Effects of biological response modifiers in psoriasis and psoriatic arthritis
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Alefacept treatment in psoriatic arthritis. Reduction of the effector T cell population in peripheral blood and synovial tissue is associated with improvement of clinical signs of arthritis

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Abstract

Objective. To investigate whether alefacept (a fully human lymphocyte function-associated antigen 3 [LFA-3]/lgG1 fusion protein that blocks the LFA-3/CD2 interaction) is able to reduce the signs and symptoms of joint inflammation in patients with active psoriatic arthritis (PsA).

Methods. Eleven patients with active PsA were treated with alefacept for 12 weeks in an open-label and explorative study. Clinical joint assessment and laboratory assessments were performed at baseline and after 4, 9, 12, and 16 weeks of treatment. Serial synovial tissue (ST) biopsy from an inflamed index joint (knee, ankle, wrist, or metacarpophalangeal joint) were obtained by arthroscopy at baseline and after 4 and 12 weeks of treatment.

Results. At the completion of treatment, 6 of 11 patients (56%) fulfilled the Disease Activity Score (DAS) response criteria. Nine patients (82%) fulfilled the DAS response criteria at any point during the study. There was a statistically significant reduction in CD4+ lymphocytes (P < 0.05), CD8+ lymphocytes (P = 0.05), and CD68+ macrophages (P < 0.02) in the ST after 12 weeks of treatment compared with baseline. The ST and peripheral blood of those patients fulfilling the DAS response criteria contained more CD45RO* cells at baseline and displayed a significant reduction in these cells compared with nonresponding patients.

Conclusion. The changes in ST, together with the improvement in clinical joint scores, after treatment with alefacept support the hypothesis that T-cell activation plays an important role in this chronic inflammatory disease. Furthermore, since alefacept, a T-cell-specific agent, led to decreased macrophage infiltration, the data indicate that T-cells are highly involved in synovial inflammation in PsA.
Introduction

Coexisting arthritis and psoriasis has been recognized as a clinical entity since the 19th century. Yet, the formal clinical distinction between psoriatic arthritis (PsA) and rheumatoid arthritis (RA) was made only in 1961, and was based on a composition of clinical features, including asymmetric pauciarticular arthritis involving the distal interphalangeal joints and dactylitis in the absence of rheumatoid factor (1). Currently, the diagnosis of PsA remains difficult due to the absence of specific markers and is therefore still mainly determined by clinical signs and symptoms (2). In the UK, the prevalence of PsA is estimated as 0.1% of the population, while RA has an estimated prevalence of 0.5–1.0% (3). Although PsA is perceived as a less aggressive disease compared with RA, it can cause severe disability in a significant proportion of patients.

Meanwhile, data on the treatment of PsA are limited. Only a few small, controlled clinical trials have been performed with interventions, such as sulfasalazine (4-6), methotrexate (7), and cyclosporine A (8, 9). The increased awareness of the success of early, aggressive, and novel treatment strategies in RA (10,11) has encouraged an identical approach to treatment of patients who have disabling PsA, but using new modalities, such as etanercept (12). More detailed information about the effects of these regimens in PsA is needed before they can be developed further. Because serial synovial tissue (ST) sampling may help to screen for possible effects at the site of inflammation and could provide insight into the mechanism of action of PsA (13), results of this screening should be included as an end point in evaluations of these new biologic therapies (14).

T lymphocytes have been proposed as key players in the pathogenesis of psoriasis and are therefore a potential target for its treatment (15). This notion is based on the presence of T lymphocytes in early psoriasis lesions (16), the beneficial effects of T-lymphocyte–targeted therapies like cyclosporine A (8), and the altered relationship between psoriatic keratinocytes and interferon-γ (IFN-γ) compared with normal keratinocytes (17). Data on the role of T cells in PsA are limited, but it has been suggested that they play a central role in its pathogenesis as well (18-20).

Alefacept (human lymphocyte function-associated antigen 3/IgG1 LFA-3/IgG1 fusion protein; Biogen, Cambridge, MA) is a recombinant protein designed to inhibit the interaction between LFA-3 and CD2. The LFA-3 portion binds to
the CD2 receptor on T lymphocytes, blocking T-cell activation and proliferation in vitro and in vivo, while the IgG1 domain interacts with Fcg receptor type III on accessory cells (e.g., macrophages and natural killer cells) to induce selective apoptosis of memory-effector T lymphocytes (21-25). In a recently completed phase II clinical trial, alefacept was documented to be safe and clinically efficacious compared with placebo in patients with active plaque psoriasis (26). In this same study, it was documented that alefacept administration resulted in a significant and selective reduction in effector T cells without major safety problems. This clinical efficacy in plaque psoriasis supports a potential role for alefacept in PsA, but its effects in these patients have as yet not been determined. Therefore, we performed an explorative, open-label clinical study with serial synovial biopsies in patients with active PsA.

Patients and methods

Patients and study protocol
In a period of 6 months, 11 patients with plaque psoriasis (diagnosed at least 12 months before enrolment) who had active joint inflammation were recruited in a prospective, single-centre, open-label, clinical trial investigating the effects of alefacept treatment. Active disease was defined as ≥2 swollen and ≥2 tender joints. In all cases, both the physician and patient assessed disease activity as being moderate or poor. All patients had at least one clinically involved knee, wrist, metacarpophalangeal (MCP) joint, or ankle joint. Prednisone therapy was not allowed. Concomitant treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) at a stable dosage was allowed. None of the patients had previously been treated with alefacept. When applicable, all treatments other than NSAIDs were stopped and, after a washout phase of 28 days, patients received 7.5 mg of alefacept intravenously once a week for 12 weeks. The criteria for administering each dose of alefacept were a total lymphocyte count ≥67% of the lower limit of the normal range within 24 hours before injection and an absolute CD4+ T lymphocyte count ≥300/μL in the previous week. All 11 patients in this study met these criteria during the entire study period.

Clinical assessments were performed at baseline and after 4, 12 (end of treatment phase), and 16 weeks, and included a 30-joint count (28-joint count (27) and both ankles) for joint swelling and tenderness, and physician and patient assessment of disease activity, morning stiffness, pain assessed by a visual analog
scale (VAS), and serum levels of serum C-reactive protein (CRP). The clinical effect after treatment was calculated using the Disease Activity Score (DAS) (28), with CRP as the acute-phase reactant and 28 joints counted. All patients gave informed consent, and the study protocol was approved by the Medical Ethics Committee of the Academic Medical Centre/University of Amsterdam.

**Arthroscopy** In all patients, 3 serial arthroscopically guided synovial biopsies of the same index joint, at baseline, after 4 weeks of treatment, and at the end of the treatment period at 12 weeks were performed under local anaesthesia (29). The joints subjected to the arthroscopic biopsy procedure were the knee joint (n=7), the wrist joint (n=2), ankle joint (n=1), and MCP joint (n=1) (30;31).

**Knee arthroscopy** The arthroscopy procedure was performed in the inflamed knee with a small-bore, 2.7-mm arthroscope (Storz, Tuttlingen, Germany) under local anaesthesia (lidocaine 1%) using an infrapatellar skin portal for macroscopic examination of the synovium and a second suprapatellar portal for the biopsy procedure. During each arthroscopy, synovial biopsy samples were obtained from the suprapatellar pouch, the synovium-cartilage junction, the patellar gutters, and the tibiofemoral junction, using a grasping forceps (Storz) (32).

**Small joint arthroscopy** Arthroscopy of the wrist, ankle, or MCP joint was performed using a small-bore 1.9-mm arthroscope (Storz) under local anaesthesia through 2 skin portals, as described previously (30). Both portals were used for macroscopic examination of the synovium and for the biopsy procedure. During each arthroscopy, synovial biopsies were obtained using a grasping forceps (Storz) (30). If there was macroscopic variation of synovitis in knee or small joint, multiple samples were obtained from both macroscopically inflamed and macroscopically noninflamed regions. To reduce sampling error, a minimum of 6 tissue specimens were processed for immunohistochemistry and for formalin fixation, each as described previously (33-35).

**Immunohistochemical analysis** The specimens for immunohistochemistry were directly collected en bloc in a mold, embedded in Tissue-Tek OCT (Miles
Diagnostics, Elkhart, IN), and subsequently snap frozen by immersion in liquid nitrogen (-180°C) after being randomly coded. 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 adhesive slides, Knittelgläser, Germany); the slides were air dried at room temperature, carefully packed, sealed airtight, and stored at -80°C until immunohistochemical analysis could be performed in a single session.

Serial sections were stained with the following mouse monoclonal antibodies (mAb): anti-CD68 (EBM11, Dako, Glostrup Denmark), anti-CD3 (SK7, Becton-Dickinson, San Jose, CA), anti-CD4 (SK3, Becton-Dickson), anti-CD8 (DK25, Dako), and anti-CD55 (Mab67, Serotec, Oxford, UK). 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 (35). Following a primary step of incubation with mAb, bound antibody was detected according to a 3-step immunoperoxidase method. The primary antibodies were incubated for 60 min. Affinity-purified and horseradish peroxidase (HRP)-conjugated goat anti-mouse antibody (DAKO) was added for 30 min, followed by subsequent incubation with affinity-purified and HRP-conjugated swine anti-goat Ig (Biosource, Etten-Leur, the Netherlands) for 30 min. HRP activity was detected using hydrogen peroxide as substrate and aminoethylcarbazole (AEC, Sigma, St. Louis, MO) as dye. Slides were counterstained with Mayer’s hematoxylin (Sigma) and mounted in Kaiser’s glycerol gelatin (Merck, Rahway, NY).

Digital image analysis Subsequently, all sections were coded and analyzed by digital image analysis in random order as described previously (36), by an independent observer (MCK), who was blinded for the clinical data. Briefly, 3 separate representative regions, including the intimal lining layer and synovial sublining, were chosen for the evaluation of each section. Six consecutive high-power fields (HPFs) from each region were captured and digitized, resulting in a total of 18 HPFs (surface area = 2.1 mm²). Subsequently, sections were examined using a specialized algorithm written in the program language QUIPS operating a Qwin-based (Qwin Pro V2.4, Leica, Cambridge, U.K.) computer-assisted color video image analysis system. (36;37).
Double-labeling measurements for $CD4^+\cdot CD45RO^+$ cells  ST samples from 8 patients with evaluable baseline and 12-week biopsies were assessed for the co-expression of CD45RO and CD4 on serial sections of the block using double immunofluorescence methods, as described previously (38). First, the anti-CD45RO (UCHL-1, CLB, Amsterdam, The Netherlands) mAb was incubated on the sections, followed by incubation with tetramethylrhodamine isothiocyanate-conjugated goat anti-mouse antibody (Nordic, Tilburg, The Netherlands). Ten percent normal mouse serum in PBS was applied as blocking serum. This was followed by incubation with fluorescein isothiocyanate (FITC)-conjugated mAb anti-CD4 (CLB-T4/2, 6D10, CLB). Subsequently, rabbit anti-FITC antibody (Dako) was incubated. Finally, FITC-conjugated swine anti-rabbit antibody (Dako) was added. The sections were embedded in Vectashield mounting medium (Vector, Burlingame, CA) and analyzed by 2 independent assessors (MCK, TJMS) who were unaware of the clinical data and the order of the biopsies (38). During the analysis, all CD4 and CD45RO double-positive cells in the entire section were counted and given as percentage of the absolute number of $CD4^+$ cells in the biopsy specimens.

Peripheral blood measurements  Flow cytometric analyses were performed at each study visit to quantify populations of $CD4^+$, $CD8^+$, $CD45RA^+$, and $CD45RO^+$ T lymphocytes. The cumulative reduction in the baseline counts over the 12-week treatment period was reported as the area under the curve.

Statistical analysis  Access database and Excel spreadsheet software (Microsoft, Redmond, WA) were used for data collection and selection. SPSS for Windows, version 9.1 (SPSS, Chicago, IL) was used for statistical analysis. The Wilcoxon's signed-rank test was used to determine significant differences between the baseline and subsequent biopsies. Kendall's coefficient was calculated to see whether changes in one variable correlated with changes in others. All statistical tests were 2-sided; $P$ values less than 0.05 were considered significant. The sponsor of the study collected the data; the authors performed the statistical analysis, interpreted the data, prepared their presentation, and wrote this report. Values are expressed as the mean ± SEM.
Results

Patients Eleven patients were included in the study and underwent all procedures without complications; 1 patient refused the third arthroscopy for personal reasons. The mean age of the patients was 46 years (range 35–70), 9 were male and 2 were female, mean disease duration was 18 months (12–124), and the mean previous number of disease-modifying arthritis drugs used was 1.3 (0–4). The study included all of the types of PsA manifestations (39); 1 patient had an isolated distal arthritis, 3 patients had asymmetric oligoarthritis, 5 patients had symmetric polyarthritis, 2 patients had arthritis mutulans, and 1 patient had spondyloarthropathy.

Clinical efficacy There was a gradual decrease in the mean DAS during the dosing period, with a sustained response after cessation of the therapy (5.0 at baseline to 3.7 after 16 weeks) (Table 1). At the end of the 12-week dosing period, 6 of 11 treated patients (55%) fulfilled the DAS response criteria; 9 patients (82%) fulfilled the DAS response criteria at any point within the study. Analysis of the individual elements of the response criteria revealed a similar pattern (Table 1). Mean tender and swollen joint counts were significantly decreased as early as 4 weeks after treatment, and this was maintained for 4 weeks after therapy was completed (week 16). Mean CRP levels decreased over the study period, with the decrease achieving statistical significance at 16 weeks. VAS scores were significantly decreased at 12 and 16 weeks after treatment. The mean Psoriasis Area and Severity index (40) was reduced by

Table 1. Clinical data on the patients.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 Weeks</th>
<th>12 Weeks</th>
<th>16 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS, mean (range)</td>
<td>5.0 (3.3-7.2)</td>
<td>4.3 (2.7-7.1)</td>
<td>4.0 (1.5-6.0)</td>
<td>3.7 (1.8-5.3)</td>
</tr>
<tr>
<td>Tender joint count§</td>
<td>7.6 ± 2.0</td>
<td>5.6 ± 2.1</td>
<td>4.5 ± 1.6</td>
<td>4.8 ± 1.4</td>
</tr>
<tr>
<td>Swollen joint count§</td>
<td>7.1 ± 2.0</td>
<td>5.9 ± 1.9</td>
<td>5.4 ± 1.5</td>
<td>4.9 ± 1.3</td>
</tr>
<tr>
<td>Disease activity, 1-10 scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigator assessment</td>
<td>3.4 ± 0.2</td>
<td>3.4 ± 0.2</td>
<td>2.8 ± 0.2</td>
<td>2.8 ± 0.3</td>
</tr>
<tr>
<td>Patient assessment</td>
<td>3.6 ± 0.2</td>
<td>2.9 ± 0.2</td>
<td>2.9 ± 0.2</td>
<td>2.7 ± 0.3</td>
</tr>
<tr>
<td>Morning stiffness, minutes</td>
<td>319 ± 28</td>
<td>174 ± 21</td>
<td>37 ± 2</td>
<td>34 ± 3</td>
</tr>
<tr>
<td>CRP, mg/liter</td>
<td>38 ± 13</td>
<td>23 ± 6</td>
<td>22 ± 6</td>
<td>14 ± 2</td>
</tr>
<tr>
<td>VAS, mm</td>
<td>53 ± 8</td>
<td>40 ± 7</td>
<td>38 ± 0</td>
<td>26 ± 7</td>
</tr>
</tbody>
</table>

*Except for the Disease Activity Score (DAS), values are the mean ± SEM. CRP = C-reactive protein; VAS = visual analog scale (100 mm). †P < 0.05 versus baseline. ‡P < 0.01 versus baseline. § Of 30 joints counted
13% at 4 weeks (SEM 8%), 23% at 12 weeks (SEM 10%), and 28% at 12 weeks
(SEM 11%).

Safety profile The aggregated safety data displayed a favourable safety profile.
The most common side effects likely or definitely associated with the study
drug were flu like syndrome (54%) and infection (18%). Two severe adverse
events were documented; both were judged as non-study related.

PB measurements Total lymphocyte counts (mean ± SEM) decreased slightly
during the dosing phase (1667 ± 124 at baseline to 1313 ± 141 after 12 weeks),
but recovered 4 weeks after cessation of the drug (1520 ± 82). CD4⁺ lymphocyte
counts displayed an identical pattern (775 ± 95 at baseline, 557 ± 66 after 12
weeks, and 602 ± 44 after 16 weeks). CD8⁺ lymphocyte counts also decreased

![Figure 1. Changes in CD4⁺, CD4⁺CD45RA⁺, and CD4⁺CD45RO⁺ cell counts in the peripheral
blood at baseline, during alefacept treatment, and after cessation of treatment. Numbers
depict the absolute number of positive cells.](image-url)
Table 2. Results of immunohistochemical staining of synovial biopsies at baseline, after 4 weeks of treatment, and at the end of the treatment phase (week 12)*.

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=9)</th>
<th>4 weeks (n=11)</th>
<th>12 weeks (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3* T cells</td>
<td>431 ± 117</td>
<td>323 ± 90</td>
<td>219 ± 67</td>
</tr>
<tr>
<td>CD4* T cells</td>
<td>384 ± 77</td>
<td>221 ± 70*</td>
<td>158 ± 56*</td>
</tr>
<tr>
<td>CD8* T cells</td>
<td>191 ± 62</td>
<td>166 ± 45*</td>
<td>77 ± 27*</td>
</tr>
<tr>
<td>Intimal lining macrophages</td>
<td>528 ± 58</td>
<td>375 ± 43</td>
<td>313 ± 63</td>
</tr>
<tr>
<td>Sublining macrophages</td>
<td>1007 ± 171</td>
<td>1009 ± 191</td>
<td>574 ± 134*</td>
</tr>
<tr>
<td>Fibroblast-like synoviocytes</td>
<td>1633 ± 1633</td>
<td>1616 ± 226</td>
<td>1599 ± 187</td>
</tr>
</tbody>
</table>

* Values are the mean ± SEM number of cells in 2.1 mm² of synovial tissue (± s.e.m.). Baseline synovial tissue biopsies of 2 patients were not assessable due to the absence of an identifiable intimal lining layer and were excluded from the immunohistochemical analysis. *P < 0.05 versus baseline.

(282 ± 39 at baseline, 203 ± 29 after 12 weeks, and 248 ± 44 after 16 weeks). The number of naïve CD4+,CD45RA+ lymphocytes in the PB remained unchanged throughout the study (284 ± 43 at baseline, 297 ± 52 after 12 weeks, and 309 ± 39 after 16 weeks).

In contrast, the number of memory-effector CD4+,CD45RO+ lymphocytes was significantly reduced during the treatment period (mean ± SEM 461 ± 67 at baseline to 236 ± 30 after 12 weeks; *P < 0.01) with sustained reductions after completion of dosing (270 ± 24 after 16 weeks) (Figure 1). Patients fulfilling the DAS response criteria at 12 weeks demonstrated a significant reduction in the percentage of CD45RO* cells (mean 65% ± 5% at baseline to 49% ± 4% after 12 weeks; *P < 0.05) compared with nonresponders, who did not have a

Figure 2. Percentage of CD4+, CD45RO+ cells in the peripheral blood and synovial tissue at baseline (shaded bars) and after alefacept treatment (open bars). Values are the mean and SEM and are for patients fulfilling the Disease Activity Score response criteria and for nonresponders.
significant reduction in the percentage of CD45RO$^+$ cells (mean of 52% ± 4% at baseline to 39% ± 6% after 12 weeks) (Figure 2).

Arthroscopy In conjunction with the clinical improvement, there was a reduction in macroscopic signs of synovitis at arthroscopy after 4 weeks, and this was even more pronounced after 12 weeks. In the absence of a validated scoring system for macroscopic synovitis, examples are provided in Figure 3.

Immunohistochemical analysis The results of the immunohistochemical analysis at baseline and after 4 and 12 weeks are depicted in Table 2. Mean macrophage numbers were significantly reduced in the synovial sublining after 12 weeks, but not in the intimal lining layer. CD3$^+$ T-cell numbers were also reduced, but this difference did not reach statistical significance. Both the CD4$^+$ T cells and CD8$^+$ T cells were significantly reduced after 4 weeks and 12 weeks. Representative examples of the immunohistochemical staining for CD3$^+$, CD4$^+$, CD8$^+$, and CD68$^+$ cells are shown in Figure 4. Fibroblast-like synoviocyte numbers did not change during the study.

Figure 3. Macroscopic appearance of the knee joint of the same patient at baseline, after 4 weeks and after 12 weeks of treatment with alefacept.
Double labelling CD4 and CD45RO The mean percentage of CD45RO⁺ lymphocytes (mean ± SEM) in the ST was gradually reduced during the treatment phase (41% ± 8% at baseline to 35% ± 9% after 12 weeks), but this reduction did not reach statistical significance, presumably due to the relatively small number of patients. Patients fulfilling the DAS response criteria at 12 weeks exhibited a reduction in the percentage of CD45RO⁺ lymphocytes (42% ± 4% at baseline to 33% ± 12% after 12 weeks), this reduction was marked but also did not reach statistical significance because of the relatively low number of patients. In contrast, the percentage of CD45RO⁺ cells in the nonresponders was unaltered after treatment (41% ± 30% at baseline to 39% ± 18% after 12 weeks) (Figure 2).

Discussion
The data presented here show for the first time a beneficial effect of alefacept, an inhibitor of the LFA-3/CD2 interaction, in patients with PsA. There was a
reduction in arthritis activity and serum levels of acute-phase reactants. Clinical improvement was associated with a reduction in the number of macrophages and T effector cells in the synovium. Recently increased awareness of the effects of chronic inflammatory joint diseases on the individual and the society, together with the expansion of treatment modalities, has increased the demand for new therapeutics. The number of treatment options available for patients with PsA is restricted to agents currently used in the treatment of RA, including sulfasalazine (4-6), methotrexate (7), and cyclosporine A (8;9). The recent development of novel agents such as etanercept (12) has shown the possibilities of targeted therapies. The importance of T cells in the pathogenesis of PsA has encouraged the development of compounds like alefacept, which interferes with T-cell activation and induces selective T-cell apoptosis (21-25). The data presented in this study support the notion that targeted therapies are effective in patients with PsA, as recently shown in plaque psoriasis (26).

To limit the placebo effects and expectation bias of an open-label design, which could suggest a more favourable response for the new treatment, we included serial measurement of biological markers that may be less susceptible to this bias (41). The relevance of ST analysis has been underscored by the observation that clinical arthritis activity is accompanied by persistent histological signs of synovitis after treatment with the mAb CAMPATH-1H, despite profound depletion of circulating lymphocytes (42). Previous work has shown that analysis of serial ST samples from RA patients who received either placebo or unsuccessful treatment with recombinant human interleukin-10 (IL-10) did not reveal any synovial changes (43). Similarly, there was no clear-cut change in serial biopsies after treatment with IL-1 receptor antagonist at 30 mg/day (44), which appears to have very limited effects on arthritis activity.

Thus, these studies support the view that changes in serial biopsy samples cannot be explained by placebo effects, regression to the mean, expectation bias, or by the arthroscopy procedure itself. Rather, they reflect biological effects of the treatment. In the present study, clinical improvement was associated with significant changes at the site of inflammation, which were consistent with the presumed mechanism of action of the compound.
Examination of serial synovial biopsy specimens may be more sensitive to change than clinical parameters (45,46), which allows its use as a screening method for novel therapies (13,45-47). However, a meaningful clinical effect obviously still needs to be shown in larger, well-controlled studies. The data presented here provide the rationale for such trials.

The suggested mechanism of action of alefacept is by interaction with T-cell activation and induction of apoptosis, resulting in reduced numbers of memory-effector T cells. For that reason, we focused on the number of memory-effector T cells in serial samples of both the PB and synovial compartment. In the PB, we confirmed the reduction of circulating CD4⁺,CD45RO⁺ T cells during the course of treatment, as previously observed in patients with plaque psoriasis (26). Moreover, there was a similar reduction in the synovial compartment. Interestingly, the 6 patients fulfilling the DAS response criteria (after 12 weeks of treatment) displayed more profound reductions in both the numbers of circulating as well as synovial memory-effector T cells compared to the 5 nonresponding patients. Since composite clinical response criteria, such as the DAS, were designed for measurement of clinically relevant disease activity, this observation supports the notion that effective blockade of the LFA-3/CD2 interaction leads to clinical improvement. It should be noted that the DAS has been validated in RA. We assume that the DAS may provide useful information in other forms of active arthritis as well, although its use in PsA remains to be validated. Using this composite index, it appears that patients with pre-existing high numbers of memory-effector T cells are more likely to respond to alefacept therapy than those with lower numbers. This could suggest that PsA is a heterogeneous disease and that activation of T-cells may be more important in the subset of patients who respond well to LFA-3/CD2 blockade.

The success of T-cell targeted therapy in PsA appears to contrast with the previous experience in RA (48). This could be explained by differences in pathogenesis, but also by differences in treatment. It has been shown previously that Th1-like cells are relatively spared treatment with anti-CD4-depleting antibody (49,50). In contrast, alefacept treatment specifically reduces the memory cell population. A potential drawback of this approach might be an increased risk of infection. However, we did not observe any increase in
infection rate, which is consistent with previous observations (26).
The favourable clinical response is also associated with a reduction in the
number of macrophages during the treatment period. This is consistent with
previous studies showing a strong correlation between macrophages and
arthritis activity (35;43;51;52). It appears unlikely that alefacept had a direct
effect on ST macrophages in light of its specificity. Therefore, we suggest that
the effect of this novel biologic therapy on effector T cells is responsible for
the observed reduction in macrophage numbers. The decrease in macrophage
infiltration after alefacept treatment supports the view that activated T cells,
presumably antigen driven (18), stimulate macrophage infiltration and
activation in patients with PsA.

In conclusion, the clinical improvement is associated with a reduction in
inflammation after treatment with alefacept. Furthermore, since alefacept, a
T cell–specific agent, leads to decreased macrophage infiltration, the data
indicate that T cells are highly involved in synovial inflammation in PsA.

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