Clinical and synovial tissue studies in psoriatic arthritis
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Detailed analysis of the cell infiltrate and the expression of mediators of synovial inflammation and joint destruction in the synovium of patients with psoriatic arthritis: implications for therapy

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Abstract

Objective
The synovial tissue is a primary target of many inflammatory arthropathies, including psoriatic arthritis (PsA). Identification of pro-inflammatory molecules in the synovium may help to identify potentially therapeutic targets. Therefore, we performed a study investigating extensively the features of cell infiltration and expression of mediators of inflammation and joint destruction in the synovium of PsA patients compared with rheumatoid arthritis (RA) patients matched for disease duration and use of medication.

Methods
Multiple synovial tissue biopsies were obtained by arthroscopy from an inflamed joint in 19 patients with PsA (8 oligoarthritis, 11 polyarthritis) and 24 patients with RA. Biopsy specimens were analyzed by immunohistochemistry to detect T cells, plasma cells, fibroblast-like synoviocytes, macrophages, pro-inflammatory cytokines, matrix metalloproteinases and tissue inhibitor metalloproteinase-1, adhesion molecules and vascular markers. Stained sections were evaluated by digital image analysis.

Results
The synovial infiltrate of PsA and RA patients was comparable with regard to numbers of fibroblast-like synoviocytes and macrophages. T cell numbers were significantly lower in the synovium of PsA patients. The number of plasma cells also tended to be lower in PsA. The expression of TNF-α, IL-1β, IL-6 and IL-18 was in PsA as high as in RA. The expression of MMPs, adhesion molecules, and vascular markers was comparable for PsA and RA.

Conclusion
These data demonstrate increased pro-inflammatory cytokine expression in PsA synovium, comparable with results obtained in RA, and support the notion that in addition to TNF-α blockade, there may be a rationale for therapies directed at IL-1β, IL-6 and IL-18.
The synovial tissue is a primary target of inflammation in many inflammatory arthropathies, including psoriatic arthritis (PsA). PsA is a chronic, progressive disease in the majority of patients (1); a polyarticular onset of PsA is associated with a more destructive course (2). PsA has some typical entities like the presence of dactylitis, enthesitis and involvement of distal interphalangeal joints. The diagnosis PsA is in the majority of cases easily made on the basis of the typical clinical signs and symptoms in combination with the presence of psoriatic lesions of skin and/or nails and often absence of rheumatoid factor.

The clinical spectrum of PsA is heterogeneous and the classification into 5 subgroups by Moll and Wright according to the phenotype (3) appears to be partially unreliable in early arthritis cohorts, with almost half of the patients classified as polyarticular in the early stages being reclassified as oligoarticular after 2 years (4). Therefore, new classifying criteria are being developed (5). In addition, there is a need for better understanding of the pathogenetic mechanisms involved in PsA.

Identification of specific features of the PsA synovial cell infiltrate and mediators of inflammation and destruction may provide insight into the pathogenesis and identify potential therapeutic targets. In the past a few studies have been performed that analyzed the characteristics of the synovium in PsA compared to RA (6-13), with variable results. Several confounding factors may have influenced the results of some of the previous work, the most important probably being differences in the use of antirheumatic drugs and corticosteroids between both groups, which can have a major influence on the features of synovial inflammation in RA (14-18) and PsA (19-23). Another confounding factor may be the selection of patients. Finally, computer assisted image analysis of stained sections is more sensitive to detect differences between groups than the semiquantitative evaluation that has been used in most previous studies. This is especially relevant for the evaluation of the expression of cytokines, adhesion molecules, and matrix metalloproteinases (MMPs) per cell, which cannot be quantified reliably by conventional microscopic evaluation (24). Therefore, we designed a comparative cohort study to investigate the features of cell infiltration, expression of pro-inflammatory cytokines, adhesion molecules, MMPs, and markers of angiogenesis in the synovium of PsA patients compared with RA. Both groups were matched for disease duration and use of medication, and stained sections were analyzed using sophisticated computer-assisted image analysis (25).
Material and methods

Patients
Nineteen patients with PsA were included. Characteristic psoriatic skin disease was present in all patients and the diagnosis psoriasis was confirmed by a dermatologist. The patients had either an oligo-articular (n = 8) or a poly-articular (n = 11) pattern of joint involvement, with or without spinal involvement. One patient with polyarticular joint involvement was classified as mutilans type. The diagnosis PsA was confirmed by two experienced rheumatologists (AWRvK and PPT). Twenty-four patients with RA served as a control group. These patients fulfilled the 1987 ACR-criteria for RA (26). The RA patients were matched for disease duration, and use of disease-modifying antirheumatic drugs (DMARDs). Patients used either methotrexate, the most commonly used DMARD in daily practice for the treatment of both RA and PsA, or no DMARD at the time of inclusion.
Clinical data on disease activity were collected at the time of the biopsy, and consisted of a tender joint count (TJC), swollen joint count (SJC), patient’s visual analog scale (VAS) for disease activity and measurement of acute phase reactants in the blood. All patients gave their informed consent before inclusion.

Arthroscopy and biopsy handling
The arthroscopy was performed in the most accessible clinically inflamed large joint (knee, wrist or ankle joint) under local anesthesia (27). To reduce sampling error an average of 15 synovial biopsies was obtained at each arthroscopy. All samples were embedded en bloc in Tissue Tec OCT (Miles, Elkhart, IN) and subsequently snap frozen. The frozen blocks were stored in liquid nitrogen until processed. Shortly before staining 5 μm sections were cut and mounted on glass slides (Star Frost; Knittelgläser, Braunschweig, Germany). The glass slides were sealed and stored at -80ºC until immunohistochemical analysis was performed in a single session.

Immunohistochemical staining
Serial sections were stained with the following mouse monoclonal antibodies (mAb): anti-CD3 (SK7, Becton-Dickinson, Mountain View, CA), anti-CD4 (SK3, Becton-Dickinson), anti-CD8 (DK25, Dako, Glostrup, Denmark), anti-CD38 (Leu-17, Becton Dickinson), anti-CD55 (Mab67, Serotec, Oxford, UK), anti-CD68 (EBM11, Dako), anti-CD163 (M0794, Dako), anti-granzyme B (GrB-7, Monosan, Uden, The Netherlands), anti-intercellular adhesion molecule 1 (ICAM-1) (CD54, BBIG-L1, R&D Systems Inc, Minneapolis, MN), anti-vascular cell adhesion molecule 1 (VCAM-1) (CD106, 51-10C9, Becton Dickinson), anti-E-selectin (BB1G-E4, R&D Systems Europe Ltd, Abingdon, UK), anti-MMP1 (36665.111 R&D), anti-MMP3 (10D6, R&D), anti-MMP13 (181-15A12,
Oncogene Research Products, Cambridge, MA), anti-tissue inhibitor metalloproteinase 1 (TIMP-1) (7-6C1, Oncogene Research Products), anti-vonWillebrand Factor (vWF) (F8/86, Dako), and anti-αvβ3 (23C6, Santa Cruz Biotechnology, Santa Cruz, CA), anti-vascular endothelial growth factor (VEGF) (C-1, Santa Cruz), anti-basic fibroblast growth factor (bFGF) (clone 6, BD Transduction Laboratories, Lexington, KY). Staining was also done with the following rabbit polyclonal antibodies: anti-TNF-α (IP-300, Genzyme, Cambridge, MA), anti-IL-1β (LP-712, Genzyme), anti-IL-6 (LP-716, Genzyme), and anti-IL-18 (2D3B6, MD Biosciences, Zürich, Switzerland).

Endogenous peroxidase activity was inhibited using 0.1% sodium azide and 0.3% hydrogen peroxide in phosphate buffered saline (PBS). Staining for cell markers and cytokines was performed as described previously (28). For control sections, the primary antibodies were omitted or irrelevant isotype-matched antibodies were applied. Following a primary step of incubation with mAb, bound antibody was detected according to a 3-step immunoperoxidase method. Alkaline phosphatase conjugated swine anti-rabbit antibodies (Dako), naphtol-AS-MX-phosphate, Fast Red Violet LB, and levamizole (Sigma, St Louis, MO) were used for detection of the rabbit polyclonal antibodies. Staining of MMPs and TIMP-1 was performed using biotinylated tyramide for amplification, as described previously (29). The primary antibodies were incubated for 60 minutes. Affinity-purified horseradish peroxidase (HRP)-conjugated goat anti-mouse (Dako) was added for 30 minutes, followed by subsequent incubation with biotinylated tyramide for 30 minutes and HRP-conjugated streptavidin for 30 minutes. HRP-activity was detected using hydrogen peroxide as substrate and amino ethylcarbazole (AEC) (Sigma) as dye. Slides were counterstained with Mayer’s hematoxilin (Merck, Darmstadt, Germany) and, after washing with distilled water, mounted in Kayser’s glycerol gelatine (Merck).

**Microscopic analysis**

The coded sections stained for CD3 (T lymphocytes), CD4 and CD8 lymphocytes, CD38 (plasma cells), CD55 (fibroblast-like synoviocytes), CD68 (macrophages), CD163 (subset of macrophages), granzyme B (cytotoxic cells), ICAM-1, VCAM-1, E-selectin, MMP1, MMP3, MMP13, TIMP1, vWF, αvβ3, VEGF, bFGF, TNF-α, IL-1β, IL-6 and IL-18 were analyzed in a random order by computer-assisted image analysis, as described previously in detail (25). Briefly, 3 separate representative regions were chosen for evaluation of each section. Six consecutive high-power fields (HPFs) from each region were captured and digitized, resulting in a total of 18 HPFs per section. We have previously shown that this results in a representative measurement. The HPF images were analyzed using the Qwin analysis system (Leica, Cambridge, UK). Additionally, vascularity was also separately scored using a semiquantitative vessel score to evaluate the VWF stained sections as described previously in detail (30).
Statistics
SPSS 11.5.1 for Windows (SPSS, Chicago, IL, USA) was used for statistical analysis. The Mann-Whitney U test was used for comparison of the various markers in synovial tissue of RA versus PsA. Results are expressed as mean ± standard error of the mean.

Results

Clinical features
The clinical and demographic data of the patients are shown in Table 1. The two groups were on average comparable with regard to disease duration and DMARD use. The PsA patients had a mean disease duration of 10 years (range 2 months - 25 years), the mean disease duration of RA patients was 9 years (range 3 months - 25 years). Four PsA patients (21%) and 6 RA patients (25%) had a disease duration of less than 1 year. Eleven PsA patients (58%) and thirteen RA patients (54%) were being treated with methotrexate (MTX) and two of these patients (one in each group) also used prednisone 10 mg/day. The other patients (8 PsA, 42% and 11 RA, 46%) were not being treated with a DMARD or corticosteroids. Thus, all patients used either MTX or no DMARD at the time of synovial biopsy (other DMARDs were not permitted to prevent bias).

As expected, the RA group comprised more women (17 RA, 71% and 7 PsA, 37%) and more RF-positive patients (18 RA, 75% and 1 PsA, 5%). RA patients had on average a higher swollen joint count (28 SJC in RA: 14.5 ± 1.6; PsA 7.6 ± 1.8 [mean ± s.e.m.], p =

Table 1 Clinical and demographic data of the patients

<table>
<thead>
<tr>
<th></th>
<th>PsA n=19</th>
<th>RA n=24</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Female (%)</td>
<td>7 (37%)</td>
<td>17 (71%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Mean age (years, range)</td>
<td>47.0 (26-72)</td>
<td>54.4 (40-76)</td>
<td>0.047</td>
</tr>
<tr>
<td>Mean disease duration (months, range)</td>
<td>122.8 (2-300)</td>
<td>106.0 (3-300)</td>
<td>n.s.</td>
</tr>
<tr>
<td>IgM-rheumatoid factor positive (%)</td>
<td>1 (5%)*</td>
<td>18 (75%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Methotrexate use (%)</td>
<td>11 (58%)</td>
<td>13 (54%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Prednisone use (%)</td>
<td>1 (5%)</td>
<td>1 (4%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>28 TJC (mean ± s.e.m.)</td>
<td>9.1 ± 1.9</td>
<td>12.6 ± 1.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>28 SJC (mean ± s.e.m.)</td>
<td>7.6 ± 1.8</td>
<td>14.5 ± 1.6</td>
<td>0.005</td>
</tr>
<tr>
<td>VAS disease activity (mm, mean ± s.e.m.)</td>
<td>51.1 ± 6.4</td>
<td>51.3 ± 4.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>ESR (mm/hr, mean ± s.e.m.)</td>
<td>34.5 ± 4.2</td>
<td>49.1 ± 6.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>CRP (mg/l, mean ± s.e.m.)</td>
<td>20.5 ± 3.4</td>
<td>41.2 ± 7.9</td>
<td>0.019</td>
</tr>
</tbody>
</table>

* IgM-rheumatoid factor was borderline positive

TJC, tender joint count; SJC, swollen joint count; VAS, visual analogue scale; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; n.s., not significant; s.e.m., standard error of the mean
Table 2 The cell infiltrate and expression of mediators of inflammation and joint degradation in synovial tissue of patients with PsA and RA

<table>
<thead>
<tr>
<th>Cell populations</th>
<th>PsA n=19</th>
<th>RA n=24</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3 T lymphocytes</td>
<td>109 ± 56</td>
<td>258 ± 61</td>
<td>0.022</td>
</tr>
<tr>
<td>CD4 T lymphocytes†</td>
<td>68 ± 22</td>
<td>144 ± 40</td>
<td>n.s.</td>
</tr>
<tr>
<td>CD8 T lymphocytes†</td>
<td>284 ± 47</td>
<td>480 ± 93</td>
<td>n.s.</td>
</tr>
<tr>
<td>CD38 plasma cells</td>
<td>206 ± 93</td>
<td>471 ± 132</td>
<td>n.s.</td>
</tr>
<tr>
<td>CD55 fibroblast-like synoviocytes</td>
<td>532 ± 93</td>
<td>346 ± 83</td>
<td>n.s.</td>
</tr>
<tr>
<td>CD68 macrophages (total)</td>
<td>648 ± 104</td>
<td>771 ± 102</td>
<td>n.s.</td>
</tr>
<tr>
<td>CD68 macrophages lining</td>
<td>223 ± 30</td>
<td>276 ± 44</td>
<td>n.s.</td>
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<tr>
<td>CD68 macrophages sublining</td>
<td>481 ± 85</td>
<td>550 ± 90</td>
<td>n.s.</td>
</tr>
<tr>
<td>CD163 macrophages</td>
<td>200 ± 34</td>
<td>342 ± 55</td>
<td>n.s.</td>
</tr>
<tr>
<td>Granzyme B (cytotoxic T cells)</td>
<td>32 ± 20</td>
<td>145 ± 101</td>
<td>n.s.</td>
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### Adhesion molecules

<table>
<thead>
<tr>
<th>Adhesion molecules</th>
<th>PsA n=19</th>
<th>RA n=24</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICAM-1</td>
<td>84,339 ± 20,153</td>
<td>151,306 ± 22,674</td>
<td>n.s.</td>
</tr>
<tr>
<td>VCAM-1</td>
<td>32,580 ± 7,115</td>
<td>23,600 ± 4,576</td>
<td>n.s.</td>
</tr>
<tr>
<td>E-selectin</td>
<td>11,964 ± 4,920</td>
<td>16,401 ± 3,437</td>
<td>n.s.</td>
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</table>

### Matrix metalloproteinases

<table>
<thead>
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<th>PsA n=19</th>
<th>RA n=24</th>
<th>P-value</th>
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<tbody>
<tr>
<td>MMP1</td>
<td>103 ± 54</td>
<td>128 ± 68</td>
<td>n.s.</td>
</tr>
<tr>
<td>MMP3</td>
<td>50,101 ± 15,418</td>
<td>32,045 ± 15,410</td>
<td>n.s.</td>
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<tr>
<td>MMP13</td>
<td>7 ± 3</td>
<td>9 ± 4</td>
<td>n.s.</td>
</tr>
<tr>
<td>TIMP</td>
<td>1,009 ± 219</td>
<td>5,206 ± 2720</td>
<td>n.s.</td>
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### Markers for angiogenesis

<table>
<thead>
<tr>
<th>Markers for angiogenesis</th>
<th>PsA n=19</th>
<th>RA n=24</th>
<th>P-value</th>
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<tr>
<td>VWF</td>
<td>73,608 ± 11,239</td>
<td>100,233 ± 11,519</td>
<td>n.s.</td>
</tr>
<tr>
<td>αvβ3</td>
<td>503 ± 110</td>
<td>376 ± 107</td>
<td>n.s.</td>
</tr>
<tr>
<td>VEGF</td>
<td>3,691 ± 1,540</td>
<td>2,754 ± 704</td>
<td>n.s.</td>
</tr>
<tr>
<td>bFGF</td>
<td>19 ± 14</td>
<td>60 ± 37</td>
<td>n.s.</td>
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### Cytokines

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>PsA n=19</th>
<th>RA n=24</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α</td>
<td>43,256 ± 19,217</td>
<td>46,054 ± 11,968</td>
<td>n.s.</td>
</tr>
<tr>
<td>IL-1β</td>
<td>5,990 ± 1,291</td>
<td>7,228 ± 2,778</td>
<td>n.s.</td>
</tr>
<tr>
<td>IL-6</td>
<td>1,086 ± 244</td>
<td>1,180 ± 290</td>
<td>n.s.</td>
</tr>
<tr>
<td>IL-18</td>
<td>458 ± 191</td>
<td>453 ± 137</td>
<td>n.s.</td>
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</table>

† PsA n=17, RA n=20

All values represent the mean ± standard error of the mean (s.e.m.). Cellular markers (CD3, CD4, CD8, CD38, CD55, CD68, CD163, granzyme B) reflect the total number of positive cells per mm², all other markers are presented as integrated optical density (IOD). PsA = psoriatic arthritis, RA = rheumatoid arthritis, n.s. = not significant, ICAM = intercellular adhesion molecule, VCAM = vascular cell adhesion molecule, MMP = matrix metalloproteinase, TIMP = tissue inhibitor metalloproteinase, VWF = vonWillebrand factor, VEGF = vascular endothelial growth factor, bFGF = basic fibroblast growth factor, TNF-α = tumour necrosis factor alpha, IL = interleukin.
and CRP (RA 41.2 ± 7.9; PsA 20.5 ± 3.4 mg/l [mean ± s.e.m., p = 0.019]). The fact that on average more joints were affected in the RA cohort may be reflected in the levels of acute phase reactants.

**Immunohistochemical features**
The results of the immunohistochemical analysis are shown in Table 2 and Figure 1. All biopsies were taken from an actively inflamed joint, shown by pain and swelling, as stated before. The synovial infiltrate of PsA and RA patients was comparable with regard to the number of fibroblast-like synoviocytes, intimal macrophages, and sublining macrophages. T cell numbers were significantly lower in the synovium of PsA patients. Consistent with this observation, both CD4 and CD8 T cells tended to be lower in PsA, but the differences did not reach statistical significance. It should be noted that CD4 is not only expressed by CD4+ T cells, but it may also be expressed by macrophages. The number of plasma cells also tended to be lower in PsA, although this difference did not reach statistical significance, possibly due to the relatively small number of patients in this type of studies. Of interest, the expression of the pro-inflammatory cytokines TNF-α, IL-1β, IL-6 and IL-18 was as high in PsA as in RA synovium. No differences between the groups were detected for MMP-1, MMP-3, MMP-13 and TIMP, or the adhesion molecules ICAM-1, VCAM-1 and E-selectin. Furthermore, results between the 2 groups were comparable for the vascular markers VEGF, vWF, αvβ3 and bFGF. This was confirmed by the semiquantitative vessel analysis on the VWF stained sections; the scores were also comparable for RA and PsA synovium. When analysis was performed between patients with oligo- versus polyarthritis, no other significant differences or trends were detected (data not shown). Within the PsA group additional analyses were performed: there were no differences between oligo- and polyarticular patients, except for IL-1β which was higher in polyarticular group (p = 0.047); no major differences between MTX users and non-MTX users were found, except for a higher MMP1 expression in the MTX users (p = 0.028).

**Discussion**
This paper is the first to study the features of the synovial infiltrate of PsA in comparison with RA taking into account disease duration and use of medication, using sophisticated digital image analysis. Interestingly, the only significant difference detected between the two groups in this study was a lower T cell count in PsA synovium. This is consistent with observations in 2 previous studies (11;13), and is perhaps remarkable because psoriasis and PsA is thought of as a T cell driven disease. The lower number of T cells in PsA synovium
Detailed analysis of the cell infiltrate

Figure 1. Synovial tissue immunohistology in patients with PsA and RA
Representative sections of staining with monoclonal antibodies for CD3, CD68, TNF-α, IL-18 and vonWillebrandfactor (vWF) are shown (magnification 400x)
Chapter 2

does not mean, however, that these cells are not important in pathogenesis: a subset of specific T cells might be sufficient to promote the inflammatory process and regulatory T cells may have anti-inflammatory effects. A trend towards a higher number of plasma cells in RA synovium was observed, but this difference was not statistically significant. Only one earlier study (10) showed a significantly higher number of plasma cells in RA compared to SpA synovium, but this could not be confirmed in a larger study by the same group (12). The most striking feature of both RA and PsA synovium is the abundant overexpression of pro-inflammatory cytokines, especially TNF-α, which was equally high in both groups. No other significant differences between PsA and RA synovium were found in synovial cell infiltrate, or in the expression of MMPs, adhesion molecules or vascularity. A few previous studies have examined the features of PsA synovium with variable results. Some studies suggested that the PsA synovium is characterized by less pronounced lining layer hyperplasia and fewer monocytes/macrophages in PsA synovium (6;11), but both findings could not be confirmed in another study that analyzed different forms of spondyloarthopathies together (10). One group found less T and B cells in PsA synovium (10), but this was not found in the other studies (6;11). The fact that the synovial tissue was collected in different ways and the use of antirheumatic medication may account for some of the observed differences (6;10;11).

Interestingly, recent studies suggested that the presence of major histocompatibility complex (MHC)-human cartilage gp39 peptide complexes in the synovium could be specific for RA (12) and that presence of p53 mutation was higher in RA than in PsA synovium (13). These data suggest that the etiology may be distinct between RA and PsA, although different processes may lead to the activation of common final pathways and similarities in synovial infiltrate in established disease.

Increased vascularity has been reported in both psoriatic skin lesions and synovial tissue. In the dermis of psoriatic skin an abundance of dilated and tortuous blood vessels is present (32). This increased dermal vascularity is believed to be mediated by angiogenetic factors (33). Several authors have reported that PsA synovium is characterized by an increase in macroscopically tortuous blood vessels, and this is more pronounced - but not exclusive - in PsA than in RA synovium (6-8;34). Consistent with the vascular abnormalities, overexpression of VEGF, which is involved in angiogenesis, has been reported in both psoriatic skin (35) and PsA synovial tissue (8;9). However, the increased vascularity in PsA compared to RA was not confirmed in all studies (11). In the present study hypervascularity could be detected in both PsA and RA. There were trends toward increased numbers of blood vessels and expression of VEGF in PsA, but the difference with RA did not reach statistical significance, possibly due to the relatively small number of patients. Blood vessels in psoriatic skin and PsA synovium express a variety of adhesion molecules, such as ICAM-1, VCAM-1 and E-selectin (6;36). These adhesion molecules are involved
in leucocyte adhesion and penetration through the endothelium. TNF-α has been shown to promote the expression of adhesion molecules as well as angiogenesis (37), while blockade of TNF-α resulted in a decrease in the expression of angiogenetic factors and adhesion molecules in psoriatic skin (22) and PsA synovium (22;23;38). In this study abundant expression of adhesion molecules was found equally in RA and PsA synovium.

The degradation of cartilage and bone, resulting in structural (radiological) damage in inflammatory arthropathies, is believed to be mediated in part by MMPs. MMPs have been shown to be abundantly present in both RA (29;31) and PsA synovium (39). It has been suggested that high MMPs expression is associated with more destructive disease (39;40). In the present study there was high expression of especially MMP3, which was comparable for RA and PsA. This is in line with recent clinical studies, which showed that joint destruction in PsA is progressive in almost 50% of PsA patients from an early arthritis clinic showing radiological damage 2 years after first presentation (1) and that the degree of radiological damage in PsA is comparable with RA (41).

Pro-inflammatory cytokines are important mediators of systemic and local inflammation, and abundant expression of IL-1 and TNF-α has been shown in psoriatic skin lesions (42), as well as synovial tissue of both RA and PsA patients (11;39;43). The success of several TNF-α blocking therapies in psoriasis and PsA (44-49) and in RA (50-53) has proven the importance of TNF-α in these inflammatory diseases. In this study there was equally high expression of TNF-α in RA compared to PsA synovium. High expression of IL-6, IL-1β and to a lesser extent IL-18 in RA and PsA synovium has also been found in the present study. These data support the view that blockade of not only TNF-α, but also IL-1β, IL-6 and IL-18 might be effective in PsA.

Consistent with previous reports, there were large differences in synovial infiltrate between individual patients within both groups. This may be caused by heterogeneity of what we diagnose clinically as being RA or PsA and may point to the presence of certain disease-subsets or pathophysiological differences, as has recently been suggested for RA (54).

There were no clear-cut differences between patients who used MTX and those who did not, which is in line with a previous cross sectional study (12). These data show that the lack of clinical response to MTX is reflected by persistent synovial inflammation.

In conclusion, although RA and PsA are clinically separate diseases, with a different etiology, the present study showed mainly similarities in the synovial infiltrate of two well matched cohorts of RA and PsA patients. This may be explained by the fact that different pathophysiological processes may lead to the activation of final common pathways. This study demonstrates increased pro-inflammatory cytokine production in PsA synovium comparable with results obtained in RA. These data support the view that in addition to TNF-α blockade, targeted therapies against other pro-inflammatory cytokines might be effective in PsA as well.
Acknowledgements
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Reference List


Detailed analysis of the cell infiltrate


