T cell differentiation in autoimmune diseases
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Chapter 5

Treatment with monoclonal anti-tumor necrosis factor α antibody results in an accumulation of Th1 CD4+ T cells in the peripheral blood of patients with rheumatoid arthritis

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TREATMENT WITH MONOCLONAL ANTIBODY RESULTS IN AN ACCUMULATION OF Th1 CD4+ T CELLS IN THE PERIPHERAL BLOOD OF PATIENTS WITH RHEUMATOID ARTHRITIS

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Objective. In rheumatoid arthritis (RA), treatment with tumor necrosis factor α (TNFα) binding agents has proven to be highly effective. Down-regulation of the proinflammatory cytokine cascade and a reduced migration of leukocytes into the joints have been proposed as modes of action of TNFα blockade. We investigated whether alterations in the number of circulating pro- and antiinflammatory T cell subsets contribute to the therapeutic effect of monoclonal antibodies (mAb) against TNFα in RA patients.

Methods. Phenotypic analysis of peripheral blood T cell subsets was performed on blood from RA patients before and after treatment with an anti-TNFα mAb.

Results. An accumulation of primed CD45RA− T cells of both the CD4+ and the CD8+ T cell population was seen shortly after treatment. Most notably, within the CD4+CD45RA− T cell subset, the number of interferon-γ-producing T cells was significantly increased after anti-TNFα mAb treatment, resulting in a significant rise in the Th1:Th2 ratio. In addition, an increase in the number of CD4+ T cells expressing the homing receptor CD49d in high density was observed after treatment, which correlated positively with the increase in the Th1:Th2 ratio.

Conclusion. We show that the Th1:Th2 ratio in the peripheral blood is raised by anti-TNFα mAb treatment.

Rheumatoid arthritis (RA) is associated with a chronic inflammation of peripheral joints and, ultimately, the destruction of joint structures. The pathogenic events that lead to the development of RA have not yet been clarified, but an immunopathogenic component has been strongly implicated. Immunohistologic examinations of RA tissues revealed an infiltration of the joints with high numbers of mononuclear cells and a local, sustained overproduction of proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF), and tumor necrosis factor (TNF) (1). In the search for agents that interrupt the immunologic cascade in RA, the effects of administering monoclonal antibodies (mAb) against cell surface molecules and soluble mediators of inflammation have been studied extensively (2–17). Extremely promising results have been reported from randomized, placebo-controlled, clinical studies in which RA patients were treated with either a chimeric fusion protein of a murine anti-TNFα mAb and a human IgG1-Fc (cA2) (5) or with a recombinant human TNFα receptor (p75)–Fc fusion protein (18).

The rationale for blockade of TNFα was based upon several observations that point to a key role of TNFα in the pathogenesis of RA. High concentrations of TNFα were found in synovial fluid, synovial fluid cells, and synovial tissue specimens of patients with RA (19–21). Moreover, injection of TNFα in animals resulted in a transient synovitis with infiltration of lymphocytes, monocytes, and neutrophils in the joint cavity (hypothetically mediated by TNFα-induced up-regulation of adhesion molecules such as intercellular
adhesion molecule 1, vascular cell adhesion molecule 1 (VCAM-1), and endothelial leukocyte adhesion molecule 1, and by local induction of chemotactic factors such as IL-8) (for review, see ref. 22). Monoclonal antibodies against TNFα were observed to diminish the production of IL-1 and GM-CSF by synovial cells in vitro (23), and to ameliorate synovial hyperplasia and joint destruction in the collagen-induced arthritis model in DBA/1 mice, even after onset of arthritis (24).

The beneficial effect of anti-TNFα mAb administration in RA patients has been attributed to down-regulation of cytokine activity and to the reduction of leukocyte trafficking to the joints, the latter being based on observations such as reduced expression of adhesion molecules on synovial endothelium, reduced cellularity of joints, and lymphocytosis in the peripheral blood of RA patients after treatment with anti-TNFα mAb (for review, see ref. 25).

We postulated that alterations in pro- and anti-inflammatory T cell subsets could contribute to the clinical effect of anti-TNFα mAb treatment. Depending upon the set of lymphokines that is secreted, T cells can be divided into discrete effector populations. Human CD4+ T cells that secrete interferon-γ (IFNγ) and TNFβ and are involved in cell-mediated immunity are called Th1 responders, and CD4+ T cells that secrete IL-4 and mediate humoral responses are called Th2 responders (26-28). These polarized sets of lymphokines exert mutual cross-regulatory or inhibitory effects (29). In organ-specific autoimmunity, the activation of proinflammatory Th1 cells and/or the insufficient counterbalance by Th2 cells is believed to be important in the development of disease and to correlate with tissue injury (30,31). In the present study, we analyzed the effects of anti-TNFα mAb on phenotypic and functional characteristics of peripheral blood T cells in RA patients.

**PATIENTS AND METHODS**

Patients and cells. Seventeen patients with severe RA were recruited from our outpatient clinic (4 men and 13 women, median age 56 years, range 41-74). Patients fulfilled the criteria of the American College of Rheumatology (formerly, the American Rheumatism Association) for the diagnosis of RA (32), had a minimum disease duration of 6 months, a history of unsuccessful treatment with ≥1 disease-modifying antirheumatic drug, and radiographic evidence of erosive disease of hands and feet. Further inclusion and exclusion criteria have been described previously (5).

A human/murine chimeric mAb of IgG1κ isotype (cA2) (Centocor, Malvern, PA) is specific for human TNFα. The construction and characterization of cA2 has previously been described (33). The antibody was supplied as a sterile solution containing 5 mg/ml of cA2 in phosphate buffered saline (PBS) containing 0.01% polysorbate 80 (pH 7.2).

On the day of entry, patients were admitted to the hospital and randomly assigned to 1 of 3 treatment groups (6 patients per group). The first group received a single infusion of placebo (0.1% human serum albumin in the same buffer as described above). The other 2 groups each received 1 infusion of cA2, either 1 mg/kg (low dosage) or 10 mg/kg (high dosage).

At several time points during treatment, starting on day 0, heparinized blood was obtained. PBMCs isolated from heparinized blood by Ficoll-Hypaque density gradient centrifugation and cryopreserved immediately. To minimize inter-assay variability, samples from individual patients from all time points were analyzed in 1 experiment.

**Membrane phenotyping.** PBMC were washed twice with PBS supplemented with 0.5% bovine serum albumin (BSA) and sodium azide (5 µg/ml). Immunofluorescence staining was performed by incubation of PBMC with saturating amounts of combinations of the following mAbs in PBS: CD4- or CD8-peridinin chlorophyll protein (PerCP) (Becton Dickinson, San Jose, CA), CD27-fluorescein isothiocyanate (FITC) (CLB-27/3; Central Laboratory of the Red Cross Blood Transfusion Service [CLB], Amsterdam, The Netherlands), and CD45RA-phycocerythrin (PE) (2H4-RD1; Coulter, Miami, FL). Stained cells were washed twice and 106 viable lymphocytes were analyzed using a fluorescence-activated cell sorter (Becton Dickinson). Percentages of positive cells of each subset were calculated. Absolute cell numbers were found by determining the percentage of CD4+ and CD8+ cells within the lymphocyte gate (defined by forward and sideward scatter) and by counting of absolute numbers of lymphocytes.

**Flow cytometric measurement of intracellular cytokine production.** Measurement of cytokine-producing cells was performed as previously described (34,35). Briefly, 0.5 × 106 cells/ml were stimulated for 4 hours with phorbol myristate acetate (1 ng/ml) and ionomycin (1 µM) in the presence of the protein-secretion inhibitor monensin (1 µM). All subsequent steps were performed at 4°C. After cell surface staining with CD4-PE or CD8-PE combined with CD45RA-FITC (Becton Dickinson), cells were washed twice with PBS and fixated for 5 minutes with PBS/4% paraformaldehyde. Fixation was followed by permeabilization for 10 minutes with PBS/0.1% saponin (Sigma, Zwijndrecht, The Netherlands)/10% human pooled serum. PBS/0.1% saponin/0.5% BSA was used for all subsequent washing and incubation steps. Staining of the cytokines with 5 µg/ml biotinylated anti-IL-4 mAb (Holzel Diagnostika, Cologne, Germany) or biotinylated anti-IFNγ mAb (MD1; gift from Dr. P. van der Meiden, Biomedical Primate Research Center, Rijswijk, The Netherlands) for 60 minutes was followed by incubation with streptavidin–RED670 (Gibco BRL, Breda, The Netherlands) for 60 minutes. Analysis was performed as described for the measurement of membrane markers.

**Determination of adhesion molecules on Th1 and Th2 cells.** CD4+ cells (>97% CD3+CD4+) of 3 healthy donors were obtained by incubating PBMC with saturating amounts of CD8, CD19, CD16, and CD14 mAb (CLB), followed by positive depletion using goat anti-mouse IgG-coupled Dynabeads (Dynal, Oslo, Norway) as previously described (36).
### Chapter 5

#### RESULTS

**Anti-TNFα treatment induces an increase in the number of CD4+, CD45RA− T cells in the peripheral blood.** In accordance with previous findings (37, 38), treatment with anti-TNFα resulted in an increase in lymphocyte numbers in the peripheral blood of RA patients shortly after infusion (Table 1). Because previous data as well as our own findings showed that the increase in lymphocyte numbers was most pronounced shortly after infusion with anti-TNFα and correlated well with clinical benefit (37, 38), we decided to analyze the alterations in circulating T cell subsets occurring 3 days after infusion with anti-TNFα mAb in RA patients.

The analysis of CD45RA expression on CD4+ T cells (Table 1) revealed a significant increase in the absolute number of both CD45RA+ (P = 0.018) and CD45RA− (P = 0.006) cells at day 3 after infusion in the group of anti−TNFα-treated patients, but not in the placebo-treated group. The increase in CD45RA− cells was far more pronounced than the increase in CD45RA+ cells, leading to an increase in the percentage of CD45RA− memory cells within the CD4+ T cell population after anti-TNFα mAb treatment. CD45RA− memory CD4+ T cells can be further subdivided into CD27+ and CD27− T cells, of which the latter subset

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### Table 1. Peripheral blood counts of lymphocytes, CD4+, and CD4+ T cell subsets in rheumatoid arthritis patients before and after treatment with monoclonal anti-tumor necrosis factor α (anti-TNFα) antibody

<table>
<thead>
<tr>
<th></th>
<th>Treatment with anti-TNFα (n = 11)</th>
<th>Treatment with placebo (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lymphocytes</strong></td>
<td>Median</td>
<td>SD</td>
</tr>
<tr>
<td>Day 0</td>
<td>1,320</td>
<td>656</td>
</tr>
<tr>
<td>Day 3</td>
<td>2,540†</td>
<td>585</td>
</tr>
<tr>
<td><strong>CD4+</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>549</td>
<td>315</td>
</tr>
<tr>
<td>Day 3</td>
<td>917†</td>
<td>364</td>
</tr>
<tr>
<td><strong>CD4+ .CD45RA+</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>176</td>
<td>129</td>
</tr>
<tr>
<td>Day 3</td>
<td>296†</td>
<td>229</td>
</tr>
<tr>
<td><strong>CD4+ .CD45RA−</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>319</td>
<td>228</td>
</tr>
<tr>
<td>Day 3</td>
<td>692†</td>
<td>242</td>
</tr>
<tr>
<td><strong>CD4+ .CD45RA−.CD27+</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>28</td>
<td>100</td>
</tr>
<tr>
<td>Day 3</td>
<td>49†</td>
<td>168</td>
</tr>
<tr>
<td><strong>CD8+</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>243</td>
<td>400</td>
</tr>
<tr>
<td>Day 3</td>
<td>488†</td>
<td>356</td>
</tr>
<tr>
<td><strong>CD8+ .CD45RA+ .CD27+</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>55</td>
<td>56</td>
</tr>
<tr>
<td>Day 3</td>
<td>85†</td>
<td>105</td>
</tr>
<tr>
<td><strong>CD8+ .CD45RA− .CD27+</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>37</td>
<td>179</td>
</tr>
<tr>
<td>Day 3</td>
<td>49</td>
<td>156</td>
</tr>
<tr>
<td><strong>CD8+ .CD45RA− .CD27+</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>88</td>
<td>62</td>
</tr>
<tr>
<td>Day 3</td>
<td>205†</td>
<td>94</td>
</tr>
<tr>
<td><strong>CD8+ .CD45RA+.CD27+</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 0</td>
<td>20</td>
<td>166</td>
</tr>
<tr>
<td>Day 3</td>
<td>39</td>
<td>111</td>
</tr>
</tbody>
</table>

* Values are the number of cells × 10⁹/liter.
† P < 0.05 by Wilcoxon’s signed rank test.

After stimulation as described above, cells were stained with antibodies against CD49d, CD29, CD11a, CD11b, CD11c, or CD2, or with negative control and FITC-coupled goat anti-mouse Ig (5 μg/ml) (all purchased from CLB). After blocking with normal mouse serum (1:10), cells were fixed, permeabilized, and stained with anti-IL-4–PE (Becton Dickinson) and biotin-coupled anti-IFNγ (MD-1) (Gibco BRL), and subsequently with streptavidin-RED670 (Gibco BRL).

Statistical analysis. Differences in the numbers of T cell subsets and in the levels of cytokine production before and after therapy were calculated using Wilcoxon's signed rank test. Correlations between increases in the Th1:Th2 ratio and the Disease Activity Score (DAS) or the number of high CD49d-expressing cells were analyzed by Spearman's rank correlation.
represents highly differentiated memory T cells that have undergone prolonged antigenic stimulation (39). Despite a significant increase in number \((P = 0.033)\) (Table 1), the percentage of CD27− T cells within the CD4+CD45RA− population did not show significant changes after treatment.

The number of CD8+CD45RA− T cells is increased after anti-TNFα treatment. Analogous to the behavior of CD4+ T cells, the number of CD45RA− T cells within the CD8+ T cell subset increased significantly after anti-TNFα therapy \((P = 0.003)\) (Table 1). As a consequence of the simultaneous increase in both CD4+ and CD8+ memory T cells, the CD4:CD8 ratio was not affected by anti-TNFα therapy (not shown). CD8+ T cells can be subdivided into naive, memory, and effector subsets based upon their CD45RA and CD27 expression pattern (40). As shown in Table 1, the number of both the naive CD45RA+CD27+ and the memory CD45RA−CD27− subset of the CD8+ population were significantly increased after treatment. However, the rise in the number of CD8+CD45RA−CD27+ T cells was greater than that of the CD8+CD45RA+, CD27+ T cells. Therefore, when calculated as a percentage of the total CD8+ population, only the CD45RA−CD27+ memory T cell population was significantly increased \((P = 0.026)\).

Increase of the Th1:Th2 ratio of CD4+CD45RA− T cells in the peripheral blood after anti-TNFα treatment. We next investigated whether anti-TNFα mAb therapy alters the amount of differentiated Th1 and Th2 cells within the peripheral blood of RA patients. Since the secretion of Th1 and Th2 cytokines is largely confined to the CD45RA− subset of CD4+ T cells, the amount of IFNγ- and IL-4–producing T cells was analyzed within this subset. The numbers of both IL-4- and IFNγ-producing CD4+CD45RA− T cells were significantly increased after anti-TNFα mAb treatment, but not after placebo treatment. However, the rise in IFNγ-producing T cells was more pronounced than the rise in IL-4-producing T cells, leading to a significant increase in the Th1:Th2 ratio in the peripheral blood \((P = 0.007)\) (Figure 1).

For CD8+ T cells, the production of IFNγ is not confined to the CD45RA− subset. Therefore, the numbers of both IFNγ- and IL-4–positive cells were calculated for the total CD8+ T cell population. In contrast to the findings for CD4+ T cells, the numbers of both IFNγ- and IL-4–positive cells, as well as their ratio, were not significantly altered within the CD8+ subset after treatment with anti-TNFα mAb (Table 2).
peripheral blood could be explained by a therapy-induced inhibition of homing of those cells to the inflamed tissues. This assumption implies a different homing pattern of Th1 and Th2 cells, which could be reflected in a difference in the expression of adhesion molecules. An important pathway in the migration of T cells to inflamed peripheral tissues involves very late activation antigen 4 (α4β1)/VCAM-1 (41), and VCAM-1 expression in the synovia of RA patients is reduced after anti-TNFα therapy (42).

### Table 2. Peripheral blood counts of interleukin-4 (IL-4)- and interferon-γ (IFNγ)-producing CD8+,CD45RA− T cells in rheumatoid arthritis patients before and after treatment with monoclonal anti-tumor necrosis factor α (anti-TNFα) antibody

<table>
<thead>
<tr>
<th></th>
<th>Treatment with anti-TNFα (n = 11)</th>
<th>Treatment with placebo (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-4+,CD8+</td>
<td>Median  SD  Range</td>
<td>Median  SD  Range</td>
</tr>
<tr>
<td>Day 0</td>
<td>16   23  0–74</td>
<td>22   22  9–61</td>
</tr>
<tr>
<td>Day 3</td>
<td>12   37  0–106</td>
<td>22   16  0–38</td>
</tr>
<tr>
<td>IFNγ+,CD8+</td>
<td>Day 0  83  309  11–1,003</td>
<td>Day 3  109  206  15–617</td>
</tr>
<tr>
<td>Day 3</td>
<td>119  336  39–916</td>
<td>69   126  36–363</td>
</tr>
</tbody>
</table>

*Values are the number of cells × 10^9/liter.

Figure 2. Comparison of the expression of adhesion molecules on IFNγ-producing Th1 and IL-4–producing Th2 CD4+ T cells from healthy individuals. The mean fluorescence intensity (MFI) for the different adhesion molecules was determined for IFNγ+IL-4− (Th1) and IFNγ−IL-4+ (Th2) cells by flow cytometry. The difference in antigen density between Th1 and Th2 cells is expressed as the MFI Th1/MFI Th2 ratio (mean and SEM of 3 donors) (A). After anti-TNFα treatment, the percentage of CD49d high-expressing CD4+ T cells in the peripheral blood of rheumatoid arthritis patients was increased and correlated significantly with the increase in the Th1/Th2 ratio (B). The alteration in the percentage of CD29-expressing CD4+ T cells did not correlate with the alteration in the Th1/Th2 ratio (C). See Figure 1 for other definitions.
To test whether CD49d (α4 integrin) is important in the homing of Th1 T cells to the synovium, we first analyzed the expression levels of CD49d and its associated β2 chain, CD29, on the cell surface of Th1 and Th2 CD4+ T cells isolated from healthy individuals. In contrast to CD29 and the other adhesion markers that were analyzed, CD49d was expressed in markedly higher density on Th1 cells when compared with Th2 cells (Figure 2A). Next, we analyzed the expression levels of CD49d and CD29 on CD4+,CD45RA− T cells in 6 RA patients before and after treatment with anti-TNFα. In contrast to CD29 (Figure 2C), the percentage of high CD49d-expressing cells was increased after treatment and, moreover, correlated significantly with the alterations in the Th1:Th2 ratio (P = 0.04) (Figure 2B).

DISCUSSION

The present study analyzed the effects of anti-TNFα mAb treatment on the phenotypic and functional characteristics of T cell subsets in the peripheral blood of RA patients. A significant increase in the number of CD45RA− memory T cells of both the CD4+ and the CD8+ T cell population was observed shortly after anti-TNFα therapy, with a concomitant rise in the Th1:Th2 ratio of the CD4+,CD45RA− T cell population, but not of the CD8+ T cell population. These findings indicate that the increase in peripheral blood T cell numbers after anti-TNFα mAb therapy is mainly due to an increase in CD45RA− memory T cells, which, with respect to the CD4+ T cell subset, have a Th1-like phenotype.

The expression of adhesion molecules on the synovial endothelium and the density of synovial infiltration of inflammatory cells were both found to be reduced after anti-TNFα mAb treatment of RA patients (42). It has been proposed that the diminished activation of endothelial cells in the synovial microvasculature leads to a decreased migration of leukocytes to the joints. In accordance with this hypothesis, the rapid increase of lymphocyte counts in the peripheral blood of treated patients correlated with clinical benefit (37,38).

In the present study, we refined the model of the mode of action of anti-TNFα therapy by demonstrating that the increase in lymphocyte numbers is greater for Th1 cells than for Th2 cells. The data therefore are consistent with the assumption that CD4+,CD45RA− Th1-like T cells preferentially migrate to the inflamed tissue in the joints of RA patients. In accordance with this, T cells isolated from synovium or synovial fluid of RA patients were observed to predominantly express Th1 cytokines (43,44), and the selective homing of Th1 cells, and not Th2 cells, into inflamed joints of mice was recently demonstrated (45). Moreover, the present data confirm the finding of an inverse relationship between serum TNFα levels and the ratio of IFNγ:IL-4 production of peripheral blood T cells (46). The finding of diminished migration of Th1-like T cells into the inflamed tissues after anti-TNFα treatment is supported by the observed increase in the proportion of high CD49d-expressing CD4+ ,CD45RA− T cells. In accordance with the finding that Th1 cells express a markedly higher density of CD49d on the cell surface when compared with Th2 cells, the increase in the number of high CD49d-expressing CD4+ T cells in anti-TNFα-treated patients correlated with the increase in the Th1:Th2 ratio. The rapid down-regulation of VCAM-1 in the synovium (42) could therefore be an important factor for inhibiting Th1 cells from migrating into the synovium.

Within the CD4+ ,CD45RA− T cell population, cells that have lost the CD27 molecule from the cell surface represent highly differentiated memory T cells that can secrete considerable amounts of either IFNγ or IL-4 upon stimulation (39). No alteration in the percentage of CD27− T cells within the CD4+,CD45RA− population was observed. It could therefore very well be that both CD27+ and CD27− memory CD4+ T cells migrate equally well to the peripheral inflamed tissues. The described increase in CD27− ,CD4+ T cells in the cellular infiltrates in the synovium (47,48) could therefore be explained by a postmigratory loss of the CD27 molecule from the cell surface, as previously proposed (47).

In a similar way of reasoning, one could hypothesize that the CD45RA− ,CD27+ subset of the CD8+ T cell population, which is also increased in both number and percentage in the peripheral blood after anti-TNFα mAb therapy, is inhibited from migrating to the inflamed tissues. Accordingly, an enrichment of CD27+ ,CD8+ T cells in the RA synovium and synovial fluid has been demonstrated (47). The recent analysis of the phenotypic and functional properties of phenotypically separated CD8+ T cell subsets revealed that this CD8+ ,CD45RA− ,CD27+ subset in healthy individuals consists of memory-type cells, which produce a wide range of cytokines and can provide helper activity for B cell differentiation (40). Thus, this CD8+ T cell subset, in addition to the previously proposed CD4+ ,CD45RA− ,CD27+ T cell subset (47), might contribute to the B cell activation and subsequent immunoglobulin production as observed in the RA synovium. However, no increase in the IFNγ:IL-4 ratio was observed in the peripheral CD8+ T
cell subset could be identified on the basis of IL-4 and IFNγ production. Selective inhibition of migration of CD45RA− T cells could contribute to the therapeutic efficacy of anti-TNFα. Patients with higher increases in the Th1:Th2 ratio after therapy tended to show higher increases in the number of circulating lymphocytes and stronger decreases in DAS (data not shown), but this did not reach statistical significance.

Previously, improved T cell mitogen- and recall antigen-induced proliferative responses of PBMC were reported to occur after anti-TNFα treatment of RA patients, which was suggested to be caused by a restoration of T cell function after removal of TNFα (49). In view of our findings, the increased responsiveness could be explained by an increase in the proportion of the memory T cell subset, which is likely to contain an increased frequency of recall-reactive T cells (50–53). Responses to recall antigens (tetanus toxoid, purified protein derivative, streptokinase-streptodornase) analyzed from anti-TNFα mAb-treated RA patients are known to be mainly mediated by Th1-like T cells (54–56), which are also found to be increased in number after anti-TNFα treatment.

In conclusion, the present findings show that after anti-TNFα treatment, the increase in lymphocyte numbers in the peripheral blood is greater for Th1 cells than for Th2 cells. Down-regulation of adhesion molecules on the synovial endothelium, selectively inhibiting the homing of Th1-like, memory CD4+ T cells to inflamed joints, might explain this observation.

ACKNOWLEDGMENT

We gratefully acknowledge Centocor, Malvern, PA, for cooperation.

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Anti-TNF-α mAb and Th1 cells in RA


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