Clinical and synovial tissue studies in psoriatic arthritis
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Chapter 1

General introduction
Psoriatic Arthritis

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy of unknown etiology that is associated with psoriasis, affecting the peripheral joints, spine, and enthesis. It has been accepted that PsA, belonging to the spondyloarthritis (SpA) family, is distinct from rheumatoid arthritis (RA), the most common inflammatory arthropathy, by infrequent seropositivity for rheumatoid factor and anti-citrullinated peptide antibodies (ACPA), as well as the presence of typical clinical features. These features include the involvement of the distal interphalangeal (DIP) joints, an asymmetric distribution of the inflamed joints, the presence of dactylitis (inflammation of an entire digit - finger or toe), enthesitis, sacroiliitis or spinal involvement, and, of course, psoriasis.

Patients with PsA are not only physically hampered by their joint disease, but they are also impaired psychologically and socially by the skin disease (1). Despite current treatment options, patients with PsA experience a significant reduction in quality of life (2;3).

Clinical phenotypes and classification of PsA

The heterogeneity in clinical presentation and the variable course have made PsA a particularly challenging disease for diagnosis, treatment, and conduct of clinical trials. Over 30 years ago, Moll and Wright described a large case series of patients with PsA, on which they based a division into 5 clinical subtypes (Table 1) (4).

Their definition of PsA as an inflammatory arthritis associated with psoriasis, usually seronegative for rheumatoid factor, was the first of many attempts to develop classification criteria (5). Recently, the Classification of Psoriatic Arthritis (CASPAR) Group published

Table 1. Clinical subtypes of PsA

<table>
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<tr>
<th>Subtype</th>
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<tr>
<td>Polyarticular, symmetrical arthritis</td>
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<tr>
<td>Oligoarticular (&lt; 5 joints), asymmetrical arthritis</td>
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<tr>
<td>Predominant DIP involvement</td>
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<tr>
<td>Predominant axial involvement</td>
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<tr>
<td>Arthritis mutilans</td>
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Table 2. CASPAR criteria for PsA

<table>
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<th>Criteria</th>
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<tr>
<td>The presence of inflammatory articular disease (joint, spine, or enthesal) plus ≥ 3 points from the following 5 items:</td>
</tr>
<tr>
<td>Psoriasis: current (2), or history (1), or family history in first or second degree relative (1)</td>
</tr>
<tr>
<td>- Nail dystrophy (1)</td>
</tr>
<tr>
<td>- Negative rheumatoid factor (1)</td>
</tr>
<tr>
<td>- Dactylitis, current (1) or history (1)</td>
</tr>
<tr>
<td>- Radiography (hands and feet), juxta-articular new bone formation (1)</td>
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a new set of PsA classification criteria based on a large prospective study conducted worldwide (Table 2)(6). The development of generally accepted classification criteria for PsA was critical, because the reliability of clinical trials depends heavily upon standardized uniform and validated enrolment criteria. With numerous therapeutic agents for PsA currently being studied and many more on the horizon, the development of the CASPAR criteria was a vital step.

**Pathogenesis of PsA**

Although the exact etiology of PsA is still unknown, there is strong evidence for a multifactorial origin of the disease, including genetic, environmental, and immunologic factors involved.

**Genes**

In psoriasis genetic involvement has long been recognized, evidenced by familial clustering of disease and concordance in monozygotic over dizygotic twins (7). The occurrence of psoriasis cannot be explained by the presence of a single gene; it has a complex and multifactorial base. Over 20 candidate gene loci associated with psoriasis have been described. However, the strongest genetic determinant of psoriasis is believed to be located in the MHC-I region on chromosome 6, also known as PSORS1 (8). Recently, it was shown that HLA-Cw6 is the PSORS1 risk factor that confers susceptibility to psoriasis (9). The presence of a single allele of the HLA-C region, HLA-Cw*0602, is associated with an early onset and a more severe course of psoriasis (10).

Recently, single nucleotide polymorphisms (SNPs) coding for interleuking (IL)-12B and IL-23R have been identified as candidate genes associated with susceptibility for psoriasis outside the PSORS1 region, using genome-wide association scans (11). It was also shown that variation within IL-23R and IL-12B is associated with susceptibility to PsA (12). The functional relevance of these SNPs remains to be elucidated, but IL-12 and IL-23 may play a key role in the pathogenesis of psoriasis. Both IL-12 and IL-23 share a p40 subunit that is highly expressed in psoriatic skin lesions (13). Moreover, neutralization of the p40 subunit with a monoclonal antibody causes marked improvement of psoriasis (14;15) and PsA (16).

There is also strong evidence for a genetic basis to PsA, indicated by an estimated risk ratio of 30 to 55 in first degree relatives (17;18). Population studies have proposed multiple susceptibility loci, mostly within the major histocompatibility complex (MHC) region, with the strongest association for HLA-Cw6 (19;20). HLA-antigens may also identify patients with a specific subtype of PsA: HLA-B27 is associated with spinal involvement, HLA-B38 and –B39 with polyarticular involvement (20). In contrast to patients with RA, the prevalence of the HLA-DRB1 shared epitope is not increased in patients with PsA; however, when present in PsA, it is associated with more erosive disease (21).
Environmental factors

Trauma and infection have been recognized as causative agents in the development of psoriasis (e.g. the Koebner phenomenon, or streptococcal infection preceding guttate psoriasis). It is uncertain if a similar phenomenon exists in the etiology of arthritis in PsA, but the identification of the synovioenthesial complex (SEC), or enthesis organ, as an immunological unit seems to support this hypothesis (22;23). Recent imaging studies have suggested that tendon and ligament insertion points to bone (entheses) are commonly subject to microdamage. While the normal enthesis is avascular in its fibrocartilaginous region, microdamage to the entheses is associated with local cytokine release, tissue repair responses and vessel ingrowth, which may evolve to subsequent inflammation. It has also been suggested that adjuvant molecules derived from bacteria may be preferentially deposited at the site of the SEC, hence microdamage and propensity for bacterial molecule deposition in the context of certain genetic factors may lead to the characteristic inflammatory changes seen at the entheses in SpA including PsA (23). Furthermore, since the nail is functionally integrated with the SEC associated to the DIP joints, this model provides a rationale for the combination of DIP arthritis and nail involvement that is often observed in PsA patients (24).

Immunologic factors

A large number of studies has elucidated immunologically mediated processes in skin and joints of patients with psoriasis and PsA, which has served as a base for potential therapeutic strategies. T cells seem to play an important role in the pathogenesis of both psoriasis and PsA (25). The infiltrate in lesional psoriasis skin mainly consists of activated T cells. In the synovial infiltrate T cells are present among other cell types, and oligoclonal T cell expansions have been demonstrated in both skin and synovium (26), suggesting that an antigen driven T cell response is behind the ongoing inflammation. The role of T cells is underlined by the beneficial effect of therapies against T cells in both psoriasis and PsA, such as ciclosporin A (27;28).

Likewise, the success of treatment with tumor necrosis factor alpha (TNFα) blocking therapy has underlined the important role of TNFα in psoriasis and PsA (29). High levels of TNFα are found in psoriatic skin lesions, synovial fluid and tissue, and serum of patients with PsA. TNFα, produced by macrophages, keratinocytes, dendritic cells, and activated T cells, upregulates nuclear transcription factors, including nuclear factor kappa B (NFκB), which results in enhanced expression of many pro-inflammatory molecules. TNFα has many immunological effects, including enhanced expression of adhesion molecules on endothelial cells, production of other pro-inflammatory cytokines and chemokines, and production of vascular growth factors, resulting in an enhanced influx of immunological cells to the site of inflammation (29). In the skin, TNFα is a direct
promoter of keratinocyte (hyper)proliferation and survival (30). In the joints, TNFα also mediates other biological processes that can result in destruction of cartilage and bone, including increased expression of matrix metalloproteinases (MMPs), and formation and activation of osteoclasts from monocytes. Histologic analysis of the synovial tissue after successful treatment with infliximab, a TNFα blocking agent, showed a reduction of the cell infiltrate and the number of blood vessels with reduced expression of adhesion molecules in a heterogeneous group of 8 SpA patients, as well as a group of 12 PsA patients (31-33). Thus, TNFα blocking treatment leads to decreased neoangiogenesis and deactivation of the endothelium, resulting in decreased cell infiltration and clinical improvement.

More recent observations indicate that interleukin (IL)-23 is highly expressed in psoriatic plaques, and this cytokine is responsible for stimulating a newly recognized T cell subset, Th17 cells, that produce IL-17 as well as TNFα, IL-21 and IL-22 (34;35). The exact role of Th17 cells in PsA is not clear at this moment, but as stated above, blocking the p40 subunit of IL-23 and IL-12 also leads to amelioration of arthritis in patients with PsA (16).

**Treatment of patients with PsA**

The management of patients with PsA should ideally take into account the skin and musculoskeletal manifestations of the disease. This is a challenge for the treating physician because of the heterogeneous presentation of the disease. The physician should always assess the severity of skin disease, arthritis, dactylitis, enthesitis and spondylitis, and base a treatment intervention on logical therapeutic reasoning for each individual patient (36). Most patients with musculoskeletal disease benefit from regular exercise and use of nonsteroidal anti-inflammatory drugs (NSAIDs). It should be noted however that NSAIDs do not modify the course of the disease or the progression of erosions.

In case of persistent arthritis, or erosive disease, patients should be treated with disease-modifying antirheumatic drugs (DMARD’s). A major problem with DMARD’s is that most of these treatments have not been well studied in controlled trials in patients with PsA. Therefore, solid evidence for efficacy is not available for most DMARD’s. Based on a Cochrane meta-analysis, performed in 2000, only iv methotrexate (which is not the common nor the recommended administration route) and sulfasalazine were considered to have some, but not very strong, effect in PsA (37). Randomized, double-blind, placebo-controlled trials of ciclosporine A for the treatment of PsA are lacking. In daily practice, based on clinical experience but not on definite evidence, methotrexate is the treatment of first choice. In 2005, leftunomide 20 mg/day was shown to be effective in peripheral joint disease in PsA (38).

The development of new biologic drugs has led to a new era of clinical trials in PsA. PsA outcome measures have generally been adapted from assessments used in RA
and psoriasis, and these have been used in clinical trials, e.g. American College of Rheumatology (ACR) 20, 50 and 70 response measures, Disease Activity Score (DAS), and the Psoriasis Area and Severity Index (PASI). These measures have been shown to effectively assess changes in peripheral joint disease and skin involvement (39).

TNFα blocking therapy has shown to be very effective for the treatment of PsA, which was shown in large phase 3 clinical trials for all drugs that are available at this moment: etanercept, infliximab, adalimumab, and also golimumab (40-43). Other biological agents have been studied with varying success, but are not available (yet) in daily practice. Efalizumab, anti CD11, was shown to be effective for treatment of skin psoriasis but not arthritis in PsA (44). For alefacept, a fusion protein blocking a costimulatory signal on T cells, beneficial effect for the treatment of PsA was demonstrated (45). Ustekinumab, a monoclonal antibody against the p40 subunit of IL-12/-23, was shown to be effective for the treatment of psoriasis and PsA (15;16). The results of studies with abatacept, IL-17 blockade, certolizumab and many other biological agents in PsA are awaited soon.

Innovative trial design

The rise in new drugs discovered has consequences for the way these potential novel therapies are tested in clinical trials. It is becoming increasingly difficult to include large numbers of patients with active disease into these placebo-controlled trials, because of the growing number of compounds to be tested, and the fact that effective treatment is now available for many patients. Therefore, in an early stage of drug development, there is a growing need for intensive trials with a small number of patients in which a large amount of data is collected to study the effects of the compound tested. The identification of biomarkers that could be used for prediction of the clinical response to treatment and evaluation of biological effects of potential novel therapies is of pivotal importance for this development. Since synovial inflammation is one of the key manifestations of PsA, we and others have focussed on the identification of synovial biomarkers (46;47). Sensitive synovial biomarkers could perhaps be used as predictors of clinical effect in small proof-of-concept trials for selection purposes, similar to the approach used in rheumatoid arthritis (RA) (48). As synovial biopsy is not available in all centres, the identification of relevant soluble biomarkers that can be measured in blood would further facilitate the feasibility of small high-density–of-data clinical trials that are conducted to screen for efficacy. Similarly, the use of biomarkers obtained from skin biopsies could be used in proof of concept studies in psoriasis.
Outline of this thesis

Chapter 2 provides an introduction to the immunohistochemical analysis of the synovial infiltrate of PsA compared to RA. The expression of TNF-like weak inducer of apoptosis (TWEAK) and its receptor Fn14, perhaps a novel therapeutic target, in RA and PsA synovium are studied in Chapter 3. In Chapter 4 the effect of adding ciclosporine A or placebo to treatment with methotrexate in patients with active PsA is studied. Chapters 5 and 6 demonstrate the changes in synovial biomarkers and soluble biomarkers of bone and cartilage metabolism after adalimumab treatment compared to placebo. Chapter 7 describes the clinical and synovial tissue response to alefacept treatment. The correlation between clinical response to adalimumab in PsA and serum levels of adalimumab and antibodies against adalimumab is studied in Chapter 8. Chapter 9 contains the summary and conclusion based upon the studies presented in this thesis.
Reference List


