by two reviewers (M.E.A.d.J. and M.M.B.S.). Of the 2649 studies found, 2533 were excluded because the abstracts showed that the studies were not eligible for inclusion. Subsequently, full text of the remaining articles was obtained. Data on study characteristics (both methodological and clinical) were independently extracted from each full text article by the same two reviewers (M.E.A.d.J. and M.M.B.S.) and recorded on a predesigned data extraction form. Finally, 64 articles were included in this review. Study characteristics included study design, study population, number of participants, duration of treatment, primary outcome, blinding, side effects, duration of remission and level of evidence (LOE). The LOEs were determined on the Oxford Centre for Evidence-based Medicine Levels of Evidence (Table 1).[6]

Table 1 Level of evidence (LOE)

1a	Systematic review of RCTs
1b	Individual RCT
2a	Systematic review of cohort studies
2b	Individual cohort study (including low quality RCT)
3a	Systematic review of case-control studies
3b	Individual case-control study
4	Case series
5	Case reports, expert opinion

Adapted from "Oxford Centre for Evidence-based Medicine Levels of Evidence" version May 2001[6]

RCT Randomized controlled trial

All case reports were considered to be equal to an expert opinion in the LOE. The conclusions are described in grades of recommendation (A to D) (Table 2), which are based on the LOE. In addition to the grade of recommendation, the numbers of patients treated were cited. In addition, a classification was made by the authors to match the different outcome measures. Clearance was defined as more than 90% improvement of the outcome parameters, whereas marked, moderate, slight, and poor improvement were defined as 70 to 90%, 50 to 70%, 30 to 50%, and less than 30% improvement of the outcome parameters, respectively, compared with baseline. Initially, a subdivision in age categories was aimed for, unfortunately, this proved impossible due to lack of age specification in the original articles. Differences among reviewers were resolved by discussion or by consulting a third investigator.

Table 2 Grades of recommendation

A	Studies with consistent LOE 1a and/or 1b (see Table 1)
B	Studies with consistent LOE 2a, 2b, 3a, or 3b; or extrapolations from studies with LOE 1a or 1b
C	Studies with LOE 4 or extrapolations from studies with LOE 2a, 2b, 3a, or 3b.
D	Studies with LOE 5 or troublingly inconsistent or inconclusive studies of any level

Adapted from "Oxford Centre for Evidence-based Medicine Levels of Evidence" version May 2001[6]

LOE Level of evidence

Results

In the results, all 116 full text articles are presented, as well as the reasons for exclusion of 52 articles. The details on the 64 studies included are summarized in Table 3.

Topical corticosteroids

Literature research revealed 11 studies.[7-17] Eight studies were excluded; two because there was no clear diagnosis of psoriasis[7, 8], one because of a vague description of treatment strategy[9], three because of the lack of an identified

outcome measure[10-12], one because of a concomitant HIV infection[16] and one because of the usage of an antipsoriatic combination therapy[13].

Herz et al[15] (LOE 4) published an open-label study on halobetasol cream 0.05%. In 72.7% of patients, lesions healed after two weeks of treatment.
A RCT performed by Kimball et al[14] (LOE 4) showed a treatment success in two of eight treated patients after two weeks of treatment with clobetasol propionate emulsion formulation 0.05%. Noteworthy is that these data come from a subgroup analysis with a control group of only one patient. Because of this, and the low number of children included in this study, the level of evidence was down-graded to level 4.
One case report (LOE 5) described the use of hydrocortisone 1% ointment in a two-year-old child with pustular psoriasis[17]; clearance was achieved with corticosteroid application.

In two of the included studies, concerning halobetasol cream 0.05% and clobetasol propionate emulsion 0.05%, adverse events were mentioned. Mild skin atrophy, erythema and depigmentation were described after a treatment period of two weeks.[14, 15] Burning at the application site was also mentioned as a side effect.[14] Unfortunately, adrenal axis testing was not performed in these studies.

Conclusion
Grade C
Number of patients treated with topical corticosteroids: 20
Halobetasol cream 0.05% and clobetasol propionate emulsion 0.05% seem to be efficacious treatments in childhood plaque psoriasis. Reported side effects were relatively mild in the treatment period of two weeks.

Vitamin D analogues

Ten publications on vitamin D treatment (eight calcipotriol and two calcitriol) in children with psoriasis were identified and assessed by data extraction forms.[18-27] One case report was excluded because of an unclear diagnosis.[27]

Oranje et al[18] (LOE 1b) performed a randomized double-blind study in 77 juvenile patients. Calcipotriol (50 μg/g) was applied twice daily for eight weeks. The investigators reported a decrease in PASI score of 52% in the vitamin D group (n = 43) and 37.1% in the placebo group (n = 34). This difference was not statistically

significant. However, reduction of the PGA at week eight and differences in morphology were statistically significant in favor of the active treatment group. Several other studies showed a positive effect of calcipotriol treatment on psoriatic lesions with an estimated outcome measure of clearance or marked improvement in at least 65% of cases.[21-26]

Calcitriol ointment (3 μg/g) was applied in a randomized double-blind study[19] (LOE 2b), showing a residual mild erythema in all 10 patients. Perez et al[20] performed a study with calcitriol of which the first part was placebo controlled (LOE 2b) and the second part was open label (LOE 4). The same four patients with plaque psoriasis participated in both studies. In the first part of the study, total severity score (range 0 - 9) was reduced from 6.0 to 2.5 in the active treatment group; in the placebo group the score decrease from 6.0 to 5.8. In the second part, a mean PASI reduction of 94% was seen after 18 months of treatment.

Irritant reactions were seen in four of the calcipotriol studies[18, 21, 23, 25]; moderate itching was seen in two studies[22, 23]. In total, 8 of 98 participants from three studies in which dropout was described ceased treatment because of side effects. No adverse events were reported in two studies.[19, 28] The two remaining studies did not mention side effects.[24, 26]

Conclusion

Grade A

Number of patients treated with calcipotriol: 155

Calcipotriol is an effective, reasonably well tolerated treatment option for childhood plaque psoriasis.

Grade B

Number of patients treated with calcitriol: 18

Calcitriol seems to be an effective treatment for childhood psoriasis with mild side effects.

Calcineurin inhibitors

Six studies were identified by literature search[29-34]; one was excluded because they used an antipsoriatic combination therapy[34]. Two studies were classified as LOE 4[29, 30] and three as LOE 5[31-33]; all described calcineurin inhibitor use in psoriasis facialis and inversa (including anogenital psoriasis).

In two non-randomized clinical trials treatment of facial and flexural psoriasis with tacrolimus 0.1% was evaluated.[29, 30] All patients showed clearance after a treatment period varying from 2 to 30 days. Tacrolimus 0.1% was also used in one case report.[33] The facial psoriasis cleared totally.
The two remaining studies were case reports on the use of pimecrolimus cream 1.0%.[31, 32] In both cases total remission was achieved.

Pruritus was noted as an adverse event in one tacrolimus study.[29] One patient discontinued the study because of this side effect. In two studies, calcineurin inhibitors (tacrolimus and pimecrolimus) were well tolerated.[30, 32] The other studies did not describe adverse events.[31, 33]

Conclusion
Grade C
Number of patients treated with tacrolimus: 20
Tacrolimus 0.1% seems an effective and safe therapeutic option for short-term treatment of facial and intertriginous childhood psoriasis. Long-term safety was not described.
No conclusion could be drawn for the use of pimecrolimus in childhood psoriasis because of a small number of patients.

Dithranol (anthralin)

Literature search revealed four studies describing dithranol treatment in children.[35-38] One was excluded because there was no outcome measure stated.[38] Two studies were classified as LOE 4[35, 36]; one was classified as LOE 5[37].

In one study short-contact dithranol treatment in 58 patients was reviewed retrospectively.[35] Of patients, 81% attained remission after a median treatment duration of two months. Guerrier and Porter[36] performed a multicentre open-label study in which they applied dithranol cream 0.1%. In all, 34 patients completed the study; mean percentage of clinical improvement (± SEM) was 64 (± 11) in centre 1 (n = 11) and 77 (± 4) in centre 2 (n = 23) after six weeks of treatment. A case report demonstrated a marked improvement of psoriatic lesions in a girl given the diagnosis of plaque psoriasis.[37] Dithranol was applied in relatively low concentration (0.016% - 0.0625%) for three months.
Overall, total remission was found in 47 of 58 patients[35] and marked improvement in 35 of 42 patients[36, 37].

Mild transient skin irritation (including burning sensation) and staining were the most frequently reported adverse events.[35, 36] In the case report of Schubert et al[37], no adverse effects were reported. In summary, 4% of all patients described ceased treatment because of side effects.

Conclusion

Grade C

Number of patients treated with dithranol: 100

Dithranol is an effective treatment in childhood psoriasis with a good margin of safety for short-term use.

Phototherapy

Of the 13 studies identified, five studies described treatment of childhood guttate and plaque psoriasis with narrowband (NB)-ultraviolet (UV) B radiation.[39-43] Photochemotherapy (psoralen plus UVA radiation (PUVA)) was the treatment examined in two case reports[44, 45] and one case series[46]. Five studies were excluded[47-51]: grounds for exclusion were systemic combination therapy in three cases[47-49], unclear diagnosis in one case[50] and unclear treatment regimen in another case[51]. All studies included were classified as LOE 4, except for two case reports which were classified as LOE 5.[44, 45]

Two open-label studies were performed. Jain et al[40] examined NB-UVB treatment for 12 weeks. PASI 90 was achieved in 60% of patients. In all, 10% had less than 50% improvement. It needs to be mentioned that all patients had skin type IV. Tay et al[43] also studied NB-UVB treatment. After a mean treatment of 11.9 weeks, clearance was reached in all patients.

Three retrospective case reviews concerning NB-UVB were found. The most recent study from 2006 reviewed 35 cases[41], which all had skin type V. Clearance or minimal residual disease was found in 63%, 9% had a poor response, and 28% of patient records could not be retrieved. Pasic et al[42] obtained records from 20 patients. PASI 90 was reached in 45% and 15% showed less than 50% improvement. al-Fouzan and Nanda[39] found a marked improvement in 88% of the 25 patients treated.

Of the case reports and case series, one used PUVA in plaque psoriasis[44], one used suit-PUVA in guttate psoriasis[45] and one used PUVA in erythema annulare centrifugum-type psoriasis[46]. In the former, lesions cleared after 18 treatments. In the second one, a marked improvement was seen after four weeks. The latter

showed clearance of lesions in two children after 36 days, in which 15 to 21 treatments were given.
In two studies erythema was reported in 10 to 30% of included patients.[40, 41] One study mentioned anxiety as adverse event in 6.75% of treated children.[41] In three studies[39, 42, 43], 55 patients in all, NB-UVB was well tolerated. The two patients who received PUVA therapy in the case series did not have any side effects.[46] The two case reports on PUVA treatmentdid not mention adverse events.[44, 45]

Conclusion
Grade C
Number of patients treated with NB-UVB: 110
NB-UVB shows good results in the treatment of plaque and guttate psoriasis in childhood and has comparatively mild side effects for the treatment duration studied.
As only four patients were treated with PUVA, a solid conclusion about the use of PUVA could not be drawn.

Antibiotics

Literature search revealed nine studies in which childhood psoriasis was treated with antibiotics.[52-60] Four were excluded because of various reasons: in one case report the treatment regimen was unclear[57] and three studies did not describe a clear outcome measure[58-60].

In one study thiamphenicol was used (LOE 4).[52] The two patients included received thiamphenicol 20 mg/kg/d; nevertheless, in both cases there was less than 50% clearance of lesions.
The four patients in the case series[53] (LOE 4) were all treated with erythromycin 50 mg/kg/d for two weeks; in all patients the psoriasis lesions disappeared completely. In the case report[54] (LOE 5), a patient with guttate psoriasis was treated with amoxicillin/clavulanic acid 50 mg/kg/d, which cleared all lesions after 20 days.
Rosenberg et al[55] performed an open-label trial (LOE 4) with both adults and children. Four juvenile patients were treated with penicillin or erythromycin for 10 to 14 days; for the last five days rifampin was added to both treatments. All patients responded very well to the treatment; three had a good response and one had an excellent response.

The only placebo-controlled study[56] (LOE 4) concerning the use of antibiotics in childhood psoriasis was performed in just three children. Group A received oral penicillin V or oral erythromycin (250 mg) four times a day for 14 days and a placebo twice a day for the last five days of the 14 days. Group B received oral penicillin V or oral erythromycin (250 mg) four times a day for 14 days and oral rifampin (300 mg) twice a day for the last five days of the 14 days. One child was randomized in group A and two were randomized in group B; in both groups no clinical change was seen. As only three children were treated in this trial, the LOE was level 4.

Gastrointestinal disturbance was mentioned as a side effect in the thiamphenicol study.[52] The remaining studies did not describe side effects.[53-56]

Conclusion

Grade C

Number of patients treated with antibiotics: 14

The efficacy of the use of antibiotics in childhood guttate psoriasis remains controversial.

Retinoids

In contrast to other treatment options, numerous studies regarding retinoid use in children with psoriasis were found. In all, 21 studies were identified[46, 49, 50, 52, 61-77], but five studies were excluded because of an unclear outcome measure[46, 67-70], nine because they used systemic antipsoriatic combination therapies[49, 50, 52, 71-76] and one case report because there was no clear diagnosis of psoriasis[77]. Therefore, six studies remained: four studies were classified as LOE 4[61, 63-65]; two were classified as LOE 5[62, 66].

In 1988 a retrospective review of 10 cases was performed[61] in which etretinate was used at an initial dose of 1 mg/kg/d, with a treatment duration varying from three weeks to more than 12 months. All patients with pustular psoriasis (n = 5) achieved complete clearance of lesions; in contrast, the erythrodermic psoriasis subgroup (n = 5) showed a complete clearance of lesions in only two and an improvement in the remaining three cases. Etretinate was also used in two case reports[62, 65], one case series[63] and one open-label trial[64]. In one case report[62] and one case series[63] 1.0 to 1.25 mg/kg/d was administered to patients with pustular psoriasis. All six patients had significant regression of erythroderma or even

clearance. In the open-label study[64], three patients with psoriasis erythroderma were treated with etretinate in a dosage ranging from 0.5 to 0.9 mg/kg/d. After four to five months of treatment, they all had complete clearance of erythema and scaling. Etretinate was used as a treatment for plaque psoriasis in two children.[65] It was administered at a dose of 25 mg/d for four to six weeks; after that, there was a dosage decrease to the maintenance dose of 12.5 mg/d. After 13 to 17 months, both patients had an excellent response. Only one case report described an excellent effect of 0.5 mg/kg/d acitretin in a child with erythrodermic psoriasis.[66] Complete remission was achieved after three months of treatment.

Cheilitis was often described as a side effect of etretinate[61, 63-65], as were pruritus and hair loss[61, 63, 64]. Skin fragility was described by two authors.[61, 64] In one case, focal osteoporosis was diagnosed 10 months after discontinuation of treatment.[61] Acitretin treatment was very well tolerated, without any side effects.[66] The authors of one case report concerning etretinate did not describe any adverse effects.[62]

Conclusion

Grade C

Number of patients treated with etretinate: 21

Etretinate is an effective treatment for pustular and erythrodermic psoriasis. However, side effects are frequently seen.

The usage of acitretin has not been sufficiently investigated in childhood psoriasis, therefore no conclusions could be drawn.

Ciclosporin

Literature search revealed nine studies on ciclosporin as a therapy for childhood psoriasis. Three case series[78-80] and six case reports[81-86] were identified. Five studies were excluded because of the use of antipsoriatic combination therapies.[80, 83-86] Of the remaining four articles, two were classified as LOE 4[78, 79] and two were classified as LOE 5[81, 82].

A case series of three patients with pustular psoriasis was described in which the administered dose was 1 to 2 mg/kg/d.[79] Complete disappearance of lesions was seen in two patients who were treated for 12 and 6 months, respectively. The third patient was still on treatment at time of publication, but showed a significant improvement after five months of treatment. Another patient with pustular psoriasis was treated with ciclosporin (3 mg/kg/d) in a different article.[81] Treatment duration

was 11 months, after which the patient was free of psoriasis. Ciclosporin in photosensitive psoriasis was also described in one patient[82], who received a dose of 3.5 mg/kg/d, leading to a complete remission after three weeks.
In contrast to the studies described above, one case series[78] did not show any response. Four patients were treated with ciclosporin, dosage ranging from 2.5 to 10 mg/kg/d, for 3.5 to 6 months. At the end of treatment none of these patients showed a response.

Ciclosporin was very well tolerated in one study.[79] The remaining three studies did not mention side effects.[78, 81, 82]

Conclusion
Grade C
Number of patients treated with ciclosporin: 9
The described efficacy of ciclosporin treatment in childhood psoriasis is ambiguous. Safety issues were sparsely described.

Methotrexate

Literature search revealed 10 studies concerning treatment of childhood psoriasis with methotrexate (MTX).[52, 87-95] Two were eliminated because of the use of anti-psoriatic combination therapies.[94, 95] The articles included consisted of four retrospectively reviewed case series (LOE 4)[52, 87-89] and four case reports (LOE 5)[90-93].

A review of 10 cases of childhood psoriasis[87] which were treated with MTX showed a complete clearance in 20%, almost complete clearance in 60% and no response in 10% of cases. MTX was given at an initial dose of 0.03 - 0.24 mg/kg/wk, and increased according to patient response to 0.10 - 0.41 mg/kg/wk; duration of treatment was 6 to 178 weeks. Authors of all other seven articles administered a MTX dosage between 0.2 and 0.4 mg/kg/wk. In all, 24 reviewed cases[88] received MTX treatment for two to 16 months with an average of 4.97 months. Almost all patients (i.e. 91.7%) reached PASI 75, whereas the remaining patients reached PASI 50. Another case series of seven patients showed control of disease, classified as more than 75% clearance of lesions and minimal scaling and erythema, in all patients after 6 to 10 weeks[89]. Subsequently, dosage was decreased to 2.5 mg/wk; total treatment duration was 31.2 - 46.4 weeks. In all other cases (n = 8)[52, 90-93], in which pustular psoriasis was treated, a marked improvement to complete remission was reached after 4 to 12 weeks of treatment.

Mild to severe nausea and vomiting were the most frequently reported side effects: in approximately 45% of patients.[87-89] In one study, transient minor elevation of liver enzymes in the serum was seen in 60% of patients; in one case leading to treatment cessation[87]. Two case reports and one case series failed to describe side effects.[52, 90, 93]

Conclusion

Grade C

Number of patients treated with methotrexate: 49

MTX is an effective treatment option in moderate to severe childhood psoriasis; the largest body of evidence is available for plaque psoriasis. Short-term side effects are usually mild and can be treated very well.

Biologics

Extensive literature review revealed 11 publications concerning treatment with biologics in children with psoriasis. They consisted of one double-blind RCT[96], two case series[97-99] and seven case reports[100-105]. Two case reports described two treatments; infliximab and etanercept.[99, 101] In one of these, the treatment period in which etanercept was used was excluded because no clear outcome measure was stated.[101] One study was excluded because of use of an antipsoriatic combination therapy.[99]

In the recent double-blind RCT[96] (LOE 1b), 211 children with plaque psoriasis were treated with once-weekly subcutaneous injections of etanercept (0.8 mg/kg), with a maximum of 50 mg. At week twelve, 27% of patients treated with etanercept reached PASI 90, in contrast to 7% of patients treated with placebo. Six other articles (LOE 4 and 5) were found regarding etanercept as a treatment in childhood psoriasis[97, 98, 100, 102, 103, 105]. Dosage was 0.4 mg/kg or 25 mg twice weekly with a treatment duration of 3 to 31 months. One patient with plaque psoriasis had no improvement of lesions after eight months of treatment[103]. Three patients had a marked improvement of lesions[97, 105] and in eight patients complete remission was achieved[97, 98, 100, 102].

Four case reports (LOE 5) described infliximab treatment in childhood psoriasis.[101, 103, 104, 106] Infliximab infusions were given in a dosage of 3.3 - 5 mg/kg. Infusions were administered at week 0, 2, and 6, and every 8 weeks thereafter. Treatment duration varied from only one administration to 10 months of treatment. All patients responded very well. The patient which was treated for 10 months had to finally

cease treatment because of loss of effect in the long term.[101]
Adverse events were described in the etanercept study[96] during the open-label part: four serious adverse events occurred, among which three infections (two cases of gastroenteritis and one of pneumonia). A serious yeast infection was described in another study with etanercept.[100] Mild injection site reaction was also seen in studies with etanercept.[98] In eight studies describing infliximab and etanercept no treatment-related side effects were described.[97, 101-106]

Conclusion

Grade A

Number of patients treated with etanercept: 117
Etanercept is an effective biologic in the treatment of plaque type childhood psoriasis. Short-term side effects during the treatment period described are usually infections.

A solid conclusion on the efficacy of infliximab could not be drawn on four patients.

Other topical and systemic therapies

The extensive literature search also revealed studies concerning Chinese medicine[107], excimer laser[108], tazarotene[109], wratizolin[110], fumaric acid[111], dapsone[52, 112] and prednisone[113, 114]. As none of these treatments were described in the literature as a monotherapy more than once, these studies were excluded.
Tonsillectomy as a treatment for childhood psoriasis was described twice in the found literature. Both were excluded, because they did not state a clear outcome measure.[115, 116]
The use of colchicine was described in two case reports.[117, 118] Both articles were classified as LOE 4. The first child[118] was administered a dose of 0.25 mg three times a day, whereas the second one[117] was administered a dose of 0.5 mg twice-daily. In both cases, the results were excellent.

Both patients treated with colchicine reported mild gastrointestinal symptoms.[117, 118]

Conclusion

Based on the paucity of evidence, a conclusion could not be drawn.

Table 3 Summary of included studies

Treatment	Author	LOE	Diagnosis (no. of patients)	Study type
Topical corticosteroids				
Halobetasol cream 0.05%	Herz et al[15]	4	PP (11)	OL
Clobetasol propionate emulsion formulation foam 0.05%	Kimball et al[14]	4	PP (9); Treated (8) Placebo (1)	RCT
Hydrocortison ointment 1%	Feicht[17]	5	GPP (1)	CR
Vitamin D analogues				
Calcipotriol 50 μg/g	Oranje et al[18]	1b	PP (77) Treatment (43) Placebo (34)	RCT
Calcipotriol 50 μg/g	Darley et al[21]	4	PP (66)	OL
Calcipotriol 0.005% in petrolatum	Fabrizi[22]	4	PP (4); IP (4); FP (2); PPP (2)	OL
Calcipotriol 50 μg/g	Park et al[23]	4	PP (12)	OL
Calcipotriol	Travis and Silverberg[24]	5	EP (1)	CR
Calcipotriol 50 μg/g	Patrizi et al[25]	4	IP (1); GP (4); PP (15)	OL
Calcipotriol	Choi et al[26]	5	GPP (1)	CR
Calcitriol ointment 3 μg/g	Saggese et al[19]	2b	PP (10)	RCT
Calcitriol 15 μg/g in petroleum jelly	Perez et al[20]	2b	PP (4)	PCT
Calcitriol 15 μg/g in petroleum jelly	Perez et al[20]	4	PP (4)	OL
Calcineurin inhibitors				
Tacrolimus 0.1%	Brune et al[29]	4	FP (5); IP (3); FP & IP (3)	OL
Tacrolimus 0.1%	Steele et al[30]	4	IP (8)	ROL
Tacrolimus 0.1%	Clayton et al[33]	5	FP (1)	CR
Pimecrolimus 1%	Amichai[31]	5	IP (1)	CR
Pimecrolimus 1 %	Mansouri and Farshi[32]	5	IP & FP (1)	CR

No. of patients (age)	Duration of treatment	Outcome
11 (5-15 y)	14 d	Healed: 72.7%; Marked improvement 18.2 %, Moderate improvement 9.1%
9 (12-17 y)	2 wk	Erythema, induration and thickness of lesions minimal or even cleared, and static PGA 'clear' or 'minimal': 25% of patients
1 (2 y)	3 wk	Clearance 100%
77 (2-14 y)	8 wk	PASI: -52% in treatment group, -37.1% in placebo group (= not significant); PGA treatment group: clearance 16%, marked improvement 44% (in placebo group clearance 0% and 44% marked improvement). Differences were statistically significant for redness and scaliness, but not for thickness.
66 (2-14 y)	8 wk	Mean (±SD) PASI 6.1 (±3.5) → 2.4 (±1.7) in 8 weeks. Clearance or marked improvement in 62-65%.
12 (4-12 y)	4-6 wk	Average PASI 3.28 → 0.28; after 2 weeks PASI50 in 60% of patients
12 (8-15 y)	12-106 wk	PASI 90: 8.3 %, PASI 75: 66.7%; Mean PASI: 18.4 (±12.2) → 6.5 (±5.4)
1 (4 mo)	3 mo	Clearance: 100%
20 (2-13 y)	8 wk	>75% improvement: 30%, 50-70% improvement: 45%
1 (6 mo)	1 mo	Lesions almost disappeared: 100%
10 (5-17y)	4 wk	Residual mild erythema: 100%
4 (13-17 y)	2 mo	Severity score (0-9) (±SD): Calcitriol: 6.0 (±0.4) → 2.5 (±0.6) ($p<0.025$). Placebo: 6.0 (±0.4) → 5.8 (±0.3) ($p=0.2$)
4 (13-17 y)	15-23 mo	Mean baseline PASI 11.0 ±2.2 reduced by 94% in 18 months
11 (2-17 y)	Maximum 180 d	12% Completely cleared; 88% 90-99% improvement; overall severity score clinically significant at day 30
8 (22 mo-16 y)	2 d - 2 wk	100% efficacy in 100%
1 (6 y)	3 d	Total clearance: 100%
1 (10 y)	3 wk	Lesions resolved: 100%
1 (10 y)	80 d	Lesions completely disappeared: 100% after 20 days

Table 3 Continued

Treatment	Author	LOE	Diagnosis (no. of patients)	Study type
Dithranol				
Dithranol cream 0.1%-2%	Zvulunov et al [35]	4	NS (58)	ROL
Dithranol cream 0.1% with 17% urea	Guerrier and Porter [36]	4	GP (6); PP (30); GP & PP (5)	OL
Dithranol 0.016%-0.0625%	Schubert et al [37]	5	PP (1)	CR
Phototherapy				
NB-UVB 50 mJ initial dose; increments of 10% at each session	Jain et al [40]	4	GP (2); PP (18)	OL
NB UVB	Tay et al [43]	4	GP (6); PP (4)	OL
NB-UVB: starting at 50% of MED with increments of 20%	Jury et al [41]	4	NS (35)	RCS
UVB	al-Fouzan and Nanda [39]	4	NS (25)	RCS
NB UVB 0.03-0.05 J/cm^2	Pasic et al [42]	4	GP (3); PP (17)	RCS
PUVA	Kim et al [44]	5	PP (1)	CR
PUVA 3.75 mg/L 8-MOP "suit" & 2.5-4.0 J/cm^2 UVA	Thappa and Laxmisha [45]	5	GP (1)	CR
PUVA 0.6 mg/kg methoxypsoralen & 0.5 – 1 Joule/cm^2 UVA	Braun-Falco et al [46]	4	EACP (2)	CS
Antibiotics				
Thiamphenicol 20 mg/kg	Juanqin et al [52]	4	GPP (2)	RCS
Amoxicillin/clavulanic acid 50mg/kg	Pacifico [54]	5	GP (1)	CR
Erythromycine 50 mg/kg	Patrizi et al [53]	4	GP (4)	CS
Rifampin	Rosenberg et al [55]	4	GP (3); PP (1)	RCT
Erythromycine or penicillin V with addition of rifampin	Vincent et al [56]	4	GP (3)	OL
Retinoids				
Etretinate 1 mg/kg	Rosinska et al [61]	4	EP (5); GPP (5)	RCS
Etretinate 10 mg	van de Kerkhof [62]	5	GPP (1)	CR
Etretinate 1 mg/kg	Pavicic et al [63]	4	GPP (5)	CS

No. of patients (age)	Duration of treatment	Outcome
58 (2-15 y)	Until remission, median 2 mo	Remission (defined as complete disappearance of scaling and erythema): 81%
41 (3-16 y)	6 wk, extension to 12 wk for 8 patients	At week 6: mean percentage clinical improvement (±SEM) 64 (±11) (n=11) & 77 (±4) (n=23)
1 (13 mo)	3 mo	Marked improvement: 100%
20 (6-14 y)	12 wk	>90% PASI reduction: 60%; 70-90% PASI reduction: 15%; 50-70% PASI reduction: 5%; <50% PASI reduction: 10%
10(14 mo-12y)	6-20 wk (mean 11.9)	Clearance: 100%
35 (4-16 y)	-	Clearance or minimal residual disease 63%; 9% no better; 28% no record
25 (5-12 y)	7.6 ± 4 wk (range 2-20 wk)	>80% clearance: 88%
20 (4-16 y)	10-39 treatments (mean 19)	PASI 90: 45%; PASI 70 65%; PASI 50: 85%
1 (17 y)	18 treatments	Lesions cleared: 100%
1 (10 y)	4 wk	PASI 14.2 → 1.6 (89% improvement)
2 (7-11 y)	15-21 treatments	Clearance: 100%
2 (2-12 y)	-	< 50 % Clearance: 100%
1 (7 y)	20 d	Cleared 100%
4 (5-10 y)	2 wk	Psoriasis completely resolved: 100%
4 (5-10 y)	5 d	Excellent response: 25 %, Good response: 75%
3 (12-15 y)	14 d	No clinical change: 100%
10 (3-15 y)	3 wk - 12+ mo	EP: 2 x complete clearing; 3x improvement; GPP: 5 x complete clearing
1 (1 y)	3 mo	Complete clearance: 100%
5 (3-11 y)	-	Complete and significant regression of erythroderma: 100%

Table 3 Continued

Treatment	Author	LOE	Diagnosis (no. of patients)	Study type
Etretinate 0.5-0.9 mg/kg	Kim et al [64]	4	EP (3)	OL
Etretinate 25 mg	van der Rhee et al [65]	4	PP (2)	CS
Acitretin 0.5 mg/kg	Salleras et al [66]	5	EP (1)	CR
Ciclosporin				
Ciclosporin A 1-2 mg/kg	Kilic et al [79]	4	GPP (3)	CS
Ciclosporin 3 mg/kg	Alli et al [81]	5	GPP (1)	CR
Ciclosporin 3.5 mg/kg	Torchia et al [82]	5	Photosensitive psoriasis (1)	CR
Ciclosporin 2.5-10 mg/kg	Mahe et al [78]	4	PPP (1); EP (1); PP (1); GPP (1)	CS
Methotrexate (MTX)				
MTX 0.03-0.24 mg/kg	Collin et al [87]	4	PP (10)	RCS
MTX 0.2-0.4 mg/kg	Kaur et al [88]	4	PPP (1); EP (3); PP (17); GPP (3)	RCS
MTX 0.2-0.4 mg/kg	Kumar et al [89]	4	EP (3); PP (2); GPP (2)	RCS
MTX 0.2-0.4 mg/kg	Juanqin et al [52]	4	GPP (4)	RCS
MTX 0.2 mg/kg	Kalla and Goyal [90]	5	GPP (1)	CR
MTX 0.4 mg/kg	Dogra et al [92]	5	GPP (1)	CR
MTX 0.3 mg/kg	Dogra et al [91]	5	GPP (1)	CR
MTX 0.3 mg/kg	Ivker et al [93]	5	GPP (1)	CR
Biologics				
Etanercept 0.8 mg/kg	Paller et al [96]	1b	PP (211) Treated (106) Placebo (105)	RCT
Etanercept 25 mg	Hoang and Burruss [100]	5	PP (1)	CR
Etanercept 0.4 mg/kg	Fabrizi et al [102]	5	EP (1)	CR
Etanercept 0.4 mg/kg	Papoutsaki et al [97]	4	GPP & EP (1); PPP (1); PP (2)	CS

No. of patients (age)	Duration of treatment	Outcome
3 (10-12 y)	4-5 mo	Clearance erythema and scaling: 100%
2 (8 y)	13-17 mo	Excellent: 100%
1 (4 y)	3 mo	Complete remission: 100%
3 (10 mo-16 y)	12, 6, 5 mo (last one still in treatment)	Almost completely disappeared: 33%; Completely disappeared: 66%
1 (9 y)	11 mo	Free of psoriasis: 100%
1 (15 y)	3 wk	Lesions healed: 100%
4 (2-10 y)	3.5-6 mo	No response: 100%
10 (5-16 y)	6-178 wk	Complete clearance: 20%; Almost complete clearance: 60%, No response 10 %
24 (2-14 y)	2-16 mo (mean 4.97)	PASI 75: 91.7%; PASI 50-75: 8.3%
7 (3-16 y)	6-10 wk to control: duration 31.2-46.4 wk (mean 38.8)	> 75% clearance: 100%
4 (2-12 y)	-	> 80% clearance: 100%
1 (4 y)	10+ wk	Marked improvement: 100%
1 (2 y)	-	Clearance of pustules: 100%
1 (4 y)	12 wk	Almost complete remission: 100%
1 (3 mo)	4 wk	Clearing: 100%
211 (4-17 y)	12 wk blind; 24 wk open; 12 wk blind	Treatment-group: PASI 90: 27% (at week 12); PASI 75: 57% (at week 12) Placebo-group: PASI 90: 7% (at week 12); PASI 75: 11% (at week 12)
1 (14 y)	8 mo	Clearance of all lesions except those plaques on elbows & knees 100%
1 (22 mo)	6 mo	PASI 37 → 1.2 in 12 weeks
4 (6-15 y)	24-86+ wk	PASI: 25.8 → 0; 21.2 → 0; 27.4 → 5.9; 9.2 → 2.2

Table 3 Continued

Treatment	Author	LOE	Diagnosis (no. of patients)	Study type
Etanercept 0.4 mg/kg	Safa et al [105]	5	EP (1)	CR
Etanercept 25 mg	Farnsworth et al [103]	5	PP (1)	CR
Etanercept 0.4 mg/kg	Kress [98]	4	PP (3)	CS
Infliximab 5 mg/kg	Farnsworth et al [103]	5	PP (1)	CR
Infliximab 3.3 mg/kg	Menter and Cush [104]	5	PP & PPP (1)	CR
Infliximab 5 mg/kg	Pereira et al [101]	5	GPP (1)	CR
Infliximab 5 mg/kg	Weishaupt et al [106]	5	GPP (1)	CR
Other therapies				
Colchicine 0.5 mg	Zachariae et al [118]	5	GPP (1)	OL
Colchicine 0.25 mg	Wahba and Cohen [117]	5	GP & PP (1)	OL

CR case report
CS case series
EACP erythema annulare centrifugum-type psoriasis
EP erythrodermic psoriasis
FP facial psoriasis
GP guttate psoriasis
GPP pustular psoriasis
IP inverse psoriasis
LOE level of evidence
MED minimal erythema dose
MOP methoxypsoralen
MTX methotrexate
NB narrowband
NS not specified
OL open-label trial
PASI Psoriasis Area and Severity Index
PCT placebo-controlled trial
PGA Physician Global Assessment
PP plaque psoriasis
PPP palmoplantar psoriasis
PUVA psoralen plus ultraviolet A
RCS retrospectively reviewed case series
RCT randomized controlled trial
ROL retrospectively reviewed open-label trial
UV ultraviolet

No. of patients (age)	Duration of treatment	Outcome
1 (7 y)	6+ mo	Significant clinical improvement: 100%
1 (14 y)	8 mo	No improvement:100%
3 (9-16y)	27; 27; 30 mo	Almost clear 100%
1 (14 y)	6+ wk	Marked clearing of psoriasis: 100%
1 (13 y)	30+ wk	Trunk and limb plaques cleared, with significant improvement of the palmoplantar disease: 100%
1 (3 y)	10 mo	Completely clear: 100% in 2 wks, after 13 wks flare, after 10 mo insufficient effect
1 (16 y)	1 administration	Pustules resolved, erythema lightened: 100%
1 (12 y)	-	Symptoms disappeared: 100%
1 (4 y)	2 mo	Excellent: 100%

Discussion

Literature concerning treatment efficacy and safety in childhood psoriasis is diverse. After thorough inspection of all literature, 64 studies could be included, describing 646 children in total. Of these 64 studies, only six were RCTs. Because of the paucity of RCTs, all LOEs were included in this study.

Most literature concerns induction of remission, rather than maintenance therapy. Although some studies describe treatment durations of up to almost 3.5 years[87], these are exceptional and comprise only a few cases. Similar data on the follow-up period and duration of remission are limited, as they are on the safety issues described. None of the studies mentioned long-term safety profiles of the treatments described. Thus, in the discussion below, efficacy refers to the induction of remission, and safety is restricted to short-term safety.

Implementation of the results on topical corticosteroids, calcipotriol, calcineurin inhibitors and dithranol and their grades of recommendation in a treatment algorithm is discussed below.

Long-term side effects of phototherapy (e.g. photo ageing, carcinogenesis) have been seen in the treatment of adults[119] and children[120]. A relationship between melanoma and UV radiation has been found.[121] In addition, anxiety can be a significant problem in the paediatric group.[41] Given the aforementioned considerations, we conclude that NB-UVB should not be used in toddlers and infants. In adolescents, it should be used carefully, especially if they have fair skin.

In contrast to two earlier publications (including a Cochrane review) in which treatment with antibiotics in guttate psoriasis was reviewed[122, 123], we only included studies reporting on the efficacy in children. The use of antibiotics in the treatment of childhood guttate psoriasis remains controversial.

Of the 22 children in whom retinoid treatment was described, 21 were treated with etretinate and its metabolite acitretin was administered to only one patient. All patients but two had pustular and erythrodermic psoriasis. An apprehension is that skeletal toxicities might occur in children on long-term retinoid therapy. In addition, all retinoids are known to be potent teratogens and the major concerns in treating fertile women with oral retinoids are fetal deformities.[124] Therefore, we advise to save retinoids for short-term treatment of pustular or erythrodermic psoriasis in infants and male adolescents.

The efficacy of ciclosporin in childhood psoriasis remains unclear. In the articles included, safety issues are rarely discussed. Studies have been published in which the drug is tolerated by children (in which ciclosporin was indicated for

another disease) at least as well as in adults.[125] Treatment periods of up to one year have been described in which the drug was well tolerated.[126] Nonetheless, caution should be taken, particularly in children, because ciclosporin has the potential of cumulative toxicity.[125] Based on the ambiguous efficacy as described in this review, treatment with ciclosporin should not be the systemic therapy of choice in childhood psoriasis.

The efficacy and safety of MTX in childhood psoriasis was described in a total of 49 patients. Long-term safety and efficacy of MTX in the treatment of childhood psoriasis has not been investigated to date. However, in juvenile idiopathic arthritis, this drug was often used for long periods of time and has a track record of safe and effective use.[127] In juvenile idiopathic arthritis MTX is described as the second-line agent of choice.[128] In case of a moderate to severe childhood plaque psoriasis, which is recalcitrant to local therapies, we consider MTX to be the systemic treatment of choice.

The efficacy and short-term safety of etanercept were studied in a large double-blind RCT (n = 211). Long-term side effects and risks were not described, as this drug has only recently been introduced for the indication of childhood psoriasis. In patients with juvenile rheumatoid arthritis, a study into safety and efficacy of up to eight years of continuous etanercept therapy was recently published. The authors state that long-term continuous treatment with etanercept was well tolerated for up to eight years, without an increase in the rates of serious adverse events over time.[129] Although this new treatment modality for childhood psoriasis seems very promising, vigilance is called for.

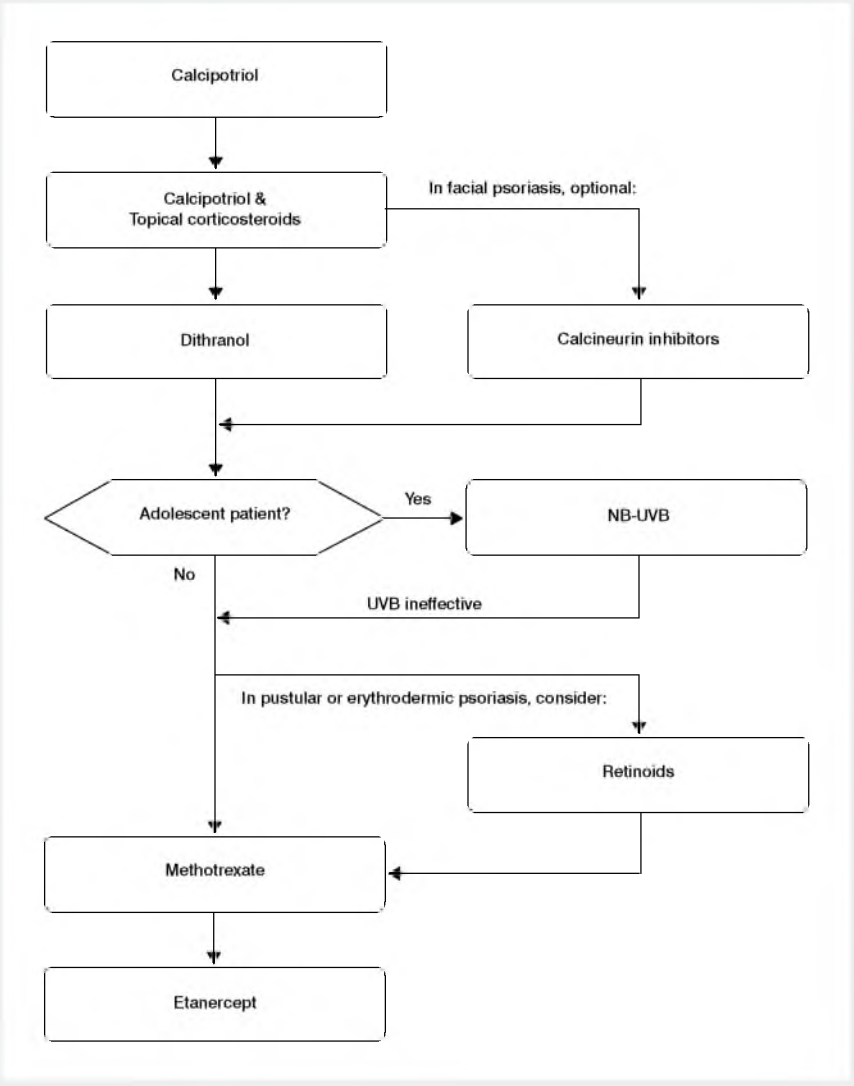
In conclusion, all available literature concerning treatment modalities of childhood psoriasis was described and assessed in this systematic review. Unfortunately, most of the evidence is of a low level, i.e. grade C and D. Only some studies describing treatment with calcipotriol and etanercept have higher LOEs (i.e. level A). Clearly, there is a need for randomized placebo-controlled trials in childhood psoriasis.

In Fig. 1 we present our recommendations based on the literature review described above. With these recommendations we hope to stimulate a fruitful discussion on this very important issue.

The treatment of choice in mild or moderate childhood psoriasis should be calcipotriol, if necessary, combined with mild to moderate topical corticosteroids. In case of treatment-resistant flexural and/or facial psoriasis, tacrolimus 0.1% can be added to the treatment regimen. If this treatment regimen is not effective, or if psoriasis is moderate to severe, treatment with dithranol is recommended. Only

in case of lack of efficacy of these modalities, treatment with NB-UVB can be considered in adolescents, but only for a short duration. Although controversial, the use of antibiotics can be considered in case of guttate psoriasis and suspicion of a streptococcal infection.
Of the systemic treatments, MTX is regarded as the therapy of choice. Retinoids should be considered in cases of pustular and erythrodermic psoriasis. Treatment with ciclosporin should only be deliberated in exceptional cases. Etanercept is a very promising new treatment modality, which should be considered as a third-line drug. Specialized centres should make alliances to provide an extensive database in which all systemic treatments will be recorded. Only then can evidence-based data be extracted on which solid conclusions can be drawn in the future.

Figure 1 Treatment algorithm



Reference List

1. Beylot C, Puissant A, Bioulac P, Saurat JH, Pringuet R, Doutre MS. Particular clinical features of psoriasis in infants and children. *Acta Derm Venereol Suppl (Stockh)* 1979; 87:95-7.
2. Farber EM, Nall L. Childhood psoriasis. *Cutis* 1999; 64:309-14.
3. Burden AD. Management of psoriasis in childhood. *Clin Exp Dermatol* 1999; 24:341-5.
4. Benoit S, Hamm H. Childhood psoriasis. *Clin Dermatol* 2007; 25:555-62.
5. Zappel K, Sterry W, Blume-Peytavi U. [Therapy options for psoriasis in childhood and adolescence]. *J Dtsch Dermatol Ges* 2004; 2:329-42.
6. Oxford Centre for Evidence-Based Medicine Levels of Evidence (May 2001). Centre for Evidence-Based Medicine website. URL: http://www.cebm.net/index.aspx?o=1025 (last accessed 19 Feb 2009).
7. Rattet JP, Headley JL, Barr RJ. Diaper dermatitis with psoriasiform iD eruption. *Int J Dermatol* 1981; 20:122-5.
8. Watanabe M, Tabata N, Tagami H. Explosive diaper pustular psoriasis. *Pediatr Dermatol* 2002; 19:564-5.
9. Carnero L, Betlloch i, Ramon R, Albares MP, Guijarro J, Botella R. Psoriasis in a 5-month-old girl with HiV infection. *Pediatr Dermatol* 2001; 18:87-9.
10. Watabe H. Childhood psoriasis associated with Turner syndrome. *J Dermatol* 2006; 33:896-8.
11. Berzel HG. Psoriasis vulgaris: The case of a 5 year old child. *TW Padiatrie* 1992; 5:56-9.
12. Allen HB, Honig PJ. Scaling scalp diseases in children. *Clin Pediatr* 1983; 22:374-7.
13. Guill CL, Hoang MP, Carder KR. Primary annular plaque-type psoriasis. *Pediatr Dermatol* 2005; 22:15-8.
14. Kimball AB, Gold MH, Zib B, Davis MW. Clobetasol propionate emulsion formulation foam 0.05%: review of phase ii open-label and phase iii randomized controlled trials in steroid-responsive dermatoses in adults and adolescents. *J Am Acad Dermatol* 2008; 59:448-54, 454.
15. Herz G, Blum G, Yawalkar S. Halobetasol propionate cream by day and halobetasol propionate ointment at night for the treatment of pediatric patients with chronic, localized plaque psoriasis and atopic dermatitis. *J Am Acad Dermatol* 1991; 25:1166-9.
16. McAleer P, Chu P, White SM, Don PC, Bamji M, Weinberg JM. Psoriasis associated with human immunodeficiency virus in an infant. *Pediatr Dermatol* 1999; 16:144-5.
17. Feicht G. Psoriasis pustulosa in children. *Z Hautkr* 1982; 57:1694-6.
18. Oranje AP, Marcoux D, Svensson A, Prendiville J, Krafchik B, Toole J, et al. Topical calcipotriol in childhood psoriasis. *J Am Acad Dermatol* 1997; 36:203-8.
19. Saggese G, Federico G, Battini R. Topical application of 1,25-dihydroxyvitamin D3 (calcitriol) is an effective and reliable therapy to cure skin lesions in psoriatic children. *Eur J Pediatr* 1993; 152:389-92.
20. Perez A, Chen TC, Turner A, Holick MF. Pilot study of topical calcitriol (1,25-dihydroxyvitamin D3) for treating psoriasis in children. *Arch Dermatol* 1995; 131:961-2.
21. Darley CR, Cunliffe WJ, Green CM, Hutchinson PE, Klaber MR, Downes N. Safety and efficacy of calcipotriol ointment (Dovonex) in treating children with psoriasis vulgaris. *Br J Dermatol* 1996; 135:390-3.
22. Fabrizi G. Calcipotriol and psoriasis in children. *J Dermatolog Treat* 1997;8:221-3.
23. Park SB, Suh DH, Youn JI. A pilot study to assess the safety and efficacy of topical calcipotriol treatment in childhood psoriasis. *Pediatr Dermatol* 1999; 16:321-5.
24. Travis LB, Silverberg NB. Psoriasis in infancy: therapy with calcipotriene ointment. *Cutis* 2001; 68:341-4.
25. Patrizi A, Neri i, Rizzoli L, Varotti C. Topical calcipotriol in childhood psoriasis. *Acta Derm Venereol* 1999; 79:477.
26. Choi YJ, Hann SK, Chang SN, Park WH. infantile psoriasis: successful treatment with topical calcipotriol. *Pediatr Dermatol* 2000; 17:242-4.

27. Patrizi A, Bardazzi F, Neri i, Fanti PA. Psoriasiform acral dermatitis: a peculiar clinical presentation of psoriasis in children. *Pediatr Dermatol* 1999; 16:439-43.
28. Perez A. Calcitriol cream shows promise for psoriasis in children. *Am Fam Physician* 1994;50:1068
29. Brune A, Miller DW, Lin P, Cotrlm-Russi D, Palier AS. Tacrolimus ointment is effective for psoriasis on the face and intertriginous areas in pediatric patients. *Pediatr Dermatol* 2007; 24:76-80.
30. Steele JA, Choi C, Kwong PC. Topical tacrolimus in the treatment of inverse psoriasis in children. *J Am Acad Dermatol* 2005; 53:713-6.
31. Amichal B. Psoriasis of the glans penis in a child successfully treated with Elidel (pimecrolimus) cream. *J Eur Acad Dermatol Venereol* 2004; 18:742-3.
32. Mansourl P, Farshi S. Pimecrolimus 1 percent cream in the treatment of psoriasis in a child. *Dermatol Online J* 2006; 12:7.
33. Clayton TH, Harrison PV, Nlcholls R, Delap M. Topical tacrolimus for facial psoriasis. *Br J Dermatol* 2003; 149:419-20.
34. Ahn SJ, Oh SH, Chang SE, Chol JH, Koh JK. A case of infantile psoriasis with pseudoalnhum successfully treated with topical pimecrolimus and low-dose narrowband UVB phototherapy. *J Eur Acad Dermatol Venereol* 2006; 20:1332-4.
35. Zvulunov A, Anlsfeld A, Metzker A. Efficacy of short-contact therapy with dlthranol in childhood psoriasis. *Int J Dermatol* 1994; 33:808-10.
36. Guerrier CJ, Porter DI. An open assessment of 0.1% dithranol in a 17% urea base ('Psoradrate' 0.1%) in the treatment of psoriasis of children. *Curr Med Res Opin* 1983; 8:446-50.
37. Schubert B, Seitz CS, Brocker EB, Hamm H. Exanthematous infantile psoriasis. *J Dtsch Dermatol Ges* 2007; 5:680-2.
38. Ghorpade A. Linear naevold psoriasis along lines of Blaschko. *J Eur Acad Dermatol Venereol* 2004; 18:726-7.
39. al-Fouzan AS, Nanda A. UVB phototherapy in childhood psoriasis. *Pediatr Dermatol* 1995 Mar; 12:66.
40. Jain VK, Aggarwal K, Jain K, Bansal A. Narrow-band UV-B phototherapy in childhood psoriasis. *Int J* Dermatol 2007; 46:320-2.
41. Jury CS, McHenry P, Burden AD, Lever R, Bilsland D. Narrowband ultraviolet B (UVB) phototherapy in children. *Clin Exp Dermatol* 2006; 31:196-9.
42. Paslc A, Ceovic R, Llpozencic J, Husar K, Susic SM, Skerlev M, et al. Phototherapy in pediatric patients. *Pediatr Dermatol* 2003; 20:71-7.
43. Tay YK, Morelli JG, Weston WL. Experience with UVB phototherapy in children. *Pediatr Dermatol* 1996; 13:406-9.
44. Kim MK, Ko YH, Yeo UC, Kim YG, Oh HY. Psoriasis and glomerulonephritis. *Clin Exp Dermatol* 1998; 23:295-6.
45. Thappa DM, Laxmlsha C. Suit PUVA as an effective and safe modality of treatment in guttate psoriasis. *J Eur Acad Dermatol Venereol* 2006; 20:1146-7.
46. Braun-Falco O, Berthold D, Ruzlcka T. [Psoriasis pustulosa generallsata--classlficatlon, clinical aspects and therapy. Review and experiences with 18 patients]. *Hautarzt* 1987; 38:509-20.
47. Rawal RC. Naevoid psoriasis? Unilateral psoriasis? *Int J Dermatol* 2006; 45:1001-2.
48. Maly J. Generalized pustular psoriasis. *Z Hautk* 1994; 69:549-50.
49. Zelickson BD, Muller SA. Generalized pustular psoriasis in childhood. Report of thirteen cases. *J Am Acad Dermatol* 1991; 24:186-94.
50. Mazzatenta C, Martini P, Luti L, Domenici R. Diffuse sterile pustular eruption with changing clinical features in a 2-year old. *Pediatr Dermatol* 2005; 22:250-3.
51. al-Fouzan AS, Hassab-el-Naby HM, Nanda A. Congenital linear psoriasis: a case report. *Pediatr Dermatol* 1990; 7:303-6.
52. Juanqln G, Zhiqlang C, Zijla H. Evaluation of the effectiveness of childhood generalized pustular psoriasis treatment in 30 cases. *Pediatr Dermatol* 1998; 15:144-6.
53. Patrizi A, Costa AM, Fiorillo L, Neri i. Perianal streptococcal dermatitis associated with guttate psoriasis and/or balanoposthitls: a study of five cases. *Pediatr Dermatol* 1994; 11:168-71.

54. Pacifico L. Acute guttate psoriasis after streptococcal scarlet fever. *Pediatr Dermatol* 1993;10:388-9.
55. Rosenberg EW, Noah PW, Zanolli MD, Skinner RB, Jr., Bond MJ, Crutcher N. Use of rifampin with penicillin and erythromycin in the treatment of psoriasis. Preliminary report. *J Am Acad Dermatol* 1986; 14:761-4.
56. Vincent F, Ross JB, Dalton M, Wort AJ. A therapeutic trial of the use of penicillin V or erythromycin with or without rifampin in the treatment of psoriasis. *J Am Acad Dermatol* 1992; 26:458-61.
57. Cassandra M, Conte E, Cortez B. Childhood pustular psoriasis elicited by the streptococcal antigen: a case report and review of the literature. *Pediatr Dermatol* 2003; 20:506-10.
58. Komine M, Tamaki K. An open trial of oral macrolide treatment for psoriasis vulgaris. *J Dermatol* 2000; 27:508-12.
59. Saraswat A. Unilateral Linear Psoriasis with Palmoplantar, Nail, and Scalp involvement. *Pediatr Dermatol* 2004; 21:70-3.
60. Herbst RA, Hoch O, Kapp A, Weiss J. Guttate psoriasis triggered by perianal streptococcal dermatitis in a four-year-old boy. *J Am Acad Dermatol* 2000; 42:885-7.
61. Rosinska D, Wolska H, Jablonska S, Konca i. Etretinate in severe psoriasis of children. *Pediatr Dermatol* 1988; 5:266-72.
62. van de Kerkhof PC. Generalized pustular psoriasis in a child. *Dermatologica* 1985; 170:244-8.
63. Pavicic Z, Kmet-Vizitin P, Kansky A. Etretinate in treating juvenile generalized pustular psoriasis. in: Farber EM, Cox AJ, editors. Proceedings of the 4th international symposium on psoriasis, Stanford University.Stanford: University Press; 1986. p. 467.
64. Kim BS, Shin S, Youn JI, Lee YS. Treatment of erythrodermic psoriasis with etretinate. *Ann Dermatol* 1991;3:107-11.
65. van der Rhee HJ, van Gelderen HH, Polano MK. is the use of Ro 10-9359 (Tigason) in children justified? *Acta Derm* Venereol 1980; 60:274-5.
66. Salieras M, Sanchez-Regana M, Umbert P. Congenital erythrodermic psoriasis: case report and literature review. *Pediatr Dermatol* 1995; 12:231-4.
67. Judge MR, McDonald A, Black MM. Pustular psoriasis in childhood. *Clin Exp Dermatol* 1993; 18:97-9.
68. Paik JH, Park PS, Choi YJ, Sung HS. Juvenile generalized pustular psoriasis treated with etretinate and methotrexate. Korean *J Dermatol* 1989; 27:64-8.
69. Shelnitz LS, Esterly NB, Honig PJ. Etretinate therapy for generalized pustular psoriasis in children. *Arch Dermatol* 1987; 123:230-3.
70. Karamfilov T, Wollina U. Juvenile generalized pustular psoriasis. *Acta Derm Venereol* 1998; 78:220.
71. Kopp T, Karlhofer F, Szepfalusi Z, Schneeberger A, Stingi G, Tanew A. Successful use of acitretin in conjunction with narrowband ultraviolet B phototherapy in a child with severe pustular psoriasis, von Zumbusch type. *Br J Dermatol* 2004; 151:912-6.
72. Law LK, Lau CY, Pang CP, Lam WY, Sweetman L, Fok TF, et al. An unusual case of multiple carboxylase deficiency presenting as generalized pustular psoriasis in a Chinese boy. *J Inherit Metab Dis* 1997; 20:106-7.
73. Li SP, Tang WY, Lam WY, Wong SN. Renal failure and cholestatic jaundice as unusual complications of childhood pustular psoriasis. *Br J Dermatol* 2000; 143:1292-6.
74. Pouessel G. Childhood pustular psoriasis associated with panton-valentine leukocidin-producing Staphylococcus aureus. *Pediatr Dermatol* 2007; 24:401-4.
75. Raynaud F, Gerbaud P, Evain-Brion D. Beneficial effect of a combination of retinoids and long-acting theophylline in the treatment of psoriasis vulgaris. *Br J Dermatol* 1994; 131:740-1.
76. Ergin S, Ersoy-Evans S, Sahin S, Ozkaya O. Acitretin is a safe treatment option for infantile pustular psoriasis. *J Dermatolog Treat* 2008: 19; 341-3.
77. Stepanova A. Psoriasis in a patient with congenital lamellar ichthyosis. *Hautarzt* 2001; 52:722-5.
78. Mahe E, Bodemer C, Pruszkowski A, Teillac-Hamel D, de Prost Y. Cyclosporine in childhood psoriasis. *Arch Dermatol* 2001; 137:1532-3.

79. Kilic SS, Hacimustafaoglu M, Celebi S, Karadeniz A, Ildirim i. Low dose cyclosporin A treatment in generalized pustular psoriasis. *Pediatr Dermatol* 2001; 18:246-8.
80. Pereira TM, Vieira AP, Fernandes JC, Sousa-Basto A. Cyclosporin A treatment in severe childhood psoriasis. *J Eur Acad Dermatol Venereol* 2006; 20:651-6.
81. Alli N, Gungor E, Karakayali G, Lenk N, Artuz F. The use of cyclosporin in a child with generalized pustular psoriasis. *Br J Dermatol* 1998; 139:754-5.
82. Torchia D, Terranova M, Fabbri P. Photosensitive psoriasis in a vitiligo patient. *J Dermatol* 2006; 33:880-3.
83. Perrett CM, Ilchyshyn A, Berth-Jones J. Cyclosporin in childhood psoriasis. *J Dermatolog Treat* 2003; 14:113-8.
84. Wollina U, Funfstuck V. Juvenile generalized circinate pustular psoriasis treated with oral cyclosporin A. *Eur J Dermatol* 2001; 11:117-9.
85. Kim HS, Kim GM, Kim SY. Two-stage therapy for childhood generalized pustular psoriasis: low-dose cyclosporin for induction and maintenance with acitretin/narrowband ultraviolet B phototherapy. *Pediatr Dermatol* 2006; 23:306-8.
86. Xiao T, Li B, He CD, Chen HD. Juvenile generalized pustular psoriasis. *J Dermatol* 2007; 34:573-6.
87. Collin B, Ogboli M, Moss C. Methotrexate therapy in 10 children with severe plaque psoriasis: P-29. *Br J Dermatol* 2006; 155:33.
88. Kaur i, Dogra S, De D, Kanwar AJ. Systemic methotrexate treatment in childhood psoriasis: further experience in 24 children from india. *Pediatr Dermatol* 2008; 25:184-8.
89. Kumar B, Dhar S, Handa S, Kaur i. Methotrexate in childhood psoriasis. *Pediatr Dermatol* 1994; 11:271-3.
90. Kalla G, Goyal AM. Juvenile generalized pustular psoriasis. *Pediatr Dermatol* 1996; 13:45-6.
91. Dogra S, Handa S, Kanwar AJ. Methotrexate in severe childhood psoriasis. *Pediatr Dermatol* 2004; 21:283-4.
92. Dogra S, Kumaran MS, Handa S, Kanwar AJ. Methotrexate for generalized pustular psoriasis in a 2-year-old child. *Pediatr Dermatol* 2005; 22:85-6.
93. ivker RA, Grin-Jorgensen CM, Vega VK, Hoss DM, Grant-Kels JM. infantile generalized pustular psoriasis associated with lytic lesions of the bone. *Pediatr Dermatol* 1993; 10:277-82.
94. Liao PB, Rubinson R, Howard R, Sanchez G, Frieden iJ. Annular pustular psoriasis--most common form of pustular psoriasis in children: report of three cases and review of the literature. *Pediatr Dermatol* 2002; 19:19-25.
95. Al-Shobaili H, Al-Khenaizan S. Childhood generalized pustular psoriasis: successful treatment with isotretinoin. *Pediatr Dermatol* 2007; 24:563-4.
96. Palier AS, Siegfried EC, Langley RG, Gottlieb AB, Pariser D, Landells i, et al. Etanercept treatment for children and adolescents with plaque psoriasis. *N Engl J Med* 2008; 358:241-51.
97. Papoutsaki M, Costanzo A, Massotta A, Gramiccia T, Soda R, Chimenti S. Etanercept for the treatment of severe childhood psoriasis. *Br J Dermatol* 2006; 154:181-3.
98. Kress DW. Etanercept therapy improves symptoms and allows tapering of other medications in children and adolescents with moderate to severe psoriasis. *J Am Acad Dermatol* 2006; 54:S126-S128.
99. Hawrot AC, Metry DW, Theos AJ, Levy ML. Etanercept for psoriasis in the pediatric population: experience in nine patients. *Pediatr Dermatol* 2006; 23:67-71.
100. Hoang JK, Burruss J. Localized cutaneous Cryptococcus albidus infection in a 14-year-old boy on etanercept therapy. *Pediatr Dermatol* 2007; 24:285-8.
101. Pereira TM, Vieira AP, Fernandes JC, Antunes H, Basto AS. Anti-TNF-alpha therapy in childhood pustular psoriasis. *Dermatology* 2006; 213:350-2.
102. Fabrizi G, Guerriero C, Pagliarello C. Etanercept in infants: suberythrodermic, recalcitrant psoriasis in a 22 month-old child successfully treated with etanercept. *Eur J Dermatol* 2007 May; 17:245.
103. Farnsworth NN, George SJ, Hsu S. Successful use of infliximab following a failed course of etanercept in a pediatric patient. *Dermatol Online J* 2005; 11:11.

104. Menter MA, Cush JM. Successful treatment of pediatric psoriasis with infliximab. *Pediatr Dermatol* 2004; 21:87-8.
105. Safa G, Loppin M, Bousser AM, Barbarot S. Etanercept in a 7-year-old boy with severe and recalcitrant psoriasis. *J Am Acad Dermatol* 2007; 56:S19-S20.
106. Weishaupt C, Metze D, Luger TA, Stander S. Treatment of pustular psoriasis with infliximab. *J Dtsch Dermatol Ges* 2007; 5:397-9.
107. Lin YK, Yen HR, Wong WR, Yang SH, Pang JH. Successful treatment of pediatric psoriasis with Indigo naturalis composite ointment. *Pediatr Dermatol* 2006; 23:507-10.
108. Pahlajani N, Katz BJ, Lozano AM, Murphy F, Gottlieb A. Comparison of the efficacy and safety of the 308 nm excimer laser for the treatment of localized psoriasis in adults and in children: a pilot study. *Pediatr Dermatol* 2005; 22:161-5.
109. Diluvio L, Campione E, Paterno EJ, Mordenti C, El Hachem M, Chimenti S. Childhood nail psoriasis: a useful treatment with tazarotene 0.05%. *Pediatr Dermatol* 2007; 24:332-3.
110. Michalowski R, Olejnicka Z, Kozak S, Urban J. Studies on the therapeutic effect of Wratizolin in selected dermatoses. *Arch Immunol Ther Exp (Warsz)* 1983; 31:649-54.
111. Gunther CH. Successive use of fumaric acid esters for the treatment of psoriasis vulgaris in a 14-year-old patient. *Hautarzt* 2004; 15:28-30.
112. Yu HJ, Park JW, Park JM, Hwang DK, Park YW. A case of childhood generalized pustular psoriasis treated with dapsone. *J Dermatol* 2001; 28:316-9.
113. Fernandes EI, Ferreira CT, Da Silveira TR, Cestari TF. Pustular psoriasis and Crohn's disease: Case report. *An Bras Dermatol* 2000; 75:57-64.
114. Tsuge I, Fujii H, Andou Y, Katayama I, Kajita M, Haga Y, et al. A case of infantile febrile psoriasiform dermatitis. *Pediatr Dermatol* 1995; 12:28-34.
115. McMillin BD, Maddern BR, Graham WR. A role for tonsillectomy in the treatment of psoriasis? *Ear Nose Throat J* 1999; 78:155-8.
116. Hone SW, Donnelly MJ, Powell F, Blayney AW. Clearance of recalcitrant psoriasis after tonsillectomy. *Clin Otolaryngol Allied Sci* 1996; 21:546-7.
117. Wahba A, Cohen H. Therapeutic trials with oral colchicine in psoriasis. *Acta Derm Venereol* 1980; 60:515-20.
118. Zachariae H, Kragballe K, Herlin T. Colchicine in generalized pustular psoriasis: clinical response and antibody-dependent cytotoxicity by monocytes and neutrophils. *Arch Dermatol Res* 1982; 274:327-33.
119. Guidelines of care for phototherapy and photochemotherapy. American Academy of Dermatology Committee on Guidelines of Care. *J Am Acad Dermatol* 1994; 31:643-8.
120. Stern RS, Nichols KT. Therapy with orally administered methoxsalen and ultraviolet A radiation during childhood increases the risk of basal cell carcinoma. The PUVA Follow-up Study. *J Pediatr* 1996; 129:915-7.
121. Dennis LK, Vanbeek MJ, Beane Freeman LE, Smith BJ, Dawson DV, Coughlin JA. Sunburns and risk of cutaneous melanoma: does age matter? A comprehensive meta-analysis. *Ann Epidemiol* 2008; 18:614-27.
122. Owen CM, Chalmers RJ, O'Sullivan T, Griffiths CE. Antistreptococcal interventions for guttate and chronic plaque psoriasis. *Cochrane Database* Syst Rev 2000:CD001976.
123. Wilson JK, Al-Suwaidan SN, Krowchuk D, Feldman SR. Treatment of psoriasis in children: is there a role for antibiotic therapy and tonsillectomy? *Pediatr Dermatol* 2003; 20:11-5.
124. Brecher AR, Orlow SJ. Oral retinoid therapy for dermatologic conditions in children and adolescents. *J Am Acad Dermatol* 2003; 49:171-82.
125. Berth-Jones J. The use of ciclosporin in psoriasis. *J Dermatolog Treat* 2005; 16:258-77.
126. Harper JI, Ahmed I, Barclay G, Lacour M, Hoeger P, Cork MJ, et al. Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *Br J Dermatol* 2000; 142:52-8.
127. Ramanan AV, Whitworth P, Baildam EM. Use of methotrexate in juvenile idiopathic arthritis. *Arch Dis Child* 2003; 88:197-200.

128. Niehues T, Horneff G, Michels H, Hock MS, Schuchmann L. Evidence-based use of methotrexate in children with rheumatic diseases: a consensus statement of the Working Groups Pediatric Rheumatology Germany (AGKJR) and Pediatric Rheumatology Austria. *Rheumatol Int* 2005; 25:169-78.
129. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, et al. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. *Arthritis Rheum* 2008; 58:1496-504.

Chapter 3.2

Dithranol therapy in childhood psoriasis

unjustifiably on the verge of falling into oblivion

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

Dermatology (2010) 220: 329 - 332

Abstract

Introduction

In childhood psoriasis, physicians aim for an effective and safe treatment, such as with dithranol. This study presents the largest study of dithranol-treated patients described in the literature.

Objective

The aim of the study was to determine the position of dithranol in the treatment strategy of psoriasis.

Methods

All juvenile patients receiving dithranol treatment at our centre were evaluated retrospectively.

Results

Sixty patients (with 82 treatment episodes in total) were included. The mean age at the start of dithranol treatment was 11.1 years (range 3.7 – 17.9). The result of treatment was: excellent (3.7%), good (69.5%), moderate (8.5%), reasonably (13.4%) or disappointing (4.9%). Mild irritation was seen in 39% and severe irritation was seen in 63% of the patients.

Conclusions

Dithranol can be regarded as an efficacious and safe topical therapy for the treatment of childhood psoriasis. It is a valuable alternative topical treatment which should not be disregarded in the treatment regimen of childhood psoriasis and should be commenced before ultraviolet or systemic treatments are initiated.

Introduction

Dithranol is one of the oldest topical therapeutics for psoriasis. More than 130 years ago, chrysarobine was shown to have an antipsoriatic effect. In 1916, dithranol, a synthetic derivative of chrysarobine, was developed by Galewski[1] and, from that time on, it was used in psoriatic patients in Europe[2]. As a result of the development of short-contact therapy with dithranol creams and ointments in the early eighties, the use of this topical agent has become more convenient over the years. The exact mechanism of action is still unknown, but it is known to induce a cascade of free radicals in the skin, resulting in antiproliferative effects and a modulation of inflammation in psoriasis.[3] No serious side effects of dithranol have been reported. It may cause a burning sensation, irritation and staining at the application site or clothing.

Especially in childhood psoriasis, there is a need for effective treatments without serious side effects. Even more than in adults, long-term side effects have to be minimized. As dithranol treatment has a long history of more than 100 years, and no serious side effects have been mentioned in the literature, dithranol is regarded as a safe treatment. To our surprise, despite one century of application in the treatment of psoriasis, only two studies have been performed concerning the use of dithranol in children.[4;5]

In order to bring forward more evidence on the safety and efficacy of dithranol in childhood psoriasis, the largest series of patients with juvenile psoriasis treated with dithranol is presented in our study.

Methods

All juvenile patients (aged < 18 years) receiving dithranol treatment at our medical centre between 1 January 1990 until 1 June 2009 were included in this study. Dithranol short-contact therapy was given at the daycare unit, using the instruction principle of daily visits during the first weeks and, thereafter, twice-weekly visits. Usually, visits last 30 - 60 min. Dithranol cream (0.01 - 4%) is diffusely applied on the trunk, arms and legs. The concentration is gradually increased after nine consecutive days of treatment, according to the tolerance and therapeutic response of the patient. Within these nine days, the dithranol cream is applied for 15 minutes at day 1 - 3, for 30 minutes at day 4 - 6, and for 45 minutes at day 7 - 9. It is washed off by shower and, afterwards, an emollient is applied on the treated

skin. An episode of dithranol treatment is finished if clearance or almost clearance is achieved or if, despite increasing the concentration of dithranol, no further favourable results are achieved. At the end of a dithranol treatment episode, predesigned data forms are completed by the dermatologist and added to the patient's records. These forms did not change in the period from 1990 until 2009. Therefore, although outcome measures are descriptive, they are standardized.
After the dithranol treatment episode is finished, patients receive prescriptions for low- to mid-potency topical corticosteroids and/or vitamin D analogues to be applied to small lesions if necessary. Multiple episodes of dithranol treatment in one patient were scored separately. Predesigned data extraction forms were used to record extracted data on treatment characteristics. The treatment outcome was determined at the end of each treatment episode. This outcome was rated as disappointing, reasonable, moderate, good (almost clearance) or excellent (clearance). End of remission is defined as the date on which more potent therapies (than the treatments prescribed at the end of dithranol treatment) were needed to control the disease. Other treatment characteristics included age at the start of treatment, antipsoriatic medication history, total duration of treatment, minimum and maximum concentration of dithranol, duration of remission, duration of follow-up and adverse events. Concomitant medication was registered throughout the whole period of dithranol treatment. The side effect irritation was divided in mild irritation and severe irritation. Severe irritation was defined as irritation due to which dithranol therapy was interrupted or adapted or topical corticosteroids were needed. All other cases of irritation were classified as mild irritation.
Descriptive statistics were provided using mean (± SD) or median (with interquartile ranges (IQR); 25^{th} - 75^{th} percentile) values depending on the (non-) parametric distribution of the measured variables. Statistical analysis was performed using SPSS16 (SPSS Inc., Chicago, IL, USA).

Results

Sixty patients were eligible for inclusion in the study. Altogether, they received 82 treatment episodes with short-contact dithranol applications. Forty-four patients received one episode of dithranol treatment, 12 patients received two episodes, three patients received three episodes and one patient received five episodes of treatment with dithranol. The mean age at the start of dithranol treatment was 11.1

years (SD: 4.0; range 3.7 - 17.9 years). Before dithranol treatment was initiated, the patients had already been treated with several other antipsoriatic therapies. Topical corticosteroids had been used prior to dithranol therapy in 90.2% of the patients. The different potencies of corticosteroids used are depicted in Table 1. Vitamin D analogues had been used in 60.0% and ultraviolet B (UVB) therapy in 46.7% of patients prior to therapy. The remaining therapies that had been used before initiation of dithranol treatment are also presented in Table 1.

Table 1 Therapies of study patients prior to dithranol treatment

Therapies	Percentage of patients
Topical corticosteroids	90.2
· Class I (e.g. hydrocortisone acetate)	13.3
· Class II (e.g. triamcinolone acetonide)	40.0
· Class III (e.g. betamethasone valerate)	80.0
· Class IV (e.g. clobetasol propionate)	28.3
Vitamin D analogues	60.0
Calcineurin inhibitors	1.7
Calcipotriol / betamethasone dipropionate	10.0
Coal tar cream / solution carbonis detergens	36.7
Keratolytic ointment	36.7
Ultraviolet B therapy	46.7
Dithranol (in other medical centres or home-treatment)	11.7
Methotrexate	3.3
Ciclosporin	3.3
Retinoids	5.0

The median minimal concentration of dithranol cream was 0.05% (IQR: 0.05 - 0.1%; range 0.01 - 0.10%), whereas the median maximum concentration was 0.2% (IQR: 0.1 - 0.4%; range 0.01 - 4.0%). The median increase in concentration was 0.1% (IQR: 0.05 - 0.35%). The duration of a treatment episode had a median of 65.0 days (IQR: 42.0 - 103.75). In 22.9% of the patients, lesions were pre-treated with 5% salicylic acid in order to reduce desquamation. Solutio carbonis detergens 10% was used in 5.4% of the patients after dithranol cream had been washed off.

A good result (almost clearance) was achieved in 69.5% of the patients, whereas 3.7% had total clearance of lesions (excellent result). The treatment outcome was moderate in 8.5% of the patients, while 13.4% had a reasonable result. In 4.9%, the treatment outcome was disappointing.

After treatment, the duration of remission was measured. For 22 treatment episodes, the remission period could not be evaluated. The remaining 60 treatment episodes had a median remission duration of 5.5 months (IQR: 1.0 - 18.0). The median follow-up duration was 12.5 months (IQR: 2.8 - 54.0).

Subanalyses were performed for 16 patients with more than one treatment episode. During the second treatment episode, median concentrations used were almost equal to those of the first episode. The median duration of treatment was 24 days longer than the initial episode (87 days versus 53 days); on the other hand, the median duration of remission was six months longer (first episode five months; second episode 11 months). In this subgroup of 16 patients, the result of the second treatment episode was somewhat better than that of the first episode. Only four patients had more than two treatment episodes. Therefore, analyses of the third, fourth and fifth episodes were not carried out because these were not representative due to the limited amount of patients.

The only side effect described was irritation; mild irritation was seen in 39% of the patients and severe irritation was seen in 63%. During the median treatment duration of 65.0 days, mild irritation occurred with a median of one time per treatment episode and severe irritation was seen a median of 1.5 times per treatment episode. None of the patients discontinued treatment because of side effects.

Discussion

These real-practice clinical data have been retrieved from the detailed patient records of our daycare unit. These results demonstrated that short-contact dithranol treatment has been an effective and safe treatment modality in as many as 73% of our children with psoriasis. A median treatment period of two months was needed to establish a median duration of remission of 5.5 months. This is comparable with results from a previous study on children, where a median treatment duration of two months resulted in a median remission duration of four months.[4] These results are superior to those of a study from 1983, in which less than 40% had more than 75% improvement in lesions after six weeks.[5] Dithranol

treatment of adults at daycare centres has been reported to result in clearing in 63 - 77% of the patients after 14 - 42 treatment days.[6-8]

Dithranol therapy is quite time-consuming for children and parents, especially in the first week when daily visits to the daycare unit are necessary. Consequently, absence from school can be a problem. Staining of skin, clothes and bathtubs should also be discussed at the start of treatment.

Although irritation was a relatively frequently seen side effect, we consider dithranol treatment to be a safe treatment. No side effects were seen during the follow-up period (median: 12.5 months), which is also supported by the literature, in which no mid- to long-term side effects are reported.[9] In the study by Zvulunov et al., 20% of the patients had adverse skin reactions such as mild transient skin irritation and staining; one patient ceased treatment due to these side effects.[4] In the treatment regimen of the former study, dithranol cream was only applied to the lesions. This could explain the fact that in the current study, where dithranol was applied diffusely, 73% of the patients had side effects. Nevertheless, none of our patients ceased treatment.

One of the aims of the study was to re-evaluate the position of dithranol in the treatment algorithm of childhood plaque psoriasis. In comparison with dithranol, ultraviolet (UV) therapy has a comparable treatment outcome and treatment duration.[10] Although there are no studies documenting the long-term safety of UVB phototherapy for childhood psoriasis, judicious use of this therapy is advised for appropriately selected patients as a second-line therapy, i.e. for children whose disease fails topical therapy.[11] For dithranol, no long-term side effects have been described.[9] Additionally, dithranol is only applied for a few months. Systemic treatments (such as methotrexate and etanercept) are usually used for a longer period. Again, more serious and long-term side effects can be seen in case of systemic treatments. Therefore, in our opinion, dithranol should be commenced before UV and systemic treatments.

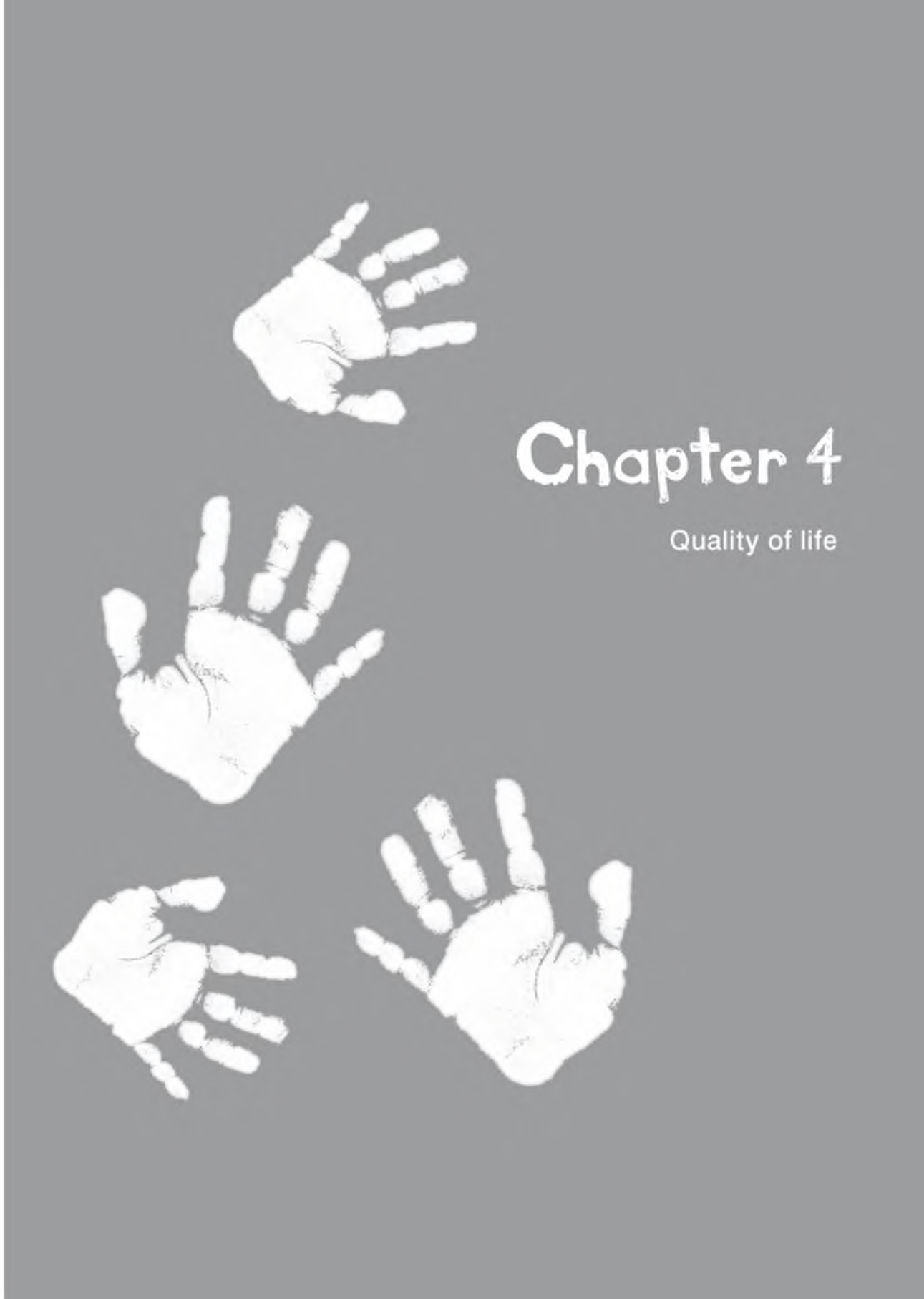
In this retrospective study, outcome measures were descriptive, but in a standardised way. Because the Psoriasis Area and Severity Index was not used, the severity of psoriasis at the beginning of the dithranol treatment could not be described objectively. In our department, however, dithranol treatment is initiated in case of moderate to severe psoriasis as it is a fairly time-consuming treatment and not easily accessible.

In conclusion, dithranol can be regarded as an efficacious and safe topical therapy for the treatment of childhood psoriasis. Even though it is a classic, rather time-consuming therapy, with obvious disadvantages such as irritation and

staining, it is a valuable alternative topical treatment which should not be disregarded in the treatment regimen for childhood psoriasis. Consequently, before UV or systemic treatment is initiated in children with psoriasis, dithranol treatment should be considered.

Reference List

1. Galewski E. Über Cignolin, ein Ersatz präparat des Chrysarobins. *Dermatol.Wochenschrift* 1916; 6: 113-5.
2. Ashton RE, Andre P, Lowe NJ *et al.* Anthraiin: historical and current perspectives. *J.Am.Acad.Dermatol.* 1983; 9: 173-92.
3. van de Kerkhof PC, Barker J, Griffiths CE *et al.* Psoriasis: consensus on topical therapies. *J.Eur.Acad.Dermatol.Venereol.* 2008; 22: 859-70.
4. Zvulunov A, Anisfeld A, Metzker A. Efficacy of short-contact therapy with dithranol in childhood psoriasis. *Int.J.Dermatol.* 1994; 33: 808-10.
5. Guerrier CJ, Porter DI. An open assessment of 0.1% dithranol in a 17% urea base ('Psoradrate' 0.1%) in the treatment of psoriasis of children. *Curr.Med.Res.Opin.* 1983; 8: 446-50.
6. Christensen OB, Holst R, Hradil E *et al.* Clinical response and side-effects in the treatment of psoriasis with UVB and a novel dithranol formulation. *Acta Derm.Venereol.Suppl (Stockh)* 1989; 146: 96-100.
7. Duschet P, Schwarz T, Pusch M *et al.* Anthraiin minute entire skin treatment: a follow-up and comparison with methoxsalen plus ultraviolet light. *Arch.Dermatol.* 1987; 123: 428-9.
8. Schwarz T, Gschnait F. Anthraiin minute entire skin treatment. A new outpatient therapy for psoriasis. *Arch.Dermatol.* 1985; 121: 1512-5.
9. van de Kerkhof PC. Dithranol treatment in psoriasis: after 75 years, still going strong. *Eur.J.Dermatol.* 1991; 1: 79-88.
10. de Jager ME, de Jong EM, van de Kerkhof PC *et al.* Efficacy and safety of treatments for childhood psoriasis: A systematic literature review. *J.Am.Acad.Dermatol.* 2010; 62: 1013-30.
11. Menter A, Korman NJ, Elmets CA *et al.* Guidelines of care for the management of psoriasis and psoriatic arthritis Section 5. Guidelines of care for the treatment of psoriasis with phototherapy and photochemotherapy. *J.Am.Acad.Dermatol.* 2010; 62: 114-35.



Chapter 4

Quality of life

Chapter 4.1

An intrapatient comparison of quality of life in psoriasis in childhood and adulthood

M.E.A. de Jager, E.M.G.J. de Jong, P.C.M. van de Kerkhof,
A.W.M. Evers, M.M.B. Seyger

Journal of the European Academy of Dermatology and Venereology
(2010) In press

Abstract

Background

Chronic diseases can have a great influence on health-related quality of life. Nevertheless, only little research has been carried out on childhood psoriasis. The perception of quality of life by adults with psoriasis of their childhood psoriasis has never been investigated.

Objectives

The aims of this study were to (i) investigate retrospectively the influence of psoriasis as experienced in childhood as compared with the current quality of life in adulthood; (ii) assess retrospectively the impact of childhood psoriasis on daily life; and (iii) compare the current quality of life in patients with childhood onset psoriasis (COP) and adult onset psoriasis (AOP).

Methods

A survey was performed among all members of the Dutch Psoriasis Society. Validated questionnaires on quality of life, impact on daily life and clinical severity were used.

Results

Questionnaires of 1762 patients were suitable for analysis. Adults with an onset of psoriasis before the age of 18 years retrospectively rate their quality of life during childhood much less as compared with their current quality of life (intrapatient comparison). Influence of psoriasis in childhood particularly had a high degree of limitations on recreational and social activities in 15 - 30% of patients. Quality of life in adulthood is not determined by age of onset of psoriasis.

Conclusions

In childhood, the quality of life is greatly influenced by psoriasis. The social development domain, which is one of the developmental milestones in a child, is particularly impaired. The current quality of life of patients with COP is equal to that of patients with AOP.

Introduction

Psoriasis is a common, inflammatory, chronic relapsing skin disease affecting approximately 2% of the worldwide Caucasian population.[1] Of the adult psoriatic patients, 35 - 50% indicates that the skin disease started before the age of 20.[2-5] Having a chronic disease in childhood can diminish a child's health-related quality of life.[6] Negative life experiences, such as a chronic disease in childhood, may also have an influence on development during childhood and on adult life.[7] In dermatological research, quality of life studies in children mainly focus on atopic dermatitis, demonstrating the burden atopic dermatitis has on children.[6;8-10] In view of the comparable impact of atopic dermatitis and psoriasis in adult patients,[11] it could be assumed that childhood psoriasis also has a comparable impairing influence on the quality of life of the children with these skin conditions. To the best of our knowledge, there are only two studies that systematically examined the quality of life of children with psoriasis, demonstrating that the quality of life of children with psoriasis is even worse than in diabetes and epilepsy in childhood.[6;12] In adult psoriatic patients, many studies have been performed on the quality of life.[13-18] Whether the age of onset of psoriasis (childhood onset vs. adult onset) influences the quality of life later in adulthood was never investigated. It could be assumed that having psoriasis as a child influences the quality of life in adult life.

The following questions were formulated: (i) How do adult psoriatic patients with childhood onset psoriasis retrospectively evaluate the quality of life in their childhood? And how does this relate to their current quality of life? (ii) How do adults retrospectively assess the quality of life of their childhood with respect to daily life? (iii) Does the age of onset of psoriasis (childhood onset vs. adult onset) influence the quality of life in the long term?

Methods

Study population

All 5300 (adult) members of the Dutch Psoriasis Society were enrolled in the present study and were sent a questionnaire. Responses were gathered from 14 February 2009 to 1 June 2009.

Patients were subdivided into two groups depending on the age of onset of disease. The first group consisted of patients who experienced an onset before

the age of 18 years (childhood onset psoriasis (COP)); the second group comprised patients with an onset of disease from the age of 18 years (adult onset psoriasis (AOP)).

Measures

Quality of life over the past year was assessed by the Dermatology Life Quality Index (DLQI).[19;20] The DLQI is a validated, self-administered, simple tool to measure how much a skin problem has affected the life of a patient. It consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their quality of life. It has been validated for dermatology patients aged 16 years and above. For this study a validated Dutch version was used. The items of the DLQI encompass aspects such as symptoms and feelings, daily activities, leisure, work or school, personal relationships and the side effects of treatment. Each item is scored on a four-point Likert scale: 0, not at all / not relevant; 1, a little; 2, a lot; and 3, very much. Scores of individual items (0 - 3) are added to yield a total score (0 - 30); higher scores mean greater impairment of the patient's quality of life.

Quality of life in childhood was questioned retrospectively with the DLQI, because the Children's Dermatology Life Quality Index (CDLQI) is not validated for adults. The questions from the DLQI were addressed for the period before the age of 18 years in patients with COP. Patients were instructed to fill out the DLQI for their average situation in childhood (i.e. until the age of 18 years) in case they had COP. For the comparison of DLQI in childhood and adulthood, patients served as their own control.

Impact of COP on daily life was measured by means of an adapted question derived from the Impact of Chronic Skin Disease on Daily Life (ISDL) questionnaire concerning this subject.[21] This 10-item generic scale measures the effect the condition has on activities of daily life including work, hobbies, holiday, sleep, sexuality, eating and relationships, with response categories on a four-point Likert scale (1, not; 2, a little; 3, strongly; 4, totally). Apart from the separate item scores, a total impact score can be calculated to reflect the overall impact of the disease on daily life. The total score ranges from 10 to 40.

Clinical severity of psoriasis was assessed by a Patient Global Assessment (PGA) and the Self-Administered Psoriasis Area and Severity Index (SAPASI)[22]. The PGA was rated on a scale from clear to very severe (0 - 5). Patients were asked to rate the current PGA and their (retrospective) PGA during childhood. The SAPASI is a one-page instrument consisting of silhouettes (front and back) of the human

body, on which patients shade areas currently affected by psoriasis. The shaded areas are assigned a numerical value of 0 to 6 for the four body regions (head, upper extremities, trunk and legs) by a physician as follows: 0, no involvement; 1, < 10%; 2, 10 - 29%; 3, 30 - 49%; 4, 50 - 69%; 5, 70 - 89%; 6, 90 - 100%. Patients also had to rate the average redness, thickness and scaliness of their lesions by means of three visual analogue scales (VAS). Similar to the PASI, scores on the SAPASI range from 0 to 72. Evidence of validity and reliability for this instrument has been provided by several studies.[22-25]

Statistics

Mean, standard deviation (SD) and range were calculated for all variables; comparisons of numeric variables were analyzed with the Student's *t*-test, paired *t*-test and χ^2 test as appropriate. P-values < 0.0025 were considered as statistically significant for the main hypotheses due to Bonferroni's correction for multiple testing. Statistical analysis was performed using SPSS16 (SPSS Inc., Chicago, IL, USA).

Results

Sample characteristics

The questionnaires were sent to 5300 psoriatic patients, of which 1963 (37.0%) were returned. Due to missing values, questionnaires of 1762 patients were suitable for analysis. The mean age of the respondents was 55.4 years (SD ± 13.3). Among the responders were 871 (49.4%) men and 891 (50.6%) women. Mean duration of psoriasis was 28.9 years (SD ± 15.2), ranging from 0 to 81 years. Mean age of onset of psoriasis was 26.5 years (SD ± 15.4); mean age at diagnosis of psoriasis was 28.3 years (SD ± 15.6). Mean age of onset was 27.6 years in men and 25.4 years in women (*t*-test; $p = 0.003$).

The total group of 1762 respondents was divided into two groups according to the age of onset of psoriasis: COP (onset of psoriasis < 18 years) consisted of 568 patients (32.2%) and AOP (onset of psoriasis ≥ 18 years) comprised 1194 patients (67.8%). There was a preponderance of women in the COP group (women: 62.3%), in comparison with the AOP group (women: 45.0%) (χ^2; $p < 0.001$). A majority of patients (51.5%) indicated that they were currently being treated by a dermatologist. On the other hand, 512 (29.3%) respondents were not currently treated by any medical professional for their skin disease. In view of treatment by a medical

professional, there were no significant differences between patients with COP and AOP (χ^2; $p = 0.233$).

Intrapatient comparison quality of life in childhood and adulthood

The retrospectively measured DLQI in childhood had a mean of 12.8 (SD ± 7.5). This mean value was significantly higher compared with the current mean DLQI of 6.8 (SD ± 5.7) of COP patients (*t*-test; $p < 0.001$). Subanalyses of separate items showed significantly higher scores for the DLQI in childhood for all questions compared with the current scores (*t*-test; $p < 0.001$). Generally, the retrospectively reported PGA was somewhat higher in childhood compared with adulthood (2.9 (SD ± 1.1) versus 2.4 (SD ± 1.0) respectively; *t*-test; $p < 0.001$).

Impact of childhood psoriasis on daily life

The impact of childhood psoriasis on daily life was retrospectively assessed by the ISDL impact scale in patients with COP. The average total score of the ISDL was 16.4 (SD ± 5.6). In patients who were currently being treated by a dermatologist, the average total score was 16.9 (SD ± 6.0). In Table 1, answers per question are displayed for all COP patients. Vacation and leisure time were affected in more than 60% of patients, whereas hobbies, sexuality and contact with friends were affected in more than 50%. In 15 - 30% of these patients, these areas were strongly or even totally influenced by the psoriasis in childhood.

Comparison current quality of life

Mean total score of the DLQI for the quality of life in the past year was 6.8 (SD ± 5.7). For COP the total score of the current DLQI was 6.8 (SD ± 5.6) compared with 6.9 (SD ± 5.8) in AOP (*t*-test; $p = 0.735$). Differences between individual questions were also not significant. The mean PGA was not significantly different between both groups: COP-group 2.38 and AOP-group 2.41 (*t*-test; $p = 0.495$). The SAPASI score in COP patients was somewhat higher than in AOP patients (7.0 versus 6.5; *t*-test; $p = 0.014$).

The results were the same for the subgroups of patients who were currently treated by a dermatologist or not.

Table 1 Impact of childhood psoriasis on daily life

Did the severity of psoriasis in your childhood had a negative influence on:					
	Number of patients	Not n (%)	A little n (%)	Strongly n (%)	Totally n (%)
Work/School	564	320 (56.3)	155 (27.3)	59 (10.4)	30 (5.3)
Household chores	554	443 (78.0)	92 (16.2)	9 (1.6)	10 (1.8)
Hobbies	560	274 (48.2)	173 (30.5)	84 (14.8)	29 (5.1)
Vacation	567	172 (30.3)	223 (39.3)	127 (22.4)	45 (7.9)
Leisure time	563	212 (37.3)	217 (38.2)	102 (18.0)	32 (5.6)
Sexuality	564	270 (47.5)	175 (30.8)	71 (12.5)	48 (8.5)
Eating habits	566	410 (72.2)	121 (21.3)	27 (4.8)	8 (1.4)
Sleeping	566	417 (73.4)	98 (17.3)	37 (6.5)	14 (2.5)
Contact with friends	568	242 (42.6)	239 (42.1)	59 (10.4)	28 (4.9)
Contact with family	568	417 (73.4)	122 (21.5)	15 (2.6)	14 (2.5)
Relationship	488*	333 (58.6)	127 (22.4)	21 (3.7)	7 (1.2)
Family life	422*	325 (57.2)	81 (14.3)	13 (2.3)	3 (0.5)

* As these items are questions about childhood psoriasis, these questions are not applicable to all patients.

Discussion

The diagnosis of childhood psoriasis raises the question among parents as to the extent to which this diagnosis can influence the quality of life of their child now and in the future.

With patients serving as their own control, retrospectively assessed DLQI scores (total scores and scores of separates questions) are significantly higher (i.e. less quality of life) in childhood (12.8) than the current DLQI scores in adulthood (6.8). Adult patients thus experienced their quality of life much worse during their childhood as compared to their current situation. This could be due to the fact that psoriasis has genuinely more impact in childhood; it is also possible that a few decades ago, treatment options for childhood psoriasis were more distressing. Another explanation could be that due to the retrospective design of this study a recall bias has occurred. Regardless of the reason for this higher retrospective

quality of life score in childhood is, the fact is that this is rated by the adults now. One can infer from the data that childhood psoriasis is experienced as incriminatory not only in adulthood, but also in childhood. So far, CDLQI scores in juvenile psoriasis have been measured in only two studies in patients who visited the dermatology outpatient department, indicating a relatively high impact of psoriasis on daily life of children.[6;12] Also, comparative CDLQI scores in children with atopic dermatitis were found in other studies.[6;8-10] Together with the high scores found in our study, when the quality of life in childhood psoriasis is retrospectively assessed, these results suggest that the impact of childhood psoriasis is at least as severe as in atopic dermatitis and can have an impairing influence on the development of children. In addition, our results of the ISDL scores showed that the influence of juvenile psoriasis on recreational and social activities (e.g. vacation and hobbies) is large in 15 - 30% of respondents. Accordingly, the social development domain, which is one of the developmental milestones in a child, is particularly impaired. In contrast, the quality of life and severity of the disease in the long term were not determined by the age of onset of psoriasis, as the current quality of life and disease severity scores of the COP- and AOP-group were comparable in adults. The conclusion could be drawn that, also in childhood, the burden of psoriasis is considerable and should not be underestimated, whereas quality of life in later life is not determined by the age of onset of psoriasis.

However, several limitations should be considered. The main limitation of this study is the retrospective design. Consequently, this could cause a recall bias, which might possibly have resulted in an overestimation or underestimation of the severity and impact of childhood psoriasis on daily life. Obviously, a prospective study would have given more reliable data. As the questionnaires were only sent to members of the Dutch Psoriasis Society, a selection bias could be present. Patients in whom psoriasis only occurred on childhood are possibly missed, because they might not be members of the Dutch Psoriasis Society in adulthood.

In summary, the current study shows that (i) retrospectively, adults rate their quality of life during childhood much less as compared with their current quality of life in adulthood, (ii) the influence of psoriasis in childhood causes a high degree of limitations on recreational activities in at least 15 - 30% of patients. Therefore, the social development domain, which is one of the developmental milestones in a child, is particularly impaired and (iii) the quality of life in the long term is not determined by the age of onset of psoriasis.

In clinical practice, there is a great challenge for dermatologists to improve the

quality of life of children with psoriasis. To do so, greater attention should be paid to the possible limitations that these children experience. As one could assume that improving the severity of psoriasis has a positive influence on quality of life, the outcome of quality of life measurements should be taken into account when deciding on treatment strategies. As a child-tailored treatment could limit the psychological impact of the disease, a more active disease-modifying approach should be considered to optimize and individualize the treatment. This might also considerably improve the quality of life of children with psoriasis.

Reference List

1. Christophers E. Psoriasis--epidemiology and clinical spectrum. *Clin.Exp.Dermatol.* 2001; 26: 314-20.
2. Swanbeck G, inerot A, Martinsson T *et al.* Age at onset and different types of psoriasis. *Br.J.Dermatol.* 1995; 133: 768-73.
3. Farber EM, Nall ML. The natural history of psoriasis in 5,600 patients. *Dermatologica* 1974; 148: 1-18.
4. Braun-Falco O, Burg G, Farber EM. [Psoriasis. A questionnaire study of 536 patients]. *Munch.Med.Wochenschr.* 1972; 114: 1105-10.
5. Raychaudhuri SP, Gross J. A comparative study of pediatric onset psoriasis with adult onset psoriasis. *Pediatr.Dermatol.* 2000; 17: 174-8.
6. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br.J. Dermatol.* 2006; 155: 145-51.
7. Haavet OR, Straand J, Saugstad OD *et al.* illness and exposure to negative life experiences in adolescence: two sides of the same coin? A study of 15-year-olds in Oslo, Norway. *Acta Paediatr.* 2004; 93: 405-11.
8. Ganemo A, Svensson A, Lindberg M *et al.* Quality of life in Swedish children with eczema. *Acta Derm.Venereol.* 2007; 87: 345-9.
9. Ben-Gashir MA, Seed PT, Hay RJ. Are quality of family life and disease severity related in childhood atopic dermatitis? *J.Eur.Acad. Dermatol.Venereol.* 2002; 16: 455-62.
10. Warschburger P, Buchholz HT, Petermann F. Psychological adjustment in parents of young children with atopic dermatitis: which factors predict parental quality of life? *Br.J.Dermatol.* 2004; 150: 304-11.
11. Evers AW, Lu Y, Duller P *et al.* Common burden of chronic skin diseases? Contributors to psychological distress in adults with psoriasis and atopic dermatitis. *Br.J.Dermatol.* 2005; 152: 1275-81.
12. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality index (CDLQi): initial validation and practical use. *Br.J. Dermatol.* 1995; 132: 942-9.
13. Jowett S, Ryan T. Skin disease and handicap: an analysis of the impact of skin conditions. *Soc.Sci.Med.* 1985; 20: 425-9.
14. Badia X, Mascaro JM, Lozano R. Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: clinical validity, reliability and sensitivity to change of the DLQi. The Cavide Research Group. *Br.J.Dermatol.* 1999; 141: 698-702.
15. Mease PJ, Menter MA. Quality-of-life issues in psoriasis and psoriatic arthritis: outcome measures and therapies from a dermatological perspective. *J.Am.Acad.Dermatol.* 2006; 54: 685-704.
16. Hong J, Koo B, Koo J. The psychosocial and occupational impact of chronic skin disease. *Dermatol.Ther.* 2008; 21: 54-9.
17. Lundberg L, Johannesson M, Silverdahl M *et al.* Health-related quality of life in patients with psoriasis and atopic dermatitis measured with SF-36, DLQi and a subjective measure of disease activity. *Acta Derm.Venereol.* 2000; 80: 430-4.
18. Krueger G, Koo J, Lebwohl M *et al.* The impact of psoriasis on quality of life: results of a 1998 National Psoriasis Foundation patient-membership survey. *Arch.Dermatol.* 2001; 137: 280-4.
19. Finlay AY, Khan GK. Dermatology Life Quality index (DLQi)--a simple practical measure for routine clinical use. *Clin.Exp.Dermatol.* 1994; 19: 210-6.
20. Basra MK, Fenech R, Gatt RM *et al.* The Dermatology Life Quality index 1994-2007: a comprehensive review of validation data and clinical results. *Br.J.Dermatol.* 2008; 159: 997-1035.
21. Evers AW, Duller P, van de Kerkhof PC *et al.* The impact of Chronic Skin Disease on Daily Life (iSDL): a generic and dermatology-specific health instrument. *Br.J.Dermatol.* 2008; 158: 101-8.
22. Feldman SR, Fleischer AB, Jr., Reboussin DM *et al.* The self-administered psoriasis area and severity index is valid and reliable. *J.Invest Dermatol.* 1996; 106: 183-6.

23. Fleischer AB, Jr., Feldman SR, Rapp SR *et al.* Disease severity measures in a population of psoriasis patients: the symptoms of psoriasis correlate with self-administered psoriasis area severity index scores. *J.Invest Dermatol.* 1996; 107: 26-9.
24. Fleischer AB, Jr., Rapp SR, Reboussin DM *et al.* Patient measurement of psoriasis disease severity with a structured instrument. *J.Invest Dermatol.* 1994; 102: 967-9.
25. Fleischer AB, Jr., Feldman SR, Dekle CL. The SAPASi is valid and responsive to psoriasis disease severity changes in a multicenter clinical trial. *J.Dermatol.* 1999; 26: 210-5.

Chapter 4.2

The burden of childhood psoriasis

M.E.A. de Jager, E.M.G.J. de Jong, A.W.M. Evers,
P.C.M. van de Kerkhof, M.M.B. Seyger

Pediatric Dermatology (2010) In press

Abstract

A pilot study on the impact on quality of life in childhood psoriasis is presented. Of the children interviewed, 65% experienced stigmatization to a certain extent, 71% reported itch and 43% complained about fatigue. Clinicians should pay attention to these items, in order to initiate a patient-tailored treatment.

Psoriasis in childhood has a prevalence of approximately 0.7%.[1] Evaluation of quality of life (QoL), defined as physical, emotional and social functioning, can display unmet medical and psychological needs of children with psoriasis. Unfortunately, this was only described in one study so far. In this study, the QoL was even worse than in diabetes and epilepsy in children.[2] Our purpose was to explore physical, emotional and social limitations children with psoriasis have to cope with in a pilot study.

Systematic, semi-structured interviews were held with 15 children with psoriasis (with their parents present) (i.e. age < 18 years). For this pilot study, the participating patients were randomly selected from a general population database. QoL was assessed with the Children's Dermatology Life Quality Index (CDLQI) questionnaire.[2] Stigmatization, severity of skin lesions and physical symptoms (degree of itch, pain and fatigue on a visual analogue scale (VAS)) were assessed with scales from the Impact of Chronic Skin Disease on Daily Life (ISDL) questionnaire.[3] Higher scores imply more feelings of stigmatization, more extended psoriasis, and more itch, pain and fatigue. All questionnaires were filled out by the children or exceptionally by the parents according to the answers given by their child.

Sample characteristics are depicted in Table 1.

From the interviews, it appeared that approximately half of the children felt stigmatized as they were bullied or called names. Three children said that they had been asked by others if lesions were contagious. One girl felt isolated because others did not want to play with her. Four children felt ashamed of their skin.

Scores on the CDLQI, severity-scale, stigmatization-scale, and the VAS are shown in Table 2. As can be appreciated by the severity score, most children had a mild psoriasis. Itch was experienced (VAS > 2) by 71% of children (n = 10), pain by 21% (n = 3) and fatigue by 43% (n = 6). Almost 65% of the patients experienced stigmatization; of this subgroup of patients, the median stigmatization-score was 11.2 (range 7 to 20).

These results implicated that juvenile psoriasis has a negative impact on the physical, emotional and social functioning of a child. Feelings of stigmatization were experienced by almost 65% of children interviewed for the current study and stigmatization-scores were nearly equal for adults in previous studies.[4] Physical symptoms (VAS) are also experienced by a substantial proportion of patients with juvenile psoriasis and the scores are similar to adult patients with psoriasis in a general practice population.[5] In contrast to the impact on pain, itch, fatigue and stigmatization, the median score of 2.9 can only be classified as a small effect on

Table 1 Sample characteristics

Age of respondents	
Mean (SD)	12.8 years (4.25)
Range	4.3 - 17.6 years
Age of onset of psoriasis	
Mean (SD)	9.4 years (5.24)
Range	2 - 16 years
	Number of patients
Gender	
Men	4
Women	11
Familial distribution	
Yes (1st degree member)	9 (5)
No	4
Unknown	2

SD standard deviation

the quality of life according to the scoring instructions of the CDLQI. Beattie et al showed a CDLQI score of 9.17, which is a moderate effect. CDLQI scores found in psoriasis and eczema were comparable, whereas scores for acne and urticaria were lower (5.4 and 6.12 respectively)[2]. The limitations of the current study are mainly contributable to the small number of patients interviewed, who also had a limited severity of disease. Therefore, the results displayed are only descriptive.
In conclusion, the 15 patients interviewed had a mild psoriasis with corresponding stigmatization- and QoL-scores. Despite this mild psoriasis, 65% experienced stigmatization to a certain extent, 71% reported itch and 43% complained about fatigue. Clinicians should pay attention to these items, in order to initiate a patient-tailored treatment. Following this small pilot study, larger studies need to be performed to accurately address the important issues raised in the current study.

Table 2 Rating of disease-related quality of life

	Minimum-maximum score	Respondents	Mean (SD)	Range
Severity of skin lesions	9 - 36	Children	12.3 (3.2)	10 - 22
Stigmatization	6 - 24	Children	9.4 (4.1)	6 - 20
CDLQI	0 - 30	Children	2.9 (2.9)	0 - 11
	Minimum-maximum score	**Respondents**	**Median (IQR)**	**Range**
VAS Itch	0 - 10	Children	3.3 (0.5 - 4.6)	0 - 8
VAS Pain	0 - 10	Children	0.8 (0.0 - 1.9)	0 - 9
VAS Fatigue	0 - 10	Children	1.5 (0.5 - 6.1)	0 - 8

SD Standard deviation
CDLQI Children's Dermatology Life Quality Index
IQR Interquartile range
VAS Visual Analogue Scale

Reference List

1. Augustin M, Glaeske G, Radtke MA *et al.* Epidemiology and comorbidity of psoriasis in children. *Br.J.Dermatol.* 2010; 162: 633-6.
2. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br.J. Dermatol.* 2006; 155: 145-51.
3. Evers AW, Duller P, van de Kerkhof PC *et al.* The Impact of Chronic Skin Disease on Dally Life (ISDL): a generic and dermatology-specific health instrument. *Br.J.Dermatol.* 2008; 158: 101-8.
4. Evers AW, Lu Y, Duller P *et al.* Common burden of chronic skin diseases? Contributors to psychological distress in adults with psoriasis and atopic dermatitis. *Br.J.Dermatol.* 2005; 152: 1275-81.
5. Verhoeven EW, Kraalmaat FW, van de Kerkhof PC *et al.* Prevalence of physical symptoms of itch, pain and fatigue in patients with skin diseases in general practice. *Br.J. Dermatol.* 2007; 156: 1346-9.

Chapter 4.3

A cross-sectional study using the Children's Dermatology Life Quality Index (CDLQI) in childhood psoriasis: the negative effect on the quality of life and moderate correlation of CDLQI and severity scores

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

British Journal of Dermatology (2010) 163: 1099 - 1101

Abstract

Background

Juvenile psoriasis is a chronic and incurable skin disease that affects approximately 0.7% of children.

Objectives

To achieve more insight into the quality of life (QoL) in childhood psoriasis and to investigate whether disease severity scores correlate to QoL scores.

Methods

All consecutive patients with juvenile plaque psoriasis (≤ 18 years old) who visited our outpatient department were included. At baseline, the Children's Dermatology Life Quality Index (CDLQI) questionnaire was completed and disease severity was assessed by the Psoriasis Area and Severity Index (PASI) and Physician Global Assessment (PGA).

Results

Thirty-nine patients were included in the study. A median CDLQI of 6 (interquartile range (IQR) 5 - 9) was reported. Median PASI was 6.3 (IQR 3.3 - 8.2) and median PGA was 2 (IQR 1 - 3). The correlation coefficient between PASI and CDLQI was 0.47 ($p = 0.003$), whereas the correlation coefficient between PGA and CDLQI was 0.51 ($p = 0.001$).

Discussion

The negative effect on QoL in juvenile psoriasis was confirmed in the largest cohort presented up to now. The correlation between disease severity scores and disease-related QoL in children with psoriasis is only moderate. Therefore, both clinical outcome parameters (PASI, PGA) and measures of QoL (CDLQI) should be included in adequate, patient-oriented clinical decision making.

Background

Juvenile psoriasis is a chronic and incurable skin disease that effects approximately 0.7% of children.[1-3] Skin disease in children can have profound effects on the quality of life (QoL), disrupting family and social relationships, interfering with play, sport and school and affecting normal development.[4]
The influence of juvenile psoriasis on QoL has only been described in two small studies.[5;6] Whether there is a correlation between QoL in these children and the severity of their disease has never been investigated before. Therefore, it is not known if one can confine evaluation to only one parameter in clinical practice.
The aim of this study was to achieve more insight in the QoL in childhood psoriasis and to investigate whether disease severity scores correlate with QoL scores. In addition, we investigated if age, gender or familiar distribution influences this correlation.

Methods

In this cross-sectional study, all consecutive patients with juvenile psoriasis (≤ 18 years old) who visited our outpatient clinic between 1 September 2008 and 1 January 2010 were assessed at their first visit. In order to create a homogeneous cohort, only patients with plaque psoriasis were included. Three patients with pustular psoriasis and one patient with guttate psoriasis were excluded. Patients with mainly nail psoriasis (n = 1) and/or arthritis (n = 1) were also excluded.
Severity of disease was measured by the Psoriasis Area and Severity Index (PASI; range 0 - 72)[7] and the Physician Global Assessment (PGA; range 0 - 5). Also, affected body surface area (BSA) was calculated. Higher scores indicate more severe psoriasis. Every child was scored by the same investigator.
Disease-related QoL was assessed with a validated Dutch version of the Children's Dermatology Life Quality Index (CDLQI) questionnaire.[8] The total score is calculated by summing the score of the 10 questions, resulting in a maximum of 30 and a minimum of 0. The higher the score, the more the QoL is impaired.
Descriptive statistics were provided using median and interquartile range (IQR) values, due to the nonparametric distribution of measured variables. Correlation coefficients were calculated with the Spearman's rho test. A test for comparing elements of a correlation matrix as described by Steiger was used to make a statistical comparison between correlation coefficients measured in the same

individuals.[9] For comparing correlation coefficients in different individuals the Fisher Z transformation was used. Statistical analysis was performed using SPSS 16 (SPSS Inc., Chicago, IL, USA) and R version 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 39 patients was included in this study. The median age at baseline was 11 years (IQR 8 - 14). Gender distribution was almost equal in our cohort. Most patients had more than a 2.5-year history of psoriasis before visiting our clinic. The vast majority (74%) had one or more family members affected with psoriasis. Patient characteristics are depicted in Table 1.

Table 1 Patient characteristics

Number of patients		39
Age (years), median (IQR)		11 (8 - 14)
Boys / girls, n (%)		18 / 21 (46 / 54)
Psoriasis history		
	Duration of psoriasis (months), median (IQR)	27.0 (12.0 - 73.0)
	Family history of psoriasis, n (%)	29 (74)
Psoriasis baseline assessments		
	CDLQI, median (IQR)	6 (5 - 9)
	PASI, median (IQR)	6.3 (3.3 - 8.2)
	PGA, median (IQR)	2 (1 - 3)
	BSA (%), median (IQR)	6.8 (2.3 - 13.5)

IQR Interquartile range
CDLQI Children's Dermatology Life Quality Index
PASI Psoriasis Area and Severity Index
PGA Physician Global Assessment
BSA Body Surface Area

The median CDLQI score was 6 (IQR 5 - 9). The following median severity scores were found: PASI 6.3 (IQR 3.3 - 8.2), PGA 2 (IQR 1 - 3) and BSA 6.8% (IQR 2.3 - 13.5). The correlation coefficient between PASI and CDLQI was 0.47 (p = 0.003), whereas the correlation coefficient between PGA and CDLQI was 0.51 (p = 0.001). According to the test for comparing elements of a correlation matrix, the difference between these correlation coefficients (i.e. 0.47 and 0.51) was not significant in our population. The distribution of individual cases is displayed in Figures 1 and 2. Subanalyses for correlation coefficients were performed on different groups according to gender, familiar predisposition, parts of the body that were affected, age at baseline and age of onset of psoriasis. No significant differences were found between the different groups using the Fisher Z transformation.

Figure 1 Children's Dermatology Life Quality Index (CDLQI) in relation to Psoriasis Area and Severity Index (PASI). A regression line is shown.

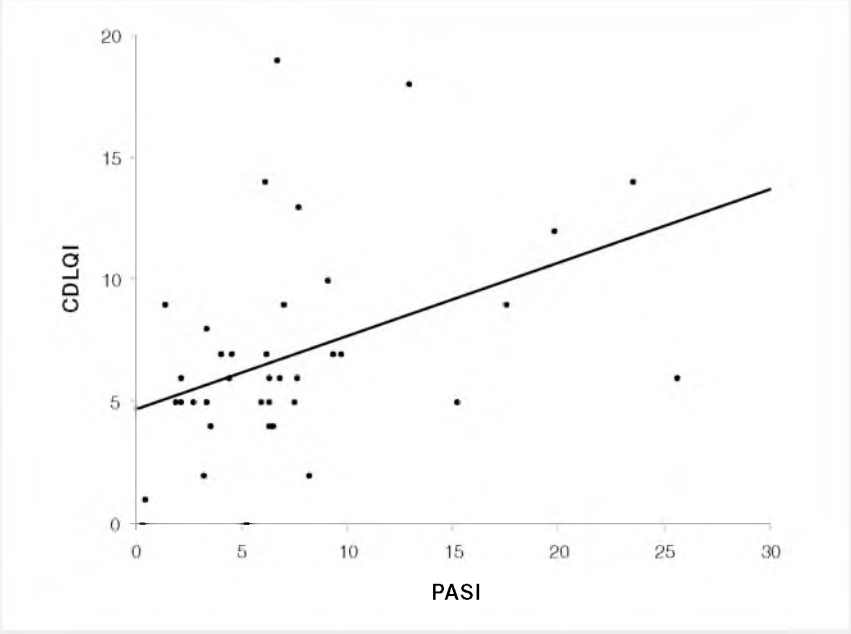
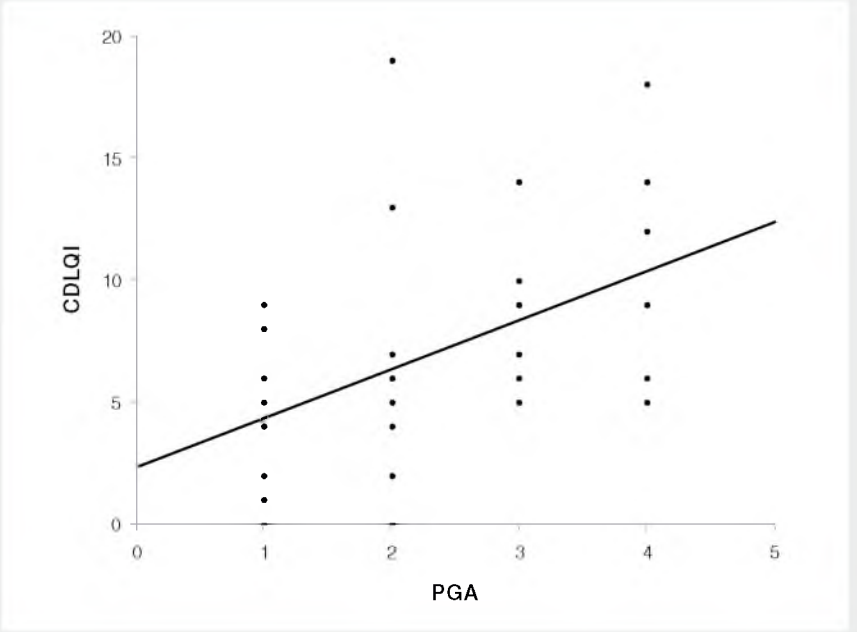


Figure 2 Children's Dermatology Life Quality Index (CDLQI) in relation to Physician Global Assessment (PGA). A regression line is shown.



Discussion

Regarding the impact of chronic diseases on the QoL, children are an especially vulnerable group because the developmental changes in this phase of life are substantial. It has been reported that the QoL of children with psoriasis is even worse than in diabetes and epilepsy in childhood.[5] Information regarding factors influencing QoL in children with psoriasis is gathering over time. Eventually, this will give us tools for combined treatment focused on the patient's disease and QoL.

In this study the negative effect on the QoL of juvenile psoriasis is demonstrated. Two previous studies have reported CDLQI scores of children with psoriasis.

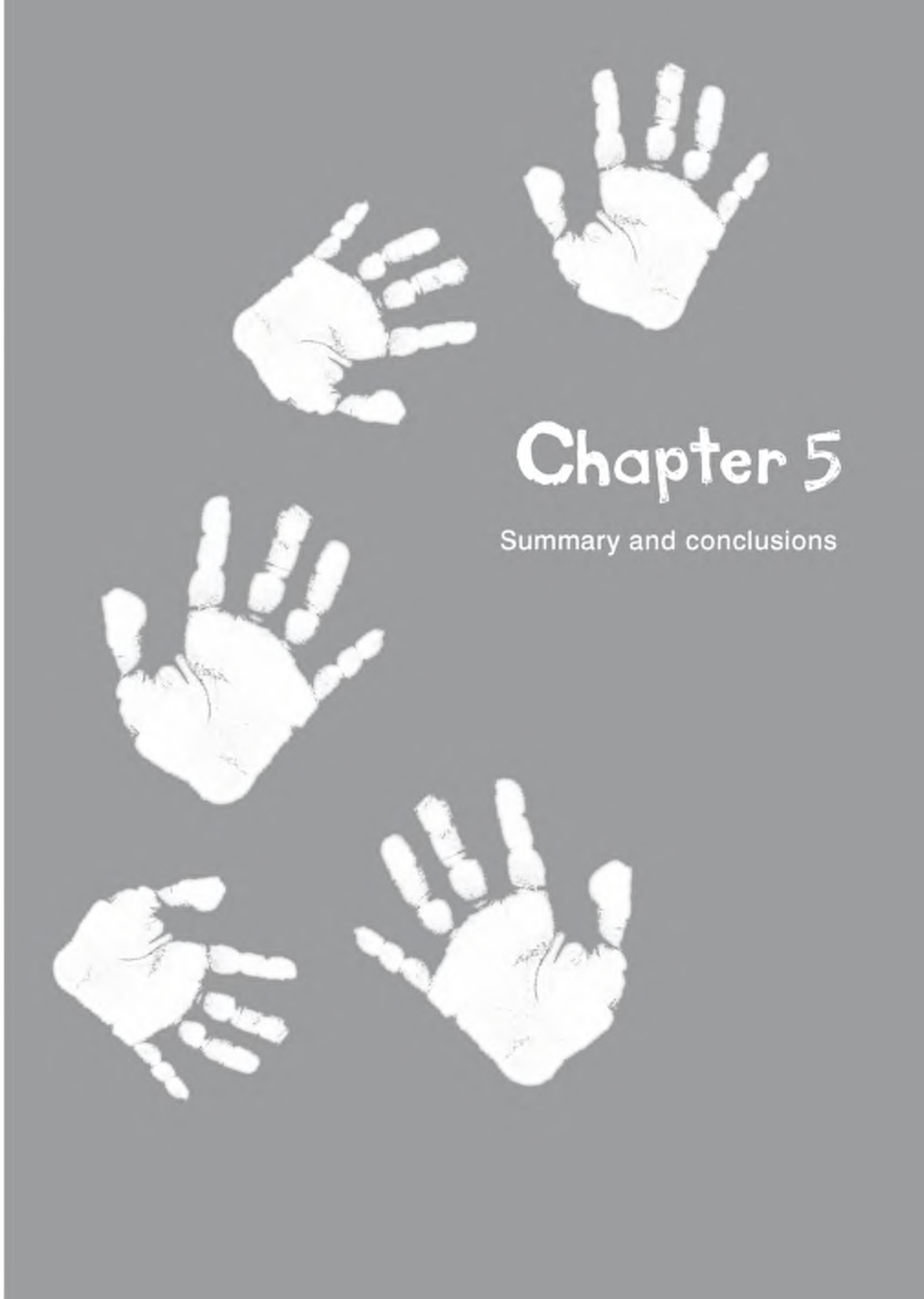
In both studies, patients attending a (paediatric) dermatology clinic were included. In the validation study of the CDLQI questionnaire, 25 patients with psoriasis were questioned.[6] The mean CDLQI score was 5.4 (SD 5.0; range 0 – 18). In another study, 29 juvenile patients with psoriasis completed the CDLQI questionnaire.[5] Their mean score was 9.17 (SD 7.83; range 0 - 27). Unfortunately, no clinical severity scores have been reported in either study, nor were correlations shown. The CDLQI score of 6 found in our cohort is in line with the previous studies and confirms the high impact of this disease on daily life.

To investigate the relation between disease severity and impact of disease, correlation coefficients were calculated. In the present study, the PGA had a higher correlation coefficient with the CDLQI (0.51) than had the PASI (0.47), although this difference was not significant. Both disease severity measures showed a moderate correlation with the QoL scores. This is roughly comparable with previous studies in adults with psoriasis which have also shown a poor to moderate correlation (i.e. range 0.15 - 0.4).[10-13] This moderate correlation could be explained by the fact that perception of QoL may depend not only on disease severity, but also on age, gender, social class, ethnicity, education, anxiety level, and the ability to minimize or exaggerate symptoms.[14] Nevertheless, a significant influence of age or gender in the perception of QoL in our cohort could not be found. Although there is not a good correlation between absolute values of the PASI and DLQI, the results of several clinical trials in adults indicate that reduction of physical severity is associated with improvement of QoL.[15] Even though this is still a relatively small sample size, the present study contributes valuable additional information on QoL in juvenile psoriasis.

In conclusion, the negative impact on QoL in juvenile psoriasis was confirmed in the largest cohort presented up to now. As the correlation between disease severity scores and disease-related QoL in children with psoriasis is only moderate, both clinical outcome parameters (PASI, PGA) and measures of QoL (CDLQI) should be included in adequate, patient-oriented clinical decision making.

Reference List

1. Augustin M, Giaeske G, Radtke MA *et al.* Epidemiology and comorbidity of psoriasis in children. *Br.J.Dermatol.* 2010; 162: 633-6.
2. Gelfand JM, Weinstein R, Porter SB *et al.* Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. *Arch.Dermatol.* 2005; 141: 1537-41.
3. de Jager ME, van de Kerkhof PC, de Jong EM *et al.* Epidemiology and prescribed treatments in childhood psoriasis: a survey among medical professionals. *J.Dermatolog.Treat.* 2009; 20: 254-8.
4. Long CC, Funnell CM, Collard R *et al.* What do members of the National Eczema Society really want? *Clin.Exp.Dermatol.* 1993; 18: 516-22.
5. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br.J. Dermatol.* 2006; 155: 145-51.
6. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality index (CDLQi): initial validation and practical use. *Br.J. Dermatol.* 1995; 132: 942-9.
7. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. *Dermatologica* 1978; 157: 238-44.
8. Holme SA, Man i, Sharpe JL *et al.* The Children's Dermatology Life Quality index: validation of the cartoon version. *Br.J. Dermatol.* 2003; 148: 285-90.
9. Steiger JH. Tests for comparing elements of a correlation matrix. *Psychological Bulletin* 1980; 87: 245-51.
10. Sampogna F, Sera F, Abeni D. Measures of clinical severity, quality of life, and psychological distress in patients with psoriasis: a cluster analysis. *J.Invest Dermatol.* 2004; 122: 602-7.
11. Fortune DG, Main CJ, O'Sullivan TM *et al.* Quality of life in patients with psoriasis: the contribution of clinical variables and psoriasis-specific stress. *Br.J.Dermatol.* 1997; 137: 755-60.
12. Touw CR, Hakkaart-Van RL, Verboom P *et al.* Quality of life and clinical outcome in psoriasis patients using intermittent cyclosporin. *Br.J.Dermatol.* 2001; 144: 967-72.
13. Schäfer i, Hacker J, Rustenbach SJ *et al.* Concordance of the Psoriasis Area and Severity index (PASi) and patient-reported outcomes in psoriasis treatment. *Eur.J. Dermatol.* 2010; 20: 62-7.
14. Annett RD, Bender BG, Lapidus J *et al.* Predicting children's quality of life in an asthma clinical trial: what do children's reports tell us? *J.Pediatr.* 2001; 139: 854-61.
15. Reich K, Griffiths CE. The relationship between quality of life and skin clearance in moderate-to-severe psoriasis: lessons learnt from clinical trials with infliximab. *Arch.Dermatol.Res.* 2008; 300: 537-44.



Chapter 5

Summary and conclusions

The present thesis intended to gain more insight in several aspects of childhood psoriasis. Therefore, six aims were formulated in **Chapter 1**.
In this chapter, a summary of the major conclusions of the presented articles will be given and discussed. In addition, practical advices for physicians treating children with psoriasis will be given, based on the most recent insights and evidence.

Aim Ia)

To further explore the epidemiology and clinical features of childhood psoriasis in The Netherlands

This aim was addressed by means of three studies presented in **Chapter 2**.
In **Chapter 2.2**, a prevalence of childhood psoriasis of 0.37% was found for the age group from 0 to 10 years old. The prevalence in the age group from 11 to 19 years old was 1.09%. The total prevalence of psoriasis in children under 20 years old was 0.7%. These figures are highly comparable with those found in other European studies (United Kingdom: 0.55% 0 - 9 years and 1.37% 10 - 19 years[1]; Germany 0.37% 0 - 9 years and 1.01% 10 - 19 years[2]). In the German study, the total prevalence of psoriasis in children up to 18 years was 0.71%.[2] If the results of our study are extrapolated across the Dutch population, a total number of 27 500 children with psoriasis should be living in The Netherlands.
In **Chapter 2.1**, 37.1% of patients reported an onset of the disease before the age of 18 years, which is comparable with literature which reports 27 - 50%.[3-9] If this number stated by the patients is correct, the supposed number of children with psoriasis in The Netherlands is even higher: 140 000 children. Several explanations for this difference in number of children with psoriasis between Chapter 2.1 and Chapter 2.2 can be considered. It may be a matter of overestimation by previous literature, as well as an overestimation of the patients who filled out the questionnaire (e.g. due to a recall bias). There could also be a selection bias present in the response group, because patients with childhood onset of psoriasis might be more inclined to fill out and return the questionnaire. It is also possible that the numbers from Chapter 2.2 are an underestimation of the actual prevalence, because this number only reflects the patients that are currently under the care of a general practitioner. On the contrary, the studies from the United Kingdom and Germany calculated their numbers from nationwide databases which contain information of 1.3 million and more than 8 million patients, respectively.
In **Chapter 2.1** only a single peak in age of onset of psoriasis was demonstrated around the age of 15 - 19 years. This single peak was also found by other

investigators.[4;10] In one study the prevalence increased in an approximately linear matter.[2] This is in contrast to the research performed by Henseler and Christophers, which showed a dual peak at the ages 16 - 22 years and 60 years.[11]

Gender distribution was also investigated. In **Chapter 2.2**, there was a male to female ratio of children with psoriasis of 1.6 : 1 in the general practitioner population, whereas there was a ratio of 1 : 1.3 in the patient population of the dermatologists. **In Chapter 2.3**, a cohort of Dutch children with psoriasis was compared with a Singaporean cohort of children with psoriasis. In the Dutch children an equal gender distribution of psoriasis was seen (male to female ratio = 1 : 1.1), whereas in Singaporean children there was a slight tendency towards a preponderance for women (male to female ratio = 1 : 1.4). Overall, one can conclude that mainly an equal gender distribution was found, which is consistent with most of the published literature.[10;12-17] Nevertheless, some cohorts consist of more girls than boys with childhood psoriasis.[18-22]

A familial distribution was revealed in 50.3 - 73.3% of the Dutch patients with juvenile psoriasis (**Chapter 2.2 and 2.3)**. In contrast, only 13.6% of Singaporean patients had a family member with psoriasis (**Chapter 2.3**). The disparity in familial distribution between Caucasian and predominantly Han Chinese patients could be due to genetic differences. An additional reason on which genetic differences as a causal factor can be proposed is that there is a difference in familial distribution across different parts of the world. The highest rates of familial distribution are found in European and Australian populations[13;21] and the lowest in Indian and Chinese communities[12;17].

The occurrence of several clinical features in childhood psoriasis was examined in our own cohort of psoriatic children (**Chapter 2.3**). The most frequently seen type of psoriasis was plaque psoriasis (88.9%), followed by pustular psoriasis (6.7%) and guttate psoriasis (2.2%). The most frequently involved sites were the scalp (88.9%) and limbs (86.7%). Intertriginous areas and the face were both involved in 24.4% of the patients. Nail changes were seen in 22.2% of the patients, with pitting as the most common abnormality. Arthritis was present in 2.2% of the children. Pruritus was reported by 80% of the patients. All these data are roughly comparable with percentages from previous reports.[10;12-24] In only 3.3% of the children precipitating factors were found. The most common factor was stress (66.7%), followed by infections (20%).

Aim Ib)

To compare differences and similarities between childhood onset psoriasis and adult onset psoriasis

In **Chapter 2.1**, a comparison was made between childhood onset psoriasis (COP) and adult onset psoriasis (AOP). A higher percentage of women was found in the COP-group (62.9%) than in the AOP-group (45.2%). A correlation of COP and a high body mass index (BMI) at adult age could not be demonstrated. In fact, the mean BMI was even slightly lower in patients with COP compared with AOP (26.2 versus 26.8 kg/m^2). Nevertheless, recent studies in children with psoriasis have demonstrated that their BMI is often too high as compared with WHO standards.[25-27] In adulthood, the most frequently reported type was plaque psoriasis in both COP and AOP patients. Guttate and erythrodermic psoriasis seemed to occur more often in adults with COP than in adults with AOP. In the majority of patients with COP, the type of psoriasis at onset remains the same when the patient grows up. Joint and nail involvement were seen in equal percentages in the COP- and AOP-group.
Psoriasis in adulthood was not more severe in patients with COP than in patients with AOP. Both scores of the Self-Administered Psoriasis Area and Severity Index (SAPASI) and Physician Global Assessment (PGA) were not significantly different in the COP- and AOP-group at adult age. In addition, there was no difference in most potent treatment prescribed at adult age between the COP- and AOP-group. This implies that the course of COP is not worse than that of AOP.
A remarkable observation was that the diagnosis delay (time from onset of symptoms to final diagnosis) was significantly longer for patients with COP than AOP. In COP, the delay in diagnosis was 3.1 years, whereas in AOP this was 1.5 years. This could be due to the fact that childhood psoriasis can mimic nummular eczema and often itches. Also, because of the relatively low prevalence in childhood, it is usually not the first diagnosis that is suspected by a physician.

Aim IIa)

To obtain an overview of efficacy and safety of treatment options in childhood psoriasis

To give an evidence-based overview of available treatments in childhood psoriasis, a systematic review was performed (**Chapter 3.1**). In **Chapter 3.2**, research was performed on short-contact dithranol therapy, a classic nearly forgotten antipsoriatic

treatment option. The major conclusions on the efficacy and safety of these treatments will now be described separately for each treatment. For references the reader is referred to **Chapter 3**.

Efficacy and safety of treatments

Unfortunately, none of the articles described in the review in **Chapter 3.1** reported data on long-term safety profiles. The median follow-up duration of dithranol treatment in **Chapter 3.2** was 12.5 months, describing an intermediate duration of follow-up.

Topical corticosteroids: Only three studies could be included in the review for evaluation, each with a treatment-period of two to three weeks. It seems that halobetasol cream 0.05% and clobetasol propionate emulsion 0.05% are efficacious treatments in childhood plaque psoriasis. Reported side effects of halobetasol cream 0.05% and clobetasol propionate emulsion 0.05% were relatively mild (mild skin atrophy, burning sensation at the application site) in the treatment period of two weeks.

Vitamin D_3 analogues: Calcipotriol is an effective treatment option for childhood plaque psoriasis as has been proven by several studies among which a randomized-controlled trial. Less research has been performed on calcitriol, but it seems to be an effective treatment. Calcipotriol is a reasonably well tolerated treatment option for childhood plaque psoriasis. The most common side effect was irritation. Calcitriol also seems to have mild side effects. Long-term side effects were not described.

Calcineurin inhibitors: Tacrolimus 0.1% is an effective and safe therapeutic option for short-term treatment of facial and intertriginous childhood psoriasis. The only side effect reported was pruritus. Again, long-term safety was not described. No conclusion could be drawn for the use of pimecrolimus due to the small number of patients in the included studies.

Dithranol: The reviewed literature shows that dithranol is an effective treatment. This was confirmed by a study performed at our department among 60 patients. Short-contact dithranol treatment was demonstrated to be an effective treatment modality in 73% of treated children with psoriasis. A median treatment period of two months was needed to establish a median duration of remission of 5.5 months

(**Chapter 3.2**). Dithranol is a treatment in childhood psoriasis with a good margin of safety for short-term use according to the review. Mild transient skin irritation and staining were the most frequently reported side effects (**Chapter 3.1**). In our own cohort (**Chapter 3.2**), skin irritation was also reported, nevertheless no severe side effects were seen during the follow-up period (median 12.5 months).

Phototherapy: Good results in the treatment of plaque and guttate psoriasis in childhood are found with narrowband (NB)-ultraviolet (UV) B radiation according to the reviewed literature. The treatment with NB-UVB shows comparatively mild side effects (e.g. erythema) for the relative short treatment duration studied. Although there are no studies documenting the long-term safety of UVB phototherapy in childhood psoriasis, the risk of photo ageing and carcinogenesis should be considered. As only four patients have been described who were treated with psoralen plus UVA radiation (PUVA), a solid conclusion about the efficacy and safety of PUVA treatment could not be drawn.

Antibiotics: The efficacy of the use of antibiotics in childhood guttate psoriasis remains controversial as two studies found no effect of this treatment and three studies showed a good to excellent effect. The safety of the use of antibiotics in childhood guttate psoriasis was not sufficiently described.

Retinoids: Previously published literature has shown that etretinate is an effective treatment for pustular and erythrodermic psoriasis. However, etretinate is not available anymore. Unfortunately, the use of acitretin has not been sufficiently investigated in childhood psoriasis; therefore no conclusions could be drawn. Nevertheless, a treatment with acitretine can be attempted in case of pustular or erythrodermic psoriasis because both treatment modalities (etretinate and acitretin) have the same mode of action, as acitretin is the active metabolite of etretinate. Side effects are frequently seen during the treatment with retinoids. Cheilitis was often described as a side effect, as well as pruritus and hair loss. No conclusions could be drawn from the review on the safety of this drug in children, because of the lack of evidence. Toxic, irreversible musculoskeletal side effects (including osteoporosis, periosteal plucking, formation of slender long bones and premature epiphyseal closure) have been associated with chronic use of high-dose systemic retinoids for other indications.[28,29] However, these adverse musculoskeletal side effects have not been associated with lower doses typically used to treat psoriasis and keratinization disorders, even when used for periods

longer than 10 years.[30-33] When retinoids are prescribed to fertile women it should be discussed that this drug is known to be a potent teratogen and pregnancies should be avoided for at least three years after discontinuing therapy.[34]

Ciclosporin: The efficacy of ciclosporin treatment in childhood psoriasis is ambiguous. In previously published literature, five patients have been treated with good effect, but four patients did not show any response. A solid conclusion could therefore not be drawn. This also applies to the safety issues which were also sparsely described. It is known from literature that the main safety concern of ciclosporin is potential nephrotoxicity. Since irreversible interstitial renal fibrosis has been reported,[35] renal function should be closely monitored.

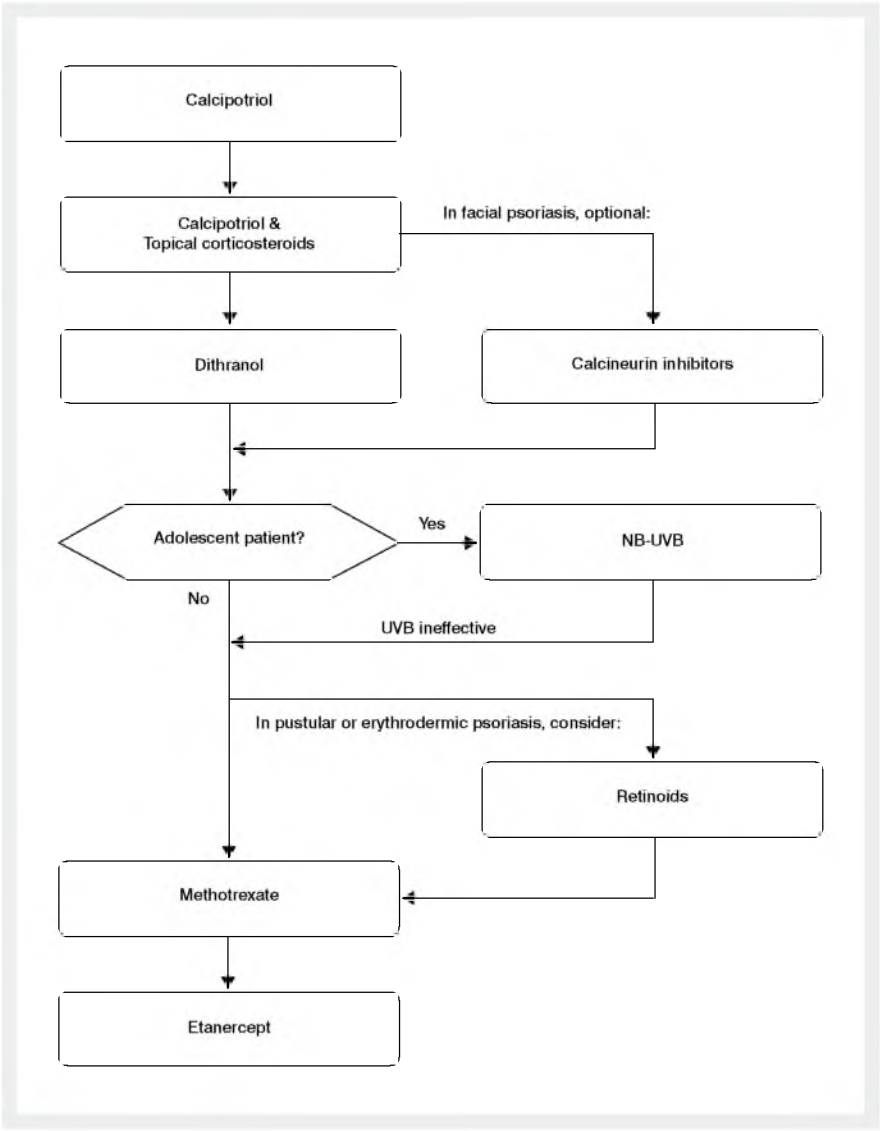
Methotrexate: Methotrexate is an effective treatment option in moderate to severe childhood psoriasis; the largest body of evidence is available for plaque psoriasis, but the use has also been described in other types of psoriasis. Short-term side effects of methotrexate in the treatment of juvenile psoriasis are usually mild and can be treated very well. The side effects include mild to severe nausea and vomiting. Also a transient minor elevation of liver enzymes was repeatedly found. Data regarding long-term safety of the use of methotrexate for childhood psoriasis is lacking. However, in juvenile idiopathic arthritis (JIA), this drug is often used for long periods of time and has a track record of safe and effective use.[36] There has been very little evidence to substantiate hepatotoxicity or clinical significant bone marrow suppression in children treated with methotrexate for JIA.[37-42]

Biologics: As has been shown in a large randomized-controlled trial (and several case reports), etanercept is an effective biologic in the treatment of plaque type childhood psoriasis. The most common short-term side effects of etanercept during the treatment period described in childhood psoriasis were upper respiratory infections, headache and nasopharyngitis. A recent study showed no new safety issues after 144 weeks of treatment in children older than eight years with severe childhood plaque psoriasis compared with the previously published randomized controlled trial.[43] Previous studies on the safety of etanercept in patients with juvenile idiopathic arthritis report few adverse events and a low rate of serious adverse events after eight years of continuous treatment with etanercept, without an increase in rates of serious adverse events over time.[44;45] However, long-term safety data are not available. Based on only four case reports, a solid conclusion on the efficacy and safety of the use of infliximab in children with psoriasis could not be drawn.

Aim IIb)

To create an evidence-based algorithm for the treatment of childhood psoriasis

Based on **Chapter 3**, the following treatment algorithm was constructed:



The treatment of choice in mild or moderate juvenile psoriasis should be calcipotriol. If necessary, this can be combined with mild to moderate topical corticosteroids. Tacrolimus can be additionally prescribed in case of treatment-resistant flexural and/or facial psoriasis. If this treatment regimen is not effective, or if psoriasis is moderate to severe, treatment with dithranol is recommended. If these treatments are not efficacious enough, a short treatment with NB-UVB can be considered in adolescents. Even though controversial, the use of antibiotics can be considered in case of guttate psoriasis and evidence of a streptococcal infection by means of a throat culture.
If systemic treatment is necessary, methotrexate is regarded as the therapy of choice. In cases of pustular and erythrodermic psoriasis retinoids can be considered. Treatment with ciclosporin should only be deliberated in exceptional cases. Etanercept should be used if the above described protocol is insufficient to control the disease.

Aim IIIa)

To get more insight in the psychological burden of psoriasis in children

To assess the burden children with psoriasis have to cope with, research was performed in children and adults with childhood onset psoriasis (COP).
In **Chapter 4.1**, 568 adults with COP were asked to (retrospectively) estimate their quality of life in childhood. Limitations were especially noted on recreational and social activities. Fifteen to 30% of the patients even indicated a large influence of the disease on these activities. Recreational and social activities are part of the social development domain, which is one of the developmental milestones in a child´s life.
In **Chapter 4.2**, a pilot study in 15 juvenile patients with a mild psoriasis was described. In the semi-structured interviews approximately half of the children said they were bullied or called names. One girl even indicated that other children did not want to play with her because of the skin lesions. Questions from others on contagiousness of the lesions were also frequent. Scores on questionnaires showed a mild effect on quality of life (mean Children's Dermatology Life Quality Index (CDLQI) score 2.9). Nevertheless, 65% experienced stigmatization, 71% reported itch and 43% complained about fatigue. These scores are comparable with scores in adult patients with psoriasis.[46;47]
Additional information on CDLQI scores was gathered in **Chapter 4.3**. In this chapter a study is presented in 39 juvenile psoriasis patients. The median CDLQI

score was 6. This is in line with previous studies which report scores of 5.4 and 9.2.[48;49] Furthermore, these scores are also comparable with results from studies in adult patients with psoriasis.[50;51] It was also investigated if disease severity scores (Psoriasis Area and Severity Index (PASI) and Physician Global Assessment (PGA) scores) correlate with quality of life scores (CDLQI scores). Both disease severity scores showed only a moderate correlation with quality of life scores. This could be explained by the fact that perception of quality of life may depend not only on disease severity, but also on age, gender, social class, ethnicity, education, anxiety level and the ability to minimize or exaggerate symptoms.[52] From the study in Chapter 4.3, the conclusion can be drawn that juvenile psoriasis has a negative effect on quality of life and both disease severity scores and measures of quality of life should be taken into account when treating a child with psoriasis.

Aim IIIb)

To compare the burden of psoriasis as experienced in childhood to the burden in adulthood

The study described in **Chapter 4.1** was set up to achieve this aim. The answers of the 1762 patients who participated in this study were analyzed after respondents were divided into two groups: childhood onset psoriasis (COP; onset of the disease before the age of 18 years) and adult onset psoriasis (AOP; onset of the disease from the age of 18 years). The COP group had a mean Dermatology Life Quality Index (DLQI) score of 12.8 in their youth (<18 years). On the contrary, their current quality of life was rated with a mean DLQI score of 6.8. The severity of disease in childhood was rated slightly worse than in adulthood. The two-fold decrease of the mean DLQI score in adulthood as compared with childhood could be justified by several explanations. The impact of psoriasis in childhood could be genuinely bigger than in adulthood. On the other hand, in prospective studies that have been performed the CDLQI scores of children with psoriasis are between 2.9 and 9.2.[48;49;53;54] Another possibility is that children rate their quality of life differently than adults and that CDLQI and DLQI scores cannot be compared. Besides that, a recall bias could be present. Another explanation could be that although quality of life scores in childhood are moderate, the same adults think that their quality of life in the past is affected more than they had realized at that time.
The current quality of life of patients with COP and AOP was also a subject of the study described in Chapter 4.1. Here it was shown that the current quality of life of (adult) patients does not differ between COP patients and AOP patients with

comparable severity scores. Therefore, the conclusion can be drawn that quality of life and severity of disease in adulthood are not determined by the age of onset of psoriasis.

Main conclusions of this thesis:

Epidemiology (Chapter 2)

- Childhood psoriasis has an overall prevalence of 0.7% in The Netherlands, which means that there should be approximately 27 500 children with psoriasis in The Netherlands. More precisely, in the first age decade the prevalence is 0.37%; in the second age decade 1.09%.
- Of the adult patients with psoriasis, 37.1% reports an onset of disease before the age of 18 years.
- Dutch juvenile psoriasis patients report a familial distribution in 50.3 - 73.3%. On the contrary, in only 13.6% of Singaporean children with psoriasis a familial distribution is noted.
- The most frequently seen type of childhood psoriasis in the Dutch cohort is plaque psoriasis (88.9%), followed by pustular psoriasis (6.7%) and guttate psoriasis (2.2%).
- Scalp (88.9%) and limbs (86.7%) are the most often affected body parts in children with psoriasis.
- Pruritus is frequently a complaint of children with psoriasis (80% of the cases).
- A correlation between childhood onset psoriasis and a high body mass index at adult age could not be found.
- The type of psoriasis at onset often remains the same throughout life in childhood onset psoriasis patients.
- The course of childhood onset psoriasis is not worse than that of adult onset psoriasis.
- Delay in diagnosis is on average twice as long in childhood onset psoriasis as in adult onset psoriasis.

Treatments (Chapter 3)

- Only two randomized controlled trials have been performed on treatments for childhood psoriasis: one with calcipotriol and one with etanercept.
- A rough summary of the proposed treatment algorithm is as follows: first,

calcipotriol with or without topical corticosteroids, followed by dithranol. Methotrexate is considered to be the systemic treatment of choice. The extended treatment algorithm can be found on page 155.
- Short-contact dithranol therapy is an effective and safe treatment option for childhood psoriasis and should be attempted first before prescribing systemic medication.

Quality of life (Chapter 4)
- The burden of psoriasis in children is substantial and mainly affects recreational and social activities.
- Disease severity scores show a moderate correlation with quality of life scores, therefore both scores should be taken into account when deciding on the treatment strategy in childhood psoriasis.
- Quality of life in adulthood is not determined by age of onset of psoriasis.

Practical clinical advises:

As has been demonstrated in this thesis, childhood psoriasis is a relatively frequently seen disease. Because it can mimic nummular eczema, it is very important for physicians to consider childhood psoriasis in case of an itching, fine-scaled, nummular, erythematous skin condition (especially if the scalp is affected). The occurrence of psoriasis in the patient's family can point in the right direction, although in Asian children this positive family history is often absent.
Childhood psoriasis can have an important influence on a child's life. Therefore, not only clinical severity should be taken into account when deciding on a treatment strategy, but also the impact of the disease on the quality of life of the child. As the correlation between these two aspects is only moderate, both a severity score (e.g. PASI, PGA) and a quality of life score (e.g. CDLQI) should be assessed. Preferably, these assessments should be made at regular time intervals to provide an overview in time of the health status of the child. Based on the repeated quality of life measurements and severity scores, the steps of the proposed treatment algorithm (page 155) can be followed. By doing so, treatment steps will be tailored for each individual child, and therefore optimal care will be provided in the treatment of childhood psoriasis.

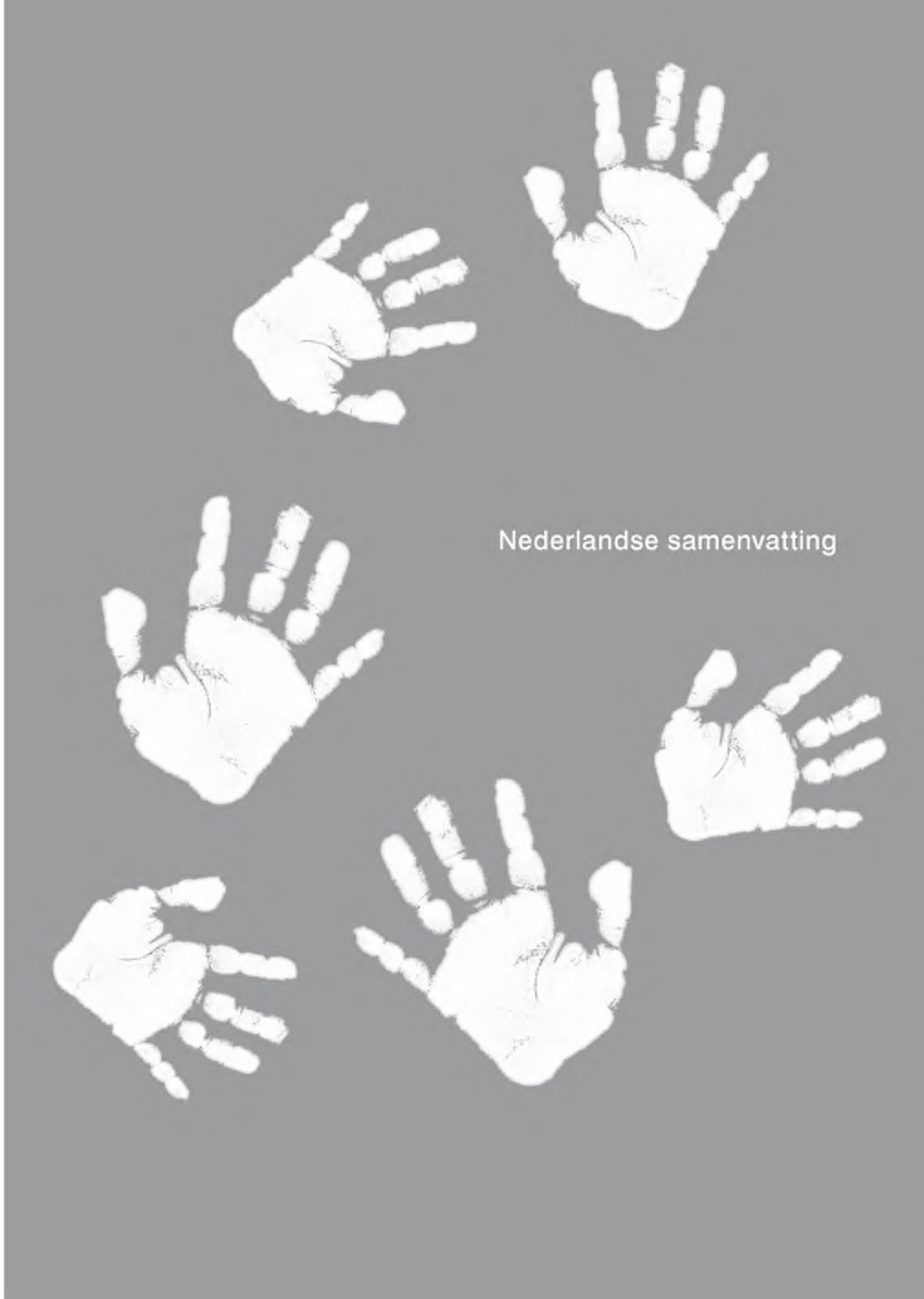
Reference List

1. Gelfand JM, Weinstein R, Porter SB *et al.* Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. *Arch.Dermatol.* 2005; 141: 1537-41.
2. Augustin M, Glaeske G, Radtke MA *et al.* Epidemiology and comorbidity of psoriasis in children. *Br.J.Dermatol.* 2010; 162: 633-6.
3. Braun-Falco O, Burg G, Farber EM. [Psoriasis. A questionnaire study of 536 patients]. *Munch.Med.Wochenschr.* 1972; 114: 1105-10.
4. Rigopoulos D, Gregoriou S, Katrinaki A *et al.* Characteristics of psoriasis in Greece: an epidemiological study of a population in a sunny Mediterranean climate. *Eur.J.Dermatol.* 2010; 20: 189-95.
5. Farber EM, Nall ML. The natural history of psoriasis in 5,600 patients. *Dermatologica* 1974; 148: 1-18.
6. Verbov J. Psoriasis in childhood. *Arch.Dis. Child* 1992; 67: 75-6.
7. Farber EM, Carlsen RA. Psoriasis in childhood. *Calif.Med.* 1966; 105: 415-20.
8. Watson W, Cann HM, Farber EM *et al.* The genetics of psoriasis. *Arch.Dermatol.* 1972; 105: 197-207.
9. Swanbeck G, inerot A, Martinsson T *et al.* Age at onset and different types of psoriasis. *Br.J.Dermatol.* 1995; 133: 768-73.
10. Tollefson MM, Crowson CS, McEvoy MT *et al.* incidence of psoriasis in children: a population-based study. *J.Am.Acad.Dermatol.* 2010; 62: 979-87.
11. Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. *J.Am.Acad. Dermatol.* 1985; 13: 450-6.
12. Kumar B, Jain R, Sandhu K *et al.* Epidemiology of childhood psoriasis: a study of 419 patients from northern india. *Int.J.Dermatol.* 2004; 43: 654-8.
13. Morris A, Rogers M, Fischer G *et al.* Childhood psoriasis: a clinical review of 1262 cases. *Pediatr.Dermatol.* 2001; 18: 188-98.
14. Nanda A, Kaur S, Kaur i *et al.* Childhood psoriasis: an epidemiologic survey of 112 patients. *Pediatr.Dermatol.* 1990; 7: 19-21.
15. Fan X, Xiao FL, Yang S *et al.* Childhood psoriasis: a study of 277 patients from China. *J. Eur.Acad.Dermatol.Venereol.* 2007; 21: 762-5.
16. Burgers SA, van Vloten WA. [Findings in children with psoriasis]. *Ned.Tijdschr. Geneeskd.* 1999; 143: 148-51.
17. Wu Y, Lin Y, Liu HJ *et al.* Childhood psoriasis: a study of 137 cases from central China. *World J.Pediatr.* 2010; 6: 260-4.
18. Seyhan M, Coskun BK, Saglam H *et al.* Psoriasis in childhood and adolescence: evaluation of demographic and clinical features. *Pediatr.Int.* 2006; 48: 525-30.
19. Sigure S. Study on children psoriasis in Latvia. *Acta Dermatovenerol Alp Panonica Adriat.* 2002; 11: 45-9.
20. Al-Fouzan AS, Nanda A. A survey of childhood psoriasis in Kuwait. *Pediatr.Dermatol.* 1994; 11: 116-9.
21. Nyfors A, Lemholt K. Psoriasis in children. A short review and a survey of 245 cases. *Br.J.Dermatol.* 1975; 92: 437-42.
22. Kim SK, Kang HY, Kim YC *et al.* Clinical comparison of psoriasis in Korean adults and children: correlation with serum anti-streptolysin O titers. *Arch.Dermatol.Res.* 2010; 302: 295-9.
23. Nanda A, Al-Fouzan AS, El-Kashlan M *et al.* Salient features and HLA markers of childhood psoriasis in Kuwait. *Clin.Exp.Dermatol.* 2000; 25: 147-51.
24. Al-Mutairi N, Manchanda Y, Nour-Eldin O. Nail changes in childhood psoriasis: a study from Kuwait. *Pediatr.Dermatol.* 2007; 24: 7-10.
25. Palier AS, Siegfried EC, Langley RG *et al.* Etanercept treatment for children and adolescents with plaque psoriasis. *N.Engl.J. Med.* 2008; 358: 241-51.
26. Boccardi D, Menni S, La VC *et al.* Overweight and childhood psoriasis. *Br.J.Dermatol.* 2009; 161: 484-6.
27. World Health Organization. *Website World Health Organization BMI classification* URL: http://apps.who.int/bmi/index.jsp?introPage=intro_3.html (last accessed 20 August 2009).
28. Halkier-Sorensen L, Laurberg G, Andresen J. Bone changes in children on long-term treatment with etretinate. *J.Am.Acad.Dermatol.* 1987; 16: 999-1006.

29. Prendiville J, Bingham EA, Burrows D. Premature epiphyseal closure--a complication of etretinate therapy in children. *J.Am.Acad. Dermatol.* 1986; 15: 1259-62.
30. Glover MT, Peters AM, Atherton DJ. Surveillance for skeletal toxicity of children treated with etretinate. *Br.J.Dermatol.* 1987; 116: 609-14.
31. Lacour M, Mehta-Nikhar B, Atherton DJ *et al.* An appraisal of acitretin therapy in children with inherited disorders of keratinization. *Br.J.Dermatol.* 1996; 134: 1023-9.
32. Katugampola RP, Finlay AY. Oral retinoid therapy for disorders of keratinization: single-centre retrospective 25 years' experience on 23 patients. *Br.J.Dermatol.* 2006; 154: 267-76.
33. Paige DG, Judge MR, Shaw DG *et al.* Bone changes and their significance in children with ichthyosis on long-term etretinate therapy. *Br.J.Dermatol.* 1992; 127: 387-91.
34. Brecher AR, Orlow SJ. Oral retinoid therapy for dermatologic conditions in children and adolescents. *J.Am.Acad.Dermatol.* 2003; 49: 171-82.
35. Hamahira K, Iijima K, Tanaka R *et al.* Recovery from cyclosporine-associated arteriolopathy in childhood nephrotic syndrome. *Pediatr.Nephrol.* 2001; 16: 723-7.
36. Ramanan AV, Whitworth P, Baildam EM. Use of methotrexate in juvenile idiopathic arthritis. *Arch.Dis.Child* 2003; 88: 197-200.
37. Graham LD, Myones BL, Rivas-Chacon RF *et al.* Morbidity associated with long-term methotrexate therapy in juvenile rheumatoid arthritis. *J.Pediatr.* 1992; 120: 468-73.
38. Hashkes PJ, Balistreri WF, Bove KE *et al.* The long-term effect of methotrexate therapy on the liver in patients with juvenile rheumatoid arthritis. *Arthritis Rheum.* 1997; 40: 2226-34.
39. Keim D, Ragsdale C, Heidelberger K *et al.* Hepatic fibrosis with the use of methotrexate for juvenile rheumatoid arthritis. *J.Rheumatol.* 1990; 17: 846-8.
40. Kugathasan S, Newman AJ, Dahms BB *et al.* Liver biopsy findings in patients with juvenile rheumatoid arthritis receiving long-term, weekly methotrexate therapy. *J.Pediatr.* 1996; 128: 149-51.
41. Lahdenne P, Rapola J, Ylijoki H *et al.* Hepatotoxicity in patients with juvenile idiopathic arthritis receiving longterm methotrexate therapy. *J.Rheumatol.* 2002; 29: 2442-5.
42. Wallace CA, Bleyer WA, Sherry DD *et al.* Toxicity and serum levels of methotrexate in children with juvenile rheumatoid arthritis. *Arthritis Rheum.* 1989; 32: 677-81.
43. Palier AS, Pariser D, Foehl J *et al.* interim results of a long-term safety and tolerability study of etanercept treatment in children and adolescents age 8 to 17 years with plaque psoriasis. *Poster Presentation at the European Society for Pediatric Dermatology Congress Lausanne* 2010; PP080.
44. Lovell DJ, Reiff A, Ilowite NT *et al.* Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. *Arthritis Rheum.* 2008; 58: 1496-504.
45. Prince FH, Twilt M, Ten CR *et al.* Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. *Ann.Rheum.Dis.* 2009; 68: 635-41.
46. Evers AW, Lu Y, Duller P *et al.* Common burden of chronic skin diseases? Contributors to psychological distress in adults with psoriasis and atopic dermatitis. *Br.J. Dermatol.* 2005; 152: 1275-81.
47. Verhoeven EW, Kraaimaat FW, van de Kerkhof PC *et al.* Prevalence of physical symptoms of itch, pain and fatigue in patients with skin diseases in general practice. *Br.J. Dermatol.* 2007; 156: 1346-9.
48. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br.J. Dermatol.* 2006; 155: 145-51.
49. Lewis-Jones MS, Finlay AY. The Children's Dermatology Life Quality index (CDLQi): initial validation and practical use. *Br.J. Dermatol.* 1995; 132: 942-9.

50. Lundberg L, Johannesson M, Silverdahl M *et al.* Health-related quality of life in patients with psoriasis and atopic dermatitis measured with SF-36, DLQI and a subjective measure of disease activity. *Acta Derm.Venereol.* 2000; 80: 430-4.
51. Reich K, Kruger K, Mossner R *et al.* Epidemiology and clinical pattern of psoriatic arthritis in Germany: a prospective interdisciplinary epidemiological study of 1511 patients with plaque-type psoriasis. *Br.J.Dermatol.* 2009; 160: 1040-7.
52. Annett RD, Bender BG, Lapidus J *et al.* Predicting children's quality of life in an asthma clinical trial: what do children's reports tell us? *J.Pediatr.* 2001; 139: 854-61.
53. de Jager MEA, de Jong EMGJ, Evers AWM *et al.* The burden of childhood psoriasis. *Pediatr.Dermatol.* 2010; In press.
54. de Jager MEA, van de Kerkhof PCM, de Jong EMGJ *et al.* A cross-sectional study using the Children's Dermatology Life Quality Index (CDLQI) in childhood psoriasis: the negative effect on the quality of life and moderate correlation of CDLQI and severity scores. *Br.J.Dermatol.* 2010; 163: 1099-101.

Nederlandse samenvatting



Psoriasis is een chronische, inflammatoire huidziekte die zich bij ongeveer 30% van de patiënten manifesteert op de kinderleeftijd. Echter, de beschikbare literatuur over de ziekte in deze leeftijdscategorie is erg beperkt. Een overzicht hiervan wordt gegeven in **hoofdstuk 1**.

In dit proefschrift zijn nieuwe gegevens verzameld omtrent juveniele psoriasis, om zo te komen tot een beter begrip van de ziekte. Daaruit voortvloeiend zijn behandelstrategieën voor kinderen met psoriasis opgesteld.

Dit proefschrift beschrijft drie verschillende aspecten van juveniele psoriasis:
1. Epidemiologie en klinische kenmerken (**hoofdstuk 2**)
2. Behandelopties (**hoofdstuk 3**)
3. Kwaliteit van leven (**hoofdstuk 4**)

Hoofdstuk 2 bestaat uit drie studies. In **hoofdstuk 2.1** worden de resultaten van een enquête onder 1926 volwassen patiënten beschreven. De respondenten werden verdeeld in twee groepen: patiënten met psoriasis die was ontstaan op de kinderleeftijd (leeftijd $<$ 18 jaar) en patiënten met psoriasis die was ontstaan op de volwassen leeftijd (leeftijd $\geq$ 18 jaar). De verschillen en overeenkomsten tussen deze twee groepen worden gepresenteerd. Middels een enquête onder huisartsen en dermatologen (**hoofdstuk 2.2**) is een prevalentie-cijfer vastgesteld van juveniele psoriasis in Nederland. Uit de literatuur is bekend dat er verschillen bestaan in klinische kenmerken en familiair voorkomen tussen verschillende bevolkingsgroepen wereldwijd. Daarom werd in **hoofdstuk 2.3** het Nijmeegse juveniele psoriasis cohort vergeleken met een cohort van kinderen met psoriasis uit Singapore.

Het doel van **hoofdstuk 3** was om de beschikbare behandelingen voor juveniele psoriasis te evalueren en een behandelalgoritme op te stellen. Daarom werd een systematisch literatuuronderzoek verricht (**hoofdstuk 3.1**). Tevens werd er aanvullend een onderzoek gedaan naar de effectiviteit en veiligheid van kort-contact dithranol behandeling (**hoofdstuk 3.2**) om de plaats van deze behandelmogelijkheid in het behandelalgoritme vast te stellen. Het behandel-algoritme is te vinden op pagina 155 van dit proefschrift.

De kwaliteit van leven bij kinderen met psoriasis staat centraal in **hoofdstuk 4**. Allereerst is onderzocht hoe de kwaliteit van leven van deze kinderen zich

ontwikkelt in de loop van het leven. Daarnaast werd vastgesteld op welke gebieden psoriasis de meeste invloed heeft gehad op de kinderleeftijd (**hoofdstuk 4.1**). Ook zijn er interviews met juveniele psoriasis patiënten verricht om deze aspecten verder uit te diepen (**hoofdstuk 4.2**). In **hoofdstuk 4.3** is de correlatie onderzocht tussen scores waarbij de uitgebreidheid van de psoriasis wordt vastgelegd (bijv. PASI, PGA) en kwaliteit van leven scores (bijv. CDLQI).

In **hoofdstuk 5** worden de bevindingen per hoofdstuk samengevat en bediscussieerd.

De belangrijkste conclusies van dit proefschrift:

Epidemiologie (hoofdstuk 2)

- Juveniele psoriasis heeft een totale prevalentie van 0.7% in Nederland, wat neerkomt op ongeveer 27 500 kinderen met psoriasis in Nederland. In de leeftijdscategorie van 0 tot 10 jaar is de prevalentie 0.37%, in de leeftijdscategorie van 11 tot 19 jaar 1.09%.
- Van de volwassen patiënten met psoriasis geeft 37.1% aan dat de huidklachten vóór het 18e levensjaar begonnen zijn.
- In Nederland is er bij 50.3 tot 73.3% van de juveniele psoriasis patiënten sprake van een belaste familieanamnese voor psoriasis. Bij kinderen uit Singapore met psoriasis is er in slechts 13.6% sprake van het familiair voorkomen van psoriasis.
- Het meest voorkomende type psoriasis bij kinderen in het Nederlandse cohort is plaque psoriasis (88.9%), gevolgd door psoriasis pustulosa (6.7%) en psoriasis guttata (2.2%).
- De hoofdhuid (88.9%) en extremiteiten (86.7%) zijn de meest aangedane lichaamsdelen bij kinderen met psoriasis.
- Jeuk komt voor bij ongeveer 80% van de kinderen met psoriasis.
- Een verband tussen psoriasis ontstaan op de kinderleeftijd en een hoge body mass index op volwassen leeftijd is niet aangetoond.
- Het type psoriasis dat ontstaat op de kinderleeftijd blijft vaak onveranderd gedurende het gehele leven.
- Het beloop van juveniele psoriasis is niet ernstiger dan die van psoriasis ontstaan op de volwassen leeftijd.
- De tijd tussen het ontstaan van klachten en het stellen van de diagnose is

gemiddeld twee keer zo lang bij juveniele psoriasis in vergelijking met psoriasis ontstaan op volwassen leeftijd.

Behandelingen (hoofdstuk 3)

- Er zijn slechts twee gerandomiseerde gecontroleerde studies verricht naar het effect en de veiligheid van medicamenteuze behandelingen bij kinderen met psoriasis: één met calcipotriol en één met etanercept.
- Een korte samenvatting van het behandelalgoritme is als volgt: geadviseerd wordt te starten met calcipotriol met of zonder topicale corticosteroïden, gevolgd door dithranol. Methotrexaat wordt beschouwd als de eerste keus systemische behandeling. Het volledige behandelalgoritme is beschreven op pagina 155 van dit proefschrift.
- Kort-contact dithranol therapie is een effectieve en veilige behandeling voor psoriasis bij kinderen en dient eerst geprobeerd te worden alvorens over te gaan op systemische medicatie.

Kwaliteit van leven (hoofdstuk 4)

- Psoriasis bij kinderen heeft een grote invloed op de kwaliteit van leven, met name op recreatieve en sociale activiteiten.
- Ziekte-ernst scores hebben een matige correlatie met kwaliteit van leven scores, waardoor er dus rekening gehouden dient te worden met beide scores in de besluitvorming over de te volgen behandelstrategie.
- Kwaliteit van leven op volwassen leeftijd wordt niet bepaald door de leeftijd waarop de psoriasis ontstaan is.

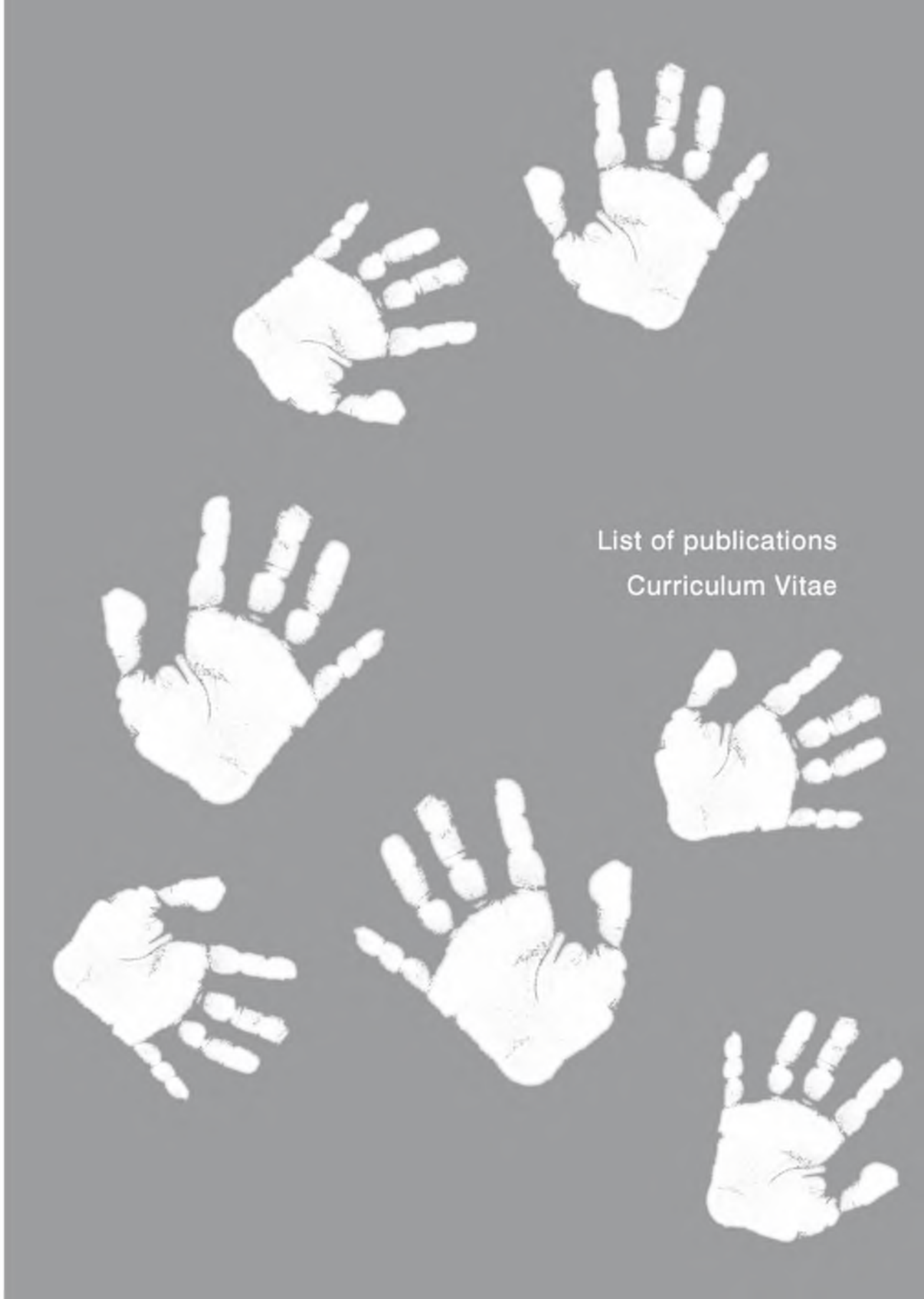
Praktische klinische adviezen:

Zoals is aangetoond in dit proefschrift is juveniele psoriasis een relatief vaak voorkomende huidziekte. Omdat de huidafwijking kan lijken op nummulair eczeem is het erg belangrijk voor artsen om de diagnose juveniele psoriasis te overwegen in geval van een jeukende, fijn schilferende, nummulaire, erythemateuze huidafwijking (vooral als de hoofdhuid is aangedaan). Het voorkomen van psoriasis in de familie van de patiënt kan wijzen in de richting van de juiste diagnose, hoewel bij Aziatische kinderen een belaste familieanamnese vaak afwezig is.
Juveniele psoriasis kan van grote invloed zijn op het leven van een kind. Daarom

moet niet alleen de ernst van de psoriasislaesies in ogenschouw worden genomen bij de beslissing over een behandelstrategie, maar ook de impact van de ziekte op de kwaliteit van leven van het kind. Omdat de correlatie tussen deze twee aspecten slechts matig is, zouden zowel een ziekte-ernst score (bijv. PASI, PGA) en een kwaliteit van leven score (bijv. CDLQI) moeten worden afgenomen. Bij voorkeur dienen deze scores te worden bepaald op regelmatige tijdstippen om een overzicht van de totale (lichamelijke en psychische) gezondheidstoestand van het kind in de tijd te verkrijgen.
Vervolgens kunnen de stappen van het behandelalgoritme (pagina 155) worden gevolgd op geleide van de ziekte-ernst scores en de kwaliteit van leven scores om zo te komen tot de meest optimale zorg voor patiënten met juveniele psoriasis.

List of publications

Curriculum Vitae



List of publications

de Jager MEA, Weemaes CMR, Blokx WAM, Seyger MMB; Niet-infectieuze cutane granulomen bij een kind met een primaire immuundeficiëntie. *Nederlands Tijdschrift voor Dermatologie en Venereologie*. 2007; 17(6): 219-21.

de Jager MEA, Blokx WAM, Warris A, Bergers AMG, Link MMG, Weemaes CMR, Seyger MMB; Immunohistochemical features of cutaneous granulomas in primary immunodeficiency disorders: a comparison with cutaneous sarcoidosis. *Journal of Cutaneous Pathology* 2008; 35(5): 467-72.

de Jager MEA, van de Kerkhof PCM, de Jong EMGJ, Seyger MMB; Epidemiology and prescribed treatments in childhood psoriasis: a survey among medical professionals. *Journal of Dermatological Treatment* 2009; 20(5): 254-8.

de Jager MEA, de Jong EMGJ, van de Kerkhof PCM, Seyger MMB; Efficacy and safety of treatments for childhood psoriasis: a systematic literature review. *Journal of the American Academy of Dermatology* 2010; 62(6): 1013-30.

de Jager MEA, de Jong EMGJ, Meeuwis KAP, van de Kerkhof PCM, Seyger MMB; No evidence found that childhood onset of psoriasis influences disease severity, future body mass index or type of treatments used. *Journal of the European Academy of Dermatology and Venereology* 2010; 24(11): 1333-9.

de Jager MEA, van de Kerkhof PCM, de Jong EMGJ, Seyger MMB; Dithranol therapy in childhood psoriasis: unjustifiably on the verge of falling into oblivion. *Dermatology* 2010: 220(4): 329-32.

de Jager MEA, de Jong EMGJ, van de Kerkhof PCM, Evers AWM, Seyger MMB; A cross-sectional study using the Children's Dermatology Life Quality Index (CDLQI) in childhood psoriasis: the negative effect on the quality of life and moderate correlation of CDLQI and severity scores. *British Journal of Dermatology* 2010; 163(5): 1099-101.

Meeuwis KAP, de Hullu JA, **de Jager MEA**, Massuger LFAG, van de Kerkhof PCM, van Rossum MM; Genital psoriasis: a questionnaire-based survey on a concealed skin disease in the Netherlands. *Journal of the European Academy of Dermatology and Venereology* 2010; 24(12): 1425-30.

de Jager MEA, van de Kerkhof PCM, de Jong EMGJ, Evers AWM, Seyger MMB; An intrapatient comparison of quality of life in psoriasis in childhood and adulthood. *Journal of the European Academy of Dermatology and Venereology* E-pub ahead of print.

de Jager MEA, de Jong EMGJ, Evers AWM, van de Kerkhof PCM, Seyger MMB; The burden of childhood psoriasis. *Pediatric Dermatology* In press.

Chiam LYT, **de Jager MEA**, Giam YC, de Jong EMGJ, van de Kerkhof PCM, Seyger MMB; Juvenile psoriasis in European and Asian children - similarities and differences. *British Journal of Dermatology* E-pub ahead of print.

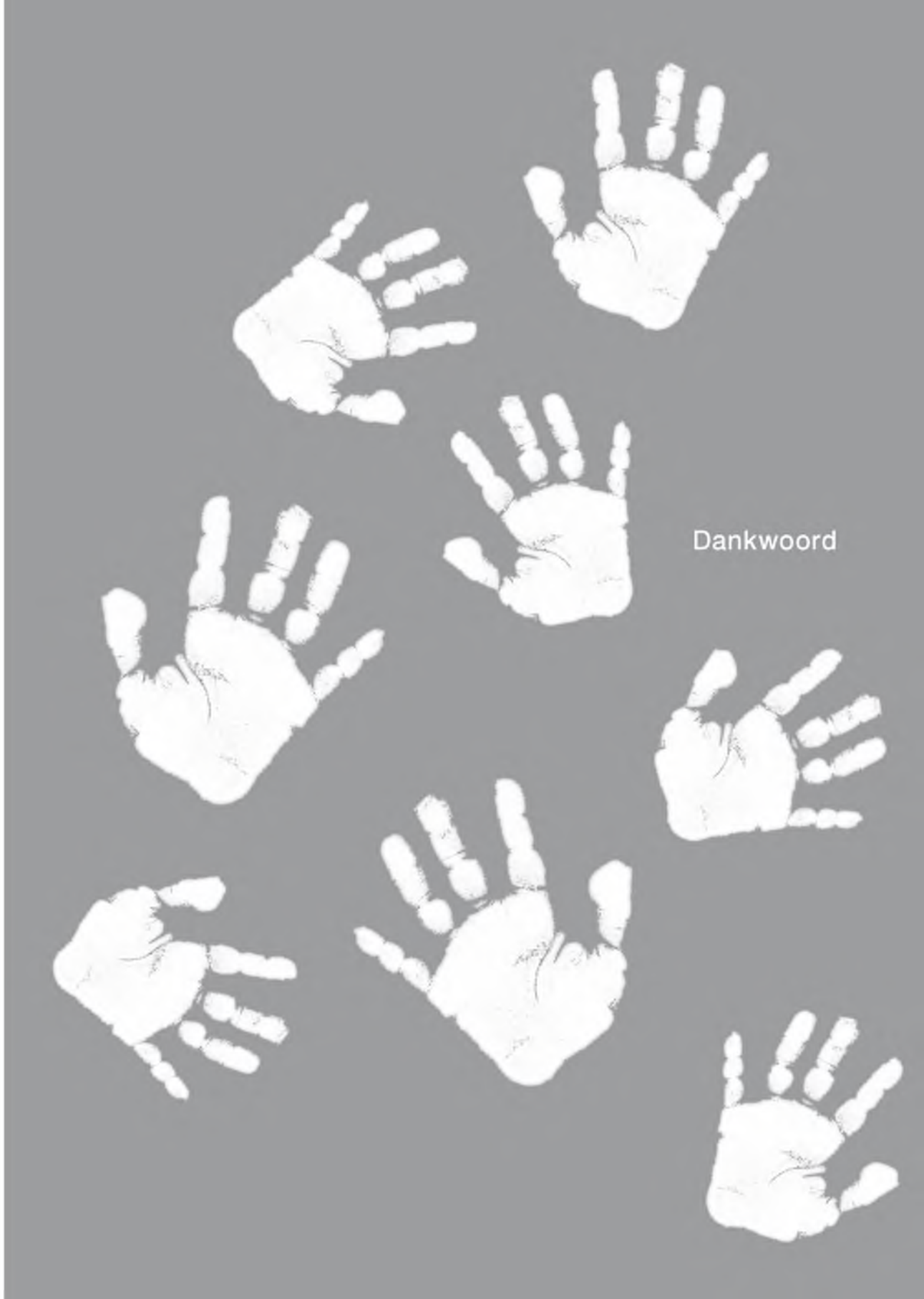
Curriculum Vitae

Michelle Elisabeth Anne de Jager werd op 1 mei 1982 geboren te Nijmegen. Zij behaalde in 2000 haar VWO diploma aan het Canisius College in Nijmegen. Omdat zij in eerste instantie werd uitgeloot voor de studie Geneeskunde, startte Michelle na haar middelbare school periode met de studie Biomedische Wetenschappen aan de Radboud Universiteit Nijmegen. Het jaar erop werd zij gelukkig ingeloot voor de opleiding Geneeskunde aan dezelfde universiteit. Michelle behaalde haar propedeuse in 2002 en haar artsexamen in 2007. Tijdens haar laatste studiejaar verrichtte zij haar onderzoeksstage naar cutane granulomen bij kinderen met een immuundeficiëntie op de afdeling Dermatologie van het UMC St Radboud onder leiding van mw. dr. M.M.B. Seyger.

Na het behalen van het artsexamen werkte zij één jaar als arts op de spoedeisende hulp van het Jeroen Bosch Ziekenhuis (locatie Carolus) in 's Hertogenbosch. Op 1 april 2008 is Michelle gestart als onderzoeker in opleiding met als onderwerp juveniele psoriasis onder leiding van prof. dr. dr. P.C.M. van de Kerkhof, mw. dr. M.M.B. Seyger en mw. dr. E.M.G.J. de Jong.

Vanaf 1 april 2010 is Michelle in opleiding tot dermatoloog in het UMC St Radboud.

Dankwoord



Dankwoord

En natuurlijk geen proefschrift zonder dankwoord!
Als eerste wil ik al "mijn" patiënten bedanken die van heinde en verre kwamen voor de regelmatige controles met het keer op keer invullen van vragenlijsten, wegen, meten en scoren. Zonder hun medewerking was dit boekje er niet geweest.
Dr. M.M.B. Seyger, beste Marieke, toen ik nog twijfelde tussen kindergeneeskunde en dermatologie heb ik gevraagd of ik misschien bij jou mijn onderzoeksstage kon doen. Het klikte meteen en we waren dan ook toen al een goed team. Desalniettemin ben ik niet alleen jouw eerste, maar ook laatste wetenschappelijke stagiaire... Gelukkig werd ik na enige tijd ook weer jouw eerste "eigen" promovenda op het gebied van de kinderdermatologie! Ik denk dat we erg trots mogen zijn op ons "kindje", waar we hard voor gewerkt hebben. Zelfs op je vakanties gingen mijn artikelen soms mee... En niet te vergeten mijn vele to-do lists die we hebben afgewerkt. Jouw gedrevenheid, positiviteit, gezelligheid en humor maakten het allemaal nog leuker. Je deur stond altijd open, ik kon altijd bij je terecht. En natuurlijk ook voor reisverhalen en koppen thee wisten we elkaar te vinden. Bedankt voor de geweldige begeleiding, ik had me geen betere kunnen wensen!
Prof. dr. dr. P.C.M. van de Kerkhof, beste professor, op de eerste plaats natuurlijk bedankt voor de kans om onderzoek te doen naar dit geweldige onderwerp. Het lag (en ligt) helemaal in mijn straatje. Uw tomeloze energie en enthousiasme en onze bijna wekelijkse "juvenile psoriasis team"-overleggen gaven altijd weer een duwtje in de goede richting. Maar ook niet-werkgerelateerde onderwerpen hebben de revue gepasseerd onder het genot van een cappuccino!
Dr. E.M.G.J. de Jong, beste Elke, mede dankzij jouw vrolijkheid, positiviteit, goede aanvullingen en ideeën ligt dit boekje er. Vaak kreeg ik mijn artikelen al weer een dag later terug met correcties, omdat jij ze vaak 's avonds op de bank las. Hopelijk houden we onze splinternieuwe traditie (met Marieke en Rieke) in stand!
Mark de Jager, lief broertje, wie had ooit gedacht dat ík degene van ons tweeën zou zijn die zou promoveren? Bedankt dat jij mijn paranimf wilt zijn.
Rieke Driessen, lieve Rieke, vele blikken werden er geworpen over onze computerschermen als er weer eens iets gebeurde in de bieb. Bedankt voor alle tips en tricks over de database en queries. Ons logo is natuurlijk ook erg mooi! Nu weer op naar ons volgende etentje!
Al mijn collega-onderzoekers (Rieke, Haike, Kim, Esther, Paula, Margit, Inge en Annet) bedankt voor de gezellige tijd. In het bijzonder de vrijdagmiddagborrels

kwamen vaak als geroepen. Annet, jij veel succes en plezier als mijn opvolgster, jouw boekje volgt vast ook snel.
Ola Marisol, gracias por enseñarme todas las cosas en el mundo de trial, juntos contigo era más agradable. Por supuesto mucha suerte con obtener tu título de doctor!
Alle collega arts-assistenten, bedankt voor het doorsturen van de patiënten, zonder jullie zou de database een stuk minder vol gezeten hebben. Ik kijk er naar uit de komende jaren met jullie samen te werken.
Onze medisch fotografen, bedankt voor het maken van de uitgebreide fotoreeksen van al mijn patiënten!
Alle medewerkers van de afdeling dermatologie, bedankt voor de fijne samenwerking en plezierige werksfeer.
Lynn, thank you for your help combining our data on children with psoriasis. I wish you the best in Singapore.
Alfons den Broeder en Martijn van Oijen, bedankt voor de consulten methodologie en statistiek.
Vrienden en familie, bedankt voor de gezelligheid en jullie interesse in mijn werkzaamheden. In het bijzonder gaat mij dank ook uit naar Edith en Stef: tijdens de weekeinden in Rees is een groot deel van dit boekje samengesteld.
Merel, Janneke en Kim (mijn oud-Kroolus collega's), bedankt dat ik af en toe bij jullie mijn hart kon luchten, voor jullie vriendschap, gezelligheid, interesse en steun. Jullie zijn me ontzettend dierbaar.
Mark, lief broertje, voor de 2e keer genoemd worden in het dankwoord, dan moet je wel erg belangrijk zijn! Maar dat is natuurlijk ook zo. Gelukkig hebben we allebei een ander vakgebied gekozen, scheelt weer wat medische en juridische consultkosten. Bedankt voor je support.
Lieve papa en mama, bedankt dat jullie altijd achter me staan en voor jullie vertrouwen en liefde.
Maar op de belangrijkste plaats, Gijs, Liefie, bedankt voor je onvoorwaardelijke liefde, steun en rotsvaste vertrouwen in mij. Zonder jou was het me nooit gelukt. Ondanks je eigen promotietraject, heb jij dit boekje vaker gelezen dan wie ook. Bedankt voor al je correcties. Toch best handig om als reumatoloog ook iets van kinderpsoriasis te weten. Nu nog de dermatoloog die iets van artrose weet, maar die volgt vast ook snel! One down, one to go!

Michelle