Chapter 1

General introduction and aims of the thesis

Ph. I. Spuls
Psoriasis is one of the most common human skin disorders. Its prevalence seems to remain stable over the last decades, although specific evidence is lacking. Psoriasis has a long history. In the beginning it was grouped together with other dry, scaly eruptions, especially with leprosy. The first description of psoriasis was published in 1808.\textsuperscript{1} In 1841 Hebra separated the clinical entity of psoriasis from that of leprosy. As with other severe skin diseases, the psychological impact may be even larger than the physical impact.

**Definition**
Psoriasis is an inherited inflammatory skin disease with increased epidermal proliferation usually characterized by sharply demarcated, erythematopapulosus or -pustulous plaques with silvery scales.

**Diagnosis**
Medical history and physical examination reliant on categorizing cutaneous features and patterns related to psoriasis lead to the diagnosis. Sometimes histopathology may be helpful.

**Aetiology**
The cause of psoriasis is not known. Psoriasis may develop in people with an inherited tendency when they come into contact with a trigger factor activating the disease. It is unknown which epidermal and/or dermal factors are primarily important in the pathogenesis.\textsuperscript{2,3}

**Clinical signs and symptoms**
Psoriasis has a large spectrum in extension and distribution. It affects different people in different ways and tends to come and go with time. Males and females are equally affected and prevalence is not linked to social class. Morphologic types are psoriasis vulgaris, guttata, nummularis, annularis, pustulosa (on the digits (acrodermatitis continua of Hallopeau), palmoplantaris, generalized (von Zumbusch), psoriasis during pregnancy (impetigo herpetiformis) and erythroderma.
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Topographic types are psoriasis vulgaris, inversa, capitis, palmo-plantaris, unguium, arthritis and generalisata. The most common type is chronic plaque type psoriasis (also named psoriasis vulgaris) with 85-90% of the cases diagnosed. Psoriasis is usually chronic and persistent, although 50% of the patients may enter spontaneous remission for varying periods of time.

The majority of the patients has a mild form and a minority a moderate to severe form. A definition of moderate to severe psoriasis is difficult to give and differs among dermatologists as well as patients. Severity depends on clinical extent, the localization, the severity of the plaques, the percentage body surface affected, physical and psychosocial disability and historical response to treatment.

This thesis deals with patients with moderate to severe plaque type psoriasis - (hereinafter simply referred to as ‘psoriasis’) - that cannot be treated with topical therapies alone (e.g. defined as affecting 10% of the skin surface area combined with the intensity of the lesions (PASI > 8)). This applies to approximately 10% of all patients with psoriasis.

Usually sharply demarcated patches varying in size, induration, redness and amount of scales are found symmetrically on the extensor aspects of elbows and knees and lumbosacral region, although almost any part of the body can be affected. The scalp, nails and joints may be involved. In about 20% of the patients with skin psoriasis the nails are affected. Nail changes, present in approximately 50% of the cases, include onycholysis and dystrophy. The nails become pitted and may mimic fungal infection.

Ten to twenty-five percent of the patients with skin psoriasis have psoriatic arthritis, a rheumatoid factor negative inflammatory arthritis localized in peripheral joints, axial joints and/or the spinal column. In 16% of the cases the arthritis begins before the skin is affected, in 7% at the same time and in 77% the arthritis follows the psoriasis. Psoriatic arthritis can develop at any time, but develops usually between the age of 30 and 50 years. Psoriatic arthritis affects both sexes equally. It can develop slowly with mild symptoms or quickly and be severe. Psoriatic arthritis causes stiffness, pain, swelling and tenderness of the joints and the tissue around them. Prompt diagnosis and treatment can relieve pain and inflammation and possibly help to prevent progressive joint involvement.
Although psoriasis is assumed to affect the skin and joints exclusively, some publications have suggested involvement of other (organ) systems such as renal abnormalities (an enhanced albumin loss, a decreased urinary excretion of epidermal growth factor, increased urinary excretion of N-acetyl-β-D-glucosaminidase), hypertension and occlusive disease. Whether or not these changes are directly related to psoriasis is not certain. Finally, though perhaps associated with arthritis rather than with skin psoriasis, there may be uveitis, scleritis, conjunctivitis and tenosynovitis.

Epidemiology
There are well-known racial differences and geographical variations in the prevalence of psoriasis. Most surveys have suggested that in Western Europe and North America about two in every hundred suffer from the condition. Nearly all data reported in the literature represent rough estimates.

From questionnaire surveys, from age of onset analysis and from gatherings of clinical data of psoriasis patients in dermatologic departments, all kinds of epidemiological aspects of psoriasis have been found. Psoriasis may start at any age. The mean age of onset is around 27 years. Based on the age of onset, two types of plaque type psoriasis can be identified. Type I (75% of the patients) has an early onset (< 40 years of age, peak of onset 16-20 years of age), association with certain HLA types like HLA-Cw6, -B57 and -DR7, and a familial inheritance. Type II has a late age at onset (> 40 years of age, peak of onset 55-60 years) with weaker HLA associations, but the most common association is with HLA-Cw2. There is no familial increased risk in type II and there is a greater likelihood of joint and nail involvement.

Inheritance
The chance of a child to have psoriasis if one parent is affected is 10-28%. With two affected parents it is 50-65%, with one parent and one sibling affected 16%, with only one sibling affected 8-10%, two siblings affected 16%, with one grandparent affected 4%, with one great-grandparent affected 1-2%. Monozygotic twins show an 80% concordance, for dizygotes 20%.
The disease has a polygenetic background and the genes involved have been localized thus far on at least 7 different loci. Of these gene loci, 6 have been officially recognized on chromosomes 6p 21.3, 17q, 4q, 1cen-q21, 3q21, 19p13 and 1p, which have been named PSOR 1, 2, 3, 4, 5 and 6.\textsuperscript{21-23}

**Trigger factors**
Exogenous factors include injury to the skin, UV-radiation, pressure (tight clothing), cold weather, drugs including beta-adrenergic receptor blockers, anti-malarials, non-steroidal anti-inflammatory drugs, lithium, the withdrawal of glucocorticosteroids, and alcohol.\textsuperscript{24} Köbner noticed that trauma to normal skin (at least into the papillary dermis) in a psoriatic patient often results within a few days in a psoriatic lesion.\textsuperscript{25} Endogenous factors are stress\textsuperscript{26} and infections, especially sore throats due to group A hemolytic streptococcus, and human immunodeficiency virus.

**Histopathology**
Hematoxylineosin staining shows an epidermal hyperplasia with abnormal keratinocytes differentiation, inflammation with infiltration of neutrophilic granulocytes with an ingrowth in the epidermis and a mononuclear infiltrate in the papillary dermis. Also a vessel proliferation high up into the dermal papillae is characteristic resulting in the Auspitz sign (pinpoint bleeding) after deliberately removing the scales.

The epidermis is much thicker and contains an increased number of cells. The time it takes for cells to move from the lowest level of the epidermis to the surface is much shorter than in normal skin, 4 days rather than 28 days. The cells on the surface are much less mature than in normal skin and therefore continue to stick to each other rather than fall off. This explains the scaly appearance. The skin becomes erythematous and inflamed. The inflammation is related to the appearance of white blood cells, cells from the immune system.
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Immunological background
A variety of humoral and cellular changes have been demonstrated. The infiltrating cells from the immune system are T lymphocytes from an activated subpopulation. These T cells interact abnormally with stem-cell keratinocytes from the epidermis through cytokines. The keratinocytes cause hyperplasia and the abnormally differentiated epidermis. The beneficial effect of immunosuppressive drugs like cyclosporin A, FK506 (tacrolimus), SDZ ASM 981 (pimecrolimus), anti-CD4 monoclonal antibody (MoAB) and immunomodulating treatments (corticosteroids, methotrexate, PUVA and UVB) in psoriasis support the hypothesis that it is a T-cell mediated disease. This is also indicated by the ability of cytokines such as IL-2, interferon (IFN)-α and INF-γ to induce psoriasis.

Differential diagnosis
The differential diagnosis for typical psoriasis is limited. For plaque type psoriasis the differential diagnosis consist of pityriasis rubra pilaris, eczema nummularis (discoid) and follicular lichen planus. Especially in erythrodermic cases with more than 80% skin involvement the diagnosis may be difficult. The differential diagnosis then may include atopic dermatitis, cutaneous T-cell lymphoma and drug eruptions. Chronic trunk lesions may be confused with nummular dermatitis, parapsoriasis, and tinea corporis. If only the scalp is affected differentiation from seborrheic dermatitis may be difficult. Scalp lesions together with lesions in a seborrheic distribution of the face is sometimes referred to as sebopsoriasis. Secondary syphilis should always be considered.

The costs of psoriasis
As psoriasis is often a chronic disease it is important to diminish the general burden of illness. Since health care resources are limited, health authorities want cost-effectiveness analysis of the therapeutic modalities in order to find efficient forms of treatment. Costs are divided into direct healthcare costs and indirect costs. Directs costs are all costs directly related to the disease itself, i.e. the costs of treatment at inpatient clinics, day-care centers and outpatient clinics, together with
the costs of first line care by general practitioners and the medication. Indirect costs are indirectly caused by the disease such as those related to the inability to work, extra washing of clothes, and traveling to clinics. \cite{37}

An anonymous mail survey to patients with psoriasis concluded that the expenses for patients with more severe psoriasis are higher than for patients with less severe psoriasis. \cite{38} A retrospective comparative cost study based on a small sample size reported that the mean total annual treatment cost per patient per year are $2604.83 (range 1356-4007) for PUVA, $1966.80 (596-3034) for outpatient UVB (3 times/week), $1381.41 (801-2293) for methotrexate, $1995.31 (1363-2927) for etretinate, and $6648.48 (5453-7750) for cyclosporin. \cite{39,40} Ellis et al. suggested that in selecting therapies for psoriasis patients, both costs and effectiveness should be considered. \cite{41}
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TREATMENT

No treatment for psoriasis is curative; at best the current treatment options result in suppression and sometimes remission of the disease.

Topical treatment
There is a large variety in topical treatments. These include bland or salicylic acid containing ointments, calcipotriol, calcitriol, corticosteroids, anthralin/dithranol, tar, tazarotene (which is not available in the Netherlands and Belgium), and unconventional topical therapies (methotrexate, 5-fluorouracil ointment, ascomycin under occlusion, and tacalcitol). Various combinations are also in use, such as calcipotriol/corticosteroid.

Although topical treatment may be time-consuming, improvement of the application frequency, smell, texture and vehicle will increase the compliance.

Photo(chemo)therapy and systemic treatment
In addition to topical treatment, photo(chemo)therapy (ultraviolet B therapy (UVB) or ultraviolet A therapy in combination with psoralens (PUVA)) and systemic treatments are available. The systemics can be divided into conventional therapies (including retinoids (RET) (etretinate (ETR) and acitretin (ACI)), cyclosporin A (CsA) and methotrexate (MTX)), unconventional therapies (including antibiotics, azathioprine, calcitriol, colchicine, FK-506, fumaric acid esters, hydroxyurea, mycophenolate mofetil, propylthiouracil, sulfasalazine and 6-thioguanine), and experimental therapies, such as ascomycin, CTLA4lg, etanercept, excimer laser, infliximab, interleukin 2 diphtheria fusion toxin, interleukin 10, alefacept, maxacalcitol, photodynamic therapy and tacalcitol.

Many different therapy combinations have been developed in order to obtain a better, safer or faster induction of remission. Nowadays, different kinds of treatment settings have become available for psoriatic patients. In addition to the in- and outpatient clinics, day care centers and even home treatment are possible options.
Introduction and aims of the thesis

This thesis will summarize the evidence of the effectiveness of monotherapy with UVB, PUVA, CsA, MTX, and ACI for the induction of remission.

Ultraviolet B therapy
The first publication of whole body UVB monotherapy (TL12) in psoriasis appeared in 1978. Previous publications concerning UVB had predominantly reported on studies of combination schedules with coal tar (Goeckerman) and dithranol (Ingram). Since 1988 narrow band UVB (311 nm, TL01 bulbs) is available in addition to broad band UVB (280-320 nm). With narrow band UVB fewer episodes of erythema occur and a lower cumulative dose of UVB is needed.

UVB treatment is antiproliferative, locally immunosuppressive and has an anti-inflammatory effect. The effect of UVB treatment depends on the dosimetry of the treatments, the frequency and continuity and the UV spectrum used. Both broad and narrow band UVB are effective modalities to induce remission. With relatively minor side-effects, a sufficient clinical result may be obtained. Many combinations with other modalities have been investigated and have been found to be effective. Topicals are advised to be used not simultaneously with the radiation because of the possibility of photosensitization and photoprotective effects.

UVB therapy is most often given on an outpatient basis. In day-care settings it is often combined with intensive topical treatment. Home-treatment with UVB is a serious option nowadays and dermatologists have been involved in this development. However, it does involve risks in case of inappropriate use. The British Photodermatology Group advises to limit the use of home UVB treatment and to reserve this for patients with good reasons not to attend outpatient clinic treatment.

Photochemotherapy
PUVA is ultraviolet A (320-400 nm) in combination with photosensitizing medication (psoralen). Psoralen may be ingested orally, given by suppository, or applied topically (bath). Only whole body monotherapy with oral PUVA is discussed in this thesis. The first study of oral PUVA monotherapy in psoriasis was published in 1974. PUVA was found to be highly effective in clearing psoriasis. There is also randomized
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controlled trial (RCT) evidence to support the combined use of ACI with PUVA.

The exact mechanism of action of PUVA is still not clarified. In addition to its anti-proliferative effect, it also has anti-inflammatory and immunosuppressive effects. Due to linkages between DNA-structures which interfere with the DNA-synthesis, cell-proliferation and hyperproliferation are blocked. Additionally, the cell mediated immune response is suppressed.\(^\text{86,89}\) PUVA therapy is most often given on an outpatient basis. In day-care settings it is often combined with intensive topical treatment.

**Methotrexate**

MTX is a folic acid antagonist. In addition to its antiproliferative effects on keratinocytes and lymphocytes, it has an immunomodulating capacity. MTX can be administered orally or intramuscularly. In addition to the usual 3-times weekly, every 12 hours, schedule, a once weekly dosage scheme has been introduced.\(^\text{70}\)

The first study of MTX for psoriasis was published in 1958.\(^\text{71}\) MTX was approved by the FDA for use in psoriasis patients in 1971. Since then, many studies have been published. In the absence of RCTs on the induction of remission of chronic plaque type psoriasis, there is still no RCT quality evidence to support the use of MTX in severe psoriasis. Clinical experience as well as open, retrospective and maintenance studies have however shown that MTX is effective in inducing remission in psoriasis.

**Acitretin**

The first study of ACI for psoriasis was published in 1984.\(^\text{72}\) Its precursor ETR, is no longer available in the Netherlands and Belgium. Using equal doses, ETR is slightly more efficient than ACI.\(^\text{73-76}\) ACI suppresses epidermal proliferation, keratinocyte differentiation and the accumulation of intra-epidermal neutrophils.

There is RCT evidence to support the moderate effectiveness of ACI at doses of 75 mg/day or 1 mg/kg/day. There is also RCT evidence to support the combined use of ACI with PUVA. Combination treatments are beyond the goal of this thesis.
Cyclosporin
Many RCTs on CsA are available, providing evidence to support the use of oral CsA in psoriasis. The first publication on CsA for severe psoriasis appeared in 1979. Originally, it is an immunosuppressive agent to prevent transplant rejection. It is a cyclic undecapeptide isolated from a Norwegian fungus. CsA is a specific and reversible suppressor of the proliferation of T-lymphocytes without myelotoxic and mutagenic characteristics. For induction of remission 2.5 to 5 mg/kg/day are used. Higher doses are associated with unacceptable side-effects although the effectiveness is dose-related. Maintenance treatment is not advisable with regards to long-term side-effects but intermittent treatment may be relatively safe. Topical and intralesional use as well as combination treatment with other antipsoriatics are beyond the goal of this thesis.

Choice of therapy
The choice of therapy depends on various factors which may relate to the psoriasis itself, the treatment, the patient and the physician. Psoriasis specific factors are the type (chronic plaque type in this thesis), the extent of involvement, the severity of scaling, inflammation and infiltration, the localization, duration and the natural course. Treatment specific factors are the efficacy of the treatment modalities, such as the percentage of patients that obtain complete clearance, good, moderate, and mild response or the percentage of patients that get worse. Further treatment specific factors are the onset of action, the duration of remission, the safety, the side-effect profiles (that may vary from mild, reversible to severe and irreversible), the inconveniences for the patient associated with the therapy, the drop-out rate and the contra-indications. Patient specific factors are the age, gender, daily activities (e.g. in relation to logistical problems such as number of outpatients visits required, and attendance for phototherapy), physical and mental health, tolerance of previous treatments with effect and impact on quality of life and the preferences of patients including expectations from treatment. Patients report ease of use and limited side-effects as important aspects of treatment. Physician specific factors like experience with and availability of treatments (in different settings and registration of drugs) play a role.
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Treatment strategy
There is not a single therapy for psoriasis that is clearly superior. Attempts have been made to develop strategies for long-term treatment in comparable patients. An evidence-based treatment strategy for comparable patients may be more than welcome, especially in times as these when many new treatments become available on the market.

Treatment outcome measurements
Efficacy is the main parameter for comparing different treatment modalities. In order to pool data from different trials the parameters for efficacy should be similar. Unfortunately many different outcome parameters have been used in various clinical studies. More objective measurements such as change in PASI and change in total BSA are used, as well as general descriptions as clear, almost clear, markedly improved, or the percentage of patients with clearance, good, moderate or poor response. In psoriasis, the effect of treatments on the quality of life is an important issue.

Quality of life
Patients with different severities of psoriasis will have different perceptions of the impact on their lives. Although psoriasis is not contagious, the disease includes visible lesions, excoriating scales, itching, pain, burning, soreness, hair loss and stains on clothing. The physical manifestations of the disease and lifestyle issues such as side-effects of treatment, negative attitudes from others and the time consuming care that is needed to treat the disease contribute a great degree to the impact the disease may have on patients.

Comparable quality of life studies with generic and disease specific questionnaires investigating the impact on the social, physical and psychological functioning and well being of patients can contribute to the optimization of the treatment. Generic quality of life questionnaires have been used (such as the Medical Outcome Survey (MOS) 36 items Short Form Health Survey (SF-36) but dermatology specific (Skindex) and disease specific questionnaires (psoriasis disability index (PDI)) are available for psoriasis.
A systematic review of the literature on quality of life in psoriasis has been performed. Many studies on quality of life in psoriasis have been published. In only a few studies quality of life was the primary goal. Validated measurements are not always used. The results of the studies are difficult to compare because different patient populations have been investigated and different outcome measurements have been used. Still, the study results show many differences in the quality of life between patients. Nine primarily quality of life studies in psoriasis showed that psoriasis has an effect on quality of life. The influence consisted predominantly of problems in the psychological functioning of the patients with a reflection on social functioning.

In most studies nearly no relation between the impact on quality of life and the severity of psoriasis could be found. A positive influence of treatment on the quality of life has been found.

Patient preferences are mentioned in lists of factors that should play a role in the selection of a specific treatment in a patient. There are different methods to investigate preferences of patients. For example, Zug concluded that with different evaluation methods, valid answers were given by patients with psoriasis to different health conditions. Different health conditions may be compared in a quantitative way. Not only the expectation related to treatment outcome plays a role but also (un)safety and (dis)ability of these therapeutic options.

Compliance
Research of studies on compliance has suggested that the rate of non-compliance in chronic conditions may be as high as 30 to 40%. Reduction of non-compliance in psoriasis will improve the management of this chronic disease. Many factors may contribute to non-compliance. Intentional adherence to treatment is affected by variables such as patients and doctors' behavior, the doctor and patient relationship, the patient's beliefs about his condition, the medication and medication side-effects. In one study, 39% of the psoriatic patients said that they 'sometimes' or 'never' complied. Given the chronicity of psoriasis, successful treatment requires full patient co-operation and the individual's active participation in the treatment. Long-term, complex and inconvenient treatments generally cause a poor compliance. Improvements in topical therapies are directed at improving compliance.
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EVIDENCE-BASED MEDICINE

The first article on evidence-based medicine (EBM) appeared in 1992. Since then, numerous articles about EBM have been published with significant overall influence on medical science. Even specific EBM journals have been initiated, summarizing the most relevant studies for clinical practice.

Definition
EBM is the integration of best research evidence with clinical expertise and patient values. In this way clinical outcomes and quality of life can be optimized. EBM has been developed in order to use the best available evidence about diagnosis, prognosis, therapy and prevention when making decisions in patient care.

Clinical decisions and clinical advice rely in many cases on traditional sources such as clinical experience, expert opinions, collegial relationships, pathophysiology, common sense, community standards, or non evidence-based published materials. EBM uses the same sources for clinical advice, but tries to support them with an explicit search for solid evidence. Traditional sources like textbooks and expert opinions are thought to be inadequate, as they may be out of date and/or based on personal experience rather then evidence, they may be ineffective for didactic continuing medical education or too overwhelming in their volume (medical journals) and too variable in their validity for practical clinical use. With the increasing number of diagnostic means and experience, knowledge must be kept up-to-date. Physicians however do not have time enough for finding and assimilating evidence.

Practicing EBM requires five steps: (1) Formulating well-built clinical questions. (2) Finding the best available evidence to answer the questions. (3) Critically appraising the evidence. (4) Applying the evidence to specific patients. (5) Saving the critical appraisal of the evidence.

With EBM RCTs, systematic reviews, meta-analysis, concise summaries of effects on health care (as collected in the Cochrane Collaboration. The Cochrane Library, Update Software, Oxford) and
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evidence-based guidelines have become more prominent. Physicians have to be educated in efficiently tracking down and appraising evidence. Information systems will be developed to make the information available within seconds (PUBMED/Cochrane database).

Limitations
There are limitations to evidence-based care. Critics have put forward that EBM may not be focused on the improvement of outcomes for individual patients. Study results are usually reported in terms of averages, or percentages in groups of patients. These findings can be extrapolated to individuals but not without a word of caution. Many flaws and fallacies have been detected while reviewing the existing evidence. The apparent shortage of coherent, consistent scientific evidence limits the use of EBM in daily practice. Additional resources, in the form of well-equipped libraries and high-speed internet access, are needed.

Some critics have suggested that EBM denigrates clinical expertise, that it is limited to clinical research, ignoring patient values and preferences and promotes a ‘cook-book’ approach to medicine.

EBM in dermatology
Uncontrolled and non systematically collected empirical data form the basis of many dermatology practices. These data may be biased, highly variable and frighteningly unreliable. When a straightforward clinical question is posed to a group of dermatologists, one is likely to receive a range of answers, not necessarily a single answer that is based on evidence. Substantial geographic variation in the use of therapeutic modalities is a fact. An evidence-based approach could narrow this variation. Evidence-based research may detect lacks of evidence.

As in general medicine, the knowledge base in dermatology is expanding. There is not enough time available to keep up with the best available evidence in the traditional way by reading and appraising all the primary literature. The EBM approach to everyday issues in the practice of dermatology has been outlined as a solution. The specific issues of the Archives of Dermatology on EBM and the start of the Cochrane Skin Group in 1996 cannot be ignored.
EBM for chronic plaque type psoriasis

The theory and practice of EBM should be incorporated in the management of chronic plaque type psoriasis. As in other fields of medical care, textbooks concerning psoriasis become quickly out of date. Expert opinions on psoriasis, however valuable, are variable and may be unreliable if based on one's own experience rather than on evidence. There is a variability in many aspects of the treatment of psoriasis, which is reflected in the existing guidelines. Examples are the necessity of trough level measurement during CsA treatment, roentgen photography before and during treatment with retinoids, liver biopsy for MTX treated patients, or calculating the maximum cumulative dose for UVB treatment.

For psoriasis, many treatments are available but the evidence for these modalities, especially the older modalities are based on reports of small series of patients. For MTX for example, one of the most often used treatments for moderate to severe psoriasis, there is no RCT evidence. Although the number of RCTs is increasing for the other treatments for severe psoriasis, the quality can still be improved. With the Consolidated Standards of Reporting Trials (CONSORT) statement supported by a growing number of medical and health care journals and editorial groups, the quality of a RCT can easily be checked and may improve in the future. Furthermore, controlled comparative studies between two modalities on large numbers of patients are still rare. No comparison studies of MTX with ACI are available. Griffiths has recommended in order of priority 8 RCTs. His number one recommendation was the comparison of CsA and MTX. The first RCT with MTX and CsA is performed (see Chapter 5: Heydendael VMR, Spuls Phl, Opmeer BC, Borgie CAJM de, Reitsma JB, Goldschmidt WFM, Bossuyt PMM, Bos JD, Rie MA de. Methotrexate versus cyclosporin in moderate to severe chronic plaque psoriasis: a randomized controlled trial. NEJM 2002, submitted).

EBM can also reduce the costs of the treatment. The costs of the management of this chronic disease are growing EBM may be able to diminish the costs if treatments for which no reliable evidence may be found, will be no longer used.


**Systematic reviews**

In a systematic review (SR), the information from the original studies is searched, selected, extracted, appraised and summarized in a transparent, valid and reproducible manner. SR's are therefore an efficient and reliable source of information for the clinician, health policy maker and researcher. The term 'systematic' is reserved for the reviews that allows others to replicate the search. With a detailed description of the extension of the search, the appraisal and synthesis methods (to minimize biases and random errors) this should be possible. The SR should be based on a carefully formulated clinical question that can be answered on the basis of data from the original studies. For appraising the quality of the SR, the following aspects are important: the question, search strategy, selection of the studies, quality assessment, data extraction and data presentation, (statistical) summary of the data, statistical and clinical heterogeneity, results and conclusion. For improving the quality of reports of meta-analyses of randomized controlled trials, the QUOROM statement has been developed.\(^{129}\) The goal of this initiative was to improve the quality of reporting of biomedical research and by doing so to bring about more effective health care.

Because there are many treatments available for psoriasis and new studies are published frequently, SR's may be helpful to compare the different aspects of these modalities. Two SR's concerning the systemic treatments of psoriasis have been carried out to compare the effectiveness of currently available treatments for severe psoriasis and to identify areas in need of further research.\(^{123,125}\)

**Levels of evidence and grades of recommendations**

Not all evidence is of the same quality. Evidence from a properly conducted randomized clinical trial is more likely to be true than evidence-based on one random physicians’s clinical experience. It is necessary to consider for each advice what the quality of the underlying evidence is. Therefore levels of evidence have been developed by Fletcher and Sackett.\(^{130}\) Over the years, this set of levels has evolved. The level of evidence has a clear relationship with the grades of the recommendations that may follow. High levels of evidence will result in a strong recommendation, while lower levels of evidence result in not more than suggestions.\(^{131,132}\) The orientation of these levels of evidence
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and the recommendations derived from both therapeutic and preventive measures are available on the internet. Updates may be downloaded from http://cebm.jr2.ox.ac.uk/docs/levels.html

In this thesis, derived levels of evidence are used. These levels came from publications in dermatological articles and are slightly adapted. (Table 1 and 2).\textsuperscript{133,134}

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Table 1. Levels of evidence concerning interventions

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Meta-analysis containing at least some trials of level A2 and of which the results of individual trials are consistent</td>
</tr>
<tr>
<td>A2</td>
<td>Randomized comparative clinical trials of good quality (randomized double-blind controlled trials) of sufficient size and consistency</td>
</tr>
<tr>
<td>B</td>
<td>Randomized clinical trials of moderate (weak) quality or insufficient size or other comparative trials (non-randomized, cohort studies, patient-control studies)</td>
</tr>
<tr>
<td>C</td>
<td>Non-comparative trials</td>
</tr>
<tr>
<td>D</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

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Table 2. Grades of recommendations

<table>
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<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>based on at least two independent performed investigations of level A</td>
</tr>
<tr>
<td>2</td>
<td>based on at least two independent performed investigations of level B</td>
</tr>
<tr>
<td>3</td>
<td>not supported by enough investigations of level A and B</td>
</tr>
<tr>
<td>4</td>
<td>advices based on non-comparative studies</td>
</tr>
<tr>
<td>5</td>
<td>advices based on the opinion of experts</td>
</tr>
</tbody>
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26
Clinical practice guidelines
Clinical guidelines are increasingly part of current practice. They may be used by clinicians to answer specific clinical questions arising from their day to day practice and physicians may detect gaps in their performance. Guidelines can be based on evidence from meta-analyses, systematic reviews, individual trials and expert advice. Levels of evidence and grades of recommendations should be indicated in these guidelines. Efforts need to be taken in order to maximize the validity of guidelines and to ensure their use within clinical practice by proper implementation. They should be adapted to local settings.

Guidelines will not address all the uncertainties of current clinical practice. Instead they should be seen as one of the attempts to improve the quality of care of patients. If guidelines are not useful in daily practice, this may be due to the fact that they are outdated, not supported or lack high level evidence to back it up.

For therapy, David Sackett has proposed the following question for a clinical guideline: ‘How to select treatments to offer patients that do more good than harm and that are worth the efforts and costs using them?’
Chapter 1

AIMS OF THE THESIS

This thesis addresses the following question: ‘In what sequence do we select the treatments available for patients with moderate to severe psoriasis. This question is raised in order to improve the recommendations for the induction of remission treatment of chronic plaque type psoriasis. The goal is to diminish the variability and subjectivity of these recommendations using the best available evidence on effectiveness from quality studies. A new guideline has been developed for this goal.

As a starting point, a systematic review of studies was conducted in which the outcome of treatment in placebo groups with chronic plaque type psoriasis was analyzed (Chapter 2). This was done in order to find out if moderate to severe chronic plaque type psoriasis is a stable disease or more fluctuating by itself as shown by studies concerning the natural history. And secondly to investigate if placebo-control groups are necessary in trials concerning chronic plaque type psoriasis.

In order to summarize the evidence that is available on the efficacy to induce remission with whole body UVB and PUVA, oral MTX, ACI and CsA, a systematic review of the literature was performed (Chapter 3). The way patients with moderate to severe psoriasis of the Department of Dermatology of the University of Amsterdam were treated, was investigated. The systematic review and the evaluation of clinical practice were used to develop a preliminary clinical practice guideline. This preliminary guideline was discussed in the department and refined. The guideline was introduced in clinical practice and its implementation was evaluated (Chapter 4).

MTX was an intervention for which firm RCT evidence of efficacy was lacking. High priority was given to an induction of remission RCT comparing MTX versus CsA. The efficacy, safety and quality of life of MTX versus CsA was investigated (Chapter 5).

The lack of evidence concerning safety parameters during treatment with CsA led to the systematic review and measuring of the trough levels in CsA treated patients (Chapter 6).
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The existing preliminary guideline has been revised using the above mentioned studies. Dimensions as side-effects, measures taken to minimize side-effects, contra-indications, interactions, and flowcharts with the regular diagnostic tests before, during and after treatment were incorporated. These aspects were abstracted from consensus reports and guideline articles of the different treatment modalities, review articles, a Dutch pharmacotherapeutic compass, and textbooks. These aspects were incorporated in the revised new version of the guideline (Chapter 7).

All the studies were performed at the outpatient clinic of the Department of Dermatology in cooperation with the Department of Clinical Epidemiology and Biostatistics, both at the Academic Medical Center of the University of Amsterdam in Amsterdam, the Netherlands.
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