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Review

Summary of the Dutch S3-Guidelines on the treatment of psoriasis 2011

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Abstract

This document provides a summary of the Dutch S3-guidelines on the treatment of psoriasis. These guidelines were finalized in December 2011 and contain unique chapters on the treatment of psoriasis of the face and flexures, childhood psoriasis as well as the patient's perspective on treatment. They also cover the topical treatment of psoriasis, photo(chemo)therapy, conventional systemic therapy and biological therapy.

Abbreviations

BCC	Basal Cell Carcinoma
BSA	Body Surface Area
CIN	Cervical Intraepithelial Neoplasia
Cr	Chromium
DLQI	Dermatology Life Quality Index
EDTA	EthyleneDiamineTetraacetic Acid
EL	Evidence Level
EMA	European Medicines Agency
FDA	Food and Drug Administration
GE	Grades of Evidence

GI	Gastrointestinal
HAART	Highly Active Anti-Retroviral Therapy
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
IGRA	Interferon-Gamma Release Assay
IL	InterLeukin
ITT	Intention To Treat
IUD	IntraUterine Divice
KIN	Keratinocytic Intraepidermal Neoplasia
LCD	Liquor Carbonis Detergens
LE	Lupus Erythematosus
LTBI	Latent TB Infection
MED	Minimal Erythema Dosage
MPD	Minimal Phototoxic Dosage
MTX	Methotrexate
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
PIIINP	Procollagen type III N-terminal Peptide
PASI	Psoriasis Area and Severity Index
PGA	Physician Global Assessment
PRO	Patient Reported Outcomes
PUVA	Psoralen (plus) UltraViolet A
QFT-G	QuantiFeron TB Gold test
SmPC	Summary of Product Characteristics

TB	Tuberculosis
TNF	Tumor Necrosis Factor
UV	UltraViolet
VAS	Visual Analogue Scale

1. Introduction to the guidelines

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1.1 Short introduction to psoriasis

Psoriasis is a chronic, inflammatory skin disease with a prevalence of 2-3% in the Western population [1, 2]. The most common clinical form of psoriasis is the chronic plaque type (90%). Abnormalities of the nails are seen in 50-80% of psoriasis patients and 20-30% also suffer from psoriatic arthritis. Other subtypes are inverse/genital, facial, scalp, guttate, erythrodermic, pustular, and palmoplantar psoriasis. Patients with psoriasis have strongly reduced quality of life scores with a quality of life similar to patients with diabetes mellitus, cardiovascular diseases, breast cancer, and depression [3]. Psoriasis is a disease that reaches further than the skin and may have systemic symptoms, such as metabolic syndrome. It may be associated with other chronic inflammatory diseases such as Crohn's disease, rheumatoid arthritis, and diabetes mellitus [4]. In psoriasis an abnormal local immune reaction can be seen, with a significantly elevated number of activated T-cells and dendritic cells and an enhanced production of cytokines. Cytokines that appear in large numbers in psoriatic lesions are TNF-alpha, type 1 and type 2 interferons, IL-12, IL-22, IL-23, and IL-17A [1, 5].

Therapies for psoriasis available in the Netherlands include topical treatments (corticosteroids, calcineurin inhibitors, Vitamin D3 analogues, coal tar, dithranol, combination preparations), photo(chemo)therapy (UVB, PUVA), and systemic therapies. The conventional systemic therapies include methotrexate, cyclosporine, acitretin, and fumaric acid esters. In targeting specific elements of the immune system, biologics have been added to the therapeutic armamentarium relatively recently. These expensive drugs are indicated for patients with moderate to severe psoriasis after ineffective phototherapy, methotrexate, or cyclosporine therapy or when these more common therapies are contraindicated or not being tolerated. Of the biologics, infliximab and adalimumab are antibodies against TNF-alpha and etanercept is a soluble TNF-alpha receptor fusion protein. Ustekinumab is a monoclonal antibody against the IL-12/IL-23 p40 protein.

1.2 Update of the Dutch S3-guidelines on the treatment of psoriasis

In 2003, the Dutch Society of Dermatology and Venereology introduced the first evidence-based guidelines on the treatment of psoriasis [6]. In 2006-2007, Germany published their first guidelines based on the Dutch guidelines of 2003 [7]. In 2009, the European S3-guidelines from the European Dermatology Forum appeared in the literature and were based on the Dutch, British, and German S3-guidelines [8].

In 2005, the Dutch Society of Dermatology and Venereology updated the practice guidelines from 2003 by updating the literature and including biologics to the guidelines. In 2009, these guidelines were revised slightly, specifically to improve the safety around prescribing methotrexate.

In 2011, the Dutch Society of Dermatology and Venereology finalized a complete update of the S3-guidelines on the treatment of psoriasis in Dutch, which is available online (Dutch S3-Guidelines on the Treatment of Psoriasis 2011; http://www.huidarts.info/documents/uploaded_file.aspx?id=579). Besides an update of the chapters on topical therapy, phototherapy, conventional systemic therapy, and biologic therapy for chronic plaque type psoriasis, these guidelines contain new chapters on the treatment of psoriasis of the face and flexures, childhood psoriasis, and the patient's perspective on treatment. The European S3-guidelines on the systemic treatment of psoriasis vulgaris by Pathirana, et al. (2009) were used as a basis for the Dutch S3-guidelines on the treatment of psoriasis 2011. We will summarize these Dutch S3-guidelines in this article.

Also in 2011, the Dutch Society for Rheumatology initiated additional, multidisciplinary guidelines (Dutch society of Rheumatology, Dermatology and Venereology, Gastroenterology and Hepatology, Physicians for Pulmonology and Tuberculosis and Internal Medicine as well as the Dutch Arthritis Association) on the use of biologics in daily practice [9] (http://www.reumabond.nl/downloads/algemeen/Mijn%20leven/Medicijnen/Biologicals/Richtlijn_biologicals_geautoriseerd.pdf).

These multidisciplinary guidelines answer questions on commonly encountered issues relating to treatment with biologics. Topics include pregnancy, surgical procedures, travelling abroad, and vaccination. We will not discuss these guidelines here.

1.3 Goals of the guidelines

The Dutch S3-guidelines on treatment of psoriasis 2011 contain recommendations in order to aid decision-making on treatment of psoriasis in daily practice. The guidelines are based on systematic reviews, primary research, and expert opinions. The guidelines are intended for dermatologists, but other personnel involved in treating psoriasis, such as general practitioners, could also benefit from it.

1.4 Composition of the working group

Dermatologists as well as patient representatives participated in the working group. Academic and peripheral centers had to be equally represented. These guidelines were developed independently of pharmaceutical companies. Conflicts of interest of working group members are mentioned within these guidelines.

1.5 Methods

The working group worked for two consecutive years (8 meetings) on a draft of the Dutch S3-guidelines. The working group formulated several key questions, which in combination with the chapters of the European S3-guidelines (Pathirana *et al*. 2009), served as the framework for these guidelines. Existing chapters of the European S3-guidelines were translated and updated. Chapters on the treatment of psoriasis of the face and flexures and on the treatment of childhood psoriasis were based on additional, separate systematic reviews (10-12). The search strategies executed to develop these guidelines are stated in appendix 1 of the Dutch S3-guidelines (appendix 1 of the Dutch S3-guidelines, available online: http://www.huidarts.info/documents/uploaded_file.aspx?id=579).

An assessment and literature evaluation form were used to select the relevant literature (appendix 2 of the Dutch S3-guidelines, available at http://www.huidarts.info/documents/uploaded_file.aspx?id=579). A full text version of the relevant studies was requested. Subsequently, these studies were selected according to inclusion and exclusion criteria and methodological quality (Table 1). Grades of evidence (GE) were assessed for selected articles (Table 2). Then, the members of the working group formulated conclusions and treatment recommendations based on included studies and provided these conclusions with an evidence level (Table 2). The final chapters were discussed and the concept guidelines were published online. Dermatologists were able to provide additional comments. These comments were implemented in the final version of the guidelines and approved by the Dutch Society of Dermatology and Venereology in December 2011.

Table 1: In- and exclusion criteria for the performed literature search*

Inclusion criteria	**Exclusion criteria**
Prospective studies (except for psoriasis in children)	Case reports (except for psoriasis in children) and abstracts
Meta-analysis and studies on induction of remission (treatment duration ≤ 16 weeks)	Studies with intralesional or topical administration of systemic treatment (instead of oral administration)
Monotherapy (except for the combination therapies retinoids/phototherapy and topical vitamin D/steroids)	Old-fashioned equipment

Dutch, English, French and German studies	Studies prescribing drugs that are not being used in the Netherlands
Studies with the following parameters: the percentage of patients with nearly complete remission (≥ 90%), the percentage of patients with partial remission (≥ 75%) (and/or duration of remission and/or percentage of improvement of psoriasis measured by PASI, PGA, global severity, body surface area, clearance)	Studies on phototherapy of only parts of the body
Dosing regimen and route of administration have to be stated in studies	Methotrexate dosage > 25 mg/week
Studies with separate data on psoriasis in adults and in children	Acitretin < 0.5 mg/kg/day
Studies with well-described separate data on several clinical subtypes of psoriasis or in case 75% of studied patients have one clinical subtype of psoriasis	Cyclosporine > 5 mg/kg/day
Studies with well-described separate data on levels of severity in patients with psoriasis or in case 75% of studied patients have moderate to severe psoriasis (PASI ≥ 8, topical therapy not sufficient)	
*Note: In case of uncertainty whether a study was performed prospectively the study was excluded. To avoid inaccuracy, data on the percentage of patients with ≥ 90% remission were not extrapolated to the percentage of ≥ 75% remission.	

Table 2: Grades of Evidence and Evidence Levels

Grades of Evidence (GE)

A1 Meta-analysis that includes at least one randomized clinical trial with a grade of evidence of A1; the results of the different studies included in the meta-analysis must be consistent

A2 Randomized, double-blind clinical study of high quality (e.g. sample-size calculation, flow chart of patient inclusion, ITT analysis, sufficient size)

B Randomized clinical study of lesser quality, or other comparative study (e.g. non-randomized cohort or case-control study)

C Non-comparative study

D Expert opinion

Evidence Levels (EL)

1 One study of level A1 or at least two independently performed studies of level A2

2 At least two independently performed studies of level B

3 One study of level A2 or B or studies of level C

4 Little or no systematic empirical evidence; expert opinions

1.6 Structure of the Dutch S3-Guidelines on the Treatment of Psoriasis 2011

The Dutch S3-guidelines are divided into different chapters, related to the different treatments of chronic plaque psoriasis, psoriasis of the face and flexures, and childhood psoriasis. A separate chapter provides an overview of the patient's perspective on treatment of psoriasis.

Every chapter starts with the key questions. Subsequently, for each treatment a short introduction is provided, followed by the mechanism of action, dosing regimen, efficacy, adverse effects/safety, contraindications, monitoring, conclusions, considerations, and treatment recommendations. Conclusions are based on current best evidence (Table 1 and 2). The working group members decided to provide conclusions on biologics solely based on grade of evidence A2. Translation of these conclusions into treatment recommendations for daily practice was established by the working group by considering different aspects, such as efficacy, safety, use, availability, and costs of treatment as well as patients' and physicians' preferences. In doing so, the Dutch Society of Dermatology and Venereology hopes to increase transparency of the Dutch S3-guidelines. A summary of the considerations of these different aspects is given in this article and can be found within the summary tables for each treatment (see below).

1.7 Legal consequences of the guidelines

Guidelines are composed in order to guide physicians in providing current, best medical care. The insights on treatment of chronic plaque psoriasis as stated in these guidelines are broadly agreed upon in the Netherlands. However, physicians are not legally

required to follow these recommendations. In individual cases it may be desired or may even be necessary to deviate from the recommendations in these guidelines. In doing so, the Dutch physician must argue and document his/her different proceedings and if possible involve the patient in the decision-making.

1.8 Authorization

The full version of the Dutch S3-guidelines on treatment of psoriasis has been authorized by the Dutch Society of Dermatology and Venereology in December 2011.

The present summary document has been agreed upon by all members of the working group who wrote chapters for the Dutch version of the S3-guidelines. The working group members approved this summary document.

1.9 Revision of the guidelines

The strength of guidelines lies in their continuous revision. Current medical studies as well as daily practice data and comments by users of these guidelines need to be implemented in future chapters. New chapters will be added to the Dutch S3-guidelines after updating searches on new developments in psoriasis treatment.

2. Treatment of psoriasis

2.1 Choice of treatment

Deciding which treatment to choose involves the ranking of different criteria. For the topical therapies, phototherapies and systemic monotherapies, the working group ranked the different drugs by different criteria, such as the degree of efficacy, safety, adverse effects, quality of life/treatment satisfaction, costs of therapy, and follow-up. Efficacy is divided into ≥90%, indicating almost complete remission, and ≥ 75%, indicating partial remission. Safety is divided into damage to vital organs, dysfunctions, teratogenicity, carcinogenicity after long-term use, toxicity in overdose, and drug interactions. In table 3, ranking is displayed from +, indicating less common or less serious, to +++, indicating most frequent or most serious. All criteria have been ranked separately for the different psoriatic treatments and cannot be calculated into a total score.

The working group did not value some of the criteria as more important as others. However, patients were able to value criteria in the evaluation of the patient's perspective (Table 3 and chapter 5). The working group holds the opinion that in choosing treatment, the decision has to be made in agreement with the patient and can deviate on individual basis from the norm outlined in these guidelines.

Table 3: Choice of treatment

	Efficacy			**Safety**						**Adverse effects**	**Quality of life/ Treatment satisfaction ****	**Costs of therapy and follow-up *****
	≥90 in %	≥75 in %	Duration of	Damage to vital	Dysfunctions*	Teratogenicity	Carcinogenicity	Toxicity in	Drug			

Topical											+	
Calcineurin inhibitors	?	?	+	0	0	?	+	0	0	+		+
Dithranol	30-70%	26-100%	+	0	0	?	0	0	0	+		+/++
Corticosteroids	25-78%	25-89%	+	+	+	0	0	0	0	+		0
Coal tar	?	45-80%	+	0	0	?	?	0	0	0		0
Vitamin D analogues	?	30-50%	+	0	0	?	0	0	0	+		+
Vitamin D/corticosteroids	?	55-76%	+	+	+	?	0	0	0	+		+
Phototherapy								****			++	
UVB	29-75%	See chapter photother.	++	0	0	0	+	+	0	+		Outpatient: ++ Home: ++
PUVA	79%	See chapter photother.	++	+	+	++/+++	++	++/+++	+	++		+++

	Efficacy			**Safety**						**Adverse effects**	**Quality of life/ Treatment satisfaction ****	**Costs of therapy and follow-up *****
	≥90 in %	≥75 in %	Duration of	Damage to vital	Dysfunctions*	Teratogenicity	Carcinogenicity	Toxicity in overdose	Drug interactions			
Systemic											+++	
Retinoids	11-50%*	25-41%	+/++	+	+/++	++	0	+/++	+/++	++		+
Methotrexate	11-40%	35-73%	+/++	++	++	++	+	++/++	++/++	+/++		+
Cyclosporine	33%	20-71%	+	++/++	++	+	++	+/++	++/++	+/++		+/++
Fumaric acid	17-46%	?	++	+/++	+/++	+	0?	+/++	+	++		+
Adalimumab	24-52%	53-80%	++	+	+	+	++	0	+	+		+++
Etanercept	11-21%	30-49%	+	+	+	+	+	0	+	+		+++
Infliximab	41-57%	64-88%	++	+	+	+	++	0	+	++		+++
Ustekinumab	36-51%	66-76%	+++	+	+	+	+	0	+	+		+++

* kidney function disorders, liver function disorders, disorders of fat metabolism+++ more 0 none

** see chapter “The patient’s perspective”: the groups are judged per group and ++ less ? unclear not per treatment. + least Phototherapy: UVB outpatient ++, UVB home +++, PUVA +

*** costs reimbursed by insurance company for treatment of 16 weeks

**** explanation (systemic/phototherapy): phototoxicity, nephrotoxicity, hepatotoxicity.

2.2 Topical therapies

P.C.M. van de Kerkhof, R.J. Borgonjen

Calcineurin inhibitors

Table 4: Calcineurin inhibitors

Recommended initial dosage	Tacrolimus (Protopic®) 0.03% ointment, followed by 0.1% ointment 1-2x daily Pimecrolimus (Elidel®) 1% ointment 1-2x daily
Recommended maintenance dosage	Apply until clearance of psoriatic lesions is reached. Then continue regular skin care (i.e., basic treatment, non-medicated ointments)
Important adverse effects (See SmPC)	Burning sensation Folliculitis, viral skin infections.
Prevention/treatment of adverse effects	Stop treatment in case of adverse effects or intolerable burning sensation. Applying topical corticosteroids or disinfectants will rapidly improve symptoms.
Absolute contraindications (See SmPC)	Hypersensitivity to calcineurin inhibitor or any other component of the preparation Primary or secondary immune deficiencies Malignant or premalignant skin lesions Pregnancy and breast feeding
Relative contraindications	Skin infections (e.g., herpes simplex,

(See SmPC)	folliculitis) UV-light exposure Liver disorder Age <2 years Live vaccines
Important drug interactions	No known drug interactions
Costs	30 g Protopic 0.03% ointment or Elidel cream = € 25.79 Protopic 0.1% ointment = €29.04
Special notes	Because of FDA warning: careful when using calcineurin inhibitors combined with phototherapy Due to lack of evidence, do not prescribe calcineurin inhibitors during pregnancy and breast feeding

Conclusions of the Dutch guidelines

EL: 2	Calcineurin inhibitors improve psoriasis compared to placebo if 1) the calcineurin inhibitor is being used under occlusion, 2) the calcineurin inhibitor is combined with a drug that enhances skin penetration (e.g. salicylic acid gel) or 3) the concentration of the calcineurin inhibitor is at least 3 times the registered concentration for atopic dermatitis in the Netherlands. It must be noted that included studies used small patient samples and suffered from substantial drop-outs (18-46%). In a larger study no difference was found between tactrolimus gel, tacrolimus cream and calcipotriol ointment.

	A2 Ortonne et al., 2006 (13) *B Carrol et al., 2005 (14)*

Treatment recommendation

Tacrolimus and pimecrolimus may be used 1-2x daily for chronic plaque type psoriasis in the face, flexures, and anogenital region (see chapter: Treatment of psoriasis of the face and flexures) as an additive (interval treatment) or as a replacement of corticosteroids. Use on other localizations is not recommended.

Be alert to adverse effects, such as burning sensation or irritation of the skin.

Calcineurin inhibitors should not be applied under occlusion or used in combination with UV-therapy.

Dithranol

Table 5: Dithranol

Recommended initial dosage	*Conventional therapy* (hospitalized patients): Initial dosage 0.1% cream or ointment 1x daily, applied on the psoriatic lesions. Do not rinse the preparation. Double concentration, guided by skin irritation, every 3 days until a concentration of 1-3% is reached. In case of extreme skin irritation, consider lowering dosage. Treatment duration: 4-6 weeks; after 2-3 weeks improvement should be noticed. No rebound-effect has been noted when treatment is terminated prematurely. *Short-contact therapy* (non-hospitalized patients): Initial dosage 0.1% cream or ointment applied on the psoriatic lesions,

	during 10-30 minutes. Rinse the preparation with lukewarm water. Increase the concentration to 1, 2 or 3% based on the amount of skin irritation. Apply during 10-30 minutes. In patients suffering from an irritative response on 0.1%, a concentration of 0.05% should be considered.
Recommended maintenance dosage	Not recommended for long-term therapy
Important adverse effects (See SmPC)	Erythema and burning sensation Discoloration of skin, hair, nails and clothing Blisters and necrosis
Prevention/treatment of adverse effects	When plaques are sharply demarcated the surrounding skin can be protected with zinc paste. Erythema and burning sensation can be treated with topical corticosteroids during 1-2 days. In case dithranol comes in contact with the eyes, this could cause strong irritation or iritis. Rinse the eyes thoroughly with water or prescribe an isotonic saline solution, followed by treatment with topical corticosteroids.
Absolute contraindications (See SmPC)	Erytrodermic psoriasis Pustular psoriasis Psoriatic plaques nearby the eyes or mucosa

Relative contraindications (See SmPC)	Pregnancy (never treat >30% of the skin surface) Children Infants
Important drug interactions	Topical preparations with salicylic acid or urea can enhance the effect of dithranol. Administration of photosensitizing agents in combination with dithranol can enhance the photosensitizing effects.
Costs	€1.83 – €3.92. Additional costs include hospitalization or outpatient treatment.
Special notes	A mild burning sensation indicates effective treatment concentration. Do not apply dithranol on the breasts in breastfeeding women. Patients not experienced with dithranol therapy should receive outpatient or hospitalized treatment.

Conclusions of the Dutch guidelines

	The results of the evaluated studies indicate a complete remission (PASI reduction of 100%) in 30-70% of patients and a partial remission (PASI reduction of 75%) in 26-100% of patients after treatment for 5-8 weeks. The differences in efficacy are probably due to the lack of a standardized dithranol treatment strategy and to the differences in clinical settings: home treatment versus outpatient treatment versus hospitalized

EL: 1	treatment. Skin irritation, burning sensation, erythema and intermittent brown discolorations are frequently reported adverse effects. Systemic adverse effects have never been reported. *A2 Monastirli et al., 2002 (15); Saraswat et al., 2007 (16)* *B Gerritsen et al., 1998 (17); Prins et al., 2001 (18); Thune et al., 1992 (19); de Mare et al., 1988 (20); Prins et al., 2000 (21); Hutchinson et al., 2000 (22); Mahrle et al., 1990 (23); Swinkels et al., 2002 (24); Van de Kerkhof et al., 2002 (25); Agrup et al., 1985 (26); de Korte et al., 2008 (27); Swinkels et al., 2004 (28); Van de Kerkhof et al., 2006 (29)* *C Agarwal et al., 2002 (30)*

Treatment recommendation

Dithranol monotherapy is recommended in patients with moderate to severe psoriasis for induction therapy during hospitalization or outpatient treatment.

Dithranol short-contact therapy may be an alternative treatment to phototherapy or systemic therapy in patients with moderate to severe psoriasis.

In patients who are unresponsive or have a contraindication to calcipotriol, corticosteroids, photo(chemo)therapy, systemic therapy, and biologics, dithranol is a last resort.

Dithranol therapy should be applied during a maximum of 4-8 weeks. Maintenance or long-term therapy is impractical and has no advantages.

In treating severe chronic plaque type psoriasis, it is recommended to add phototherapy or topical preparations (Vitamin D3 analogues, corticosteroids) to dithranol treatment because of higher efficacy.

Corticosteroids

Table 6: Corticosteroids

Recommended initial dosage	1x daily
Recommended maintenance dosage	Taper when psoriasis improves, for example beta methasone dipropionate 1x daily for 3 weeks, then 1x / 2 days for 1

	week, followed by 1x / 3 days for 1 week and then ceasing medication
Important adverse effects (See SmPC)	Skin atrophy, teleangiectasias, secondary infection, rosacea, perioral dermatitis, corticosteroid-induced acne
Prevention/treatment of adverse effects	Adverse effects occurring after long-term treatment include skin atrophy and teleangiectasias. These adverse effects are hard to treat. Try to avoid these adverse effects by taking into consideration therapeutic class of drug, location of drug use and treatment duration. A higher therapeutic class means a higher risk of adverse effects. Long-term treatment with a high potent corticosteroid increases the risk of skin atrophy. The face, genitals, neck and flexures are especially prone to skin atrophy. In the flexures a secondary infection could occur. The face is prone to rosacea, perioral dermatitis and corticosteroid-induced acne. The scalp and the soles of hands and feet can be treated with potent corticosteroids for months or sometimes years before skin atrophy appears.
Absolute contraindications	None
Relative contraindications	Rosacea, perioral dermatitis

(See SmPC)	Skin infections with bacteria (tuberculosis, lues), fungi, viruses (herpes simplex, herpes zoster, chicken-pox) Adverse effects of vaccines
Important drug interactions	None
Costs	€2.44 daily for topical corticosteroids (10 most prescribed preparations were taken into account) €57.24 per month for mometasone furoate (based on 100g / week)
Special notes	Most patients are afraid to use corticosteroids. Consequently, a detailed advice on benefits and disadvantages needs to be given to patients. During pregnancy, potent corticosteroids may induce intrauterine growth restriction when used on large surfaces for a long time period. During breastfeeding, do not apply corticosteroids on the breasts in order to avoid hospitalization of the infant. The mother must stop breastfeeding in case of long-term treatment with potent corticosteroids.

Conclusions of the Dutch guidelines

	After applying high potent corticosteroids (beta methasone dipropionate

EL: 1	2x daily) a substantial improvement or complete remission of skin lesions is seen in 46-56% of psoriasis patients *A1 Mason et al., 2009 (12)* *A2 Papp et al., 2003 (31); Douglas et al., 2002 (32); Kaufmann et al., 2002 (33)* *B Weston et al., 1988 (34); Bagatell, 1988 (35)*

EL: 1	Therapy with corticosteroids of very high potency (clobetasol-17-propionate 2x daily) has a similar efficacy in 68-89% of psoriasis patients *A2 Gottlieb et al., 2003 (36); Lowe et al., 2005 (37)* *B Decroix et al., 2004 (38); Lebwohl et al., 2002 (39); Weston et al., 1988 (34); Lee et al., 2009 (40)* *C Mazzotta et al., 2007 (41)*

EL: 2	Due to the small number of available studies and varying study-outcome it is unclear whether clobetasol-17-propionate is more effective as a cream, lotion, spray or foam. *A2 Lowe et al., 2005 (37)* *B Lebwohl et al., 2002 (39); Lee et al., 2009 (40)* *C Mazotta et al., 2007 (41)*

	Owing to the small number of available studies it is unclear whether 1x daily application of topical corticosteroids is more effective than 2x daily

EL: 2	application. *A2 Kaufmann et al., 2002 (33)*

Treatment recommendation

Topical corticosteroids are recommended for the treatment of mild to severe chronic plaque psoriasis. Combination therapy with calcipotriol, phototherapy, or systemic therapy may be prescribed, thereby reducing the total dosage of corticosteroids significantly.

The class of corticosteroids prescribed depends upon the areas of skin affected.

It is important to be aware of the occurrence of skin atrophy or teleangiectasia, especially when corticosteroids are used as long-term therapy and are being applied in areas prone to these adverse effects.

Owing to lack of evidence for 2x daily application of corticosteroids over 1x daily application, it is recommended to start with 1x daily.

Coal tar

Table 7: Coal tar

Recommended initial dosage	No recommended initial dosage; the dosage of coal tar may vary
Recommended maintenance dosage	It is not recommended to use coal tar for maintenance or long-term therapy
Important adverse effects (See SmPC)	Coal tar odor, staining,phototoxicity
Prevention/treatment of adverse effects	The brown-black stains in clothing and the penetrating odor are unavoidable. Patients should exercise caution with exposure to sunlight in order to avoid UV-erythema.
Absolute contraindications (See SmPC)	Pregnancy and breastfeeding Xeroderma pigmentosum, dysplastic nevus syndrome, basal cell nevus syndrome

Relative contraindications (See SmPC)	Intense exposure to sunlight or UV-light during treatment Prior history of skin cancer
Important drug interactions	There are no drug interactions reported for topical use of coal tar products
Costs	€3.51 daily
Special notes	The Goeckerman-method consists of application of coal tar during 1-2 hours followed by UVB therapy. Optimal dosage of UVB is reached when the treated skin does not become erythematous. In outpatient care, pix lithantracis is often used and in combination with UV-therapy shows a higher efficacy when compared to liquor carbonis detergens (LCD)/UV-light combination therapy.

Conclusions of the Dutch guidelines

EL: 3	Coal tar monotherapy (10% LCD) seems to improve psoriatic lesions when compared to placebo, but is less effective than betamethasone valerate. *B Thawornchaisit et al., 2007 (42)*

EL: 2	Coal tar (5%) is being used in clinical studies combined with phototherapy. When combined with UV-light a reduction of 75% in PASI score (PASI 75) was reached in 45-80% of participants after 15-20

	applications. The evidence on the additive effect of coal tar when combined with phototherapy is insufficient. The addition of coal tar might result in a faster and longer remission. *B Bagel, 2009 (43); Belsito et al., 1982 (44)* *C Frost et al., 1979 (45)*

Treatment recommendation

Coal tar is not the first-choice of treatment for chronic plaque psoriasis.

Coal tar as a monotherapy is outdated. Nowadays, treatment options exist that are less hazardous and more practical.

Only when therapeutically necessary, coal tar or pix lithanthracis may be used in combination with UVB or PUVA to treat recalcitrant chronic plaque psoriasis.

Tazarotene

Tazarotene is not available in the Netherlands and therefore not included in these guidelines.

Vitamin D3 analogues

Table 8: Vitamin D3 analogues

Recommended initial dosage	Calcipotriol: 2x daily on affected areas of the skin Calcitriol: 2x daily on affected areas Calcipotriol/betamethasone: 1x daily on affected areas
Recommended maintenance dosage	Calcipotriol: ≤15g cream or ointment daily and ≤100g weekly Calcitriol: ≤30g ointment daily and ≤35% of body surface area Calcipotriol/betamethasone: continuous use during 4 weeks. Owing to lack of

	evidence on long-term continuous therapy, intermittent use of this drug is recommended
Important adverse effects (See SmPC)	Burning sensation, redness Overdosing: hypercalcemia, bone resorption, possibly uric acid kidney stones, or even kidney failure
Prevention/treatment of adverse effects	Do not treat unaffected skin areas. In case of skin irritation, adjust frequency of therapy or stop briefly. Topical corticosteroids may reduce irritation.
Absolute contraindications	None
Relative contraindications (See SmPC)	Pustular psoriasis Diseases involving disorders of calcium metabolism Treatment with medication that can cause hypercalcemia Serious kidney or liver disease Due to lack of experience, treatment during pregnancy and breastfeeding should be avoided
Important drug interactions	Topical salicylic acid (inactivation), avoid other topical irritating preparations Oral calcium supplementation, oral vitamin D3, thiazide diuretics: check serum calcium levels
Costs	120g calcipotriol cream: €37.26

	100g calcitriol ointment: €23.70 100g Dovobet (calcipotriol/betamethasone): €68,-
Special notes	Do not apply calcipotriol before treatment with UV-light. It can diminish the effect of UV-therapy. Calcipotriol may be administered after phototherapy.

Conclusions of the Dutch guidelines

EL: 1	After topical application of vitamin D3 analogues 30-50% of patients with mild to moderate chronic plaque psoriasis improved substantially or even achieved almost complete remission within several weeks *A2 Camarasa et al., 2003 (46); Kragballe et al., 2004 (47); Zhu et al., 2007 (48); Guenther et al., 2000 (49)*

EL: 1	Efficacy and tolerance of vitamin D3 analogues are enhanced by combining therapy with topical corticosteroids during the first phase of treatment. Usage of calcipotriol/betamethasone dipropionate ointment or gel is preferred because of a higher patient compliance with 1x daily application *A2 Papp et al., 2003 (31); Douglas et al., 2002 (32); Kaufmann et al., 2002 (33); Tabolli et al., 2009 (50); Guenther et al., 2002 (51); Kragballe et al., 2004 (47); Ortonne et al., 2004 (52); Kragballe et al., 2006 (53); Peeters et al., 2005 (54); Saraceno et al., 2007 (55)*

Treatment recommendation

Vitamin D3 analogues are recommended as topical therapy for chronic plaque psoriasis.

Efficacy and tolerance is higher for the combination of vitamin D analogues with corticosteroids when compared to both monotherapies. The combination preparation is preferred because of its 1x daily application.

For treatment of moderate to severe chronic plaque psoriasis the use of topical vitamin D3 analogues combined with UV-therapy or systemic therapy is recommended.

2.3 Phototherapy

E.P. Prens, W.J.A. de Kort, M.B.G. Koek

Table 9: Phototherapy

Registration for psoriasis	More than 50 years of experience with the oldest modality (Goeckerman)
Recommended control parameters before starting treatment	Regular inspection of skin every 8 to 10 treatments. Ask for UV-erythema.
Recommended initial dosage	Individual dosage depends on skin type; follow one treatment regimen until erythema occurs, then: - UVB: 70% of the minimal erythema dosage (MED) - Oral PUVA: 75% of the minimal phototoxic dosage (MPD) - Bath/cream PUVA: 30-50% of MPD
Recommended maintenance dosage	Increase dosage (10-30%) based on erythema
Onset of effect	After 2-3 weeks
Response rate	UVB: 75% of patients a PASI 75 after 4-6 weeks (EL: 2) PUVA: complete clearance of skin lesions in 75-90% of patients (EL: 2)

Absolute contraindications	Photodermatoses/photosensitivity, skin malignancies, treatment with cyclosporine (immunosuppressant) and expected treatment with cyclosporine in future. PUVA: pregnancy or lactation. This is a relative contraindication for bath PUVA.
Relative contraindications	Epilepsy, pregnancy or lactation (for bath PUVA), unavoidable therapy with photosensitizing agents, skin type I, dysplastic melanocytic nevi, prior history of skin cancer, poor compliance, physical or emotional inability to sustain therapy (heart failure NYHA class III-IV, claustrophobia), presence of actinic skin damage, children < 18 years, high cumulative number of treatments or dosage (for UVB: 400 treatments, this equals approximately 600-800 J/cm^2 for narrow band UVB and 120-180 J/cm^2 for broadband UVB therapy). For oral PUVA: High cumulative number of treatments (1000 J/cm^2 or 150-200 treatments), prior arsenic treatment or ionizing radiation, significant liver damage.
Most common adverse effects	≥1/10: Erythema, itch, hyperpigmentation. Only for PUVA:

	nausea. Only for excimer laser: blistering.
Important drug interactions	Note: medication capable of inducing phototoxicity or photoallergy.
Special notes	Combination with topical preparations may work synergistically. PUVA should not be combined with cyclosporine. Eyes must be protected during phototherapy, as well as the penis and scrotum.

Table 10: Important adverse effects of UVB and PUVA therapy

Most frequently	Erythema, itch, hyperpigmentation Only PUVA: nausea Only excimer laser: blistering
Frequently	-
Sometimes	Blistering
Rarely	Oral PUVA: squamous cell carcinoma, basal cell carcinoma
Very rarely	-

Table 11: List of medication capable of inducing phototoxicity and photoallergy

Drugs inducing phototoxicity	**Drugs inducing photoallergy**
Tetracyclines	Tiaprofenic acid
Phenothiazine	Promethazine
Griseofulvin	Chlorpromazine
Nalidixine acid	Hydrochlorothiazide
Furosemide	Quinine
Amiodarone	Para-aminobenzoic acid (PABA) ointments

Piroxicam	Desinfectants (hexachlorophene, others)
Tiaprofenic acid	

Table 12: Starting dosage UVB therapy (56)

Skin type	**UVB broadband** (mJ/cm^2)	**Narrow band UVB** (mJ/cm^2)
I	20	200
II	30	300
III	50	500
IV	60	600

Table 13: Treatment regimen UVB phototherapy (56)

Step 1 Assessment of MED	Assess after 24 hours	
Step 2 Start of therapy	Starting dosage	According to skin type or 70% of MED
Step 3 Treatment 2-3 times per week	No erythema	Increase by 30%
	Minimal erythema	Increase by 20%
	Persisting asymptomatic erythema	Do not increase dosage
	Painful erythema	Interrupt treatment until symptoms disappear
Step 4 Resume treatment	After disappearance of symptoms	Lower last dosage by 50% Increase further by 10%

Table 14: Treatment regimen localized UVB phototherapy (excimer laser or lamp) (57)

Step 1 Assessment of MED	Assess after 24 hours	
Step 2 Start of therapy	Starting dosage	2x-4x of MED
Step 3 Treatment 2 times per week	Persisting asymptomatic erythema	Increase with 1x-2x MED
	Painful erythema	Interrupt treatment until symptoms disappear
Step 4 Resume treatment	After disappearance of symptoms	Repeat last dosage

Table 15: PUVA: most commonly used photosensitizing agents and their dosage (56, 58)

Modality	**Photosensitizing agent**	**Dosage or concentration**
Oral PUVA	8-methoxypsoralen (8-MOP) 5-methoxypsoralen (5-MOP)	0.6 mg/kg 1.2 mg/kg
Bath PUVA	8-MOP	0.5-5.0 mg/L
localized PUVA (emulsion or gel)	8-MOP	1%-0.005%

Table 16: PUVA starting dosages (57)

Skin type	**Oral PUVA**		**Bath PUVA**
	8-MOP (J/cm^2)	**5-MOP** (J/cm^2)	**1.0 mg/L 8-MOP** (J/cm^2)
I	0.3	0.4	0.2
II	0.5	1.0	0.3
III	0.8	1.5	0.4

IV	1.0	2.0	0.6

Table 17: PUVA treatment regimen (57)

Step 1 Assessment of minimal phototoxic dosage	Oral PUVA: assess after 72-96 h Bath PUVA: assess after 72-96 h	
Step 2 Start of therapy	Starting dosage	Oral PUVA: According to skin type or 75% of MPD Bath PUVA: According to skin type or 30-50% of MPD
Step 3 Treatment 2x per week	No erythema, good response	Increase by 30% (max. 2 times per week)
	Minimal erythema	Do not increase
	Persisting asymptomatic erythema	Do not increase
	Painful erythema	Interrupt treatment until symptoms disappear
Step 4 Resume treatment	After disappearance of symptoms	Lower last dosage by 50%; increase further by 10%

Conclusions of the Dutch guidelines

UVB (broadband)

EL: 2	About 75% of all patients treated with broadband UVB 2-3 times per week achieved at least PASI 75 response after 4-12 weeks (depending on UV schedule) and clearance was reached in most cases. *A2 Dover et al., 1989 (59)*

	B Coven et al., 1997 (60); Orfanos et al., 1979 (61); Petrozzi, 1983 (62); Ramsay et al., 2000 (63)

UVB (narrow band)

EL: 2	63% - >75% of all patients treated with narrow band UVB 2-3 times per week reached at least PASI 90 response within 20 weeks of treatment. Presumably higher response percentages are achieved for PASI 75. Exact data are not available since performed studies date before the "PASI-era". *B Arnold et al., 2001 (64); Gordon et al., 1999 (65); Markham et al, 2003 (66); Youssef et al., 2008 (67)*

EL: 2	It is unclear whether phototherapy > 3 times per week results in a higher efficacy and faster response. *B Coven et al., 1997 (60); Grundmann-Kollmann et al., 2004 (68); Leenutaphong et al., 2000 (69)*

EL: 2	The percentage of patients achieving PASI 75, PASI 90 or complete clearance is equally high for home UVB phototherapy as for outpatient phototherapy. *A2 Koek et al., 2009 (70)* *B Cameron, 2002 (71)*

	No significant difference exists between home and outpatient

EL: 2	phototherapy for total cumulative dosage of UVB at the end of treatment. There is also no difference between both therapies for percentage of adverse effects as for the number of adverse effects experienced at least once by psoriasis patients. *A2 Koek et al., 2009 (70)* *B Cameron, 2002 (71)*

UVB 308 nm

EL: 2	Individual plaques disappear completely (in 33-37%) or almost completely (about 70%) after treatment with the excimer laser for 8-16 weeks. *B Hacker et al., 1992 (72); Taibjee et al., 2005 (73); Trehan et al., 2002 (74); Goldinger et al., 2006 (75)* *C Feldman et al., 2002 (76); Han, 2008 (77)*

EL: 3	There is evidence the results of the excimer lamp equal the excimer laser. *B Kollner et al., 2005 (78)*

Oral PUVA

	After 12-16 weeks, 75-90% of patients achieve near complete clearance of skin lesions when treated with oral PUVA 2-4 times per week *A2 Yones et al., 2006 (79)*

EL: 2	*B Caca-Biljanovska et al., 2002 (80); Barth et al., 1978 (81); Berg et al., 1994 (82); Buckley et al., 1995 (83); Calzavara-Pinton et al., 1992 (84); Collins et al., 1992 (85); Cooper et al., 2000 (86); Diette et al., 1984 (87); Hanke et al., 1979 (88); Khurshid et al., 2000 (89); Kirby et al., 1999 (90); Park et al., 1988 (91); Parker et al., 1984 (92); Parrish et al., 1974 (93); Rogers et al., 1979 (94); Vella Briffa et al., 1978 (95); El-Mofty et al., 2008 (96)* *C Henseler et al., 1981 (97)*

Bath PUVA

EL: 2	The results of bath PUVA equal oral PUVA when treatment frequencies are similar. *B Caca-Biljanovska et al., 2002 (80); Barth et al., 1978 (81); Berg et al., 1994 (82); Buckley et al., 1995 (83); Calzavara-Pinton et al., 1992 (84); Collins et al., 1992 (85); Cooper et al., 2000 (86); Diette et al., 1984 (87); Hanke et al., 1979 (88); Khurshid et al., 2000 (89); Kirby et al., 1999 (90); Park et al., 1988 (91); Parker et al., 1984 (92); Parrish et al., 1974 (93); Rogers et al., 1979 (94); Vella Briffa et al., 1978 (95); El-Mofty et al., 2008 (96)*

Retonoid plus PUVA / UVB

EL: 2	There is evidence that combination therapy with PUVA / acitretin or narrow band UVB / acitretin achieves higher efficacy and is dose-sparing in regard to cumulative UV dosage. *B Saurat et al., 1988 (98); Carlin et al., 2003 (99); Lauharanta et al., 1989*

	(100)

Instructions for phototherapy

Prior to treatment

- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Medical history and physical examination need to be directed at prior exposure, melanocytic nevi (in particular dysplastic type) and skin cancer.
- Additional UV exposure due to recreational activities should be taken into account
- Prescription of UVA protecting sunglasses is obligatory before commencing oral PUVA therapy.

During treatment

- Physical examination
- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- UV dosages should be documented with precise cumulative units (J/cm^2 or mJ/cm^2) and number of treatments.
- Ask for the occurrence of erythema on a regular basis in order to accurately determine treatment dosage
- Physicians should report adverse effects, therapeutic response and concomitant treatments within the medical record
- Eyes should always be protected during phototherapy with sunglasses with UV-protection as well as at least 8 hours after oral-PUVA treatment
- Cover the genital area when skin lesions are absent. If desired, healthy skin of

the face and other unaffected areas may be covered (possibly with adequate sunscreens). The area of covered skin needs to be the same during every treatment since a shift of 1 cm may cause burns due to unequal sensitivity of this area to UV light.

- It is essential for the patient to avoid additional sun exposure and/or to use sunscreens

After treatment

- After a treatment course, cumulative UV-dosage and number of treatments should be registered
- Especially patients with high number of treatment episodes (200-250x PUVA) need to be screened routinely for skin cancer during their entire life.

Treatment recommendation

Phototherapy is recommended for induction therapy of moderate to severe chronic plaque psoriasis. Narrow band UVB is recommended as first choice; PUVA is advised in case UVB is ineffective.

8-MOP or methoxsalen is preferred for PUVA therapy. This preparation, however, is being withdrawn from the market. The manufacturer states Oxsoralen (methoxsalen 10 mg capsules) can be imported by the pharmacist with a delivery time of a week.

Oxsoralen is not registered in the Netherlands and will not be reimbursed. The dermatologist should contact the health insurance of the patient to arrange a reimbursement for a non-registered drug.

The use of excimer lasers should be limited to treatment directed at single, therapy resistant psoriatic plaques.

UV maintenance therapy is not recommended owing to decreased efficacy after repetitive UV-exposure and increased chance of UV skin damage. The number of treatment courses should be limited to a maximum of 2 per year.

UV-therapy after or during immunosuppressant drugs, especially cyclosporine, demands special attention.

Both home and outpatient UVB phototherapy are available for the treatment of psoriasis. The dermatologist should, in consultation with the patient, decide which treatment setting is preferred.

2.4 Conventional systemic therapies

Methotrexate

E.M.G.J. de Jong

Table 18: Methotrexate

Registration for psoriasis	1958
Recommended control parameters before starting treatment	Hb, leucocytes and differential, thrombocytes, liver enzymes, serum creatinine, urine sediment, pregnancy test, HBV/HCV, serum albumin, PIIINP if available, X-thorax in case of suspected tuberculosis on anamnesis.
Recommended initial dosage	5-10 mg weekly
Recommended maintenance dosage	5-22.5 mg weekly (oral, subcutaneous or intramuscular)
Onset of effect	After 4-12 weeks
Response rate	PASI 75 in 35-73% of patients after 16 weeks
Absolute contraindications (See SmPC)	Severe infections, serious kidney and liver diseases, bone marrow diseases, substantial hematologic abnormalities, men and women planning to have children, pregnancy, breastfeeding, pulmonary fibrosis or poor lung function, alcohol abuse, immune deficiencies, acute peptic ulcer, drug abuse.
Relative contraindications (See SmPC)	High age, less serious kidney and liver diseases, ulcerative colitis, history of HBV or HCV, poor compliance, gastritis, diabetes, history of malignancies, heart failure, drug interactions

Most common adverse effects (See SmPC)	≥1/10: stomatitis, dyspepsia, nausea, loose of appetite. Increase of serum transaminases. ≥1/100 - ≤1/10: oral ulcers, diarrhea. Exanthema, erythema, itch. Headache, fatigue, sleepiness. Interstitial alveolitis or pneumonitis: symptoms of potentially severe damage are dry, unproductive cough, dyspnoe and fever. Leukopenia, anemia, trombopenia.
Important drug interactions	Trimethoprim, probenecide, retinoids, NSAIDs
Special notes	Dosing once a week; overdose may lead to leukocytopenia or pancytopenia which may be life-threatening. Continue oral contraceptives until 3 months after cessation of MTX. Alcohol consumption, obesity, hepatitis and diabetes increase the risk of hepatotoxicity. In geriatric patients a lower dose of MTX is usually prescribed and kidney function should be monitored on a regular basis.

Conclusions of the Dutch guidelines

	Methotrexate is effective for the treatment of plaque psoriasis in adults. After 16 weeks, in 35-73% of psoriasis patients a PASI 75 response was

EL: 1	reached on 15-22.5mg methotrexate weekly. *A2 Flystrom et al., 2008 (101); Ranjan et al., 2007 (102); Saurat et al., 2008 (103); Heydendael et al., 2003 (104); Akhyani et al., 2010 (105)*

Table 19: Important adverse effects of MTX

Most frequently	Stomatitis, dyspepsia, nausea, loose of appetite. Increase of serum transaminases. Hair loss.
Frequently	Oral ulcers, diarrhea. Leukopenia, anemia, trombopenia.
Sometimes	Fever, shivers, depression, infections
Rarely	Nephrotoxicity, liver fibrosis / cirrhosis
Very rarely	MTX alveolitis or pneumonitis.

Table 20: List of medication and drug interactions

Medicine	**Type of drug interaction**
Colchicin, cyclosporine, NSAIDs, penicillin, probenecide, salicylic acids, sulfonamides	Reduced renal clearance of MTX
Chloramphenicol, co-trimoxazol, cytostatics, ethanol, NSAIDs, sulfonamides	Increased risk of bone marrow and gastrointestinal toxicity
Barbiturates, co-trimoxazol, phenytoin, probenecide, NSAIDs, sulfonamides	Interaction with plasma protein binding
Ethanol, leflunomide, retinoids, tetracyclines	Increased risk of hepatotoxicity

Instructions for MTX use

Prior to treatment

- Medical history and physical examination
- Assessing disease severity, preferably with PASI or PGA
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Laboratory controls (Table 21)
- Start contraceptives in fertile women (start after menstruation), contraceptive measures in men
- In case liver function screening shows abnormalities, refer to specialist for further evaluation
- Influenza vaccination is recommended
- X-thorax in case of suspected tuberculosis on anamnesis.

During treatment

- Objective assessment of disease severity using PASI or PGA
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Medical history
- Physical examination
- Laboratory controls (Table 21)
- Contraceptive measures in fertile women and men
- Administer folic acid once weekly at least 24 hours after MTX*
- Intake of MTX with milk reduces the absorption of MTX

After treatment

- Women should not become pregnant and men should not conceive children during MTX treatment and 3 months thereafter.

* Folic acid dosage varies in the literature between 1 to 5mg daily and 1 to 2.5-10mg weekly (Prey, 2009).

The working group of these guidelines holds the opinion that dosage of folic acid should be flexible with 1mg daily (except for the day of MTX intake) to 5-10mg once weekly administered at least 24 hours after MTX intake. The guidelines of the Dutch Society of Rheumatology advice to prescribe at least 5mg of folic acid weekly, at least 24 hours after MTX intake. It is recommended to double this dosage in case MTX dosage becomes ≥15mg weekly.

Table 21: Laboratory controls

Parameter*	**Prior to treatment**	**After the first week of treatment**	**During the first two months 1x every 2 weeks, thereafter every 2-3 months.**
Hb, leucocytes and differential, thrombocytes, erythrocytes	X	X	X
Liver enzymes (ALAT, AP, yGT)	X	X	X
Serum creatinine	X	X	X
Urine sediment	X	X	X
Pregnancy test	X		
HBV/HCV	X		
Serum albumin**	X	X	X

PIIINP if available	X	Every 3 months***

Further testing may be required based on patient's status, risk and exposures.

* Decrease MTX dosage or stop MTX in case leukocytes are <3.0, neutrophils <1.0, thrombocytes<100 or liver enzymes >2x the upper limit normal range

** In certain patients (e.g. suspicion of hypoalbuminemia or patients using other medication with strong serum albumin binding properties)

*** Liver biopsy should be considered in selected patients, e.g. patients with a continuous elevated PIIINP level (>4.2 mcg/l in at least 3 samples during a 12 month time period)

Table 22: PIIINP (amino-terminal propeptide of type III pro-collagen) cut-off levels and clinical guidance

PIIINP (amino-terminal propeptide of type III pro-collagen) for psoriasis
Reference range: 1.7 – 4.2 mcg/L. First serum sample before starting MTX, thereafter 1x every 3 months. Confounding factors: arthritis, age <18 years, scleroderma, myeloproliferative disorders, malignancies (breast carcinoma, hepatocellular carcinoma, ovarian carcinoma), recent myocardial infarction.
A gastroenterologist should be consulted (after exclusion of confounding factors) when: PIIINP value is >8.0 mcg/L prior to starting MTX PIIINP value is >4.2 mcg/L in at least 3 samples during a 12 month time period PIIINP value is >8.0 mcg/L in at least 2 consecutive samples PIIINP value is >10 mcg/L in 1 sample. In this case, provisionally stop MTX.

Table 23: Liver biopsy: Roenigk classification of liver damage and its therapeutic consequences

Histological classification:

Grade I: Normal
Grade II: Changes, no fibrosis
Grade IIIA: Mild fibrosis
Grade IIIB: Moderate to severe fibrosis
Grade IV: Cirrhosis
Therapeutic consequences:
Grade I and II: MTX may be continued
Grade IIIA: MTX may be continued, but liver biopsy needs to be repeated after 6 months
Grade IIIB and IV: stop MTX

Table 24: Folic acid dosage in case of MTX overdose

Serum MTX (M)	Parenteral administration of folic acid once every 6 hours (dosage in mg)
5 x 10-7	20
1 x 10-6	100
2 x 10-6	200
>2 x 10-6	Increase dosage proportionally

Treatment recommendation

Treatment with methotrexate (15-22.5 mg/week) is effective for plaque psoriasis and induces a reduction of PASI score of at least 75% (PASI75) in 35-73% of patients after 16 weeks of treatment. Owing to its slow onset of effect, methotrexate is less suitable for short induction treatment than for long-term therapy.

It is recommended to supply folic acid to reduce the risk of hepatic adverse effects. The dosage may vary from 1mg daily (except for the first day of MTX intake) to 5-10mg once weekly, with a time interval between MTX intake and start of folic acid of at least 24 hours.

Before starting MTX therapy and every 3 months thereafter, it is recommended to monitor for liver damage by measuring liver enzymes and PIIINP.

PIIINP measurement should be available for all Dutch dermatologists. Values should be given preferably with interpretation of the results and advice. Several hospitals should offer the possibility of PIIINP measurement. Currently, PIIINP measurement is available in the University Medical Centre Nijmegen and VU Medical Centre Amsterdam.

Because of the occurrence of overdosing of MTX (e.g. prescribed once daily instead of once weekly) with sometimes lethal consequences it is recommended to prescribe the recipe for MTX carefully. It must be clearly stated that dosage is once weekly. It is strongly advised by The Dutch health inspection that physicians should state the indication of MTX on the recipe. Patients should be informed about the once weekly treatment regimen.

Owing to the possible mutagenic effects of MTX fertile men and woman should be strongly advised to use reliable contraceptives.

Cyclosporine

Ph.I. Spuls, M. de Groot

Table 25: Cyclosporine

Registration for psoriasis	1993
Recommended control parameters before starting treatment	Hb, leucocytes and differential, thrombocytes, serum creatinine, urea, uric acid, liver enzymes (ASAT, ALAT), bilirubin,

	alkaline phosphatase, yGT, LDH, albumin, sodium, potassium, magnesium only in case of muscle cramps, urine sediment, cholesterol / triglycerides, pregnancy test, blood pressure.
Recommended initial dosage	2.5-3 (max. 5) mg/kg per day for 4-6 weeks. When skin does not improves, increase to 5 mg/kg/day
Recommended maintenance dosage	Lower dosage every two weeks until a maintenance dosage of 0.5-3 mg/kg/day is reached, divided into 2 doses. Increase dosage in case of recurrence of psoriasis. Maximal total duration of therapy: 2 years. (EDF guidelines, 2009)
Onset of effect	After 4 weeks
Response rate	The response is dose-dependent. After 8-16 weeks of treatment with 3 mg/kg/day, PASI 75 is reached in approximately 50% of patients after 8 weeks.
Absolute contraindications (See SmPC)	History of serious adverse effects on or hypersensitivity to cyclosporine, poor kidney function, severe liver disease, severe hypertension, serious infections, malignancy (current or past, especially hematologic or cutaneous malignancies except for basal cell carcinoma), concurrent PUVA treatment, contra-indicated concomitant medication,

	vaccination with live vaccines, gout.
Relative contraindications (See SmPC)	Prior potential carcinogenic treatment (arsenic, PUVA > 1000 J/cm^2 or 150-200 applications), prior long-term MTX use, psoriasis induced by serious infection or medication (beta blocker, lithium, antimalarial medication), liver function disorders, hyperuricemia, hyperkalemia, epilepsy/convulsions, inadequate efficacy in the past, simultaneous treatment with nephrotoxic drugs, polypharmacy (e.g., HIV patients), simultaneous use of other systemic immunosuppressive drugs, concurrent phototherapy, simultaneous use of systemic retinoids or retinoid therapy 4 weeks prior to commencing cyclosporine treatment, drug or alcohol related diseases or substance abuse or alcohol abuses, pregnancy/breastfeeding, current treatment with ricinus oil preparations.
Most common adverse effects (See SmPC)	≥1/100 - <1/10: kidney insufficiency (dose-dependent), irreversible kidney damage (long-term therapy), hypertension, gingival hyperplasia, reversible gastrointestinal complaints (dose-dependent), tremor, fatigue, headache, burning sensation of hands and feet, reversible hyperlipidemia

	(especially in combination with systemic corticosteroids), hypertrichosis, abnormal liver function tests.
Important drug interactions	Many different drug interactions: see SmPC text and Dutch guidelines (http://www.huidarts.info/documents/uploaded_file.aspx?id=579)
Special notes	Increased risk of lymphoproliferative diseases in transplant patients. Increased risk of squamous cell carcinoma in psoriasis patients after photo(chemo)therapy (106). *Special warnings:* - The capsules contain a small amount of alcohol (intake of 100 mg capsules equals 0.1 g alcohol) - There is a potential risk of drug interactions, especially with statins (increased risk of myopathy). - When idiopathic intracranial hypertension is diagnosed, cyclosporine should be stopped in order to avoid permanent decline in vision. - Yearly assessment of GFR is the most accurate method in order to assess kidney tolerance to cyclosporine in long-term therapy. - Supplementation with magnesium seems to protect against loss of kidney function as well

	as chronic cyclosporine nephrotoxicity by adapting the activity of nitrogen monoxide synthase (107). *Special attention to switching therapies:* - Switching from cyclosporine to other cyclosporine (other manufacturer): be aware of differences in biological availability and if necessary adjust dosage. - Cyclosporine may be used after systemic retinoid therapy, that is 4 weeks after cessation of retinoid treatment. - Fumaric acid esters and cyclosporine are usually not combined. - In case of insufficient response to cyclosporine a switch to a biological agent may be considered. A period of simultaneous usage of both biological agent and cyclosporine may be considered in spite of synergistic toxicity (infections, hepatotoxicity).

Conclusions of the Dutch guidelines

	Cyclosporine is effective for the treatment of moderate to severe chronic plaque psoriasis in adults. PASI 75 was reached in 20-71% of psoriasis patients on 2.5-5 mg/kg/day cyclosporine at week 8-16 and PASI 90 was reached in 33% of patients on 3-5 mg/kg/day at week 16. Most included

EL: 1	studies showed a clinical relevant response 4-6 weeks after commencing therapy. *A2 Heydendael et al., 2003 (104); Gisondi et al., 2008 (108); Koo, 1998 (109); Ellis et al., 1991 (110)*

Table 26: Important adverse effects of cyclosporine

Frequently	Kidney insufficiency (dose-dependent), irreversible kidney damage (long-term therapy), hypertension, gingival hyperplasia, reversible gastrointestinal complaints (dose-dependent), tremor, fatigue, headache, burning sensation of hands and feet, reversible hyperlipidemia (especially in combination with systemic corticosteroids), hypertrichosis, abnormal liver function tests.
Sometimes	Convulsion, gastrointestinal ulcers, weight gain, hyperglycemia, hyperuricemia, hyperkalemia, hypomagnesemia, acne, anemia.
Rarely	Ischemic heart disease, pancreatitis, polyneuropathy (motoric), decreased eyesight, decreased hearing, central ataxia, myopathy, erythema, itch, leucopenia, thrombocytopenia.
Very rarely	Microangiopathic hemolytic anemia,

	hemolytic uremic syndrome, colitis (isolated cases), papillary oedema (isolated cases), idiopathic intracranial hypertension (isolated cases).

Instructions for cyclosporine use

Prior to treatment

- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Medical history and physical examination need to be directed at prior diseases and current comorbidity (e.g., serious infections, (skin) malignancies, kidney and liver diseases). Also, possible drug-interactions involving current concomitant medication and contraindications should be ruled out.
- Measure blood pressure at two separate consultations if first measurement was elevated.
- Laboratory controls (Table 27)
- Reliable contraceptive (note: contraceptives with progesterone become less effective)
- Gynecological screenings should be performed on a regular basis according to the Dutch national guidelines on cervix carcinoma.
- Inform patients about vaccination (especially live attenuated vaccines), patient's susceptibility to infections (take infections serious, apply adequate medical assistance), drug interactions (inform other treating physicians on therapy), avoidance of excessive sun exposure, advice the use of sunscreens.

During treatment

- Objective assessment of disease severity (such as PASI / BSA / PGA; arthritis)
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Physical examination should include examination of skin and mucous membranes for formation of skin malignancies (also inspect for increase of hair growth on the body, gingival changes), signs of infections, gastrointestinal or neurological symptoms.
- Repeat the advice on avoidance of excessive sun exposure and using sunscreens
- Check concomitant medication
- Measure blood pressure
- Laboratory controls (Table 27)
- If creatinine levels are increased or if patient is treated > 1 year, assess the creatinine clearance (or 51 Cr-labeled EDTA clearance if available)
- Routine assessment of cyclosporine serum levels is not recommended (see Dutch S3-guidelines for details: http://www.huidarts.info/documents/uploaded_file.aspx?id=579)
- Reliable contraceptive

After treatment

- After cessation of cyclosporine, the dermatologist needs to inspect the patient for the formation of skin malignancies, especially in cases in which extensive UV-therapy or UV-exposure preceded cyclosporine treatment.

Table 27: Laboratory controls

Parameter	Prior to treatment	Treatment period (in weeks)				
		2	4	8	12	16
Blood count*	X	X	X	X	X	X

Liver values**	X	X	X	X	X	X
Electrolytes***	X	X	X	X	X	X
Serum creatinine	X	X	X	X	X	X
Urine sediment	X		X			X
Urea and uric acid	X		X	X	X	X
Pregnancy test (urine)	X					
Cholesterol, triglycerides	X****			X		X
Magnesium*****	X			X		X

* Leucocytes, thrombocytes, erythrocytes

** Transaminase, AP, yGT, bilirubin, LDH, albumin

*** Sodium, potassium

**** Recommended 2 weeks prior to treatment and on the first day of treatment (fasting).

***** Only if indicated (e.g., muscle cramps). Also consider CPK.

Treatment recommendation

3-5 mg/kg/day Cyclosporine is recommended for induction therapy in patients with moderate to severe plaque psoriasis. Because of its fast onset of action, cyclosporine is appropriate for short-term induction therapy or crisis intervention.

Cyclosporine may be used to induce remission in adults with moderate to severe chronic plaque psoriasis who are undertreated with topical preparations or phototherapy.

Cyclosporine may be used for long-term treatment (up to 2 years) in individual cases, but patients must be screened intensively for signs of toxicity, especially for decrease in kidney function and the development of hypertension.

Retinoids

M. te Booij, P.C.M. van de Kerkhof, M.C. Pasch

Table 28: Retinoids

Registration for psoriasis	1992 (Germany)

Recommended control parameters before starting treatment	Hb, Hct, leukocytes, trombocytes, liver enzymes (ASAT, ALAT), AP, yGT, serum creatinine, pregnancy test, blood glucose (fasting), triglycerides/cholesterol/HDL, perform X-ray examination of bones when symptoms exist (Ormerod, 2010)
Recommended initial dosage	0.3-0.5 mg/kg/day during 4 weeks, followed by 0.5-0.8 mg/kg/day
Recommended maintenance dosage	Individual dosage depends on response and tolerance
Onset of effect	After 4-8 weeks
Response rate	Varies strongly and is dose-dependent, unambiguous conclusions cannot be stated, 25-75% reach partial remission (PASI 75) (30-40 mg/day) (Level of evidence: 3)
Absolute contraindications (See SmPC)	Kidney and liver damage, fertile women planning to have children, concomitant medication interacting with retinoids, hepatotoxic concomitant medication, pregnancy, breast-feeding, alcohol abuse, blood donation.
Relative contraindications (See SmPC)	Alcohol use (111), diabetes mellitus, use of contact lenses, children, history of pancreatitis, hyperlipidemia (especially hypertrygliceridemia) and hyperlipidemia treated with medication, atheroclerosis.

Most common adverse effects (See SmPC)	≥ 1/10: vitamin A toxicity (cheilitis, xerosis, epistaxis, alopecia, increased skin fragility) ≥ 1/100 to < 1/10: conjunctivitis (be aware of contact lenses), hair loss, photosensitivity, hyperlipidemia.
Important drug interactions	Phenytoin, tetracycline, methotrexate, alcohol, minipill, lipid lowering drugs (see also table 30).
Special notes	Continue contraceptive use at least 2 years after cessation of medication in fertile women

Conclusions of the Dutch guidelines

EL: 2	Acitretin is effective in the treatment of adult patients with moderate to severe plaque psoriasis. 11% (A2) – 50% (B) of psoriasis patients treated with 0.5 mg/kg/day acitretin reached PASI 90 response at week 8-12 and 25-41% of patients reached PASI 75 at week 8-12 when treated with 10-75 mg/day acitretin. *A2 Kragballe et al., 1989 (112)* *B Gupta et al., 1998 (113); van de Kerkhof et al., 1998 (114)*

Table 29: Important adverse effects of retinoids

Most frequently	Vitamin A toxicity (xerosis, cheilitis)
Frequently	Conjunctivitis (be aware of contact lenses), hair loss, photosensitivity,

	hyperlipidemia.
Sometimes	Muscular, joint and bone pain, retinoid-induced dermatitis
Rarely	Gastrointestinal complaints, hepatitis, jaundice. Bone changes with long-term use.
Very rarely	Idiopathic intracranial hypertension, decreased color vision, nyctalopia

Table 30: List of medication and drug interactions

Medicine	**Type of drug interaction**
Tetracycline	Induction of idiopathic intracranial hypertension
Phenytoin	Shift of plasma proteins
Vitamin A	Increasing the effect of retinoids
Methotrexate	Hepatotoxicity
Low dosage of pill with progesterone	Insufficient contraceptive effect
Lipid lowering drugs	Increased risk of myotoxicity
Antifungal imidazoles	Hepatotoxicity

Instructions for retinoid use

Prior to treatment

- Medical history and physical examination should be directed at muscle and skeletal problems. When patients experience symptoms supplementary imaging studies may be performed.
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)

- Exclude the possibility of pregnancy/lactation: patients have to be extensively informed about the teratogenic risk of the drug, the necessity of long-term effective contraceptives up to 2 years after cessation of acitretin therapy and the possible consequences of pregnancy during retinoid use: this must be well documented by the physician.
- Patients should be informed about the specific risks of excessive alcohol consumption. Inform female patients about the increased conversion of acitretin into etretinate.
- Direct the patient that blood donation is not allowed during and until 1 year after treatment
- Laboratory controls (Table 31)

During treatment

- Capsules should be taken during a meal or with milk
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- It is required to avoid pregnancy. Treatment is started at the second or third day of the menstruation cycle after adequate contraceptive use for at least 1 month prior to treatment. It is recommended to use 2 contraceptives simultaneously (e.g., condom + pill; IUD/NuvaRing + pill; note: avoid the use of preparations with low dose progesterone / mini-pill) during treatment and up to 2 years after cessation of treatment.
- Avoid excessive usage of alcohol
- Ask patient about symptoms of the back and joints. When patients experience symptoms supplementary imaging studies may be performed.
- Laboratory controls (Table 31)

After treatment

- Reliable contraceptives in fertile women up to 2 years after cessation of treatment
- It is recommended to use 2 contraceptives simultaneously, as stated above
- Patients are not allowed to be blood donors for 1 year after cessation of treatment

Table 31: Laboratory controls

Parameter	Prior to treatment	Treatment period (in weeks)					
		1	2	4	8	12	16
Blood count*	X				X		X
Liver values**	X		X	X	X		X
Serum creatinine	X						
Pregnancy test (urine)	X	Monthly during treatment					
Blood glucose (fasting)	X						
Tryglicerides, cholesterol, HDL	X			X			X
Further testing may be required based on clinical symptoms, risk and exposures							

* Hb, Hct, leukocytes, thrombocytes

** ASAT, ALAT, AP, yGT

Treatment recommendation

0.5mg/kg/day acitretin is recommended for induction therapy of moderate to severe psoriasis.

When induction therapy is considered to be effective after 10 – 16 weeks, maintenance therapy may be considered using the lowest effective dosage.

When conventional systemic therapies are indicated, acitretin is not recommended as first-choice monotherapy.

Fertile women planning to have children should not be treated with acitretin owing to its teratogenic properties.

Fumaric acid esters

H.B. Thio, E.P. Prens

Table 32: Fumaric acid esters

Registration for psoriasis	1994 (Germany), not registered in the Netherlands
Recommended control parameters before starting treatment	Complete blood count, liver enzymes serum creatinine, urine sediment, pregnancy test.
Recommended initial dosage	See dosing scheme (Table 33)
Recommended maintenance dosage	Determine individually
Onset of effect	After 6 weeks
Response rate	18-46% PASI 90 after 16 weeks of treatment 50-70% PASI 75 after 16 weeks of treatment
Absolute contraindications (See SmPC)	Severe liver and/or kidney diseases, gastrointestinal diseases, hematological malignancies, pregnancy or breastfeeding
Relative contraindications (See SmPC)	Hematological diseases (deviation in blood count), simultaneous usage of drugs that have the potential to induce nephrotoxicity

Most common adverse effects (See SmPC)	≥ 1/10: diarrhea, flushing ≥ 1/100 to < 1/10: cramps, flatulence, lymphocytopenia, eosinophilia
Important drug interactions	No known drug interactions
Special notes	Especially applicable for long-term therapy

Conclusions of the Dutch guidelines

EL: 2	Fumaric acid esters result in almost complete remission in 24% (weighted average, 18-46%) of patients after 16 weeks of treatment. Partial remission (PASI 75) is seen in 50-70% of patients after 16 weeks of treatment. Good efficacy was reached in both short-term and long-term (maintenance) therapy. *A2 Altmeyer et al., 1994 (115); Gollnick et al., 2002 (116)* *B Nugteren-Huying et al., 1990 (117); Kolbach et al., 1992 (118); Nieboer et al., 1990 (119)* *C Altmeyer et al., 1996 (120); Bayard et al., 1987 (121); Litjens et al., 2003 (122); Carboni et al., 2004 (123); Mrowietz et al., 1999 (124)*

Table 33: Dosing scheme for dimethyl fumarate

Time	Dimethyl fumarate 30 mg Number of tablets / day	Dimethyl fumarate 120 mg Number of tablets / day
Week 1	0-0-1	-
Week 2	1-0-1	-
Week 3	1-1-1	-

Week 4	-	0-0-1
Week 5	-	1-0-1
Week 6	-	1-1-1
Week 7	-	1-1-2
	Evaluate clinical response: In case PASI response ≥ 50% In case PASI response ≤ 50%	 Maintain 1-1-2 Proceed to 2-1-2 (week 8)
Week 8	-	2-1-2
Week 9	-	2-2-2

Table 34: Important adverse effects of fumarates

Most frequently	Diarrhea, flushing
Frequently	Cramps, flatulence, lymphocytopenia, eosinophilia
Sometimes	Nausea, dizziness, headache, fatigue, proteinuria, increase of creatinine levels, increase of liver enzymes levels
Rarely	Isolated increase of ALAT or bilirubin

Instructions for use of fumaric acid esters

Prior to treatment

- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Medical history and physical examination

- Laboratory controls (Table 35)

During treatment

- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Physical examination
- Laboratory controls (Table 35)

After treatment

- None

Table 35: Laboratory controls

Parameter	**Prior to treatment**	**Treatment period (months)**		**3rd month, thereafter once every 3 months, followed by once every 6 months after 1 year of treatment**
		1	**2**	
Total blood count (leucocytes, differential)	X	X	X	X
Liver enzymes (yGT, ALAT, ASAT)	X	X	X	X
Serum creatinine	X	X	X	X

Urea	X	X	X	X
Cholesterol	X	X	X	X
Urine sediment	X	X	X	X
Urine protein	X	X	X	X
Pregnancy test (urine)	X			

Treatment recommendation

Fumaric acid esters are recommended according to dosing scheme for induction therapy of patients with moderate to severe chronic plaque psoriasis

When induction therapy is considered to be effective after 10 – 16 weeks, maintenance therapy may be considered using the lowest effective dosage.

Fumaric acid esters may be considered as first-choice systemic monotherapy.

2.5 Biologics

Biologics in general

T.E.C. Nijsten

Therapeutic response

The primary outcome in the evaluation for therapeutic response of psoriatic drugs remains the improvement of clinical disease severity (PASI 75 or PGA mild to absent), but patient-reported outcome measures (e.g. patient preference, treatment satisfaction and/or improvement in quality of life) are increasingly important [125]. The momentum of treatment evaluation is preferentially 24 weeks (initiation period), but for some treatments this may be at 16 weeks (e.g. adalimumab and infliximab).

When therapeutic response is considered suboptimal (PASI 75%-50% and PASI 50%) or insufficient by the patient several alternatives are possible: increase dosage or dosage frequency, combination therapy (for example adding topical therapies, UV-therapy and/or methotrexate or acitretin) or switch to another (biologic) therapy.

Transition

Clinical experience shows that switching between biologics of the same or different class may be effective in patients not responding to an anti-TNF alpha agent. Insufficient therapeutic response to a TNF-alpha antagonist does not imply ineffectiveness of the other biologics inhibiting TNF alpha. Of course patients can be switched to ustekinumab, a biologic with a completely different mode of action. The same applies vice versa. The evidence of the effectiveness of switching between biologics is derived from small observational studies and (retrospective) case series [126, 127].

Hepatitis / HIV

Owing to the immunosuppressive properties of biologics it is advised to exclude chronic and active infections with HBV, HCV, and HIV in psoriasis patients before commencing biologic therapy. The following recommendations are based upon small case-series since solid clinical studies are lacking.

In chronic carriers of hepatitis B (HBsAg positive), there is a risk of reactivation of the virus (with the complication of acute liver failure). Therefore, these patients should not be treated with biologics, except when simultaneously treated with nucleoside analogues and guided by a gastrointestinal (GI) specialist.

In HCV infected psoriasis patients, biologic therapy may be started with adequate monitoring and in consultation with a GI specialist. HCV, in contrast to HBV, lacks the possibility of integrating into the DNA of hepatocytes and thus the risk of HCV flares is absent.

In HIV infected psoriasis patients, anti-TNF alpha therapy may be prescribed when the infection is controlled by HAART therapy. Additional controls are required given the possibility of drug interactions. Naturally, the patient should be treated in close consultation with the treating physician. Such experiences are lacking for ustekinumab therapy.

Malignancies

The risk of the occurrence of malignancies (especially lymphomas and cutaneous squamous cell carcinomas) related to immunosuppressive agents such as biologics remains an issue of concern. Psoriasis patients may already have an increased risk of developing skin cancer because of prior UV-phototherapy (especially PUVA), which is further increased after initiation of immunosuppressive drugs (e.g., cyclosporine and biologics) in patients with a history of high levels of UV exposure [128, 129, 130, 131]. Therefore, all patients and especially those with a prior history of intensive immunosuppressive therapy or PUVA therapy should be examined for melanoma and non-melanoma skin cancer prior to and during anti-TNF alpha treatment.

Spontaneous reporting registries have identified an increased risk of hepatosplenic T-cell carcinoma, which is often lethal, in patients using infliximab and adalimumab.

Long-term effects of ustekinumab are likely to be comparable to other biologics but relatively little is known because relatively few patients have used these drugs for a long period compared to the TNF antagonists. In clinical trials, some patients developed a basal cell carcinoma during ustekinumab treatment. Hence, screening for malignancies by physical examination (mainly the skin) and a complete blood sample is being advised before commencing therapy with ustekinumab.

In order to optimally assess the long-term safety and stimulating effects on the carcinogenesis of biologics well-designed and independent post-marketing studies (phase IV) are needed. Until now, few studies on the long-term safety are published [132, 133]. Large (inter)national prospective registers (e.g. PsoNet) of patients on biologic therapy may be helpful in detecting and estimating the risks associated with the use of biologics. Physicians are therefore encouraged to participate in patient registers (if available).

Demyelinating diseases

TNF-alpha antagonists are associated with the development or worsening of demyelinating diseases and multiple sclerosis.

Cardiovascular diseases

TNF-alpha antagonists are able to worsen (pre-existing) heart failure and should not be prescribed to psoriasis patients with severe congestive heart failure (NYHA class III or IV). Patients with a mild form of heart failure being administered an anti-TNF alpha agent for psoriasis should be carefully monitored and also guided by a cardiologist.

Data from a meta-analysis seem to implicate a short-term increased risk for myocardial infarction, cerebrovascular accident, and cardiovascular mortality for ustekinumab (and briakinumab) [134]. Further studies are required, but this seems to be a specific complication of this class of biologics.

Infections

TNF-alpha antagonists increase the risk of infection including tuberculosis (TB). Reactivation of (latent) TB seems to occur more often with infliximab and adalimumab therapy compared to etanercept. It is mandatory to screen for latent TB before commencing therapy with a biologic (see chapter: screening for tuberculosis). Other infections include upper and lower respiratory tract infections, urinary tract infections and skin infections [135].

Pregnancy

The experience with biologics just before and during pregnancy is too limited to claim safety of its (continuous) use.

Fertility

It is uncertain whether biologics reduce spermatogenesis [136, 137, 138]. No data has been published about the influence of TNF-alpha blockade on female fertility.

Transplacental passage

Biologics (adalimumab, infliximab and etanercept) may pass the placental barrier during the first, second, and especially third trimester [139].

Lactation

Mothers wishing to breastfeed their child have to be informed about the uncertainty of the influence of biologics on children and need to be advised about alternatives for lactation.

Biologics and antibody formation

L.L.A. Lecluse

As with other foreign proteins, treatment with biologics may cause antibody formation.

Neutralizing antibodies have been shown against adalimumab, infliximab, and ustekinumab, but not against etanercept [132, 140, 141]. For adalimumab and infliximab routine screening can be done. Antibodies against ustekinumab are tested in an experimental setting at this moment.

When to check for antibodies

Assessment of antibody titer may be indicated in patients treated with adalimumab or infliximab when:

I There is a significant decrease in effectiveness of the agent involved

II The psoriasis is recalcitrant to improvement since commencing therapy

III An infusion reaction occurs (only with infliximab)

How to interpret and act on antibody titers

Situation I

The effectiveness of the biologic declines, the antibody titer is low, and serum concentration value of the biologic is decreased.

The biologic may be continued, but dosing frequency or dosage of this drug may be increased to reduce antibody formation. Costs of treatment will rise.

Situation II

There is no clinical sign of effectiveness of the biological agent, the antibody titer shows high levels of antibodies, and the biologic serum concentration is undetectable.

The biologic should not be continued because the antibodies are neutralizing the biological agent. Consider switching to a biologic of a similar or different therapeutic class.

Situation III

There is no clinical sign of effectiveness of the biological agent, the antibody titer shows no antibodies, and the biologic serum concentration is within normal range.

The patient does not respond to therapy. Consider switching to a biologic of a different therapeutic class.

Screening for tuberculosis

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Table 36: Plan of action for tuberculosis screening

Diagnostic approach to TB, regardless of BCG vaccination status, prior to and during follow-ups of treatment with biologic agents. Physicians should be alert to the occurrence of TB during treatment and 6 months thereafter [142]. During treatment yearly screening is advised for latent TB. Medical history, Mantoux and IGRA are recommended. To limit the influence of immunosuppressive drugs on Mantoux and IGRA a treatment-free interval may be introduced a week before screening.

Medical history:

- Symptoms indicating possible TB
- Prior history of TB, possibly treated sufficiently
- Exposition to TB
- Originating from or recent long stay in an epidemic area
- Risk patient
- BCG vaccination status

Physical examination, consider:

- Auscultation of lungs when symptomatic (non-specific for TB diagnosis)
- Scar (left) upper arm (possible BCG vaccination)

Chest X-ray

- Signs of active or past TB?

  ➔ Consult pulmonologist in case of abnormalities

Mantoux

- ≥ 5mm induration → positive → consider latent TB infection (LTBI) or active TB infection (TBI) → consult pulmonologist
- < 5mm induration:

  - age < 65 years: draw blood for IGRA test

  - age ≥ 65 years: repeat Mantoux after 2 weeks

  • ≥ 5mm induration → positive → consult pulmonologist

  • < 5mm induration → draw blood for IGRA test

IGRA (Altena, 2010)

Mantoux	**IGRA**	**Diagnosis**	**Management**
< 5mm	Negative	Depending on medical history	- Start a biologic agent when medical history (symptoms, prior history, exposition, origin, recent stay, risk patient) reveals no signs of or risk to TB - In case medical history reveals signs of or risk to

			TB, consult a pulmonologist for further diagnostics and treatment - HIV-infected patients with a low CD-4 count could still have a TB infection
≥ 5mm < 10mm	Negative	Strongly consider LTBI and active TB	Consult pulmonologist for further diagnostics and treatment
> 10 mm	Negative	LTBI	Consult pulmonologist for further diagnostics and treatment
Every value	QFT-G 0.2-0.35 U/ml	Strongly consider LTBI	Consult pulmonologist for treatment
Every value	Positive (QFT-G > 0.35 U/ml)	LTBI	Consult pulmonologist for treatment

Treatment:

A

- Active TB or (considered) LTBI → consult pulmonologist for treatment, in some

cases for 9 months (143).

- During treatment of LTBI a biologic agent may be started after 1-3 months. There is no consensus about this issue, thus, it is recommended to start treatment in consultation with a pulmonologist (142, 143).

B

- **Preference of biologic agent:** (see also table 37) Studies suggest that reactivation of latent TB is less common in etanercept compared to adalimumab or infliximab (143, 144). This could be related to the different mode of action and binding to TNF-alpha. For ustekinumab, at present, there is no available data.

Table 37: Biologic agents classified by TB risk

High risk (143, 144)	Infliximab Adalimumab Prednisone ≥ 15mg/day Cytostatic agents
Average risk (143, 144)	Etanercept
Low risk	Methotrexate (one case reported at Lareb) Cyclosporine (one case reported at Lareb)
Too little evidence	Ustekinumab

Adalimumab

H.B. Thio

Table 38: Adalimumab

Registration for psoriasis	December 2007 (EMA)
Recommended control parameters before starting treatment	Complete blood count, liver enzymes, erythrocyte sedimentation (ESR) / CRP, serum creatinine, urine sediment, pregnancy test, HBV / HCV, HIV (prior to treatment). TB screening summarized: medical history, physical examination, chest X-ray, Mantoux test, Quantiferon test.
Recommended initial dosage	Loading dosage: 80 mg subcutaneous
Recommended maintenance dosage	40 mg subcutaneous 1x every 2 weeks
Onset of effect	After 4 weeks
Response rate	53-80% PASI 75 24-52% PASI 90
Absolute contraindications (See SmPC)	Hypersensitivity to adalimumab, severe active infections, chronic HBV, active TB, heart failure (NYHA III/IV), pregnancy or lactation, malignancy or lymphoproliferative disorder in recent history (< 5 years and excluded are BCC, KIN III, CIN III), demyelinating disorders, vaccination with live vaccines.
Relative contraindications (See SmPC)	Heart failure (NYHA I/II), hepatic and biliary disorders, HCV, PUVA >1000J/cm^2 or 150-200 treatments (especially when cyclosporine has been prescribed afterterwards), HIV or AIDS, Wegener's granulomatosis.

Most common adverse effects (See SmPC)	≥ 1/10: respiratory tract infections (including lower and upper respiratory tract infections, pneumonia, sinusitis, pharyngitis, nasopharyngitis, and viral herpes pneumonia), leucopenia (including neutropenia, agranulocytosis), anemia, increased lipid levels, headache, abdominal pains, nausea and vomiting, increased liver enzymes, rash (including scaly rash), myalgia, injection site reactions (including injection site erythema). ≥ 1/100 to < 1/10: systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including viral gastroenteritis), skin and subcutaneous infections (including paronychia, cellulitis, impetigo, necrotizing fasciitis and herpes zoster), etc. (see SMPC or http://www.huidarts.info/documents/uploaded_file.aspx?id=579)
Important drug interactions	Abatacept, Anakinra
Special notes	Vaccination with live vaccines should not be administered during treatment with a biologic. Depending on the drug's half-life, the biologic must be stopped 4-8 weeks prior to immunization and may be restarted 2-3 weeks after vaccination.

Conclusions of the Dutch guidelines

EL: 1	Adalimumab is effective for the treatment of moderate to severe chronic plaque psoriasis in adult patients. After 16 weeks of treatment (Gorden et al., at week 12), PASI 75 was reached in 53-80% and PASI 90 in 24-52% of patients with psoriasis treated with adalimumab. *A2 Gordon et al., 2006 (145); Menter et al., 2008 (146); Saurat et al., 2008 (103)*

Table 39: Important adverse effects of adalimumab

Most frequently	Injection site reactions, respiratory tract infections, headache, abdominal pains, nausea and vomiting, rash, myalgia, bone marrow depression
Frequently	(Severe) infections, benign tumors, skin cancer, mood swings (inter alia depression), anxiety, fatigue, sensory disturbances, migraine, dizziness, itch, pyrosis
Sometimes	Tuberculosis, lymphoma
Rarely	-
Very rarely	Drug-induced lupus, sudden cardiac death, multiple sclerosis

Table 40: List of medication and drug interactions

Medicine	**Type of drug interaction**
Anakinra	Increased risk on serious infection
Immunosuppressive mediation	Increased immunosuppression

(cyclosporine, other biologics)	
PUVA	Risk of skin cancer

Instructions for adalimumab use

Prior to treatment

- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider assessing HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Medical history and physical examination should be directed at therapeutic history, malignancies, infections, congestive heart failure and neurological symptoms
- Recommended actions are:
- Check for skin cancer
- Check for lymphadenopathy
- Laboratory controls (Table 41)
- Chest X-ray, Mantoux test and QuantiFERON-TB Gold test
- Pregnancy test
- Contraception

During treatment

- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Perform a TB screening annually (medical history, mantoux and IGRA)
- Consider the assessment of HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Physical examination should be directed at malignancies, risk factors for serious infections, congestive heart failure and neurological symptoms
- Recommended actions are:
- Check for skin cancer

- Check for lymphadenopathy
- Laboratory controls (Table 41)
- Urine sediment
- Contraception

After treatment

- After treatment with adalimumab physicians are advised to perform regular follow-ups with medical history and physical examination
- Reliable contraceptives until 5 months after treatment, if indicated
- Physicians are encouraged to document their patients' parameters into registers (if available) to evaluate long-term efficacy and safety of biologics.

Table 41: Laboratory controls

Parameter	**Prior to treatment**	**Treatment period (weeks)**		**Thereafter once every 3 months**
		4	**12**	
Total blood count	X	X	X	X
Liver enzymes	X	X	X	X
Serum creatinine	X	X	X	X
Urine sediment	X	X	X	X
Erytrocyte sedimentation (ESR), CRP	X	X	X	X
Pregnancy test (urine)	X	X	X	X

HBV / HCV	X			
HIV	X			
Further testing may be required based on clinical symptoms, risks and exposure				

Treatment recommendation

Adalimumab is recommended for induction therapy (80 mg at week 0, followed by 40 mg every 2 weeks) in patients with moderate to severe chronic plaque psoriasis, when photo(chemo)therapy and conventional systemic treatments are ineffective, contraindicated, or not being tolerated.

Etanercept

T.E.C. Nijsten

Table 42: Etanercept

Registration for psoriasis	September 2004 (EMA)
Recommended control parameters before starting treatment	Complete blood count, liver enzymes, ESR / CRP, serum creatinine, urine sediment, pregnancy test, HBV / HCV, HIV. TB screening summarized: medical history, physical examination, chest X-ray, Mantoux test, Quantiferon test.
Recommended initial dosage	2x25 mg/week, 1x50 mg/week or 2x50 mg/week (week 0-12)
Recommended maintenance dosage	2x25 mg/week, 1x50 mg/week or 2x50 mg/week
Onset of effect	After 6-8 weeks
Response rate	PASI 75 in 33 or 49% after 12 weeks (2x25 or 2x50 mg/week)
Absolute contraindications (See SmPC)	Hypersensitivity to etanercept, severe active infections, chronic HBV, active TB, heart failure (NYHA III/IV), pregnancy or

	lactation, malignancy or lymphoproliferative disorder in recent history (< 5 years and excluded are BCC, KIN III, CIN III), demyelinating disorders, vaccination with live vaccines.
Relative contraindications (See SmPC)	Heart failure (NYHA I/II), hepatic and biliary disorders, HCV, PUVA >1000J/cm^2 or 150-200 treatments (especially when cyclosporine has been prescribed afterterwards), HIV or AIDS, Wegener's granulomatosis.
Most common adverse effects (See SmPC)	≥ 1/10: infections (including lower and upper respiratory tract infections, pneumonia, bronchitis, cystitis and skin infections), injection site reactions (including bleeding, bruising, erythema, itch, pain, swelling). ≥ 1/100 to < 1/10: allergic reactions, auto-antibody formation, pruritus, fever.
Important drug interactions	Anakinra, Abatacept, immunosuppressives (cyclosporine, other biologics), PUVA.
Special notes	Weight gain

Conclusions of the Dutch guidelines

	Etanercept is effective for the treatment of moderate to severe plaque psoriasis in adult patients. At week 12, PASI 75 was reached in 30-34% and PASI 90 in 11% of patients when etanercept was prescribed in a

EL: 1	dosage of 2 x 25 mg per week. When 2 x 50 mg etanercept is administered, PASI 75 and PASI 90 are reached in 47-49% and 21% of patients, respectively, at week 12. These percentages increase with 10% at week 24. *A2 Gottlieb et al., 2003 (147); Leonardi et al., 2003 (148); Tyring et al., 2006 (149); Papp et al., 2005 (150)*

Table 43: Important adverse effects of etanercept

Most frequently	Infusion reactions, infections (upper respiratory tract, bronchitis, skin infections)
Frequently	Pruritus, antibody formation, allergy
Sometimes	Thrombocytopenia, urticaria, angioedema, severe infections (for example: pneumonia, cellulitis and sepsis), uveitis, Non-melanoma skin cancer, interstitial lung disease, rash
Rarely	Anemia, leucopenia, neutropenia, pancytopenia, vasculitis, subacute and discoid LE, demyelinating disease, TB reactivation, convulsions, heart failure, severe allergy, liver function abnormalities
Very rarely	Aplastic anemia

Table 44: List of medication and drug interactions

Medicine	**Type of drug interaction**

Anakinra	Neutropenia and severe infections
Immunosuppressive mediation (cyclosporine, other biologics)	Increased immunosuppression
PUVA	Risk of skin cancer (especially squamous cell carcinoma)

Instructions for etanercept use

Prior to treatment

- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider the assessment of HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Medical history and physical examination should be directed at therapeutic history, malignancies, infections, congestive heart failure and neurological symptoms
- Recommended actions are:
- Check for skin cancer
- Check for lymphadenopathy
- Laboratory controls (Table 45)
- Chest X-ray, Mantoux test and QuantiFERON-TB Gold test
- Pregnancy test
- Contraception

During treatment

- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Perform a TB screening annually (medical history, mantoux and IGRA)
- Consider the assessment of HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)

- Physical examination should be directed at malignancies, risk factors for serious infections, congestive heart failure and neurological symptoms
- Recommended actions are:
- Check for skin cancer
- Check for lymphadenopathy
- Laboratory controls (Table 45)
- Urine sediment
- Contraception

After treatment

- After treatment with etanercept physicians are advised to perform regular follow-ups with medical history and physical examination
- Physicians are encouraged to document their patients' parameters into registers (if available) to evaluate long-term efficacy and safety of biologics.

Table 45: Laboratory controls

Parameter	**Prior to treatment**	**Treatment period (weeks)**		**Thereafter once every 3 months**
		4	**6**	
Total blood count	X	X	X	X
Liver enzymes	X	X	X	X
Serum creatinine	X	X	X	X
Urine sediment	X	X	X	X
Erytrocyte sedimentation	X	X	X	X

(ESR), CRP				
Pregnancy test	X	X	X	X
HBV / HCV	X			
HIV	X			
Further testing may be required based on clinical symptoms, risks and exposure				

Treatment recommendation

Etanercept is recommended for induction therapy (2 x 25 mg, 1 x 50 mg or 2 x 50 mg per week) (maximum of 24 weeks) in patients with moderate to severe chronic plaque psoriasis, when photo(chemo)therapy and conventional systemic treatments are ineffective, contraindicated, or not being tolerated.

When induction therapy with etanercept is effective after 10-16 weeks, low dose etanercept (2 x 25 mg per week or 1 x 50 mg per week) should be prescribed as maintenance therapy.

Infliximab

M. de Groot

Table 46: Infliximab

Registration for psoriasis	September 2005 (EMA)
Recommended control parameters before starting treatment	Complete blood count, liver enzymes, ESR / CRP, serum creatinine, urine sediment, pregnancy test, HBV / HCV, HIV. TB screening summarized: medical history, physical examination, chest X-ray, Mantoux test, Quantiferon test.
Recommended initial dosage	5 mg/kg body weight
Recommended maintenance dosage	5 mg/kg body weight week 2, 6, and thereafter every 8 weeks
Onset of effect	After 2-5 weeks
Response rate	PASI 75 in 80% of patients after 10 weeks
Absolute contraindications	Hypersensitivity to infliximab, severe

(See SmPC)	active infections, chronic HBV, active TB, heart failure (NYHA III/IV), pregnancy or lactation, malignancy or lymphoproliferative disorder in recent history (< 5 years and excluded are BCC, KIN III and CIN III), demyelinating disorders, vaccination with live vaccines.
Relative contraindications (See SmPC)	Heart failure (NYHA I/II), hepatic and biliary disorders, HCV, PUVA >1000J/cm^2 or 150-200 treatments (especially when cyclosporine has been prescribed afterterwards), HIV or AIDS, Wegener's granulomatosis.
Most common adverse effects (See SmPC)	≥ 1/10: none ≥ 1/100 to < 1/10: viral infections (e.g., flu, viral herpes infection), serum sickness-like symptoms, headache, vertigo, dizziness, flush, lower respiratory tract infection (e.g., bronchitis, pneumonia), upper respiratory tract infections, sinusitis, dyspnoea, abdominal pains, diarrhea, nausea, dyspepsia, elevated transaminases, urticaria, rash, pruritus, hyperhidrosis, dry skin, infusion related reactions, chest pain, fatigue, fever
Important drug interactions	Abatacept, Anakinra
Special notes	Reliable contraceptives in fertile women

	until 6 months after infliximab treatment

Conclusions of the Dutch guidelines

EL: 1	Infliximab is effective for the treatment of moderate to severe chronic plaque psoriasis in adult patients. About 64% - 88% of patients treated with 5mg/kg infliximab reached PASI 75 at week 10. About 41% - 57% of patients treated with infliximab (5mg/kg) reached PASI 90 at week 10. *A2 Antoni et al., 2005 (151); Menter et al., 2007 (152); Reich et al., 2005 (153); Gottlieb et al., 2004 (154)*

Table 47: Important adverse effects of infliximab

Most frequently	Infusion reactions, infections, nausea, diarrhea, difficulty breathing, dizziness, fatigue
Frequently	Headache, flushing, pruritus, urticaria, fever, elevated transaminases
Sometimes	Serum sickness-like disease, cutaneous lupus erythematosus, severe infections, anaphylactic reaction, circulation problems, depression
Rarely	Opportunistic infections, tuberculosis, pancytopenia, vasculitis, demyelinating diseases
Very rarely	Myelitis transversa, psoriasis (including pustular psoriasis), hepatocellular

	damage. In patients with Crohn's disease and ulcerative colitis hepatosplenic T-cell lymphoma may be induced.

Instructions for infliximab use

Prior to treatment

- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider the assessment of HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Medical history and physical examination should be directed at therapeutic history, malignancies, infections, congestive heart failure and neurological symptoms
- Recommended actions are:

- Check for skin cancer
- Check for lymphadenopathy
- Laboratory controls (Table 48)
- Urine sediment
- Chest X-ray, Mantoux test and QuantiFERON-TB Gold test
- Pregnancy test

- Contraception

During treatment

- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Perform a TB screening annually (medical history, mantoux and IGRA)
- Consider the assessment of HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Physical examination should be directed at malignancies, risk factors for serious infections, congestive heart failure and neurological symptoms

- Recommended actions are:
- Check for skin cancer
- Check for lymphadenopathy
- Laboratory controls (Table 48)
- Urine sediment
- Contraception

After treatment

- After treatment with infliximab physicians are advised to perform regular follow-ups with medical history and physical examination
- Reliable contraceptives until 6 months after cessation of treatment, if indicated
- Physicians are encouraged to document their patients' parameters into registers (if available) to evaluate long-term efficacy and safety of biologics.

Table 48: Laboratory controls

Parameter	**Prior to treatment**	**Treatment period (weeks)**		**Thereafter, prior to every infusion**
		4	**6**	
Total blood count	X	X	X	X
Liver enzymes	X	X	X	X
Serum creatinine	X	X	X	X
Urine sediment	X	X	X	X
Erytrocyte sedimentation	X	X	X	X

(ESR), CRP				
Pregnancy test	X	X	X	X
HBV / HCV	X			
HIV	X			
Further testing may be required based on clinical symptoms, risks and exposure				

Treatment recommendation

Infliximab is recommended for induction therapy when photo(chemo)therapy and conventional systemic treatments are ineffective, contraindicated, or not being tolerated.

It is advised to prescribe infliximab 5mg/kg in patients with moderate to severe chronic plaque psoriasis at week 0, 2, 6, and every 8 weeks thereafter.

When induction therapy with infliximab is effective after 10-16 weeks, maintenance therapy with infliximab is recommended for every 8 weeks.

It is advised to combine infliximab therapy with 7.5 mg methotrexate per week in order to prevent antibody formation and to lower the risk of infusion reactions.

Ustekinumab

Ph.I. Spuls, P.A. Poblete-Gutiérrez, J. de Bes

Table 49: Ustekinumab

Registration for psoriasis	20th November 2008 (EMA)
Recommended control parameters before starting treatment	Complete blood count, liver enzymes, ESR / CRP, serum creatinine, urine sediment, pregnancy test, HBV / HCV, HIV. TB screening summarized: medical history, physical examination, chest X-ray, Mantoux test, Quantiferon test.
Recommended initial dosage	45 mg, patients > 100 kg 90 mg at week 0, 4 and 16
Recommended maintenance dosage	45 mg/12 weeks, patients > 100 kg 90 mg/12 weeks

Onset of effect	After 2 weeks
Response rate	PASI 75 in 66-76% of patients
Absolute contraindications (See SmPC)	Hypersensitivity to ustekinumab, severe active infections, chronic HBV, active TB, heart failure (NYHA III/IV), pregnancy or lactation, malignancy or lymphoproliferative disorder in recent history (< 5 years and excluded are BCC, KIN III and CIN III), demyelinating disorders, vaccination with live vaccines.
Relative contraindications (See SmPC)	Heart failure (NYHA I/II) and a prior history of or increased risk for cardiovascular accident or acute myocardial infarction. Hepatic and biliary disorders, HCV, PUVA >1000J/cm^2 or 150-200 treatments (especially when cyclosporine has been prescribed afterterwards), HIV or AIDS, Wegener's granulomatosis.
Most common adverse effects (See SmPC)	≥ 1/10: nasopharyngitis and upper respiratory tract infections ≥ 1/100 to < 1/10: inflammation of subcutaneous connective tissue (cellulitis), viral infection of the upper respiratory tract, hypersensitivity reactions (including rash and urticaria), depression, dizziness, headache, sore

	throat, stuffy nose, diarrhea, pruritus, back pain, myalgia, fatigue, erythema on injection site
Important drug interactions	Unknown
Special notes	Reliable contraceptives are mandatory in fertile women until 15 weeks after ustekinumab treatment

Conclusions of the Dutch guidelines

EL: 1	Ustekinumab is effective for the treatment of moderate to severe chronic plaque psoriasis in adult patients. PASI 75 was reached in 67% of patients treated with ustekinumab (45 mg at week 0, 4 and 16) at week 12. PASI 75 was reached in 66-76% of patients treated with ustekinumab 90 mg (week 0, 4 and 16). A maximum effect was observed in more than three-quarters of the research population (PASI 75) after 24 weeks. *A2 Leonardi et al., 2008 (155); Papp et al., 2008 (132)*

Table 50: Important adverse effects of ustekinumab

Most frequently	Nasopharyngitis, upper respiratory tract infections, headache, arthralgia
Frequently	Cellulitis, viral infections of upper respiratory tract, depression, dizziness, headache, sore throat, stuffy nose, diarrhea, pruritus, back pain, myalgia, fatigue, erythema on injection site,

	urticaria
Very rarely	Severe infections or allergy

Instructions for ustekinumab use

Prior to treatment

- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Consider the assessment of HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Medical history and physical examination should be directed at therapeutic history, malignancies, infections, TB, heart and kidney diseases and neurological symptoms
- Recommended actions are:
- Check for skin cancer
- Check for lymphadenopathy
- Laboratory controls (Table 51)
- Urine sediment
- Chest X-ray, Mantoux test and QuantiFERON-TB Gold test
- Vaccinations in concordance with the National Immunization Program
- Pregnancy test
- Reliable contraceptives in fertile women during treatment and until 15 weeks after cessation of treatment

During treatment (every 3 months)

- Objective assessment of psoriasis (such as PASI / BSA / PGA; arthritis)
- Perform a TB screening annually (medical history, mantoux and IGRA)
- Consider the assessment of HRQoL (e.g. DLQI, Skindex-29 or Skindex-17 or VAS)
- Recommended actions are:

- Check for skin cancer
- Laboratory controls (Table 51)
- Urine sediment

After treatment

- Follow-up visits for assessing symptoms of psoriasis
- Reliable contraceptives until 15 weeks after cessation of treatment, if indicated
- Physicians are encouraged to document their patients' parameters into registers (if available) to evaluate long-term efficacy and safety of biologics.

Table 51: Laboratory controls

Parameter	Prior to treatment	After 4 weeks	Thereafter once every 12 weeks
Total blood count	X	X	X
Liver enzymes	X	X	X
Serum creatinine	X	X	X
Urine sediment	X	X	X
Erytrocyte sedimentation (ESR), CRP	X	X	X
Pregnancy test	X	X	X
HBV / HCV	X		
HIV	X		
Further testing may be required based on clinical symptoms, risks and exposure			

Considerations when prescribing biologics

The following table highlights the considerations per biologic.

Table 52: Considerations when prescribing biologics

Etanercept (E)	**Adalimumab (A)**	**Infliximab (I)**	**Ustekinumab (U)**
Less efficacy compared to A, I and U. However, maximum efficacy may be reached after 24 weeks	Higher efficacy compared to E (after 12 and 24 weeks)	Higher efficacy compared to E (after 12 and 24 weeks)	Higher efficacy compared to E (after 12 and 24 weeks)
		Fast initial response	
Less effective than U	No head-to-head trials with this biologic	No head-to-head trials with this biologic	More effective than E
Drug survival rate below I (daily practice data)	Drug survival rate below I (daily practice data)	Highest drug survival rate compared to A and E (daily practice data)	Drug survival rate is high during 1 year (daily practice data)
Injection side reaction	Injection side reaction	Infusion reaction	Injection side reaction
Thrombocytopenia, leucopenia and pancytopenia	Thrombocytopenia, leucopenia and pancytopenia	Thrombocytopenia, leucopenia and pancytopenia	Thrombocytopenia, leucopenia and pancytopenia
Less TB reactivation compared to A and I	More TB reactivation compared to E	More TB reactivation compared to E	Little long-term experience

Non-neutralizing antibody formation	Neutralizing antibody formation, possibly clinically relevant	Neutralizing antibody formation, clinically relevant	
High dosage (2x50 mg/week) leads to high costs	Loading dosage at start increases cost at start.	In extreme obese patients (> 100kg) costs will rise. Loading dosage at start increases cost at start.	In extreme obese patients (> 100kg) costs will rise. Loading dosage at start increases cost at start.
Subcutaneously	Subcutaneously	Intravenously	Subcutaneously
			Long treatment interval (3 months). (Higher user friendliness)
Daily practice data indicate biologics to be less effective when compared to data from randomized controlled trials. Hence, the dosage of biologics is higher in daily practice.			

This table is a summary of the paragraph "considerations when prescribing biologics" within the Dutch guidelines on the treatment of psoriasis 2011 (http://www.huidarts.info/documents/uploaded_file.aspx?id=579). The content of this table is based upon the following references: [125-127, 134, 156-160].

Conclusions

Adalimumab or low-dose etanercept (1x50 mg/week) are the preferred first-choice treatments in otherwise healthy, biologic-naïve psoriasis patients. Adalimumab seems to be more effective than etanercept in the short-term, but may be related to clinically relevant antibody formation. Infliximab is preferred in acute situations (e.g., severe exacerbation of plaque psoriasis, off-label for psoriatic erythroderma or generalized pustular psoriasis) because of high efficacy and fast clinical response, followed by a maintenance dosage of this agent. Also, infliximab is important in patients not responding to other TNF-alpha agents. Although ustekinumab is highly effective, the working group holds the opinion that until long-term efficacy and safety are elucidated this agent should be reserved for patients responding insufficiently to TNF-alpha antagonists.

3. Treatment of psoriasis of the face and flexures

P.C.M. van de Kerkhof, C.L.M. van Hees

Epidemiology

Conclusions of the Dutch guidelines

	Psoriasis of the face is present in 17-46% and psoriasis of the flexures in 6.8-36% of psoriasis patients. Hence, psoriasis cannot be regarded as a rare manifestation in these areas.
EL: 3	*C Fauéré et al., 2005 (161); Dubertret et al., 2006 (162); van de Kerkhof et al., 2000 (163); Farber et al., 1968 (164); Farber et al., 1974 (165); Wang et al., 2005 (166); Nanda et al., 1990 (167); Puissant, 1970 (168); Nyfors et al., 1975 (169)* *D van de Kerkhof et al., 2007 (10)*

Recommendation

It is recommended to further study the efficacy and safety of treatments (preferably by randomized, double blind, controlled trials), given the frequency of psoriasis of the face and flexures.

Clinical signs

Conclusions of the Dutch guidelines

	Psoriasis of the face is a prognostic marker for a severe form of psoriasis. Psoriasis of the flexures is not a prognostic marker.
EL: 4	*C Park et al., 2004 (170)* *D van de Kerkhof et al., 2007 (10)*

	Psoriasis of the face and psoriasis of the flexures should not be considered two different disease entities, but as a variation of localization of the same disease.
EL: 4	*D van de Kerkhof et al., 2007 (10)*

EL: 3	Clinical signs of facial psoriasis suggest there are three forms: hairline psoriasis, sebo-psoriasis and true facial psoriasis. *C Woo et al., 2008 (171)* *D van de Kerkhof et al., 2007 (10)*

EL: 4	Otitis externa and ocular manifestations may drastically decrease quality of life and should therefore not be neglected. *D van de Kerkhof et al., 2007 (10)*

Pathogenetic aspects

Conclusions of the Dutch guidelines

EL: 3	Evidence is small to absent on the role of microbiological factors in the pathogenesis of psoriasis of the face and flexures. *C Rosenberg et al., 1989 (172)* *D van de Kerkhof et al., 2007 (10)*

EL: 3	The reaction to UV radiation differs between patients with facial psoriasis. At least 5% of psoriasis patients has photosensitive psoriasis. *C Farber et al., 1968 (164); Farber et al., 1974 (165); Lane et al., 1937 (173); Lomholt et al., 1963 (174); Braun-Falco et al., 1972 (175)* *D van de Kerkhof et al., 2007 (10)*

Recommendation

It is recommended to exclude photosensitive diseases such as lupus erythematosus and polymorphic light eruption in patients with photosensitive psoriasis.

Antimicrobial treatment

Conclusions of the Dutch guidelines

EL: 3	There is no evidence that antimicrobial treatment is effective for psoriasis of the flexures. *C Leigheb et al., 2000 (176)*

EL: 3	There is evidence antifungal treatment may be effective for sebo-psoriasis of the face. *C Doering., 1985 (177); Faergemann, 1985 (178)*

Considerations

The efficacy of antiseptic, antibacterial, and antifungal treatments has sparsely been investigated in comparing studies. Randomized and double blind trials are lacking.

Treatment recommendation

Antimicrobial treatment is not indicated for the treatment of psoriasis of the face and flexures.

Dithranol and coal tar

Conclusions of the Dutch guidelines

EL: 3	The efficacy of dithranol combined with coal tar is similar as for fluocinolone acetonide cream. *B Heller, 1989 (179)*

Considerations

The evidence of the efficacy of dithranol is also being supported by decades of clinical experience.

Skin irritation and stains in textile limit the use of these treatments.

Treatment recommendation

Discoloration and skin irritation limit the use of dithranol and coal tar. Dithranol and coal tar are not indicated for first-line therapy, except in cases in which first-line therapies fail.

Topical corticosteroids

Conclusions of the Dutch guidelines

EL: 3	Evidence about the efficacy and safety of topical corticosteroids comes from a non-comparative study (topical corticosteroids until 12 weeks) and a double blind, randomized vehicle-controlled study (topical corticosteroids during 4 weeks). *B Kreuter et al., 2006 (180)* *C Lebwohl et al., 2001 (181)*

Considerations

Textbooks state that low-potent (class 1-2) topical corticosteroids are effective and safe, whereas mid-potent (class 2-3) topical corticosteroids induce perioral dermatitis and striae, especially during long-term use.

Treatment recommendation

Topical corticosteroids class 1-2 (low-potency) are first-choice treatments for psoriasis of the face and flexures during a limited treatment period. Subsequently, topical non-steroidal agents should be prescribed.

Vitamin D3 analogues

Conclusions of the Dutch guidelines

EL: 2	Vitamin D analogues are effective for the treatment of psoriasis of the face and flexures. *A2 Liao et al., 2007 (182)* *B Ortonne et al., 2003 (183)*

	C Duweb et al., 2003 (184); Kienbaum et al., 1996 (185); Langer et al., 1996 (186)

EL: 3	Calcitriol is superior over calcipotriol regarding safety profile. *B Ortonne et al., 2003 (183)*

Treatment recommendations

Vitamin D3 analogues are first-choice treatments for psoriasis of the face and flexures. Calcitriol induces less adverse effects, such as erythema and irritation, than calcipotriol.

Calcineurin inhibitors

Conclusions of the Dutch guidelines

EL: 1	The efficacy of calcineurin inhibitors for the treatment of psoriasis of the face and flexures has been assessed in 4 independent A2-studies (2 placebo-controlled studies, 1 comparative study with clobetasone butyrate and 1 comparative study with calcitriol). *A2 Lebwohl et al., 2004 (187); Gribetz et al., 2004 (188); Kleyn et al., 2005 (189); Liao et al., 2007 (182)*

Considerations

Calcineurin inhibitors are not registered for this treatment indication.

Treatment recommendations

Low-potent (class 1-2) topical corticosteroids *during 2-4 weeks* are the first-choice treatment of psoriasis of the face and flexures. Calcineurin inhibitors or Vitamin D3 analogues may also be prescribed. Calcineurin inhibitors may be used for long-term treatment.

Photo(chemo)therapy

Conclusions of the Dutch guidelines

EL: 4	No studies have been conducted measuring the efficacy and safety of photo(chemo)therapy. However, clinical experience shows these treatments improve psoriasis of the face and flexures. *D van de Kerkhof et al., 2007 (10)*

Treatment recommendations

When topical therapies provide insufficient disease control, phototherapy is an option for the treatment of psoriasis of the face and flexures.

Systemic therapies

Conclusions of the Dutch guidelines

EL: 4	No studies have been conducted measuring the efficacy and safety of methotrexate, cyclosporine, acitretin, fumaric acid esters and biologics for the treatment of psoriasis of the face and flexures. However, clinical experience shows these treatments improve psoriasis in these locations. *D van de Kerkhof et al., 2007 (10)*

EL: 3	There is evidence available indicating botulinum toxin is effective for the treatment of psoriasis of the flexures. *C Zanchi et al., 2008 (190)*

Considerations

Botulinum toxin is not registered for the treatment of psoriasis. The costs of this treatment are substantial.

Treatment recommendations

When topical therapies provide insufficient disease control, systemic therapies are an option.

4. Treatment of childhood psoriasis

M.M.B. Seyger

Introduction

All drugs mentioned in these guidelines have not been registered for the treatment of childhood psoriasis. Thus, usage of these drugs is off-label, with the exception of etanercept, which is registered for plaque psoriasis in children aged eight years or older. Off-label use of drugs is not uncommon, according to the Medicine Evaluation Board (MEB; Netherlands: CBG) and Inspection for Health Care (IGZ), if justified. The treating physician is obligated to inform the patient about the advantages and disadvantages of off-label drug use.

Topical corticosteroids

Conclusions of the Dutch guidelines

EL: 3	Halobetasol cream 0.05% and clobetasol proprionate emulsion 0.05% twice daily may be effective treatments for childhood psoriasis. Reported adverse effects during treatment were relatively mild. *C Herz et al., 1991 (191); Kimbal et al., 2008 (192)* *D Feicht, 1982 (193)*

Considerations

Published literature on the use of topical corticosteroids in childhood psoriasis is scarce. The number of treated patients is low and the treatment period short. Also, different vehicles were being used. Nonetheless, topical corticosteroids are important in the physician's treatment arsenal for treating childhood psoriasis.

Treatment recommendations

The use of topical corticosteroids is rewarding in childhood psoriasis. It is recommended to use topical corticosteroids of class 2-3 (mild-potency).

Vitamin D3 analogues

Conclusions of the Dutch guidelines

EL: 3	Calcipotriol is an effective and mostly well tolerated treatment option for plaque type childhood psoriasis. Adverse effects are mild. *A2 Oranje et al., 1997 (194)*

EL: 3	Calcitriol seems to be an effective treatment for childhood psoriasis with mild adverse effects. *B Perez et al., 1995 (195)*

Considerations

Both calcipotriol and calcitriol are not registered for use in children. Calcipotriol is no longer available as monotherapy in the Netherlands.

Treatment recommendations

Given the efficacy and mild adverse effect profile of Vitamin D3 and analogues (calcipotriol), these agents are recommended as first-choice therapy for childhood psoriasis. A combination with topical corticosteroids class 2-3 (mild potency) is recommended.

Calcineurin inhibitors

Conclusions of the Dutch guidelines

EL: 3	Tacrolimus 0.1% seems to be effective and safe for short-term treatment of childhood psoriasis of the face and flexures. Long-term efficacy has not been described in studies. *C Brune et al., 2007 (196); Steele et al., 2005 (197)*

EL: 3	Due to small numbers of treated patients, no conclusions can be drawn on the use of pimecrolimus for childhood psoriasis. *C Amichai, 2004 (198); Mansouri et al., 2006 (199)*

Considerations

Studies covered by these guidelines only describe the efficacy of 0.1% tacrolimus in children with psoriasis of the face and flexures. Calcineurin inhibitors are not registered for this treatment indication. In children (≤ 16 years) with eczema, tacrolimus 0.03% is registered.

Treatment recommendations

It is recommended to consider treatment with tacrolimus 0.03% or 0.1% in children with therapy resistant psoriasis of the face and flexures.

Dithranol

Conclusions of the Dutch guidelines

EL: 3	Dithranol is effective and safe for treatment of childhood psoriasis. *C Zvulunov et al., 1994 (200); Guerrier et al., 1983 (201)* *D Schubert et al., 2007 (202)*

Considerations

To reduce the risk of adverse effects (discolorations and skin irritation) dithranol should be used in a daycare unit setting. This also increases compliance and guarantees a more effective treatment regimen.

Treatment recommendations

It is strongly recommended to prescribe dithranol treatment for children with psoriasis if treatment with topical corticosteroids and vitamin D3 analogues failed. This should preferably take place in a daycare unit.

Phototherapy

Conclusions of the Dutch guidelines

EL: 3	Narrowband UVB treatment for children with plaque psoriasis or guttate psoriasis has positive results and a relatively mild adverse effect profile during a mean treatment period of 12 weeks. *C Al-Fouzan et al., 1995 (203); Jain et al., 2007 (204); Jury et al., 2006 (205); Pasic et al., 2003 (206); Tay et al., 1996 (207)*

No conclusion possible	Evidence on the efficacy of PUVA treatment for childhood psoriasis is too limited. *D Kim et al., 1998 (208); Thappa et al., 2006 (209)*

Considerations

Uncertainty persists on the long-term safety of UVB phototherapy. UVB therapy results in actinic damage and premature skin aging. UVB is carcinogenic. Oral PUVA has a carcinogenic effect.

Treatment recommendations

It is recommended to limit the use of UVB phototherapy in children with psoriasis. Especially in children less than 12 years of age and a fair skin type, UVB should be considered with great care. PUVA therapy is contraindicated in children with psoriasis given its carcinogenic effect.

Antibiotics

Conclusions of the Dutch guidelines

EL: 3	The efficacy of oral antibiotics and its use in children with guttate psoriasis remains controversial. *C Patrizi et al., 1994 (210)* *D Pacifico, 1993 (211)*

Considerations

If, on anamnesis, the psoriatic plaques erupted after a severe throat infection or the psoriasis deteriorated after a throat infection, it is recommended to perform a throat culture.

Treatment recommendations

When, on anamnesis, a throat infection may have induced or worsened the psoriasis and the performed throat culture is positive, it is recommended to consider the use of oral antibiotics.

Retinoids

Conclusions of the Dutch guidelines

EL: 3	Etretinate is effective in treating pustular or erytrodermic psoriasis. However, adverse effects are frequently encountered. *C Rosinska et al., 1988 (212); van de Kerkhof, 1985 (213); Pavicic et al., 1986 (214); Kim et al., 1991 (215); van der Rhee et al., 1980 (216)*
No	The use of acitretin in childhood psoriasis has not been thoroughly

conclusion possible	studied. Therefore, no conclusions can be stated in these guidelines. However, given the positive experiences with etretinate, it is likely that acitretin is also effective in pustular and erythrodermic childhood psoriasis.

Considerations

Etretinate is no longer available. Acitretin is a metabolite of etretinate, therefore, the efficacy of acitretin is probably similar to etretinate. Considerations about general safety are described in the chapter of retinoids in the full Dutch S3-guidelines: http://www.huidarts.info/documents/uploaded_file.aspx?id=579. Special attention should be given to the occurrence of skeletal toxicities in children on long-term retinoid therapy [217].

Treatment recommendations

It is recommended to consider the use of acitretin in children with pustular or erytrodermic psoriasis. It is firmly recommended not to treat adolescent women, given the potential teratogenic effects.

Treatment with acitretin may be considered in other types of childhood psoriasis.

Cyclosporine

Conclusions of the Dutch guidelines

EL: 3	The described efficacy of cyclosporine treatment in childhood psoriasis is ambiguous. Safety aspects were sparsely described. *C Mahe et al., 2001 (218); Kilic et al., 2001 (219); Alli et al., 1998 (220); Torchia et al., 2006 (221)*

Considerations

Adverse effects of cyclosporine in children with psoriasis were sparsely described in studies. In children with atopic dermatitis, this agent was well tolerated for a period of one year [222]. Given the potential cumulative toxicity, especially children should be treated with caution [223].

Treatment recommendations

Given the previous considerations and the contradictive evidence on cyclosporine for childhood psoriasis, it is recommended to use this agent only in exceptional cases.

Methotrexate

Conclusions of the Dutch guidelines

EL: 3	Methotrexate is effective for the treatment of moderate to severe childhood psoriasis. Most evidence is on plaque psoriasis. Short-term adverse effects are relatively mild and can easily be treated. *C Collin et al., 2006 (224); Kaur et al., 2008 (225); Kumar et al., 1994 (226); Kalla et al., 1996 (227); Dogra et al., 2004 (228); Dogra et al., 2005 (229); Ivker et al., 1993 (230)*

Considerations

Long-term safety of methotrexate for childhood psoriasis has not been studied. However, this drug has been used for decades for the treatment of juvenile idiopathic arthritis without severe adverse effects. Therefore, this treatment is considered safe [231].

Treatment recommendations

Methotrexate is recommended as first-choice systemic treatment in children with moderate to severe plaque psoriasis. Dosage is between 0.2-0.4 mg/kg/week. Folic acid 5mg should be administered 24 hours after methotrexate intake. Methotrexate should not be administered with milk products as this negatively affects its efficacy.

Biologics

Conclusions of the Dutch guidelines

EL: 3	Etanercept is effective for the treatment of plaque psoriasis in children. Dosage was 0.8 mg/kg/week. Short-term adverse effects are usually infections. *A2 Paller et al., 2008 (232)*

No conclusion possible	Infliximab seems effective for induction of remission. However, firm conclusions cannot be made on the results of 4 patients. *D Pereira et al., 2006 (233); Farnsworth et al., 2005 (234); Menter et al., 2004 (235); Weishaupt et al., 2007 (236)*

Considerations

Knowledge on long-term adverse effects of biologics is insufficient. It is unknown whether biologics increase the risk of lymphoma and skin cancer in psoriasis patients. The safety and effectiveness of etanercept was registered for children with juvenile idiopathic arthritis during 8 consecutive years. In these 8 years, the authors found no increase of severe adverse effects [231].

Treatment recommendations

Given the uncertainty concerning long-term safety of biologics, care should be taken in prescribing these agents in children with moderate to severe psoriasis. Etanercept is recommended when topical therapies, e.g. dithranol, as well as UVB (in older children) and methotrexate are ineffective, contraindicated, or not being tolerated.

The working group holds the opinion that children treated with etanercept should be registered in a national database to evaluate long-term safety.

Other topical and systemic therapies

Conclusions of the Dutch guidelines

No conclusion possible	No conclusions can be drawn on the efficacy and safety of Chinese drugs, excimer laser, tazarotene, wratizolin, fumaric acid esters, dapsone, prednisone, tonsillectomy and colchicine. *C Lin et al., 2006 (237); Pahlajani et al., 2005 (238); Diluvio et al., 2007 (239); Michalowski et al., 1983 (240); Gunther et al., 2004 (241); Yu et al., 2001 (242); Fernandes-EI et al., 2000 (243); Tsuge et al., 1995 (244); McMillin et al., 1999 (245); Hone et al., 1996 (246); Wahba et al., 1980 (247); Zachariae et al., 1982 (248)*

Considerations

None

Treatment recommendations

No conclusions can be drawn from the literature on the efficacy and safety of other therapies. These therapies are not recommended.

5. The patient's perspective

J. de Korte, O.D. van Cranenburgh

The experiences and opinions of patients with chronic skin diseases are becoming increasingly important for the assessment of their general and skin-related health status, and for the treatment of their skin disease. These patients' perspectives are generally

captured with so-called Patient Reported Outcomes (PROs). PROs are reports or assessments of any aspect of a patient's health status and/or treatment impact that are directly expressed by the patient, i.e. without the interpretation of others [249]. Examples of PROs are: disease severity, health-related quality of life, cost-benefit, safety, compliance, treatment preference, and satisfaction with treatment.

Health-related quality of life (HRQoL) of patients with psoriasis, i.e. the physical, emotional and social functioning and well being of patients, has been referred to throughout the Dutch S3-guidelines on the treatment of psoriasis 2011. The practice guidelines 'Photo(chemo)therapy and systemic therapy in severe chronic plaque-psoriasis' 2003 (updated 2005 and 2009) also addressed that, in exceptional cases, patients with less severe psoriasis may be prescribed a biological agent when there is a considerable loss of quality of life (Skindex-29 $\geq$ 35, combined with a PASI $\geq$ 8) (6).

In order to gain insight into psoriasis patients' satisfaction with treatment, we conducted a cross-sectional, national, web-based, survey. Aims of this survey were to assess the degree of patients' satisfaction with prior and current dermatological treatments and to study how patients value 1) effectiveness, 2) safety, 3) convenience and 4) organization of treatment, 5) information about treatment,and 6) the doctor-patient relationship.

Our study comprised 2070 patients (response rate: 43%), aged $\geq$ 18 years, with a self-reported diagnosis of psoriasis and treated or being treated with topicals, phototherapy, and/or systemic therapies. The questionnaire survey was preceded by literature search, results from a focus group session (N=9), and results from a previous survey (conducted for the first Dutch *evidence-based* psoriasis guidelines, 2005). The literature search revealed the importance of specifying domains of treatment satisfaction [250, 251].

The questionnaire survey was comprised of 27, mainly multiple-choice questions on patient characteristics, disease duration and severity, prior and current treatments, as well as generic and specific treatment satisfaction. Questions about treatment satisfaction were answered on a 5-point scale: 1 = very dissatisfied and 5 = very satisfied. The group of "Satisfied patients" was defined as the group of patients with scores of 4 and 5 and the group of "Dissatisfied patients" as the group of patients with a score of 1. Patients with scores 2 and 3 were excluded from analysis.

For an extensive report on methodology, patient characteristics, data analysis, and results we refer to the complete Dutch S3-guidelines on the treatment of psoriasis 2011: http://www.huidarts.info/documents/uploaded_file.aspx?id=579. An international peer-reviewed publication is in preparation [252].

Conclusions

Following conclusions and recommendations are based on the research report.

EL: 3	1. About 1 out of 3 psoriasis patients (32.4%) was satisfied with prior treatments. About 1 out of 14 patients (7.0%) was dissatisfied with prior treatments. 2a. About half of psoriasis patients (53.8%) was satisfied with their current treatment. Patients with topical therapies were least satisfied, patients with systemic therapies were most satisfied. 2b. Patients receiving a topical therapy were least satisfied with effectiveness and convenience of treatment. Patients receiving

	phototherapy were least satisfied with effectiveness of treatment. Patients with systemic treatment were least satisfied with safety of treatment. 3. Patients value the effectiveness of treatment as the most important domain of satisfaction. The doctor-patient relationship was valued as important as treatment safety, and more important than convenience.

Recommendations on quality of life and treatment satisfaction

1. In dermatological practice, it is recommended to explicitly address the influence of psoriasis on quality of life by:

   a) Asking patients directly about their quality of life or by means of standardized questionnaires such as the DLQI or Skindex, if applicable and relevant.

   b) Modifying treatment and care, if necessary, based on current evidence.

2. In dermatological practice, it is recommended to explicitly address treatment satisfaction by:

   a) Asking patients directly about their treatment satisfaction (general as well as specific) regarding: 1) effectiveness, 2) safety, 3) convenience, 4) organization of treatment, 5) information about treatment, and 6) the doctor-patient relationship).

   b) Modifying treatment and care, if necessary, based on current evidence.

3. Additionally, it is recommended to professionals to determine norms or cut-off points for the interpretation of scores of satisfaction and dissatisfaction with treatment, based on evidence, suitability, and feasibility.

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