Anti-TNFα Therapy Modulates the Phenotype of Peripheral Blood CD4+ T Cells in Patients with Posterior Segment Intraocular Inflammation

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PURPOSE. Posterior segment intraocular inflammation (PSII) is a putative Th1 CD4+ cell mediated autoimmune disorder. In experimental autoimmune uveoretinitis, neutralization of tumor necrosis factor (TNF)-α induces suppression of Th1 cells, macrophage activation, and target organ damage. Previous studies implicated an efficacy of anti-TNFα therapies in patients with PSII. This study investigated the immunomodulatory effect of anti-TNFα therapy to find predictors of effective immunosuppression in PSII.

METHODS. Fifteen patients with PSII refractory to conventional immunosuppressive therapy received a single infusion of a recombinant protein generated by fusing the p55 TNFα receptor with human IgG1. During 17 treatment periods, visual acuity (logarithm of the minimum angle of resolution [logMAR]) was monitored as a response criterion. Phenotype markers of CD4+ T cells were analyzed before and 2, 4, and 12 weeks after therapy. Expression of intracellular cytokines (interferon [IFN]-γ, interleukin [IL]-10, and TNFα) and Th1/Th2-specific chemokine receptors (CXCR3, CCR4, and CCR5) on peripheral blood CD4+ T cells was determined using flow cytometry.

RESULTS. The fraction of IL-10–expressing CD4+ T cells was increased during 12 of 17 treatment periods within 2 weeks after treatment. During eight treatment periods, this increase was associated with an improvement of visual acuity of at least 0.2 logMAR within 4 weeks (P = 0.029). The ratio between IL-10- and IFNγ-expressing CD4+ T cells was significantly increased 2 weeks after therapy (P = 0.015).

CONCLUSIONS. Neutralizing TNFα activity in PSII increases the fraction of peripheral blood CD4+ T cells expressing IL-10, which correlates with a recovery of visual function. (Invest Ophthalmol Vis Sci. 2004;45:170–176) DOI:10.1167/iovs.03-0659

The pleiotropic cytokine tumor necrosis factor (TNF)-α is produced by a variety of cell types, including T lymphocytes, and mediates its effects through two receptors, p55 (TNFr1) and p75 (TNFr2).1,2 During inflammation, TNFα activates T cells and macrophages and upregulates endothelial adhesion molecules and proinflammatory cytokines, playing a central part in both the induction and maintenance of inflammation in autoimmune reactions.1,3,4

Noninfectious posterior segment intraocular inflammation (PSII) is a putative antigen-specific CD4+ T-cell-mediated autoimmune disease that includes intermediate, posterior, and panu veinitis.5,6 The experimental model of PSII, experimental autoimmune uveoretinitis (EAU), which parallels the clinicopathological features of PSII, is mediated by T-helper type 1 (Th1) CD4+ T cells, and TNFα plays a key role in its pathogenesis.7–9 The presence of elevated TNFα in the aqueous humor and serum of patients with uveitis,10 and the recent successful use of anti-TNFα therapies in neutralizing TNFα activity in patients with various forms of uveitis,11–14 implicates TNFα as a crucial mediator of inflammation in PSII, similar to its role in rheumatoid arthritis.15 Commercially available anti-TNFα preparations administered in these studies include etanercept, a p75 TNFα receptor fusion protein,16 and infliximab, a chimeric IgG monoclonal antibody directed against TNFα.17

In EAU, we showed that TNFα inhibition with a p55 TNFα receptor fusion protein (TNFR-Ig) ameliorated intraocular inflammation and led to decreased interferon (IFN)-γ and increased interleukin (IL)-4 production by the retinal T-cell infiltrate, suggesting that TNFR-Ig caused deviation of the immune response toward the Th2 type in parallel with the improvement in clinical activity.18 However, the immunomodulatory effects of anti-TNFα therapy in patients with PSII have not been elucidated. We conducted a phase I/II trial to investigate the clinical benefit of TNFR-Ig in patients with PSII refractory to conventional immunosuppression and found a significant amelioration of inflammatory activity and improvement of visual function (Murphy et al., manuscript submitted). In this study, we evaluated the effect of TNFR-Ig therapy on peripheral blood CD4+ T cell phenotype using cytokine (TNFα, IFNγ, and IL-10) and chemokine receptor (Th1-associated CCR5 and CXCR3, and Th2-associated CCR4) expression to look for evidence of systemic immunomodulation after treatment and to find predictors of effective immunosuppression.19–21

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Materials and Methods

Patients and Treatment Regimen

Fifteen patients were recruited from the uveitis clinics of the Aberdeen Royal Infirmary and the Bristol Eye Hospital in an open-label pilot study of TNFr-Ig for refractory PSII (5 men and 10 women; mean age, 42 years; range, 25–60). Ethics committee approval for this study was received, and informed consent was obtained from all participants. The study adhered to the principles of the Declaration of Helsinki. All patients had active chronic relapsing PSII at study entry that had not been improved by prednisolone (Pred) or by at least one immunosuppressive agent (cyclosporin A [CSA], tacrolimus [Tacr], methotrexate [MTX], azathioprine [AZA], or mycophenolate mofetil [MMF]), either because of drug intolerance or refractory disease. Each patient’s current immunosuppression was continued during the study. Dose reduction was attempted when disease control was achieved. The clinical data of the patient population are shown in Table 1. Thirteen patients were diagnosed with idiopathic PSII after a comprehensive clinical and laboratory workup and two patients had Behcet’s disease, but clinically apparent nonocular manifestations of the disease were absent in both cases.

TNFr-Ig is a chimeric molecule comprising the extracellular domain of the human p55 TNFr receptor fused to the hinge, CH2, and CH3 domains of the human IgG1 heavy chain and was manufactured as follows by the Therapeutic Antibody Centre (University of Oxford). A portion of cDNA coding for the extracellular domain of the p55 human TNFr receptor was amplified from a cDNA library kindly provided by Brian Seed. The DNA was ligated in frame to cDNA encoding the hinge, CH2 and CH3 domains of human IgG1. This construct is similar to the one described by Peppel et al.22 The chimeric gene was introduced into the glutamine synthetase expression vector and transfected into CHO-K1 cells using methionine sulfoximine as a selective agent.23 A transformant was obtained from each patient. The isolated lymphocytes were washed twice with culture medium) at 37°C for 4 hours. Brefeldin A (Golgiplug; BD Biosciences, Franklin Lakes, NJ) was added to the culture before receiving TNFr-Ig and 2 weeks, 4 weeks, and 3 months after treatment. Isolation reagents (Prepacyte and VitaLyse; BioErgonomics, St. Paul, MN) were used for the isolation and preparation of peripheral blood lymphocytes from 10 mL of heparinized venous blood obtained from each patient. The isolated lymphocytes were washed twice with phosphate-buffered saline (PBS).

To study intracellular cytokine expression, lymphocytes were cultured in PMA (phorbol 12-myristate 13-acetate) with ionomycin (ActiCyte PMMA BioErgonomics) at a volume of 1 mL of culture medium to the lymphocytes isolated from 1 mL of blood (<1 × 10^6 cells/mL of culture medium) at 37°C in 5% CO₂ for 4 hours. Brefeldin A (Golgiplug; BD Biosciences, Franklin Lakes, NJ) and monensin (Golgistop, BD Biosciences) were added at recommended concentrations immediately before cell culture. After surface staining for CD3 and CD4, cells were washed twice with flow cytometry (FACS) buffer (PBS with 1% bovine serum albumin and 0.1% sodium azide), fixed (Cellfix; BD Biosciences) for 20 minutes at 4°C, then washed a further two times before being

Phenotype Analysis of Peripheral Blood CD4+ T Cells

Patients underwent peripheral blood CD4+ T cell analysis immediately before receiving TNFr-Ig and 2 weeks, 4 weeks, and 3 months after treatment. Isolation reagents (Prepacyte and VitaLyse; BioErgonomics, St. Paul, MN) were used for the isolation and preparation of peripheral blood lymphocytes from 10 mL of heparinized venous blood obtained from each patient. The isolated lymphocytes were washed twice with phosphate-buffered saline (PBS).

Best corrected logMAR visual acuity was determined immediately before therapy with TNFr-Ig and during the follow-up period at 4 and 12 weeks. It was used as the primary clinical outcome measure. Visual acuity of the worse eye affected by PSII was considered for further analysis, unless an irreversible disease that compromised visual acuity and was unrelated to PSII was present in this eye. In such cases, the fellow eye if affected by PSII was considered for further analysis. Response to treatment was defined as an improvement in visual acuity of at least 2 lines (i.e., a decrease in logMAR score of at least 0.2), within 4 weeks after administration of TNFr-Ig in the eye selected by the criteria as defined earlier. To ensure the validity of visual acuity as a response criterion, we carefully monitored cataract formation and progression by the LOCS III method.23 Cataract was present in all but three patients. A limited progression of cataract by one grade of the LOCS III scale was observed in four patients (Table 1).
kept overnight in flow cytometry (FACS) buffer at 4°C. The following morning, the cells were permeabized using 0.1% saponin and intracellular cytokine staining with saturating concentrations of the following directly conjugated monoclonal antibodies (mAb) was performed before cytometry acquisition: IL-10-PE, IFNγ-PE, and TNFα-APC (BD Biosciences).

To study expression of chemokine receptors, lymphocytes were cultured in basal medium containing RPMI (ActiCyte basal medium; BioErgonomics) at a volume of 1 mL of culture medium to the lymphocytes isolated from 1 mL of blood (< 1 × 10^6 cells/mL of culture medium) at 37°C in 5% CO2 for 4 hours and immunofluorescence staining with saturating concentrations of the following directly conjugated mAbs was performed: CD3-FITC, CD4-PerCP, and either CCR4-PE, CCR5-PE, or CXCR3-PE. Isotype-matched antibodies were used as a negative control. All mAbs were acquired from BD Biosciences. The cells were incubated with the mAb for 30 minutes at 4°C in the dark and then washed twice in flow cytometry (FACS) buffer immediately before cytometry data acquisition.

Samples were acquired using a flow cytometer (FACSCalibur; BD Biosciences) and analyzed with the accompanying software (CellQuest; BD Biosciences). Ten thousand cells were analyzed in each sample. After setting the detection thresholds using isotype controls, the fraction of positive cells was calculated for each marker by gating on the CD3^+ CD4^+ cell population.

**Cytometric Analysis of Secreted Cytokines**

A flow cytometric cytokine bead array determination of IL-2, IFN-γ, IL-4, IL-5, and IL-10; TNFα; and IFNγ released from unstimulated and activated lymphocytes was performed in accordance with the instructions of the manufacturer (BD Biosciences). After peripheral blood lymphocyte isolation, 5 × 10^6 lymphocytes were incubated in 0.5 mL of unstimulated culture medium (ActiCyte basal medium) or activated culture medium (ActiCyte PMA) in 5% CO2 at 37°C for 4 hours. The samples were then centrifuged and the supernatants removed and stored frozen until cytokine bead array analysis, which was performed as described elsewhere.25

**Statistical Analysis**

The Wilcoxon signed rank test and the sign test were used in a longitudinal investigation of the patient population. Significance levels for individual tests were adjusted with respect to the Bonferroni correction for multiple tests to reach an overall significance level of 0.05. Cross-tabulation analysis was performed using the Fisher exact test.

**RESULTS**

**Clinical Observations**

In the severity grading of clinical uveitis, visual acuity is the best single determinant of disease activity.26 In 15 patients during 17 treatment periods, visual acuity was analyzed in worse eyes or only in eyes affected by PSII. LogMAR visual acuity in these eyes significantly improved 4 weeks after treatment with TNFr-Ig (P = 0.012, Fig. 1). Eyes with an irreversible disease unrelated to PSII were excluded from the analysis. During 8 of 17 treatment periods (47%), visual acuity improved by at least 0.2 logMAR (2 lines) in the first 4 weeks after treatment, which is the criterion for response to treatment. At 12 weeks, visual acuity no longer differed significantly from baseline (Murphy et al., manuscript submitted).

Doses of prednisolone, CSA or tacrolimus concomitantly administered with TNFr-Ig was reduced during 11 treatment periods (Table 1).

**Phenotype of Peripheral Blood CD4^+ T Cells**

In EAU, IFNγ, IL-10, and TNFα have important roles for the induction, progression and remission of ocular inflammation.27–29 In this study, the percentage of stimulated peripheral blood CD3^+ CD4^+ IFNγ^+ and CD3^+ CD4^+ TNFα^+ cells in patients with PSII did not change significantly during treatment according to the Wilcoxon test (Figs. 2B, 2C). In contrast, the percentage of stimulated CD3^+ CD4^+ IL-10^+ cells was found to be significantly higher 12 weeks after TNFr-Ig treatment in comparison to baseline values at day 0 using the Wilcoxon test (P < 0.01, Fig. 2A). To ensure that this significant difference was not due to the three patients with CD3^+ CD4^+ IL-10^+ fractions above 10% at 12 weeks, we verified this result with the sign test, which is independent of the extent of changes. This test also yielded a significant difference (P < 0.01) between the fractions of CD3^+ CD4^+ IL-10^+ cells at baseline and 12 weeks. Furthermore, we determined the ratio between IL-10 expressing and IFNγ expressing CD3^+ CD4^+ T cells. This ratio was significantly higher in PSII patients 2 weeks after TNFr-Ig administration in comparison to baseline values at day 0 (Fig. 3). Cytometric bead array analysis was performed to quantify the release of cytokines from unstimulated and activated lymphocytes obtained from patients immediately before TNFr-Ig therapy and after 2 weeks, 4 weeks, and 3 months. There was no significant change in IL-2, IFNγ, and IL-10; IFNγ; or TNFα concentrations in cell culture supernatants (data not shown).

Given that chemokine receptor expression on CD4^+ T cells correlates with Th1/Th2 phenotype,31 we determined whether there was any evidence of CD4^+ T cell phenotype switch. Furthermore, in EAU, chemokine receptor expression has been shown to be elevated in mononuclear cell infiltrates.30 In the present study, the expression of the chemokine receptors CXCR3, CCR4, and CCR5 on peripheral blood CD3^+ CD4^+ cells from PSII patients was not significantly altered by treatment with TNFr-Ig (Table 2).

**Association between Concomitant Immunosuppression and CD4^+ T Cell Phenotype**

Changes of CD4^+ T cell phenotype could have been due to immunomodulation induced by concomitantly administered immunosuppressants. Thus, treatment periods were classified into periods with CSA or tacrolimus versus periods without...
patients showed a rapid decrease of the percentage of CD3⁺CD4⁺IL-10⁺ cells 2 weeks after treatment. In four of them, visual acuity improved. However, this improvement was less than the threshold set for clinical response (ΔlogMAR ≥ 0.2). To further investigate this issue in a quantitative way we performed a correlation analysis. The extent of improvement of visual acuity at 4 or 12 weeks was not correlated with the extent of change of the fraction of IL-10 expressing CD4⁺ T cells at any time point analyzed. These findings indicate that the patients with the highest rise of IL-10 expressing CD4⁺ T cells are not necessarily those with the most extensive improvement of visual function.

Next, we analyzed the relationship between the recovery of visual acuity and changes of the fraction of CD4⁺ T cells expressing IL-10 in a qualitative way. Treatment periods were classified according to the extent of improvement of visual acuity. During eight treatment periods, patients exhibited an improvement of logMAR visual acuity of at least 0.2 within 4 weeks after treatment (i.e., these patients showed a clinical response). Modulation of the immune response should precede improvement of visual function. Therefore, IL-10 expression in CD3⁺CD4⁺ cells was determined at the earliest time point available after therapy (2 weeks). Table 3 depicts the relationship between the occurrence of an increase of IL-10 expressing CD3⁺CD4⁺ cells 2 weeks after TNFr-Ig infusion and the occurrence of clinical response to treatment (ΔlogMAR ≥ 0.2). The Fisher exact test revealed a significant difference (P = 0.029) in the frequency of the increase of IL-10 expression between the two classes of treatment periods (ΔlogMAR < 0.2 vs. ΔlogMAR ≥ 0.2). These data indicate a qualitative association between the occurrence of an increase of IL-10 expression in peripheral blood CD4⁺ T cells within 2 weeks after therapy and clinical remission of PSII.

Dose reduction of concomitantly administered immunosuppressives can be considered a criterion of response to treatment with TNFr-Ig. The association between IL-10 expression in CD3⁺CD4⁺ cells 2 weeks after therapy with TNFr-Ig and dose reduction of prednisolone, CSA, or tacrolimus within 4 weeks after treatment was analyzed with the Fisher exact test (Table 4). There was a significant difference (P = 0.028) in

Figure 2. Intracellular expression of cytokines (A: IL-10, B: IFNγ, C: TNFα) in stimulated peripheral blood CD4⁺ T cells before and after treatment with TNFr-Ig. n.s., not significant.

Figure 3. Ratio between IL-10- and IFNγ-expressing peripheral blood CD4⁺ T cells immediately before and 2 weeks after treatment with TNFr-Ig.
changes of IL-10 expression between the two classes of treatment periods (reduced doses versus constant doses).

**DISCUSSION**

TNFα is a principal mediator of inflammatory eye disease and inhibition of its activity in EAU ameliorates ocular inflammation by modulating the phenotype of retinal T-cell infiltrates and downregulating macrophage activity.10,28,31–33 The role of cytokines in PSII has been extensively studied in the EAU model, giving rise to the notion that TNFα is a pivotal mediator of tissue destruction.19 A 16-fold increase in TNFα mRNA expression has been detected in EAU mice, most likely produced by infiltrating T cells and macrophages.34

In this study, we investigated the effect of TNFα blockade on the phenotype of peripheral blood CD4+ T cells in patients with PSII. The rationale for studying peripheral blood T cells is that experimental models of organ specific ocular disease strongly suggest that systemic CD4+ cell activation occurs and is manifested by circulating T cells en route between the eye, regional lymph nodes and spleen (for review see Forrester and McMenamin).15. We found that the anti-TNFα agent TNFr-Ig induced an upregulation of IL-10 expression in peripheral blood CD4+ T cells and an alteration in the ratio of IL-10- and IFNγ-producing CD4+ T cells. These findings were associated with a recovery of visual function even in patients with longstanding retinal inflammation refractory to previous combination therapies of immunosuppressants. Although spontaneous remissions of PSII seem unlikely in view of these patients characteristics, a randomized trial will be necessary to confirm the results of this study.

In EAU, uveitogenic T cells are typically high IFNγ producing. These cells are overridden by IL-10 expressing CD4+ T cells. Moreover, the ratio between IL-10 expressing CD4+ T cells and an alteration in the ratio of IL-10- and IFNγ-producing CD4+ T cells. These findings were associated with a recovery of visual function even in patients with longstanding retinal inflammation refractory to previous combination therapies of immunosuppressants. Although spontaneous remissions of PSII seem unlikely in view of these patients characteristics, a randomized trial will be necessary to confirm the results of this study.

**TABLE 2.** Fraction of Peripheral Blood CD4+ T Cells Expressing Selected Chemokine Receptors before and after Therapy with TNFr-Ig

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>2 Weeks</th>
<th>4 Weeks</th>
<th>12 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CXCR3</td>
<td>24.0</td>
<td>24.2</td>
<td>26.2</td>
<td>29.5</td>
</tr>
<tr>
<td>CCR4</td>
<td>29.9</td>
<td>41.8</td>
<td>35.4</td>
<td>35.6</td>
</tr>
<tr>
<td>CCR5</td>
<td>22.5</td>
<td>36.9</td>
<td>24.0</td>
<td>19.3</td>
</tr>
</tbody>
</table>

Data are expressed as the mean percentage, with the range in parentheses.

**TABLE 3.** Contingency Table Showing Changes of IL-10 Expression of Peripheral Blood CD4+ T Cells 2 Weeks After Treatment with TNFr-Ig

<table>
<thead>
<tr>
<th></th>
<th>Δ logMAR &lt;0.2</th>
<th>Δ logMAR ≥0.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased IL-10 expression</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Decreased IL-10 expression</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are the number of patients showing a change in expression of IL-10 within 2 weeks after TNFr-Ig treatment (P = 0.029), as determined by changes in logMAR visual acuity within 4 weeks after treatment.

revealed a shift of the Th1/Th2 balance toward Th1 cells.30 Furthermore, during the recovery phase of PSII, the Th1/Th2 balance appears to be inverted with a predominance of Th2 cytokines such as IL-10.40 In this study, we did not detect changes of the fraction of IFNγ or TNFα expressing peripheral blood CD4+ T cells. However, we observed an increase of IL-10 expressing CD4+ T cells after TNFr-Ig treatment comparable to the reported increase of serum IL-10 levels during anti-TNFα therapy for patients with rheumatoid arthritis.41 Regarding the entire patient population (i.e., when patients were not classified into responders versus nonresponders), the fraction of IL-10 producing CD4+ T cells was found to be significantly increased from baseline values only at 12 weeks after treatment with TNFr-Ig. At this time point, visual acuity already declined and was no longer significantly different from baseline values. These findings suggest that the anti-inflammatory effects of peripheral blood CD3+ CD4+IL-10+ cells are overridden by pro-inflammatory processes in the retina at this time point. Despite the increase in intracellular cytokine production, the quantification of secreted IL-10 performed by cytometric bead array analysis did not show significant changes after TNFr-Ig therapy. However, this assay was performed on an unselected lymphocyte population and not isolated CD4+ T cells.

The occurrence of a rapid increase of CD3+ CD4+IL-10+ cells within 2 weeks after treatment was significantly associated with an improvement of visual function above the threshold set for clinical response and the possibility of reducing doses of concomitant immunosuppressants within 4 weeks after treatment with TNFr-Ig. This finding supports the hypothesis that systemic immunomodulation is linked to clinical remission of PSII. The extent of increase of the IL-10 expressing CD4+ T cell population, however, was not correlated with the extent of improvement of visual acuity. The heterogeneity of pretrial conditions in patients eyes as reflected by the variability of visual acuity at baseline may have contributed to the quantitative dissociation between these two parameters. However, we cannot exclude that the recovery of visual function could have been independent of the changes in CD4+ T cells expressing IL-10. Moreover, the ratio between IL-10- and IFNγ-producing CD4+ T cells 2 weeks after treatment was significantly increased in comparison to baseline values suggesting modulation of the T-cell response. Whether these changes

**TABLE 4.** Contingency Table Showing Changes of IL-10 Expression of Peripheral Blood CD4+ T Cells 2 Weeks After Treatment with TNFr-Ig

<table>
<thead>
<tr>
<th>Constant Dose of Pred/Tacr/CSA</th>
<th>Reduced Dose of Pred or Tacr or CSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased IL-10 expression</td>
<td>2</td>
</tr>
<tr>
<td>Decreased IL-10 expression</td>
<td>4</td>
</tr>
</tbody>
</table>

Data are the number of patients showing a change in expression of IL-10 within 2 weeks after TNFr-Ig treatment, in association with reduced or constant doses of immunosuppressants, measured within 4 weeks of TNFr-Ig treatment.
represents a shift in Th1/Th2 balance is not supported by our observations of chemokine receptor expression. However, data from in vitro experiments have suggested that expression of chemokine receptors CXCR3, CCR4, and CCR5 may not be specific for Th1 or Th2 cells as previously assumed by other investigators.

In all patients where IL-10 was not upregulated after treatment with TNF-R-Ig, pretreatment IL-10 expression was already relatively high and improvement of visual acuity, if it occurred at all, was rather limited. This latter finding may indicate a previous but failed attempt of the immune system to down-regulate ocular inflammation. The results of the cytokine expression analysis could also be due to an increase in T regulatory cells expressing IL-10. Further subtyping of CD4+ T cells (e.g., by CD25 or CD45RA), would have been necessary to elaborate this issue. In the context of the increased fraction of CD4+CD45RA+ memory T cells observed by Maurice et al. after anti-TNFα therapy in patients with rheumatoid arthritis, our data may lead to speculations about a specific population of memory CD4+ T cells induced by TNF-R-Ig. The alterations observed in peripheral T cells could be due to modulation of ocular inflammation or could represent side effects of TNF-R-Ig unrelated to the control of ocular inflammation. This issue is strongly associated with the question of whether TNF-R-Ig exerts its effects only on peripheral blood lymphocytes or whether it is also present and active in ocular tissues, which remains unresolved. Despite knowledge of strong chemokine receptor CXCR3 and CCR5 expression in the posterior segment of eyes of mice with EAU associated with infiltrating mononuclear cells, the current findings are in keeping with EAU data where TNF-R-Ig did not modulate T cell migration into retinal tissue.

In the clinical management of uveitis, the evaluation of parameters such as visual acuity or BIO score can be compromised by cataract formation, especially in patients with long-standing disease. Thus, assessment of other indicators of disease activity are needed to guide therapy for these patients. Nonspecific laboratory tests of inflammatory activity (e.g., C-reactive protein), are usually normal in isolated ocular inflammation. Monitoring of peripheral blood T cell markers during treatment might help to identify predictors of relapse or indicators of response to new therapies. Importantly, the increase of CD3+CD4+IL-10+ cells above baseline induced by TNF-R-Ig preceded or coincided with the clinical response (i.e., the improvement of visual acuity), if it occurred. Thus, IL-10 appears to have at least the potential to serve as a surrogate marker of TNF-R-Ig efficacy in PSII.

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