A prospective, randomised, placebo-controlled study to identify biomarkers associated with active treatment in psoriatic arthritis: effects of adalimumab treatment on synovial tissue

A W R van Kuijk, D M Gerlag, K Vos, G Wolbink, M de Groot, M A de Rie, A H Zwinderman, B A C Dijkmans, P P Tak

ABSTRACT

Objective: To determine which of the changes in synovial tissue correlates best with clinical response associated with effective therapy (adalimumab) to facilitate the planning of future studies with therapeutic agents for psoriatic arthritis (PsA).

Methods: A total of 24 patients with active PsA were randomised to receive adalimumab (n = 12) or placebo (n = 12) for 4 weeks. Synovial biopsies were obtained before and after 4 weeks of treatment. Immunohistochemical analysis was performed to characterise the cell infiltrate, expression of cytokines and matrix metalloproteinases (MMPs) and vascularity. Sections were analysed by digital image analysis. Statistical analysis was performed using covariance analysis.

Results: The mean Disease Activity Score in 28 joints (DAS28) after 4 weeks was 1.92 units lower (95% confidence interval (CI) 1.07 to 2.77) after adalimumab therapy compared with placebo. Paired pretreatment and post-treatment synovial samples were available from 19 patients. Many cell types were reduced after adalimumab treatment compared to placebo. After applying a ranked analysis of covariance (ANCOVA) model to correct for baseline imbalances, a significant effect of treatment was observed on CD3-positive cells: there was a median reduction of 248 cells/mm² after adalimumab versus placebo treatment (p = 0.035). In addition, the expression of MMP13 was significantly reduced after active treatment: the integrated optical density (IOD)/mm² was 18 190 lower after adalimumab treatment as compared to placebo (p = 0.033).

Conclusion: Adalimumab therapy in PsA is associated with a marked reduction in T cell infiltration and MMP13 expression in synovial tissue, suggesting that these parameters could be used as biomarkers that are sensitive to change after active treatment in small proof of concept studies in PsA.

Because the synovium is a primary site of inflammation, there is increasing interest in studying the synovial tissue (ST) of patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA). In addition to the use of synovial biopsies for diagnostic purposes and pathogenetic studies, serial synovial biopsies have been used to evaluate the effects of novel treatments. This approach has been proposed to screen for efficacious novel antirheumatic interventions.

PATIENTS AND METHODS

Patients

Patients with PsA fulfilling the ClASsification of Psoriatic ARthritis (CASPAR) criteria for PsA, aged 18–80 years, were included into the study after written informed consent was obtained. Patients had to have active disease at time of enrolment, defined by the presence of at least 2 tender and 2 swollen joints out of the 68 joints for tenderness and 66 joints for swelling assessed. One of the swollen joints had to be a knee, ankle or wrist joint that was accessible for arthroscopy. Patients were allowed to use concomitant methotrexate, which had to be stable for at least 28 days. They were not allowed to use any other disease-modifying antirheumatic drugs (DMARDs).
1 month prior to baseline. For leflunomide, a 2-month washout period was required. Use of non-steroidal anti-inflammatory drugs was allowed, provided that the dose had been stable for at least 28 days. Parenteral, intra-articular or oral use of cortico-
teroids within 28 days before enrolment into the study was not allowed. Topical treatments for psoriasis were not allowed 14 days prior to baseline, with the exception of low potency (class I) topical steroids to be used on scalp, palms, groin and/or soles only. Other exclusion criteria were the use of any biological agent or investigational drug within the previous 6 months and having a history of tuberculosis or a malignancy in the past 10 years. Infection with HIV, hepatitis B or C virus was excluded via serological testing. Patients with another serious infection within 4 weeks before baseline, or a significant history of cardiac, renal, neurological or metabolic disease were excluded from the study. Female patients who were pregnant or breastfeeding were not allowed to enter the study.

**Study protocol**

This was a randomised, double-blind, placebo-controlled, single centre study performed at the Academic Medical Center of the University of Amsterdam. The study protocol was approved by the Medical Ethics Committee of the institute and all patients signed informed consent before the start of the study. They had a complete medical history taken and underwent a full physical examination, including joint assessment by a rheumatologist and skin assessment by a dermatologist. Routine clinical chemistry, haematology and urinalysis assessments were performed, as well as a chest x-ray and purified protein derivative (PPD) skin test prior to baseline to exclude patients with (latent) tuberculosis. Eligible patients were included into the study within 2 weeks after screening, and were seen at baseline, week 4 and week 12.

Clinical assessment included a 68 joint count for tenderness and 66 joint count for swelling, a psoriasis area and severity index (PASI), a subject's visual analogue scale (VAS) score for possible pain), a subject's and investigator's global disease index (PASI), a subject's visual analogue scale (VAS) score for possible pain), a subject's and investigator's global disease index (PASI), a subject's visual analogue scale (VAS) score for possible pain). The PASI was calculated using the Psoriasis Area and Severity Index (PASI) formula. PASI is a measure of psoriasis severity and is calculated as the sum of the product of the severity of each of the six body areas (head, neck, trunk, upper extremities, lower extremities, and arms) with the percentage body surface area (BSA) occupied by psoriasis in each area. Clinical assessment also included the Health Assessment Questionnaire (HAQ) for functional (dis)ability. Furthermore, C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR) were determined. A blinded, independent assessor performed the clinical evaluation. The 28-joint Disease Activity Score (DAS28), which has been shown to discriminate between active drug and placebo in clinical trials in PsA, was chosen to monitor changes in clinical disease activity after therapy. In addition, the American College of Rheumatology (ACR) criteria for improvement were assessed.

**Treatment**

Patients were randomised to receive subcutaneous injections with either adalimumab 40 mg or matching placebo at baseline (day 1) and day 15 in a 1:1 ratio. After the second arthroscopy all patients received adalimumab 40 mg every other week.

**Arthroscopy**

A needle arthroscopy of an actively inflamed joint (knee, ankle, or wrist) was performed under local anaesthesia in all patients before treatment and 28 days after initiation of study medication from the same joint. The procedures for needle arthroscopy and tissue processing were performed as described previously in detail. In summary, to minimise sampling error biopsies were taken from six or more sites of the joint during each procedure. ST biopsy specimens were immediately embedded in TissueTek OCT (Miles Diagnostics, Elkhart, Indiana, USA), snap frozen by immersion in methylbutane (−80°C) and stored in liquid nitrogen until further processing. Before staining, coded ST samples were cut with a cryostat (5 µm), fixed with acetone and endogenous protease activity was blocked with 0.3% hydrogen peroxide.

**Immunohistochemical analysis**

Serial sections were stained with the following antibodies: anti-
CD3 (SK7; BD Biosciences, San Jose, California, USA), anti-
CD4 (SK3; BD Biosciences), anti-CD8 (C8/114B; Dako, Glostrup, Denmark), anti-CD15 (C3D-1; Dako), anti-CD22 (CLB-B-ly/1,6B11; Sanquin, Amsterdam, The Netherlands), anti-CD38 (1,6B11; BD Biosciences; anti-CD55 (clone 67; Serotech, Oxford, UK), anti-CD68 (EMB11; Dako) and anti-CD163 (5C6 FAT; Bachem Peninsula Laboratories, San Carlos, California, USA) to analyse the cell infiltrate. Antibodies against myeloid-related protein (MRP)3 (B-5C2; BMA Biomedicals, Augst, Switzerland) and MRP14 (S64.48; BMA Biomedicals) were used to detect infiltrating monocytes/macrophages in an early stage of differentiation.

For immunohistochemical analysis of cytokine expression, interleukin (IL)1β (2D8; Immunokontakt, Stockholm, Sweden) and IL6 (B-E8; Invitrogen, Breda, The Netherlands) were stained. Furthermore, von Willebrand factor (vWF) (F8/86; Dako) was used as a marker to detect blood vessels. Additionally, the expression of matrix metalloproteinase (MMP)3 (MAB1359; Bio-Connect, Huisgen, The Netherlands) and MMP13 (VIIIA2; Oncogene, Cambridge, Massachusetts, USA) was determined.

Sections with non-assessable tissue, defined by the absence of an intimal lining layer, were excluded from analysis. Staining for cellular markers was performed using a three-step immunoperoxidase method as previously described. For the determination of cytokine expression, biotinylated tyramine (BT) was used for amplification after incubation with the secondary antibody and incubation with streptavidin-horseradish peroxidase (HRP) conjugate was followed by detection with aminomethylcarbazole (AEC), as previously described. For control sections, the primary antibodies were omitted or irrelevant antibodies were applied.

**Digital image analysis**

After immunohistochemical staining, all sections were coded and randomly analysed by computer-assisted digital image analysis (DIA). For all markers, 18 high-power fields were analysed. CD68 and CD163 expression (macrophage markers) were analysed separately in the intimal lining layer and the synovial sublining. The images of the high-power fields were analysed using the Qwin analysis system (Leica, Cambridge, UK), as described in detail previously.

**Statistical analysis**

SPSS for Windows (V 12.0.2; SPSS, Chicago, Illinois, USA) was used for statistical analysis. Baseline characteristics between the two groups were compared using a Student t test for normal distributed data and a Mann–Whitney U test for variables with a very skewed distribution. Correlations of changes in clinical parameters and immunohistochemical markers were analysed with Spearman rank correlation. Additionally, each of the end points was analysed using an analysis of covariance model (ANCOVA) after rank transformation to correct for baseline
differences. The model included terms for treatment as a fixed effect and the baseline measurement as a covariate. The aim was to assess the treatment difference.

RESULTS

Demographic features
A total of 24 patients (15 men, 9 women) were included in the trial, 12 patients were randomised to receive adalimumab and 12 placebo treatment. The mean age was 42.8 (range 21–61) years for the patients in the adalimumab group and 47.2 (25–78) years in the placebo group (table 1). The mean PsA disease duration was comparable in both groups. Concomitant methotrexate was used by seven patients in the adalimumab group and five patients in the placebo group in a comparable dose (mean 18.2 mg/week and 19.0 mg/week, respectively). None of the patients had used tumour necrosis factor (TNF) inhibitors in the past. Most patients (n = 16) had polyarticular involvement according to the Moll and Wright classification, a minority had an oligoarticular phenotype (n = 7) or predominantly distal interphalangeal involvement (n = 1). Two of the patients with polyarticular disease also had axial involvement. The PsA phenotypes were not equally distributed between the 2 groups, with the placebo group harbouring more patients with polyarticular disease than the adalimumab group (10 versus 6). Despite this difference, the patient groups were comparable with regard to disease activity markers, such as CRP and DAS28.

All patients received the two injections with study medication according to the protocol. Overall study medication was well tolerated. No infections other than common cold were reported in the 4-week study period. One patient in the placebo group complained of more pain in her ankle after the first arthroscopy, but could undergo the second arthroscopy.

Clinical response
As anticipated, a markedly positive effect of adalimumab treatment was seen on the DAS28,23 which was 1.92 units lower compared to placebo after 4 weeks of treatment (95% confidence interval (CI) 1.07 to 2.77, p<0.001) (fig 1). The mean PASI score after 4 weeks of adalimumab treatment was 2.61 points lower compared to placebo (95% CI −0.08 to 5.30, p = 0.056). The mean PASI decreased from 5.89 (4.25) to 4.01 (2.49) in the adalimumab group, whereas there was a slight increase in the placebo group from 4.72 (2.55) to 5.45 (4.05).

At 4 weeks the ESR and CRP levels were respectively 58% (95% CI 30% to 86%, p = 0.001) and 57% (95% CI 29% to 84%, p<0.001) lower after adalimumab treatment than after placebo treatment. The mean ESR was reduced from 24.2 (21.7) mm/h to 8.1 (7.5) mm/h after adalimumab treatment, and the mean CRP from 19.9 (25.7) mg/litre to 2.1 (1.4) mg/litre, whereas after placebo treatment there was no clear cut change: ESR from 72.8 (55–91) mm/h and CRP from 9.9 (9.1) to 9.2 (10.0) mg/litre, respectively.

Immunohistochemical analysis
Paired pretreatment and post-treatment synovial samples from 19 patients were available for analysis. The pretreatment ST biopsies of three patients did not contain an intimal lining layer and therefore did not pass the quality control tests. Due to an unfortunate freezer accident ST biopsies of two other patients were lost. The remaining 19 paired ST samples were analysed, 10 were in the adalimumab group and 9 in the placebo group. The results of this analysis are shown in table 2.

Table 1 Demographic and clinical features of the 24 patients with psoriatic arthritis (PsA) enrolled in the study

<table>
<thead>
<tr>
<th></th>
<th>Adalimumab (n = 12)</th>
<th>Placebo (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>42.8 (21–61)</td>
<td>47.2 (25–78)</td>
</tr>
<tr>
<td>No. men/women</td>
<td>9/3</td>
<td>6/6</td>
</tr>
<tr>
<td>No. (%) currently MTX</td>
<td>7 (58)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>Dose MTX, mg/week</td>
<td>18.2 (10–25)</td>
<td>19.0 (15–25)</td>
</tr>
<tr>
<td>PsA disease duration, years</td>
<td>5.5 (0.4–14.1)</td>
<td>8.4 (1.9–18.2)</td>
</tr>
<tr>
<td>No. (%) RF positive</td>
<td>2 (17)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>No. (%) anti-CCP positive</td>
<td>1 (8)</td>
<td>0</td>
</tr>
<tr>
<td>No. (%) erosive</td>
<td>7 (58)</td>
<td>5 (42)</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>24.2 (4–66)</td>
<td>22.4 (3–66)</td>
</tr>
<tr>
<td>CRP, mg/litre</td>
<td>19.9 (2.3–81.6)</td>
<td>9.9 (1.3–26.7)</td>
</tr>
<tr>
<td>DAS28 score</td>
<td>4.67 (3.0–5.78)</td>
<td>5.07 (2.21–6.83)</td>
</tr>
<tr>
<td>Patient global assessment of disease activity (VAS 0–100 mm)</td>
<td>73 (45–94)</td>
<td>62.8 (18–92)</td>
</tr>
<tr>
<td>Patient assessment of pain (VAS 0–100 mm)</td>
<td>72.8 (55–91)</td>
<td>67.4 (11–89)</td>
</tr>
<tr>
<td>PASI</td>
<td>5.89 (0–14.0)</td>
<td>4.72 (0–7.0)</td>
</tr>
</tbody>
</table>

All values are mean (range) except where indicated otherwise.

CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; ESR, erythrocyte sedimentation rate; MTX, methotrexate; PASI, psoriasis area and severity index; RF, rheumatoid factor; VAS, visual analogue scale.

Figure 1 Effect of treatment with either adalimumab or placebo on the individual 28-joint Disease Activity Score (DAS28). A marked reduction is seen after adalimumab treatment for 4 weeks.
Despite randomisation, there were clear differences at baseline for several synovial markers between adalimumab and placebo groups, as shown in table 2 (adalimumab and placebo before). Most of these baseline differences were not statistically significant except for the number of CD8-positive cells, CD163-positive cells and MMP3 expression, which were significantly higher in the adalimumab group. A marked reduction was observed in most cell types after active treatment. The effect after adalimumab was significant for CD3-positive T cells: there was a median decrease of 248 cells/mm$^2$ after adalimumab compared to placebo, but the differences were not statistically significant. There was considerable reduction of expression of MMP3 and MMP13 in the adalimumab group as compared to placebo. The expression of MMP15 was decreased with 9188 (8653) IOD/mm$^2$ (median (SE)) after adalimumab treatment as compared to an increase of 9002 (5469) IOD/mm$^2$ after placebo. When ANCOVA was applied to correct for baseline imbalances, the effect of treatment after 4 weeks was significant only for the number of CD3-positive cells ($p = 0.035$) and MMP13 expression ($t = 0.035$).

### Table 2: Median values (standard error (SE) of the median) for the synovial biomarkers before treatment and median reduction (SE of the median) after 4 weeks of treatment in each group and p value of the ranked analysis of covariance (ANCOVA) applied

<table>
<thead>
<tr>
<th></th>
<th>Adalimumab</th>
<th>Placebo</th>
<th>ANCOVA p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>Reduction</td>
<td>Before</td>
</tr>
<tr>
<td>CD68 total</td>
<td>1927 (133)</td>
<td>435 (197)</td>
<td>835 (516)</td>
</tr>
<tr>
<td>CD68L</td>
<td>378 (28)</td>
<td>236 (61)</td>
<td>177 (140)</td>
</tr>
<tr>
<td>CD68SL</td>
<td>1423 (262)</td>
<td>147 (59)</td>
<td>753 (628)</td>
</tr>
<tr>
<td>CD163 total</td>
<td>1243 (208)</td>
<td>765 (309)</td>
<td>480 (178)</td>
</tr>
<tr>
<td>CD163L</td>
<td>426 (203)</td>
<td>167 (72)</td>
<td>68 (8)</td>
</tr>
<tr>
<td>CD163SL</td>
<td>1081 (155)</td>
<td>674 (265)</td>
<td>468 (206)</td>
</tr>
<tr>
<td>CD3</td>
<td>533 (36)</td>
<td>212 (230)</td>
<td>144 (66)</td>
</tr>
<tr>
<td>CD4</td>
<td>1130 (265)</td>
<td>386 (278)</td>
<td>184 (21)</td>
</tr>
<tr>
<td>CD8</td>
<td>177 (103)</td>
<td>103 (72)</td>
<td>27 (7)</td>
</tr>
<tr>
<td>CD15</td>
<td>35 (13)</td>
<td>22 (8)</td>
<td>13 (1)</td>
</tr>
<tr>
<td>CD22</td>
<td>306 (167)</td>
<td>210 (145)</td>
<td>44 (7)</td>
</tr>
<tr>
<td>CD38</td>
<td>15 (11)</td>
<td>4 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>CD55</td>
<td>660 (218)</td>
<td>85 (145)</td>
<td>681 (30)</td>
</tr>
<tr>
<td>vWF</td>
<td>137 853 (42 944)</td>
<td>47 107 (25 755)</td>
<td>87 300 (8092)</td>
</tr>
<tr>
<td>IL1β</td>
<td>515 740 (200 575)</td>
<td>272 189 (74 412)</td>
<td>620 179 (485 911)</td>
</tr>
<tr>
<td>IL6</td>
<td>169 164 (181 653)</td>
<td>39 063 (49 052)</td>
<td>38 671 (12 175)</td>
</tr>
<tr>
<td>MRP8</td>
<td>1483 (1550)</td>
<td>1313 (1644)</td>
<td>396 (139)</td>
</tr>
<tr>
<td>MRP14</td>
<td>3976 (1380)</td>
<td>2814 (2339)</td>
<td>1837 (1360)</td>
</tr>
<tr>
<td>MMP3</td>
<td>247 021 (101 010)</td>
<td>138 679 (99 428)</td>
<td>17 680 (1913)</td>
</tr>
<tr>
<td>MMP13</td>
<td>25 822 (15 822)</td>
<td>9188 (8653)</td>
<td>14 673 (10 350)</td>
</tr>
</tbody>
</table>

CD68$^+$ macrophages (total), CD68$^+$ macrophages in the intimal lining layer (L) and in the synovial sublining (SL), CD163$^+$ cells (subset of macrophages) (total), CD163$^+$ cells in L and SL, CD3$^+$ T cells, CD4$^+$ and CD8$^+$ T cells, CD15$^+$ neutrophils, CD22$^+$ B cells, CD38$^+$ plasma cells and CD55$^+$ fibroblast-like synoviocytes are provided as cells/mm$^2$.

Expression of von Willebrand Factor (vWF), interleukin (IL1β), IL6, myeloid related protein (MRP8, MRP14), matrix metalloproteinase (MMP3, MMP13, MMP3, MMP13, are provided as median (SE of the median)) integrated optical density (IOD)/mm$^2$. Differences before treatment between the groups were statistically significant for CD163$^+$ cells (total, L and SL), CD68$^+$ cells and MMP3 expression, which were higher in the adalimumab group. After ANCOVA was applied to correct for baseline imbalances, the effect of treatment after 4 weeks was significant only for the reduction in the number of CD3-positive cells ($p = 0.035$) and MMP13 expression ($t = 0.035$).

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**Correlation between clinical improvement and changes in synovial biomarkers**

For the cellular markers clinical improvement was strongly correlated with a decrease in CD3-positive T cells (Spearman $\rho = 0.644$, $p = 0.003$), CD4-positive cells ($\rho = 0.649$, $p = 0.003$) and MRFP8-positive macrophages ($\rho = 0.561$, $p = 0.012$) (fig 3), but there was no statistically significant correlation with changes in other cell types. There was also a strong correlation between clinical improvement and the reduction of MMP15 ($\rho = 0.619$, $p = 0.005$) (fig 3) and MMP3 ($\rho = 0.560$, $p = 0.013$).

**DISCUSSION**

This placebo-controlled study with adalimumab was conducted to address the question which features in PsA ST samples could be used as a biomarker for clinical efficacy on the group level in relatively small studies of short duration. The results presented...
**Figure 2** Representative photograph showing CD3+ T cells (red–brown) in psoriatic arthritis synovial tissue before and after treatment with adalimumab (upper panel left and right) or placebo (lower panel left and right). Magnification ×200. A marked reduction of the number of CD3+ T cells was observed after 4 weeks of adalimumab treatment.

**Figure 3** Scatter plots showing individual data points for the correlation between change in 28-joint Disease Activity Score (ΔDAS28, a positive value represents clinical improvement) on the y axis and change in biomarker (a positive value represents a reduction of the expression) on the x axis after 4 weeks for CD3-positive cells (rho = 0.644, p = 0.003), CD4-positive cells (rho = 0.649, p = 0.003), expression of myeloid-related protein (MRP)8 (rho = 0.561, p = 0.012) and matrix metalloproteinase (MMP)13 (rho = 0.619, p = 0.005).
here show that clinically effective adalimumab therapy is particularly associated with a marked reduction in CD3-positive T cell infiltration and expression of MMP13 in the ST of patients with PsA 4 weeks after initiation of treatment.

Previous work on synovial biomarkers in patients with PsA has been mainly limited to open studies, mostly of longer duration. Open label treatment of 10 patients with PsA with methotrexate resulted in a decrease in T cells and macrophages as well as reduced expression of IL8, E-selectin, intercellular adhesion molecule 1 (ICAM-1) and MMP3 after 6 to 12 months of treatment. In another study 52 patients with peripheral arthritis due to spondyloarthritis were included; 16 of these had PsA. The patients underwent synovial biopsy at baseline and 12 weeks following different treatment regimens (infliximab, etanercept, sulfasalazine or no DmARD). Clinical improvement correlated with a decrease in CD16S-positive macrophages, polymorphonuclear cells (PMNs) and MMP3 expression. A study on the effects of TNF blockade showed in 11 patients with PsA, who were treated with infliximab (5 mg/kg) combined with stable methotrexate treatment, a significant reduction of ICAM-1, vWF and αvβ8 expression. There was also a trend towards a reduction of T cells and macrophages. Similarly, another study demonstrated a decrease in macrophage numbers and vascular markers in the synovium of nine patients with PsA 8 weeks after initiation of infliximab (5 mg/kg) treatment. A study on the effects of alefacept revealed a significant decrease in T cell numbers after 4 weeks of treatment, and a significant reduction of T cells and macrophages after 12 weeks of treatment in 11 patients with PsA. Finally, experimental treatment with IL10 subcutaneously for 4 weeks resulted in decreased T cell and macrophage infiltration in the synovium.

The present study was designed to determine which synovial biomarkers are associated on the group level with active treatment, identical to the approach that we have previously described in patients with RA. In RA macrophage numbers were previously identified as synovial biomarkers associated with active treatment. These results have been confirmed and validated in various studies. Of interest, although we did observe clear trends towards decreased numbers of macrophages and macrophage subsets after active treatment, analysis of covariance indicates that in PsA especially the number of CD3-positive T cells and the expression of MMP13 could be used to screen for potentially active drugs in small proof of concept studies of short duration. The results presented here underscore the important role of T cells in the pathogenesis of PsA, consistent with the observation that specific targeting of T cells may result in clinical benefit in this disease.

A potential drawback of this study is the fact that there were baseline differences—in clinical and synovial variables—between the adalimumab and placebo group despite randomisation, which is probably related to the relatively small number of patients. The ANCOVA model, however, includes the baseline value for each marker as a covariate, thereby correcting for these baseline imbalances. Using this model to describe the relationship between clinical improvement and changes in ST, the effect of treatment was sustained for a reduction of T cells and MMP13 expression. Another potential limitation of this exploratory study is related to the high number of synovial parameters tested and the chance of erroneously reporting statistical significance in the context of multiple comparisons. The limited power of our study did not allow a conservative Bonferroni correction. Of importance, other investigators have very recently independently confirmed the specific decrease in CD3+ T cells in the synovium after initiation of TNF blockade in patients with PsA. Thus, it appears unlikely that the identification of CD3+ T cells as a key synovial biomarker associated with active treatment can merely be explained by chance.

The reduction of synovial inflammation associated with clinical improvement of the joint and skin after adalimumab treatment is also consistent with previous reports showing a decrease in leukocyte numbers (including T cells and macrophages), as well as reduced vascularity and expression of proinflammatory cytokines and MMPs in the synovium of patients with PsA after infliximab treatment. The cellular changes might be explained in part by changes in cell migration due to reduced neoangiogenesis and reduced expression of adhesion molecules and chemokines, as suggested previously.

Analysis of molecular markers in synovial tissue is increasingly used in clinical trials on targeted therapies. With this approach, tissue specificity is not a problem and examination of serial biopsy samples can be used to monitor the response in individual patients and screen for interesting biological effects at the site of inflammation. This study clearly shows that changes in T cell numbers and the expression of MMP13 in the synovium of patients with PsA may be used as biomarkers to screen for effective therapies during early drug development. It can be anticipated that future developments will include the use of more extensive markers of synovial inflammation and joint degradation as well as the use of panels of biomarkers in serum and synovial tissue samples.

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Competing interests: This publication reflects only the author’s views; the European Community is not liable for any use that may be made of the information herein. This research is integrated in the work of the OMERACT Special Interest Group on Synovial Analysis in Clinical Trials.

Ethics approval: The study protocol was approved by the medical ethics committee of the institute and all patients signed informed consent before start of the study.

REFERENCES


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