Innovative therapies and new targets in psoriasis

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1  GENERAL INTRODUCTION AND AIMS OF THE THESIS
INTRODUCTION

Psoriasis is one of the most common skin diseases and has been recognized since ancient times. Although sometimes mixed up with for example leprosy in early times, psoriasis is viewed as a separate entity since 1841. Psoriasis is estimated to have an incidence of 1-3% worldwide and prevalence rates varies from 0.5% in China to 4.8% in Norway.

This thesis focuses on psoriasis vulgaris, also known as chronic plaque psoriasis, and this is the most common form of psoriasis occurring in more than 80% of cases. It is characterized by symmetrical red scaly well-demarcated plaques that are typically found on elbows, knees, the scalp, buttocks and genitalia. There are clinical variants of psoriasis, defined as subsets, with identical histopathological changes in the skin. These subsets are described based on their form (guttate, pustular, annular) or their distribution (inversa, palmoplantar, erythrodermic). Occasionally combinations of the different types develop simultaneously or sequentially over time in the same patient. About 50% of patients with psoriasis have distinctive nail changes, e.g. pitting, onycholysis, oil-spots and dystrophy, related to the disease.

In addition to the skin and nail involvement, a seronegative inflammatory arthritis can develop in 7-39% of psoriasis patients. This wide range is probably due to variable methods of assessment. More recent studies suggest that the prevalence of psoriatic arthritis tends towards the higher end of this range. The course of psoriatic arthritis varies, with some having mild changes and others severe, rapid destruction of joints. Usually the skin lesions precedes the involvement of the joints or tendons, but in 19% the arthritis is present before skin lesions appear.

Psoriasis is classified as mild, moderate, or severe. This classification takes account of the severity of cutaneous manifestations, which are usually rated with the Psoriasis Area and Severity Index (PASI). This index is based on the degree of erythema, infiltration, and scaling and the extent of involvement of the four body areas (head, trunk, arms and legs). Psoriasis is classified as mild if the PASI is below 10, and moderate to severe if it is 10 or above; the highest possible PASI value is 72. Total body surface area (BSA) is another method to classify the severity of psoriasis, and then BSA >10 is the criterion for moderate to severe psoriasis.

Once psoriasis appears, it is usually a life-long disease characterized by a variable and unpredictable course and spontaneous remissions is uncommon. Psoriasis patients need long-term therapy, which often give rise to a variety of side-effects, including organ-toxicity. Although psoriasis itself is not life-threatening, it causes significant psychosocial morbidity and a decrease in health-related quality of life. Quality of life in psoriasis patients equals or exceeds that due to other severe disorders such as diabetes, rheumatoid arthritis, or cancer. The combined costs of long-term therapy and social costs of the disease due to reduced levels of employment have a major impact on health care systems and on society in general.
There is increasing awareness that psoriasis as a disease is more than skin deep. Co-morbidities thought to have an increased prevalence in psoriasis include cardiovascular disease, lymphoma, non-melanoma skin cancer, Crohn’s disease and metabolic disorder. The relative influence of known confounders like concomitant therapy with immunosuppressants and phototherapy, smoking and alcohol is currently unknown.

Although there is currently no cure for psoriasis, there are several treatment options comprising topical therapy, phototherapy and systemic agents. In Table 1 an overview of currently applied (and widely approved) treatments of psoriasis is given.

**Table 1**

<table>
<thead>
<tr>
<th>Topical</th>
<th>Photo(chemo)therapy</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Broadband UVB (290-320nm)</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Dithranol1</td>
<td>Narrowband UVB (311 nm)</td>
<td>Cyclosporine A</td>
</tr>
<tr>
<td>Tar1</td>
<td>PUVA (320-400 nm)</td>
<td>Acitretin</td>
</tr>
<tr>
<td>Tazarotene</td>
<td>Excimer laser (308)</td>
<td>Fumaric acid</td>
</tr>
<tr>
<td>Vitamine D analogues</td>
<td></td>
<td>Biologicals</td>
</tr>
</tbody>
</table>

**IMMUNOPATHOGENESIS**

The cause of psoriasis can be considered multifactorial, resulting from an interaction of genetic, environmental, and immunological factors.

Twin and family studies have shown that psoriasis has a strong genetic component although the inheritance pattern is still unclear. In patients with childhood psoriasis 71% have a positive family history. Siblings and first-degree relatives of psoriasis patients show a four-fold or more increased risk in developing psoriasis. Studies of disease concordance among twins show a risk of psoriasis that is two to three times as high among monozygotic twins as among dizygotic twins. At least ten chromosomal loci have been identified that are evidently linked to psoriasis (PSOR1-10), the most important of which is PSOR1 on chromosome 6p21 and is considered to be responsible for up to 50% genetic susceptibility.

Environmental factors that trigger psoriasis in genetically predisposed individuals are suggested with the finding that psoriasis often manifests itself initially, or is worsened at some point in its further course, after exposure with factors of various types. The main ones that have been identified are streptococcal upper respiratory infections, certain medications (beta-blockers, ACE-inhibitors, lithium salts, interferon-alpha, anti-malarials) and stress.

With regard to immunological factors, the hypothesis of the pathogenesis of psoriasis is continuously evolving with new developments achieved in immunology.
Until the early 1980s, psoriasis was believed to be a disease primarily of epidermal keratinocyte proliferation. Along with the development of immunohistochemical staining techniques, it was discovered that the leukocyte infiltrate consists mainly of CD4 positive and CD8 positive T cells. Furthermore, reported beneficial effects of specific T-cell therapies, such as cyclosporin A and DAB389IL-2 suggesting a prominent role for T cells in the pathogenesis of psoriasis. Some years later, when the T cells were divided into Th1 and Th2 on the basis of the cytokine production profile, the T-cell hypothesis was refined and psoriasis was considered a Th1-cell-associated disease with a prominent role for interferon (IFN)-γ.

In recent years, clinical and basic science observations have shown that innate immunity as well as adaptive immunity is crucial in the initiation and maintenance of psoriatic plaques. Innate immunity comprises the immediate response against pathogens and usually precedes the adaptive immunity, which requires several days to develop. The division in innate and adaptive immunity is not so clear-cut, however, as some overlap exists. In addition, these two branches do not operate independently, but rather are able to influence each other. Practically all cellular and humoral elements of the innate part of the skin immune system are upregulated or increased in lesional skin of psoriasis patients. Keratinocytes, neutrophils, natural killer (NK) cells, NK T cells and dendritic cells are all part of the cutaneous inflammation in psoriasis. Of the dendritic cells specifically plasmacytoid dendritic cells are of importance. This specific type of dendritic cell accumulates in the skin of psoriasis patients and produces IFN-α early in the development of psoriasis. This activates and expands the autoimmune T cell cascade leading to psoriasis, and may provide an unique link between the innate and adaptive immune system in driving inflammation in psoriasis.

In 2005, a new type of T cell, Th17, was described. Th17 cells are distinguished from both Th1 and Th2 cells in that they secrete a distinct set of proinflammatory cytokines, including IL-17A (IL-17), IL-17F, IL-6, and, to a lesser extent, TNF-α and IL-22. Th17 cells and Th17-related cytokines play a pivotal role in the pathogenesis of psoriasis. IL-17 potently stimulates keratinocytes to produce proinflammatory cytokines and IL-22 induces proliferation of keratinocytes and production of antimicrobial peptides as well as chemokines. Furthermore, successful anti-TNF treatment reduces Th17 cells in psoriasis lesions. Th17 cells activation is induced by IL-23, which is overproduced by activated dendritic cells in psoriasis lesions and keratinocytes. Biologically active IL-23 is a heterodimer molecule consisting of a unique p19 subunit and a p40 subunit shared with heterodimer IL-12, which combines the p40 subunit with a specific p35 subunit. IL-12 is a cytokine that promotes Th1 cell differentiation and production of IFN-γ. Both IL-23 p19 and IL12/IL-23 p40 mRNA are increased in skin lesions of psoriasis patients, but in contrast IL-12 p35 mRNA expression is decreased compared with uninvolved skin.

More recently, in 2009, inflammatory CD4+ T cells were described, that produced IL-22, but do not express IL-17A or IFN-γ, the so-called Th22 cells, which are...
also increased in psoriasis. Concentration of plasma IL-22 is higher in psoriatic patients and levels are highly reflective of skin disease activity. In the skin, IL-22 induces antimicrobial peptides, promotes keratinocyte proliferation, and inhibits keratinocyte differentiation, which suggests a role in remodeling wound healing and in innate defense mechanisms.

At present it is unknown whether Th1, Th17 and Th22 cells might cooperate in order to amplify immune responses or whether these cells are involved at different stages during development of the inflammation in psoriasis. In model systems cross-regulation between Th1 and Th17 was demonstrated, suggesting important functional interactions. Lowes et al. demonstrated Th17 to be a discrete population localized predominantly to the dermis of psoriasis skin lesions, separate from Th1 cells, suggesting a mixed Th1 and Th17 inflammatory environment. Th17 cells might participate in the initial acute inflammation, while Th1 cells are involved in prolonging and perpetuating tissue inflammation. The clinical relevance of Th22 remains to be determined.

During the last decade a tremendous progress in understanding of the pathogenesis of psoriasis was made. Discovery of new cell types (e.g. plasmacytoid dendritic cells, NK T cells), new cytokines, and other developments in fundamental and clinical immunology have all been incorporated in the etiology of this skin disease. The current model comprises a complex network with many different cell types that can reciprocally stimulate each other by a still growing list of bound and soluble factors (see Figure 1). What causes this cascade of immunological events in skin of psoriasis patients is still a mystery. Due to its complexity it is as yet (and perhaps will always be) impossible to pinpoint a single cell, factor, or gene as the culprit of psoriasis.

CHEMOKINES AND CHEMOKINE RECEPTORS IN PSORIASIS

For psoriatic lesions to develop, inflammatory cells must be able to migrate into lesional skin. Chemokines are small (8-14kD) chemotactic peptides that have an important role in host defence by regulating the migration of passing immune cells. More than 45 chemokines have been identified and their secretion can be controlled by various agents including cytokines and lipopolysaccharide. They have been grouped into four classes -CXC, CC, CX3C and C- on the basis of their disposition and number of invariant cysteines. A common feature of most chemokines is a heparin-binding domain comprised mainly, but not exclusively, of residues in an α-helical region near the C-terminus. This allows chemokines in the blood to bind to glycosaminoglycans that are exposed on the cell surface of endothelial cells, thus rapidly forming a solid-phase chemotactic gradient. By this means they are able to attract and activate passing immune cells. Chemokines exert their biological effects by binding to and activating cell-surface receptors that belong to the G-protein-coupled receptor (GPCR) superfamily. Currently, 19 chemokine receptors have been identified. They are
expressed on a variety of cells including immune cells, endothelial cells and neurons and are either constitutively activated or induced by agents such as cytokines and lipopolysaccharide. Each receptor has a repertoire of chemokine ligands that activates it. These range from CCR1, which has at least nine ligands that bind with
high affinity, to specific receptors such as CCR8, which only has one ligand. So, it seems that there is a great degree of redundancy in the chemokine receptor system. This is accentuated even further by the fact that some chemokines can bind with high affinity to more than one receptor. For example, CCL5 (also known as RANTES) can bind to CCR1, CCR3 and CCR5. By contrast, others such as CCL1 (also known as I-309) only bind a single receptor (CCR8). In addition, chemokines that are agonists for one receptor can be natural antagonists for others.

Various studies have documented a strong chemokine expression in keratinocytes in psoriatic skin, and the production of chemokines by keratinocytes may contribute relevantly to the formation of the inflammatory infiltrate. The intra-epidermal accumulation of neutrophils, a characteristic feature of psoriasis, is caused by CXCL8 (also known as IL-8) and CXCL1 (also known as GRO-α), which were found to be in a high content within psoriatic scales. In addition, the infiltrating neutrophils in psoriatic skin express the corresponding receptors CXCR1 and CXCR2, of which CXCR2 is overexpressed in psoriatic skin. The monocytes and Th1 cells found in psoriatic lesions are attracted predominantly by CCL2 (also known as MCP-1), CCL5, CXCL9 (also known as Mig) and CXCL10 (also known as IP-10).

The predominant chemokine receptors expressed on Th1-cells are CCR5 and CXCR3. Besides its preferential expression on Th1 cells, CCR5 is also expressed on monocytes, macrophages, natural killer and dendritic cells: all thought to be significant elements in the pathogenesis of psoriasis. The ligands of CCR5 (CCL3, CCL4 and CCL5 (also known as MIP1α, MIP1β and RANTES, respectively)) are highly expressed by keratinocytes in psoriatic tissue. Furthermore, it has been demonstrated that the proinflammatory cytokines IFN-γ and TNF-α can induce the expression of these chemokines and that treatment of psoriasis resulted in a significant decrease of CCL5, as well as a reduction of CCR5+ T cells in the skin.

The other chemokine receptor predominantly expressed on Th1 lymphocytes, CXCR3, has been suggested to be one of the major chemokine receptors responsible for their recruitment to inflamed sites in vivo. Besides its importance in recruitment, CXCR3 is also found on natural killer (NK) cells, B cells, plasmacytoid dendritic cells and myeloid dendritic cells. The presence of infiltrating CXCR3+ T cells in psoriasis as well as other inflammatory skin disorders has been reported. The cognate ligands of CXCR3, CXCL9, CXCL10 and CXCL11 (also known as ITAC) are induced by IFN-γ and have been shown to be expressed by inflammatory cells and/or keratinocytes in psoriatic skin and lesional skin of other inflammatory skin disease.

Another important chemokine receptor in the pathogenesis of psoriasis is CCR6. This chemokine receptor is expressed on the Th17 subsets of CD4+ T cells and, together with its ligand, CCL20 (also known as MIP-3α), it is expressed at statistically higher levels in lesional psoriatic skin than in non-lesional or normal donor skin. Furthermore, studies have shown that CCR6 is necessary for the pathology induced in a mouse model of psoriasis-like inflammation. A nice overview on chemokines and chemokine receptors that have been associated with psoriasis is published by Homey.
NEW DIRECTIONS IN PSORIASIS THERAPY

Although there are several systemic treatments for patients with moderate to severe psoriasis, they do not fully meet the needs of patients. The toxicity, inefficacy and often inconvenience of current conventional treatments, in addition to the impaired quality of life in psoriasis patients, call for new therapeutics options.

With the growing knowledge and understanding of the pathogenesis in psoriasis, more specific immunomodulating therapies are being developed, the so-called ‘biologic response modifiers’ or ‘biologics’. These custom-made, protein-like molecules can target specific parts of the activated immune system in psoriasis, e.g. activation, co-stimulation, or proliferation of T cells, their trafficking into the skin, or effector cytokines. Since 1989 several biological therapies have been tested for psoriasis and in January 2003 Alefacept (Amevive®), anti-CD2, was the first biological that was approved by the US Food and Drugs Administration (FDA). In Table 2 an overview is given of all biological therapies registrated by the European Medicines Agency (EMEA) and the FDA for the treatment of moderate to severe plaque type psoriasis.

Alefacept is an intravenously or intramuscularly administered fusion protein which contains of human immunoglobin (IgG) and the binding site of lymphocyte function-associated antigen-3 (LFA-3). It binds to the CD-2 receptor located on T cells, resulting in inhibition and memory T cell activation and proliferation. Beside T cells, CD2 is also expressed on NK cells and a small population of CD14+ DC’s. Two randomized, double-blind, placebo-controlled trials showed an improvement of PASI with 75% (PASI-75) after 12 weeks of treatment in 28 to 40% of the patients. Alefacept is currently approved in the USA and in Europe only in Switzerland.

Another anti-CD2 therapy, which is currently still under investigation, is siplizumab (MEDI-507). In vitro studies of this humanized monoclonal anti-CD2 antibody have shown that high doses of siplizumab cause depletion of lymphocytes, whereas lower doses induce T-cell hyporesponsiveness. Currently, clinical studies in psoriasis patients are going on.

### Table 2

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>Mode of action</th>
<th>registrated indications beside psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>alefacept</td>
<td>Amevive®</td>
<td>anti-CD2</td>
<td>-</td>
</tr>
<tr>
<td>efalizumab</td>
<td>Raptiva®</td>
<td>anti-CD11a</td>
<td>-</td>
</tr>
<tr>
<td>etanercept</td>
<td>Enbrel®</td>
<td>anti-TNF-α</td>
<td>Pediatric plaque psoriasis, RA, PsA, JIA, AS</td>
</tr>
<tr>
<td>infliximab</td>
<td>Remicade®</td>
<td>anti-TNF-α</td>
<td>RA, PsA, AS, Crohn's disease (children and adults), ulcerative colitis</td>
</tr>
<tr>
<td>adalimumab</td>
<td>Humira®</td>
<td>anti-TNF-α</td>
<td>RA, PsA, JIA, AS, Crohn's disease (adults)</td>
</tr>
<tr>
<td>ustekinumab</td>
<td>Stelara®</td>
<td>anti-p40 IL12/IL23</td>
<td>-</td>
</tr>
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</table>

RA, rheumatoid arthritis; PsA, psoriatic arthritis; JIA, polyarticular juvenile idiopathic arthritis; AS, ankylosing spondylitis
Efalizumab was also designed to interfere with T-cell adhesion and co-stimulation. This humanized murine monoclonal antibody targets CD11a, which is a subunit of leukocyte function-antigen-1 (LFA-1) that is expressed on all leukocytes. In order for leukocytes to bind to other cell types, CD11a needs to bind to intercellular adhesion molecule-1 (ICAM-1). Efalizumab blocks this binding, which interrupts many processes, including the activation of T cells, adhesion of T cells to endothelial cells and migration of T cells to sites of inflammation, including psoriatic skin. In clinical trials PASI-75 was achieved in 22-39% of patients after 12 weeks of treatment with 1 mg kg⁻¹/Avk efalizumab subcutaneously. In February 2009 the European Medicines Agency (EMEA) has recommended the suspension of the marketing authorization for efalizumab after concluding that the benefits of efalizumab no longer outweighed its risks, because of safety concerns, including the occurrence of progressive multifocal leukoencephalopathy (PLM) in three patients treated with efalizumab.

Currently there are three registered TNF-α inhibitors for the treatment of psoriasis. Etanercept was the first to be approved and is a human TNF-α receptor and immunoglobulin fusion protein that binds TNF-α and lymphotoxin-α, rendering TNF-α biologically inactive. As a result etanercept modulates multiple biological responses induced or regulated by TNF-α, including serum levels of cytokines, expression of adhesion molecules responsible for leukocyte migration and, to a lesser extent, ICAM-1. About 30% of patients treated in doses of 25 mg twice weekly and 50% of patients treated in doses of 50 mg twice weekly achieve PASI 75 in 12 weeks. Continuing therapy up to 6 months improves response rates further to 43% and 57% for 25 mg biweekly and 50 mg biweekly, respectively.

While etanercept is a fusion protein, infliximab and adalimumab are both monoclonal antibodies directed at TNF-α. Infliximab is a chimeric monoclonal antibody given intravenously every 2 months after a loading period. Onset of action is rapid, with evidence of significant improvement within the first 2 weeks of treatment and maximum benefit by week 10, when 79% of patients achieve PASI-75.

Adalimumab is a human monoclonal antibody given subcutaneously once every other week. As with infliximab, onset of action is rapid, with significant improvements in disease severity within 2 weeks of treatment initiation. At week 12, 69% of patients treated with 40 mg every other week achieve PASI-75.

Currently, two new monoclonal antibodies against TNF-α are on the horizon, golimumab and certolizumab. Golimumab (Simponi®) is the first transgenic human monoclonal antibody against TNF-α approved for the treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. It is synthesized using conventional hybridoma technique after immunizing transgenic mice containing human immunoglobulin genes. The constant region of golimumab is identical to that of infliximab, but the variable regions of golimumab have fully human sequences. Certolizumab (Cimzia®) is a PEGylated Fab’fragment of an anti-TNF-α monoclonal antibody. The compound binds to TNF-α and prevents binding to cell surface receptors. As certolizumab does not contain an Fc region, unlike infliximab and adalimumab, it does not fix complement or cause antibody-dependent cell-mediated
introduction & aims

Cytotoxicity in vitro. It has been approved for the treatment of Crohn’s disease and rheumatoid arthritis. Although both medications are currently not registered for the treatment of psoriasis, given their mechanisms of action, it is likely to have similar benefits as other TNF-α inhibitors and therefore in the future they may be added to the treatment options for patients with moderate to severe psoriasis.

More recently, monoclonal antibodies directed against p40, a polypeptide shared by IL-12 and IL-23, are being tested in clinical trials. Ustekinumab is the first registered IL-12/IL-23 inhibitor in Europe and the US for the treatment of moderate to severe plaque psoriasis. In total 2,666 patients were investigated in three large randomized controlled clinical trials and both doses of ustekinumab (i.e. 45 mg and 90 mg) were highly effective in psoriasis. Onset of action is evident within 2 weeks, with 67% and 72% of patients achieving PASI 75 by week 12 for the 45 mg and 90 mg doses, respectively, and maximal efficacy evident between week 20 and week 24. Remarkable is the low dosing frequency: at week 12 only two administrations of the drug have been given to the patients. Ustekinumab has a median half-time of approximately 3 weeks, yet the dosing frequency is once every three months, after a loading period. Although this appears to be favorable for the patient, in case of an infection or non-elective surgery treatment cannot be antagonized. Recently, ustekinumab was compared with etanercept in chronic plaque psoriasis in a large phase II randomized controlled trial. The percentage of patients achieving PASI 75 by week 12 with ustekinumab 90 mg and 45 mg at week 0 and 4 was 74% and 68%, respectively, compared with 56% for patients randomized to etanercept 50 mg biweekly for 12 weeks. Besides psoriasis, ustekinumab is currently also being evaluated for the treatment of psoriatic arthritis.

ABT-874 (Briakinumab®) is another monoclonal antibody directed against p40 IL-12/IL-23 and is in the pre-registration phase for treatment of chronic plaque psoriasis. A phase II randomized placebo-controlled trial showed that over 90% of patients receiving more than one dose (100 or 200 mg) of ABT-874 achieved a PASI 75 by 12 weeks.

With the increasing knowledge and understanding of psoriasis, new treatment options are now available without the cumulative organ toxicity of systemic treatments like methotrexate and cyclosporine. The usefulness of this new generation of sophisticated therapeutical agents is a good example that fundamental research in immunology is indispensable for human health. With these more specific immunomodulating therapies, the treatment of patients with moderate to severe psoriasis has shifted to long-term disease management, and hence, requires long-term evaluation of efficacy and safety. For this purpose patient registers are indispensable.

And although tremendous progress has been made in the last decade regarding the understanding of the pathogenesis of psoriasis, and subsequently the treatment of psoriasis patients, psoriasis still remains a chronic disease, which we cannot cure. Therefore, the ultimate challenge for the next decade will be the determination of the factor or factors that actually trigger psoriasis, enabling the possibility to prevent this skin disorder in genetically predisposed individuals.
AIMS OF THE STUDIES

The first part of this thesis considers the clinical and/or the effects on different leukocyte subsets in situ of several registered biological treatments for psoriasis. The last two chapters consider possible treatment targets for psoriasis patients.

Although biologics are a big leap forward for the treatment of moderate to severe psoriasis, these effective treatments still show side-effects. In Chapter 2a a case-report on a clinical side-effect is described of a psoriasis patient treated with efalizumab. Chapter 2b is a written response to a comment made in the discussion of another case-report, which referred to the case-report mentioned in 2a.

Randomized clinical trials regarding biologics show large clinical improvement in patients with moderate to severe psoriasis. Yet, patients included in these studies did not have to fit strict criteria regarding unresponsiveness to several systemic treatments, contrary to patients in daily practice. Chapter 3 describes the results of a retrospective clinical study evaluating the non-trial based clinical response of normal and high dosed etanercept treatment in psoriasis patients.

The remarkable improvements of psoriasis seen in clinical trials with tumor necrosis factor (TNF)-α antagonist, together with the discovery of activation of several cellular and humoral components of the innate immune system, suggests that aggravation of innate immunity plays an important role in the pathogenesis of psoriasis. We hypothesizes that, if malfunctioning of the innate immune system is somehow a pivotal initiator of psoriasis, successful treatment of psoriasis would diminish the expression of markers of innate immunity. The in situ effects of etanercept treatment in psoriasis patients, specifically on different inflammatory markers, are described in Chapter 4.

In Chapter 5a, the same inflammatory markers as in Chapter 4 are examined in psoriasis skin lesions, but now after treatment with adalimumab in a prospective, randomized, placebo-controlled study in patients with psoriatic arthritis. Chapter 5b describes the results of study in synovial tissue. Both studies were done in order to identify biomarkers associated with effective treatment.

Although the specific effector cells responsible for the inflammatory process in psoriasis are not known, T cells play a role in the pathogenesis. The trafficking of T cells from blood to tissues is essential in chronic inflammatory diseases such as psoriasis. Key factors in this migration are chemo-attractant cytokine molecules known as chemokines and their receptor. The predominant chemokine receptors expressed on Th1-cells are CCR5 en CXCR3. In Chapter 6 the expression of the chemokine receptor CCR5 and its ligands in lesional and non-lesional psoriatic skin are described. In addition, the clinical and immunohistochemical results of a randomized placebo controlled trial with a CCR5 inhibitor are presented. In Chapter 7, the expression of another chemokine receptor, namely CXCR3, and its ligands are investigated in lesional and non-lesional psoriatic skin.
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