Psoriasis. Present therapies and new developments

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CHAPTER 1
General introduction

1.1 Clinical manifestations of psoriasis
Psoriasis is a skin disease affecting 1.5-3% of the population in Western Europe and Northern America. Lesions are characteristically indurated, erythematous and with adherent silvery scales. They can occur anywhere on the skin, but the elbows, knees and lower back are more frequently involved. Psoriasis can also affect the joints (psoriatic arthritis). Many clinical manifestations are known, and there are two ways to classify them, morphologically and topographically (table 1). In both these classifications two diseases are missing, morbus Andrews-Barber (localized erythematousquamous and pustulous processes, only occurring on the palms and soles) and acrodermatitis continua of Hallopeau (localized erythematousquamous and pustulous processes, only occurring at the tips of fingers). It is still a matter of debate whether or not these two diseases form part of the psoriasis spectrum.

All subtypes of psoriasis can occur as a single feature or in combination with other types. In this way the disease called psoriasis variâtes in severity between individuals. Even in the same individual there are large fluctuations in the severity of the disease over time.

The prevalence of psoriatic arthritis is described in several studies as varying from 0.7 to 40% in patients with psoriasis, depending on the definition used. The classification of psoriatic arthritis has always been under discussion. Because of the description in literature of two new clinical entities, the Synovitis-Acne-Pustulosis-Hyperostosis-Osteomyelitis (SAPHO) syndrome and the Psoriatic-Onycho-Pachydermo-Periostitis (POPP) syndrome of psoriatic arthritis, the classification became even more complicated. Ruzicka recently developed a classification based on the Moll and Wright model (table 2).

Table 1. Morphologic and topographic variants of psoriasis

<table>
<thead>
<tr>
<th>Morphologic</th>
<th>Topographic</th>
</tr>
</thead>
<tbody>
<tr>
<td>psoriasis guttata</td>
<td>psoriasis vulgaris</td>
</tr>
<tr>
<td>psoriasis &quot;en plaque&quot;</td>
<td>psoriasis inversa</td>
</tr>
<tr>
<td>psoriasis nummularis</td>
<td>psoriasis capitis</td>
</tr>
<tr>
<td>psoriasis annularis</td>
<td>psoriasis palmoplantarlis</td>
</tr>
<tr>
<td>psoriasis pustulosa (generalisata)</td>
<td>psoriasis unguium</td>
</tr>
<tr>
<td>erythrodermia</td>
<td>psoriatic arthritis</td>
</tr>
<tr>
<td></td>
<td>psoriasis universalis</td>
</tr>
</tbody>
</table>
Table 2. Different types of psoriatic arthritis according to Ruzicka.

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymmetric oligoarticular arthritis</td>
</tr>
<tr>
<td>2</td>
<td>Distal interphalangeal arthritis</td>
</tr>
<tr>
<td>3</td>
<td>Symmetric polyarthritis (Rheumatoid arthritis-like)</td>
</tr>
<tr>
<td>4</td>
<td>Mutilating psoriatic arthritis</td>
</tr>
<tr>
<td>5</td>
<td>Spondyloarthritis</td>
</tr>
<tr>
<td>6</td>
<td>Pustulosis palmoplantaritis associated with osteoarthritis of sternoclavicular joints</td>
</tr>
<tr>
<td>7</td>
<td>Psoriatic Onycho Pachydermo Periostitis (POPP)</td>
</tr>
</tbody>
</table>

This classification is probably the most practical one for dermatologists; they should be aware of the different clinical phenomena existing in psoriatic arthritis to be able to inform their patients about it. However, until now assigning a patient to a specific subgroup has had no therapeutic consequences since therapy for all subtypes is similar.

If the nails are involved, they show hyperkeratosis, onycholysis and discoloring to yellow or brown. Pitting of the nails is common, but not specific. In patients with psoriatic arthritis 80% of patients have nail involvement. For the treatment of nail lesions and for psoriatic arthritis, local therapies are not effective, and systemic treatment is sometimes necessary in severe cases.

In the classification of psoriasis of the skin, little has changed during the past few decades. Based on two different age peaks that have been recognized for the development of the first signs of psoriasis, the categories type I psoriasis (early onset < 40 yrs and a positive family history) and type II psoriasis (late onset and often a negative family history) have been proposed. It seems indeed that genetic predisposition is more strongly associated with type I than with type II psoriasis.

1.2 Pathogenesis of psoriasis

The exact cause of psoriasis is still unknown despite all the efforts that are being made throughout the world. Most investigators believe in the concept of psoriasis as a T-cell mediated disease. Also, it is accepted that there is a genetic background. A shift from genotype to phenotype may be triggered by outside factors which then initiate a deviation in immunologic and keratotic processes, e.g., stress, infection (especially upper respiratory tract infections with streptococci), particular drugs (beta-blocking agents, lithium, chloroquine), and physical trauma to the skin causing the Koebner phenomenon.

Psoriasis is believed to be a disorder at the T-cell level. This is suggested by the fact that cyclosporine, tacrolimus, methotrexate and prednisone, all immunosuppressive drugs, lead to very good improvement. These drugs all have a direct effect on T cells. Also, the serum levels of soluble T-cell activation molecules (sIL-2R, sCD27) are elevated in patients with psoriasis, and they are correlated with disease activity, e.g., the level of sIL-2R decreases
with the improvement seen during immunosuppressive therapy.\textsuperscript{9,10} Further evidence is found in reports indicating clearance of psoriasis or occurrence of psoriasis after bone marrow transplantation.\textsuperscript{11,12}

**Genetics**

Psoriasis is believed to be a multigenetic disease whose expression is in part dependent on external factors. This is best demonstrated in sibling and twin studies. It was noted that the risk for the sibling of developing psoriasis was higher if one of the parents had psoriasis than if none of the parents had psoriasis (14\% versus 6.6\%, respectively). In twin studies a concordance rate of 56 to 70\% for identical twin pairs was found.\textsuperscript{13,14} This proves that there must be another factor in addition to genetic predisposition, possibly initiating or activating the genetic deviation. A recent publication from Swanbeck et al, concerning the lifetime risk of developing psoriasis in the Swedish population, showed a 4\% risk if neither parent has psoriasis, 24\% risk if a sibling has psoriasis, 28\% risk if one parent has psoriasis, and 65\% if both parents have psoriasis. If both parents and a sibling have psoriasis, the lifetime risk was 83\%.\textsuperscript{15} The empirical data obtained from these studies\textsuperscript{13-15} can help patients with psoriasis estimate the risk of having a child with psoriasis.

The immunogenetic research in psoriasis has focussed on HLA molecules. Certain HLA haplotypes are associated with psoriasis. Frequently mentioned gene associations involve class I HLA antigens Cw6, B13, B17, and B57 and with class II HLA antigens DR7, DQA1, DQB1.\textsuperscript{16-18} Association with the major histocompatibility complex (MHC) antigen Cw6 has been found in different populations in Europe, Japan and Israel.\textsuperscript{19,20} Most studies concentrate on a combination of these HLA antigens as the suspected genetic predisposition to psoriasis. The haplotypes Cw6-B57-DRB1*0701-DQA1*0201-DQB1*0303, A2-Cw11-B46-C2C-BFS-C4A4-C4B2-DR8, A2-B13-Cw6-DR7-DQA1*0201, A1-B17-Cw6-DR7-DQA1*0201 are most frequently found.\textsuperscript{19,21} Type I psoriasis seems to be associated more strongly with haplotype Cw6-DR7-DQA1*0201 according to Ikäheimo et al.\textsuperscript{21} A gene association on the distal end of the long arm of chromosome 17 has been found in three out of eight tested families.\textsuperscript{22} It was suggested that within the same region of 17q, a gene responsible for the activation of T cells is present. Recently, this association with 17q was confirmed by a group in Ann Arbor.\textsuperscript{23} Newly suggested associations include 16q, p20, and the TNF-α promoter polymorphism 238.2 in juvenile onset psoriasis.\textsuperscript{23,24} TNF-α is thought to be an important mediator in the initiation phase of cutaneous inflammation in psoriasis.\textsuperscript{25}

**Keratinocytes and T cells**

How these genetic deviations can affect the keratotic processes in psoriatic lesions is not known. The epidermis exists primarily of keratinocytes. The keratinocyte stem cells are localized in the basal cell layer, and in the normal situation, only a few of them are involved in active cell cycling. The lesional epidermis in psoriatic patients could be the result of an increase in the per-
percentage of stem cells involved in cell cycling or an increase in the number of cell cycles of dividing cells (prolonged apoptotic process), or a combination of both.\textsuperscript{26,27}

T cells are an important part of the inflammatory reaction in the papillary layer of psoriatic lesions. They are also present within the hyperplastic epidermis of psoriatic lesions.

As Bos et al. suggest in their manuscript,\textsuperscript{28} psoriasis could be the result of a disturbed interaction between activated T cells and keratinocytes. The simplest and perhaps most elegant hypothesis is that in psoriasis, T cells are able to induce keratinocyte hyperproliferation through the secretion of relevant cytokines that are able to bring resting keratinocytes in cell cycling.\textsuperscript{29-31}

T cells, however, are present in the papillary dermis of all individuals,\textsuperscript{32} just like keratinocytes in the epidermis. The question remains why only patients with psoriasis suffer from the results of their interaction.

**MHC and superantigens**

The interaction of major histocompatibility molecules (MHC) and T-cell receptors might additionally be involved in the interaction of T cells with keratinocytes, as a result of which costimulation is increased. This might occur as a result of endogenous antigens (MHC class I expression), or by expression of exogenous antigens (MHC class II).

The role of superantigens in psoriasis has been studied by different groups. When it became known that certain superantigens derived from bacteria such as \textit{Staphylococcus aureus} and \textit{Streptococcus pyogenes} may form a bridge between the antigen-presenting cell and the T cell by binding to MHC class II and the TCR, respectively, an antigen-independent mechanism of T cell activation in psoriasis was hypothesized.\textsuperscript{33}

In summary, in the immunopathogenesis of psoriasis, we can assume that all of the mechanisms described operate together in the stimulation of keratinocyte growth. It is as yet unclear whether epidermal hyperproliferation is the result of an increase in the number of stem cell keratinocytes in active cell cycling or the result of an increase in the number of cell cycles of the transiently amplifying cell population, or a combination of both.\textsuperscript{31}

It is also unclear how T cells become involved in this epidermal hyperproliferation, i.e., by direct interaction with keratinocytes or indirectly with a role for autoantigens, superantigens and/or antigen-presenting cells.

### 1.3 Present therapies

As there is such a large variety in the clinical manifestations of psoriasis, it is difficult to give a standard protocol for treatment. Minor clinical signs sometimes need no treatment at all, whilst severe psoriasis with arthritis and nail involvement often requires aggressive systemic treatment. In between these extremes, there is a broad range of therapies.

Not all drugs accepted as therapy for psoriasis (especially the older drugs) have been studied properly, following the current stringent regulations of the Food and Drug Administration (FDA) and Good Clinical Practice (GCP) guidelines.
This means that new drugs tested in studies performed according to these rules are not infrequently compared with a "golden standard" therapy that is based solely on clinical experience.

In general, there are three types of therapies for psoriasis: topical therapy, photo(chemo)therapy, and systemic therapy. All of them have their own side-effects. For this reason, therapies are sometimes combined in order to reduce these side-effects, or rotational therapy is used. A therapy that could cause side-effects is replaced by another therapy before any obvious side-effect has occurred, to prevent the development of long-term side-effects. In addition, patient education and acceptance form an important factor. A patient with knowledge of his or her disease and the possible therapies who receives optimal psychosocial guidance (if necessary) will benefit more from the therapy, resulting in a better quality of life.

**Topical therapy**

Tar, dithranol, and topical corticosteroids combined with indifferent ointments, were the only therapies for many years for localized psoriasis. In this way, the majority of patients could be treated to some extent. Tar products are still used because of their positive effect. Their exact mode of action is unknown, but an antiinflammatory and antiproliferative effect has been found. Today, it is often used in a day-care setting.

Dithranol is effective in many patients. Its exact mechanism of action is not known, but it seems to have a primary effect on the keratinocytes of the epidermis.

Topically applied corticosteroids are most often used by patients with psoriasis because of their good clinical efficacy and acceptable side-effects. Their efficacy is based on their immunosuppressive, antiinflammatory and antiproliferative activity.

In 1993, an ointment with a vitamin D derivative (i.e., calcipotriol) was introduced, which had an effect almost comparable to potent corticosteroids like betamethasone. The mechanism of action is a combination of a decreased proliferation of undifferentiated keratinocytes, stimulation of differentiated keratinocytes and an immunoregulatory effect which is not completely understood. Calcipotriol ointment is now the therapy of first choice.

An important help during all therapies for psoriasis is the use of emollients. They have an important effect on the psoriatic plaque as they remove scales. In contrast to all other drugs they do not cause side-effects.

**Side-effects**

Tar can irritate the skin, especially in combination with sun exposure. The issue of carcinogenicity is old but has recently resurfaced. Tar may potentially induce skin cancer, but appears to be a sufficiently safe therapy for psoriasis. Tar products do have an unpleasant odour, and patients dislike using them in their bathroom at home.

Dithranol can also irritate the skin as well as the eyes. The cosmetic acceptance is limited. It can cause discolouring of skin, hair, clothing, and furniture.
Topical corticosteroids are the therapy of choice of many patients but can cause atrophy of the skin and local immunosuppression. When used in large amounts, they can lead to adrenal insufficiency, and tachyphylaxis occurs when applied daily. It is advised to use topical corticosteroids in pulse therapy.

The side-effects of calcipotriol are limited to some irritation of the skin in a number of patients, and if used in an amount of more than 100 g per week, there is a risk of disturbance in the calcium metabolism.

A disadvantage of all topical therapies for the more extended forms of psoriasis is the fact that it is time consuming to apply, and patients simply get tired of it. This results in poor patient compliance.

**Photo(chemo)therapy**

If topical therapy is not an option in generalized psoriatic lesions, or if it is not effective, photochemotherapy (psoralen + UVA; wavelength 320-400nm) or phototherapy (UVB broad band; wavelength 280-350nm: TL12) is a good second choice. This therapy can be given in a course of around 16 weeks, two to three times a week. The potentially long period of remission without further treatment makes the therapy attractive to many patients with psoriasis.

Sometimes it is used in combination with other systemic therapies. Its mechanism of action is an antiproliferative effect, combined with a local immunosuppressive effect and an antiinflammatory effect. Despite the unwanted side-effects, this therapy is used widely because the risk/benefit ratio is better than that of most systemic therapies.

A more recent therapy utilises narrow-band ultraviolet B therapy (wavelength 311-312nm: TL01). This therapy gives better results compared to broad band ultraviolet B and is comparable to photochemotherapy. The development of erythema of the skin is much less, and therefore the minimal erythema doses are higher. This is an advantage for patients with skin type I or II.

**Side-effects**

Frequent short-term side-effects of photo(chemo)therapy include burned skin and itching during therapy, as well as nausea and photosensibility if methoxy-psoralen is used.

The most worrying long-term side-effect is the induction of (skin) cancer, because of DNA damage. Photo(chemo)therapy alone has the capacity to induce skin cancer, especially squamous cell carcinoma. However, patients treated in the past with carcinogenic therapies, or those predisposed to skin cancer because of a genetic disorder, immunosuppressive disease or therapy, or earlier skin malignancies have a higher risk to develop these skin cancers.

These high-risk patients should not be treated with photo(chemo)therapy. The British Photodermatology Group developed guidelines for treatment with photochemotherapy. Especially with respect to skin cancer, they advise limiting photochemotherapy to a total of 150-200 therapy sessions or 1000-1500 J/cm² per patient, whenever possible.
Systemic therapies

Patients who fail to react to local and photo(chemo)therapy or, for other reasons, are not able to undergo these treatments are considered for systemic therapy, e.g., acitretin, cyclosporine A or methotrexate. While these therapies are very potent in reducing the symptoms of psoriasis, they have considerable side-effects which limit their use.

The order in which these therapies should be given is not fully established, and often depends on the patient. The retrospective systematic review by Spuls et al. revealed some aspects of the efficacy and side-effects of systemic therapies. In their study retinoids produced the lowest proportion of patients (56%) with a good response (defined as 75 to 100% improvement). Nevertheless, for the pustular forms of psoriasis and acrodermatitis continua of Hallopeau acitretin is the treatment of first choice. Cyclosporine appeared second best (64%), while photochemotherapy and ultraviolet B therapy gave the best results (83% and 68% of patients with a good response, respectively). As well-documented clinical studies with methotrexate are lacking, no estimate of patients with a good result is given in the review of Spuls et al. Clinical experience with methotrexate, however, suggests that the percentage will be in the range of cyclosporine. Methotrexate is accepted as the treatment of first choice in patients with psoriasis associated with psoriatic arthritis. In addition to these registered therapies, there is another therapy, with fumaric acid esters. A combination of dimethylfumarate and monoethylfumarate combined with calcium, magnesium or zinc salts is used, also known as Fumaderm. Although not officially recognized as a therapy for severe psoriasis, it is not seldom used as such with good results.

Side-effects

The first retinoic acid marketed for psoriasis vulgaris was etretinate. Its metabolite acitretin is now used in most countries because its elimination rate is 50 fold faster than that of etretinate. It was thought that the teratogenicity of acitretin could be restricted to two months instead of the 18 months recommended for etretinate. Unfortunately, it has been proven that acitretine can be isomerized in the body to etretinate, probably under the influence of ethanol. Retinoids cause in vitro inhibition of cell proliferation, keratinization and differentiation of epithelial cells, and have an anti-inflammatory effect. Also, there are some indications of immunomodulatory effects in vitro. Which of these effects is most important in the efficacy in psoriasis is not known. The growth and differentiation of epidermal keratinocytes decrease significantly under treatment with retinoids in vivo.

The side-effects of retinoids include dry mucosae, granulomas and furunculosis, hyperostosis, and thinning of the epidermis. An increase of serum triglycerides and sometimes cholesterol can occur, rarely an increase of liver enzymes. Generally, side-effects with acitretine are manageable and reversible if therapy is discontinued.

Methotrexate, a folic acid antagonist, was first thought to have a cytotoxic effect on proliferating epidermal cells. In high dosages it indeed causes dam-
age to epidermal cells. However, recent data showed that methotrexate in a
dose of 2.5-5 mg effectively killed lymphoid cells, while human keratinocytes
were not affected. In this way, methotrexate can have its beneficial effect on
psoriatic lesions by influencing the immune system. The side-effects of
methotrexate can be quite severe, e.g., methotrexate pneumonia, toxicity of
the liver (sometimes resulting in fibrosis or cirrhosis of the liver), and bone
marrow suppression, but fortunately these side-effects occur rarely. If
monitored closely this therapy is safe. Side-effects like hepatotoxicity, nau­
sea, ulcerative stomatitis, bone marrow suppression and osteopathy are
reversible if discovered in time.

Cyclosporine, a cyclic polypeptide with strong immunosuppressive activity,
has been extensively studied and has proven to be a potent drug in the treat­
ment of psoriasis. The side-effects include hypertension, nephrotoxicity,
disturbed liver functions, gastro-intestinal complaints, headache, and paraes­
thesia. All of them are reversible if discovered in time. There is, however,
some evidence that although the creatinine clearance may return to the pre-
treatment level, nephropathy can be demonstrated in biopsies of the kidneys
and this is irreversible. Furthermore, it is reported that patients using cyclo­
sporine develop skin cancer more rapidly. Cyclosporine itself is neither
mutagenic nor carcinogenic.

Fumaric acid esters, products in the citric acid cycle (Krebs cycle), are still
under investigation but are already being used as a therapy for psoriasis. The
working mechanism is based on the assumption that the natural fumaric acid
storage in patients with psoriasis is lower than in controls. The side-effects of
fumaric acid esters are especially nephrotoxicity, disturbance of liver enzymes,
as well as a mild decrease in leucocyte count.

1.4 Aim of this thesis
The search for other treatments for psoriasis is continuing. The new area of
research concerns the genetic background of psoriasis, but gene therapy is
not yet possible. For now, interest is focussing on immunosuppressive drugs,
retinoids, photo(chemo)therapy and vitamin D derivatives and combinations
of them. In this perspective many studies were and are performed with sev­
eral systemic and topical drugs.

The aim of this thesis is to participate in the search for new therapies.
When the studies in this thesis started, in 1992, regulations for the registra­
tion of drugs were under development. Since then, it has become more diffi­
cult to conduct a study that is approved for registration purposes. Many older
studies, and unfortunately some current ones do not fulfill the modern crite­
ria for Good Clinical Practice of investigational drugs and the regulations of the
Food and Drug Administration. Nowadays, a drug therapy for psoriasis can­
not have a place in therapies of psoriasis based on clinical experience only.
There are just a few comparative studies of therapies used to treat psoriasis.
This makes it difficult to give a minimum of effectiveness necessary to accept a
new drug as useful in the treatment of psoriasis.

Before investigating new therapies, first a study was made of the existing
therapies. Methotrexate was among the first systemic therapies for psoriasis and was introduced in the 1950s. It has many side-effects that are known by dermatologists who prescribe this drug. This thesis starts with a report concerning one side-effect of methotrexate, methotrexate osteopathy, which was thought to occur only in children suffering from leukemia who were treated with high doses of methotrexate and was therefore unknown to dermatologists (chapter 2, section 2.1). As only a few comparative studies exist, this thesis includes a comparative study of two established therapies (e.g., cyclosporine A and photochemotherapy). Because cyclosporine A was very successful in reducing psoriatic lesions, even patients with less severe psoriasis were treated with this drug. To be able to place cyclosporine A better between the other therapies it was decided to compare this drug with photochemotherapy, its main competitor. The evaluation had to be done retrospectively, because it is almost impossible to perform a double-blind study with photochemotherapy and cyclosporine A therapy due to their different natures (chapter 2, section 2.2). Chapter 3 is about possible new therapies and starts with a study investigating ranitidine a new and promising drug for the treatment of psoriasis. Being a H$_2$-antagonists, ranitidine has a well documented record of safety, also for long-term use.\textsuperscript{78} It would therefore offer an attractive alternative. Witkamp et al.\textsuperscript{79} studied these reports and noted that positive results with H$_2$-antagonists were found in those patients who were treated for a period of at least 16 weeks. They found encouraging results in their open prospective study with ranitidine for 16 weeks in 20 patients with moderate to severe psoriasis. The mechanism of action postulated was a delayed immunosuppressive effect of ranitidine due to partial blockade of CD8$^+$ cells and an increased histamine production from positive feedback mechanisms.\textsuperscript{80} As placebo-controlled studies were lacking, a double-blind, placebo-controlled, multicenter dose-comparing study in 201 patients with chronic psoriasis was performed to confirm the results of the study of Witkamp et al (chapter 3, section 3.1). A study with a new derivative of cyclosporine, IMM 125 (cyclosporine S or exaclosporine), was performed because laboratory studies and animal studies suggested that it had a better safety profile, especially regarding nephrotoxicity than cyclosporine A. The results of this study are described in chapter 3, section 3.2. As well as creating new derivatives of cyclosporine A, an improvement of the current drug can make a difference as well. This has been found in a new pharmaceutical preparation of cyclosporine A, a cyclosporine micro-emulsion. This new formula claimed to have a better pharmacokinetic profile with an Area Under the Curve (AUC) greater than the old cyclosporine A formula, and a more stable blood concentration without the high peak concentrations known from the old formula. In this chapter the effects of the change to this new cyclosporine micro-emulsion in patients currently treated with cyclosporine A are studied (chapter 3, section 3.3). In addition, a new cyclic immunosuppressive drug was found, a macrolide called tacrolimus (FK506). It has been studied as a systemic therapy, and
proven to be effective in psoriasis (chapter 3, section 3.4), and as a topical formulation for the treatment of plaque-type psoriasis. The results are described in chapter 3, section 3.5.

This thesis ends with a summary of the results of the clinical trials. It became a proclamation to perform the best possible study, and as soon as possible, for any new drug being claimed as a treatment for psoriasis. In this way we can protect our patients against false hope, and protect society against a waste of money for therapies that are ineffective.
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