Cyclosporine vs Tacrolimus Therapy for Posterior and Intermediate Uveitis

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Objectives: To compare the efficacy and tolerability of tacrolimus and cyclosporine therapy for noninfectious posterior segment intraocular inflammation and to evaluate their effect on peripheral blood CD4+ T-cell phenotype and activation status.

Methods: Thirty-seven patients who required second-line immunosuppression for posterior segment intraocular inflammation were enrolled in this prospective randomized trial of tacrolimus vs cyclosporine therapy. The main outcome measures were visual acuity, binocular indirect ophthalmoscopy score, adverse effects, and quality of life. In addition, peripheral blood CD4+ T-cell phenotype and activation status were evaluated by flow cytometry before treatment and at 2, 4, and 12 weeks using CD69, chemokine receptor (CCR4, CCR5, and CXCR3), and intracellular cytokine (tumor necrosis factor α, interferon-γ, and interleukin 10) expression.

Results: Thirteen patients (68%) taking tacrolimus and 12 patients (67%) taking cyclosporine responded to treatment. Cyclosporine therapy was associated with a higher incidence of reported adverse effects. Mean arterial pressure and serum cholesterol level were significantly higher at 3 months in the cyclosporine group than the tacrolimus group. No significant difference was detected with regard to effect on quality of life or CD4+ T-cell phenotype.

Conclusions: Tacrolimus and cyclosporine were similar with regard to efficacy for posterior segment intraocular inflammation, but the results suggested a more favorable safety profile for tacrolimus therapy.

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Cyclosporine is an effective treatment for noninfectious posterior and intermediate uveitis and is now in widespread use in cases where prednisolone therapy has failed.1-3 However, enthusiasm is tempered by its toxic effect profile, which includes renal impairment, systemic hypertension, and metabolic abnormalities. Furthermore, it is estimated that approximately 20% of patients with uveitis are refractory to cyclosporine, indicating the need to evaluate more potent and safer treatment strategies.4

Tacrolimus, a natural metabolite of the bacterium Streptomyces tsukubaensis, is 10 to 100 times more potent than cyclosporine on a weight-for-weight basis.5 It shares many features with cyclosporine, in particular its modulation of CD4+ T-cell activity through the inhibition of interleukin 2 (IL-2) production, a mechanism that is pertinent to the treatment of noninfectious posterior uveitis. Several uncontrolled cohort studies6-8 have demonstrated the efficacy of tacrolimus in the treatment of posterior uveitis.

The safety and efficacy of tacrolimus- and cyclosporine-based immunosuppression have been extensively studied in solid organ transplantation. Tacrolimus has demonstrated a significant advantage over cyclosporine in relation to the incidence of transplant rejection episodes following kidney, liver, and pulmonary transplantation.9-11 In addition, it has a more favorable effect on systemic hypertension and lipid abnormalities after solid organ transplantation, giving it a safer cardiovascular risk profile.12-15 In contrast, substantive randomized trials that compared immunosuppressive agents for the treatment of noninfectious posterior segment intraocular inflammation (PSII), a term that encompasses intermediate, posterior, and panuveitis of presumed autoimmune etiology, are

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notably lacking. The aim of this study was to compare the efficacy and tolerability of tacrolimus and cyclosporine therapy for noninfectious PSII in a prospective randomized trial. In addition, we undertook a longitudinal study of the effect of tacrolimus and cyclosporine therapy on peripheral blood CD4\(^+\) T-cell phenotype and cytokine and chemokine receptor expression to assess if changes in CD4\(^+\) T-cell phenotype correlated with effective immunosuppression.

**METHODS**

**PATIENTS**

A total of 37 patients were recruited to this prospective randomized study of tacrolimus vs cyclosporine therapy for noninfectious PSII from 2 regional referral centers for uveitis in the United Kingdom (Bristol Eye Hospital [Bristol, England] and Aberdeen Royal Infirmary [Aberdeen, Scotland]) between May 2001 and April 2003. All patients who were invited to enroll in the study during this period agreed to participate. The study was approved by the ethics committee of each center, and informed consent was obtained from all patients. Inclusion criteria were chronic, noninfectious, sight-threatening PSII, which was defined as (1) unacceptably high doses of prednisolone (>10 mg/d), (2) recurrent high-dose steroid rescue for recurrent relapsing disease (>2 relapses per year despite maintenance prednisolone of >10 mg/d), or (3) severe sight-threatening disease that warranted immediate institution of high-dose prednisolone and a second-line agent. Reasons for exclusion from the study were pregnancy, diabetes mellitus, renal disease, concurrent infection, and recent live vaccinations.

**IMMUNOSUPPRESSION PROTOCOL**

Patients were randomized using a computer-generated non-stratified random-allocation sequence to receive either tacrolimus or cyclosporine at doses of 0.03 to 0.08 mg/kg daily and 2.5 to 5.0 mg/kg daily, respectively, with doses adjusted based on the clinical response and drug levels in the blood. Target whole blood trough levels were 8 to 12 ng/L for tacrolimus and 100 to 225 ng/L for cyclosporine, although trough levels below these ranges were acceptable, provided remission was achieved. All patients were analyzed in the group to which they were randomized. Neither the patients nor the investigators were masked to the treatment.

**CLINICAL ASSESSMENT**

Systemic and ophthalmic evaluation was undertaken before commencing tacrolimus or cyclosporine therapy, at 2 and 4 weeks, and then every 4 to 6 weeks thereafter according to clinical activity and response to treatment. Baseline assessment included history, general physical and ophthalmic examination, blood pressure, urinalysis, chest x-ray examination, and blood tests, including complete blood cell count, liver function tests, and creatinine, glucose, urate, C-reactive protein, and random serum cholesterol measurement. Patients were evaluated at each follow-up visit for adverse effects and clinical response to therapy. The International Uveitis Scoring System was used to assess clinical disease activity.

**OUTCOME MEASURES**

The main outcome measures were best-corrected logMAR visual acuity measured at 4 m with the Early Treatment Diabetic Retinopathy Study\(^{17}\) chart scored for individual letters and the binocular indirect ophthalmoscopy (BIO) score. Secondary outcome measures were adverse effects, vision-related quality of life, and health-related quality of life. Treatment response was defined as an improvement in visual acuity of at least 2 lines (a decrease in logMAR score of at least 0.2) in either eye or a decrease in BIO score to 0 in either eye within 3 months of commencing treatment with cyclosporine or tacrolimus. Patients who did not achieve these clinical criteria were defined as having had failed treatment. Relapses of intraocular inflammation were defined by a decrease in visual acuity of at least 2 lines or an increase in BIO score of at least 1 grade after achieving a clinical response. The duration of response to treatment was defined as the interval between commencing treatment and when relapse occurred or final follow-up if the response was maintained for the duration of the study. Treatment outcome was evaluated in this way for all 37 patients who entered the trial, with no exclusions.

**QUALITY-OF-LIFE ASSESSMENT**

Three self-administered questionnaires were used to assess health-related quality of life, vision-related quality of life, and adverse effects experienced before treatment with cyclosporine or tacrolimus and after 1, 3, 6, and 12 months. The health-related quality of life was evaluated using the UK standard version of the 36-item Short-Form Health Survey (SF-36),\(^{16}\) which consists of 36 items grouped into 8 scales to measure health, including physical functioning, social functioning, role limitations because of physical problems, role limitations because of emotional problems, mental health, energy or vitality, bodily pain, and general health perception. The vision-related quality of life was measured using the Vision Core Module-1 (VCM-1), a 10-item questionnaire that provides a subjective measure of concern regarding vision, with scores ranging from 0.0 (best score) to 5.0 (worst score) with 50 intervals.\(^{10}\) Finally, patients completed an adverse-effect questionnaire that contained a comprehensive list of well-recognized adverse effects to immunosuppressive agents. This questionnaire, which addressed the overall effect of the adverse effects on quality of life by asking the question “How much have these problems interfered with your quality of life?,” was scored from 0 to 5, which corresponded to the answers “not at all,” “hardly at all,” “a little,” “a fair amount,” “a lot,” and “an extreme amount,” respectively.

**PERIPHERAL BLOOD CD4\(^+\) T-CELL ANALYSIS**

Patients underwent peripheral blood CD4\(^+\) T-cell analysis before receiving tacrolimus or cyclosporine and after 2, 4, and 12 weeks, as described elsewhere.\(^{20}\) In brief, the expression of the activation marker CD69, the chemokine receptors CXC\(_R3\), CCR4, and CCR5, and the intracellular cytokines tumor necrosis factor \(\alpha\) (TNF-\(\alpha\)), interferon-\(\gamma\) (IFN-\(\gamma\)), and interleukin 10 (IL-10) by peripheral blood CD4\(^+\) T cells was determined using flow cytometry after a 4-hour incubation in either basal medium (unstimulated culture) for CD69 and chemokine receptors or phorbol-12-myristate 13-acetate with ionomycin and Golgi inhibitor (activated culture) for intracellular cytokines.

Statistical analysis was performed using the Wilcoxon signed rank test for paired data and the Mann-Whitney \(U\) test for unpaired data. Prism statistical software version 3.02 (GraphPad Software Inc, San Diego, Calif) was used for all statistical calculations, and significance was attributed at \(P<.05\). To detect a difference in efficacy between cyclosporine and tacrolimus, we estimated that 72 patients would need to be recruited to each
treatment group. This estimate was performed using a $\chi^2$ test with a 2-sided significance level of .05 and 80% power.

### RESULTS

#### DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Eighteen patients were randomized to cyclosporine, and 19 patients were randomized to tacrolimus. No major differences occurred between the groups with regard to clinical and demographic characteristics (Table 1). The dosage of oral prednisolone, the only other immunosuppressant allowed for the duration of the study, was similar in both groups (Table 2). All patients were followed up for a minimum of 3 months.

#### CLINICAL EFFICACY

A response to treatment, defined by an improvement in visual acuity of at least 2 lines in either eye or a decrease in BIO score to 0 in either eye within 3 months of commencing treatment, occurred in 13 patients (68%) taking tacrolimus and 12 patients (67%) taking cyclosporine. Nine patients (50%) taking cyclosporine and 8 patients (42%) taking tacrolimus achieved the visual acuity outcome measure within 3 months of commencing treatment. Nine (64%) of 14 patients taking cyclosporine and 8 (62%) of 13 patients taking tacrolimus who had a BIO score of greater than 0 at baseline achieved a decrease in BIO score to 0 in either eye within 3 months of commencing treatment. The significant improvements in visual acuity and BIO score were equivalent for cyclosporine and tacrolimus ($P=.56$ and $P=.65$, respectively, when comparing the groups) (Figure 1). Of the responders, 4 patients (33%) taking cyclosporine had a relapse during the follow-up period compared with 6 patients (46%) receiving tacrolimus. The median duration of response to cyclosporine and tacrolimus was 7 months (interquartile range, 4-13 months) and 6 months (interquartile range, 3-9 months), respectively. No difference was found between the 2 groups with regard to ability to taper oral prednisolone (Table 2).

#### TOLERABILITY

The occurrence of adverse effects to tacrolimus and cyclosporine is presented in Table 3. Cyclosporine therapy was associated with a higher incidence of adverse effects, including headache, gingival hyperplasia, fatigue, and palpitations. Seven patients (37%) taking tacrolimus experienced no adverse effects compared with only 1 patient (6%) taking cyclosporine. Urinary frequency, which was not due to urinary tract infection, occurred exclusively in 2 female patients taking tacrolimus and improved with dose reduction.

The biochemical and cardiovascular adverse effects of tacrolimus and cyclosporine are given in Table 4. Hypertension (blood pressure $>$140/90 mm Hg on 2 or more consecutive visits) developed in 4 patients (22%) taking cyclosporine and 1 patient (5%) taking tacrolimus. Despite comparable mean arterial pressure (MAP) at baseline, this was significantly higher in the cyclosporine group at 3 months ($P=.02$). Although no increase in median MAP occurred with tacrolimus therapy, a significant increase in MAP was detected at 1 and 3 months after commencing cyclosporine therapy compared with baseline ($P=.002$ and $P=.003$, respectively). Total serum cholesterol level was significantly higher in the cyclosporine group at 1 month ($P=.02$) and 3 months ($P=.04$). No patient started taking cholesterol-lowering agents during the study, and only 1 patient (in the cyclosporine group) commenced antihypertensive treatment. No significant difference in serum creatinine level was detected between the treatment groups. Two patients taking cyclosporine and 1 patient taking tacrolimus experienced a greater than 30% increase in serum creatinine level during the study, requiring discontinuation of treatment for 1 patient in each treatment group. Hypomagnesemia (magnesium level below normal range on 2 or more consecutive visits) developed in 3 patients (17%) taking tacrolimus and 1 patient (6%) taking cyclosporine. Only 1 of these patients (in the tacrolimus group) received magnesium supplements. One patient (6%) taking cyclosporine, who was also taking prednisolone, developed hyperglycemia (serum glucose level $>$144 mg/dL [$>$8.0 mmol/L]). No patients taking tacrolimus developed hyperglycemia.

#### TREATMENT FAILURES

Six patients in each treatment group were switched to alternative immunosuppression because of treatment fail-
ure, which was defined as failure to achieve an improvement of visual acuity of 2 or more lines in either eye or a decrease in BIO score to 0 in either eye within 3 months of commencing treatment. One of the patients in whom tacrolimus therapy failed was diagnosed as having intraocular lymphoma secondary to a systemic B-cell lymphoma 6 months after enrollment in the trial. This was characterized by chronic low-grade intermediate uveitis with cystoid macular edema, which rapidly resolved with systemic chemotherapy, having failed to respond to immunosuppressive therapy.

Two patients discontinued cyclosporine therapy because of toxic effects, one because of severe treatment-related hypertension and adverse effects, including nausea, vomiting, fatigue, and headache, and another because of nephrotoxicity. One patient discontinued tacrolimus therapy as a consequence of nephrotoxicity. Overall, in 7 patients (37%) taking tacrolimus and 8 patients (44%) taking cyclosporine, treatment failed because of either refractory disease or drug toxicity.

**EFFECT OF CYCLOSPORINE AND TACROLIMUS ON QUALITY OF LIFE**

Both tacrolimus and cyclosporine therapy led to significant improvements in vision-related quality of life (Figure 2). When comparing changes in VCM-1, the adverse effect questionnaire, and the SF-36 subscales after commencing treatment, we found no significant difference between the tacrolimus and cyclosporine groups. A significant improvement in the SF-36 mental health subscale was detected at 6 months for the tacrolimus group ($P=.01$). No significant changes in the other SF-36 subscales or the adverse effect questionnaire score were detected.
EFFECT OF CYCLOSPORINE AND TACROLIMUS ON CD4 T-CELL PHENOTYPE

Results pertaining to peripheral blood CD4 T-cell activation status and phenotype are given in Table 5. No significant difference was found on comparing the 2 treatment groups. A significant decrease in the percentage of CD4 T cells expressing the proinflammatory cytokine TNF-α occurred in the cyclosporine-treated group within 2 weeks of commencing treatment in parallel with the improvement in clinical activity (P = .03). No other significant changes in chemokine receptor, cytokine, or CD69 expression by CD4 T cells were detected in either group after commencing tacrolimus or cyclosporine therapy. When comparing treatment responders and nonresponders for the entire group, CD4 T-cell expression of TNF-α was significantly lower 2 and 4 weeks after commencing cyclosporine or tacrolimus therapy in the responder group, despite being comparable at baseline (Figure 3). No significant differences were found for the other cytokines, chemokine receptors, or CD69 when comparing responders and nonresponders.

COMMENT

Retrospective case series and uncontrolled observational studies have demonstrated a benefit for the use of cyclosporine and tacrolimus for sight-threatening PSII disease in combination with corticosteroids. In this prospective, randomized open-label trial, we observed that tacrolimus and cyclosporine had comparable efficacy (response rates of 67% and 68% with cyclosporine and tacrolimus, respectively) in the treatment of noninfectious PSII but that tacrolimus had a superior adverse-event profile. These findings are similar to those reported in the transplantation literature, in which tacrolimus has been shown to cause significantly fewer toxic effects, particularly with regard to systemic hypertension and hyperlipidemia.

Gingival hyperplasia was notably absent in the tacrolimus group, whereas it occurred in 5 patients (28%) taking cyclosporine. Fatigue and headache were also markedly more common with cyclosporine therapy, whereas urinary frequency, which was probably secondary to neu-
rotoxicity, occurred exclusively in 2 patients taking tacrolimus. A key outcome measure with respect to adverse effects was the adverse-effect questionnaire. In contrast to the frequency of reported adverse effects in each group, which was greater for cyclosporine, no difference was found for the adverse-effect questionnaire score. This may reflect the relatively low impact of these adverse effects on quality of life in the present study (the median scores for tacrolimus and cyclosporine at 1 month were 1 and 2, respectively, indicating that the adverse effects affected quality of life “hardly at all” and “a little”). Thus, although adverse effects were more common with cyclosporine therapy, their overall effect on patient well-being was not significantly greater than for tacrolimus therapy.

A potential benefit of tacrolimus over cyclosporine therapy observed in this study was its more favorable effect on systemic blood pressure and serum cholesterol level. Since hypertension and hyperlipidemia are known to have a major impact on cardiovascular health, it is possible that a sustained increase in blood pressure and cholesterol level above pretreatment levels increases the risk of cardiovascular morbidity in patients with uveitis, especially if added to other risk factors, such as smoking, obesity, physical inactivity, and family history. The cardiovascular risks of tacrolimus and cyclosporine therapy have been extensively compared in solid organ transplantation, in which similar findings to the present study have been observed. In a prospective study of 41 patients with uveitis treated with cyclosporine for 1 year at a mean daily dose of 4.1 mg/kg, a 78% incidence of systemic hypertension was noted, and after 5 years of treatment, hypertension persisted in 81% of the cohort despite cyclosporine dose reduction. Significant increases in serum cholesterol level in patients treated with cyclosporine for amyotrophic lateral sclerosis have also been reported. These problems are therefore not unique to the renal and hepatic transplantation population, in which metabolic and cardiovascular problems might be expected to occur. However, the significance of the increased cardiovascular risk, if any, presented by increases in serum cholesterol level and blood pressure in patients with uveitis and the decreased propensity to develop these adverse effects with tacrolimus compared with cyclosporine therapy is unknown at present and warrants further evaluation in long-term studies. Although hypertension and hypercholesterolemia may be controlled pharmacologically, complicating immunosuppressive regimens by the addition of these agents may lead to further adverse effects and poorer compliance. The more favorable toxic-effect profile of tacrolimus observed in this study may in part be explained by the relatively lower tacrolimus doses administered, as reflected by the drug trough levels. Equally, however, the results suggest that a similar efficacy to cyclosporine can be achieved with lower doses of tacrolimus. Therefore, in the treatment of uveitis, it may be more appropriate to aim for tacrolimus trough levels in the range of 5 to 10 µg/L, rather than 8 to 12 µg/L as in the present study.

Table 5: CD4⁺ T-Cell Phenotype and Activation Status

<table>
<thead>
<tr>
<th>Status</th>
<th>Cyclosporine Group (n = 14)</th>
<th>Tacrolimus Group (n = 7)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD69 unstimulated, %</td>
<td>27.5 (23.8–46.8)</td>
<td>26.4 (17.5–52.4)</td>
<td>.90</td>
</tr>
<tr>
<td>Week 2</td>
<td>24.7 (22.3–40.8)</td>
<td>28.5 (17.5–37.2)</td>
<td>.81</td>
</tr>
<tr>
<td>Week 4</td>
<td>26.2 (21.9–36.0)</td>
<td>39.0 (36.7–46.6)</td>
<td>.06</td>
</tr>
<tr>
<td>Week 12</td>
<td>35.0 (27.8–37.0)</td>
<td>20.5 (14.1–44.1)</td>
<td>.53</td>
</tr>
<tr>
<td>IL-10 activated, %</td>
<td>2.8 (0.9–3.8)</td>
<td>1.3 (1.1–2.1)</td>
<td>.62</td>
</tr>
<tr>
<td>Week 2</td>
<td>1.4 (1.0–2.9)</td>
<td>0.6 (0.4–1.4)</td>
<td>.17</td>
</tr>
<tr>
<td>Week 4</td>
<td>4.0 (1.2–4.9)</td>
<td>0.7 (0.2–2.2)</td>
<td>.08</td>
</tr>
<tr>
<td>Week 12</td>
<td>1.1 (0.7–1.3)</td>
<td>0.6 (0.3–1.5)</td>
<td>.53</td>
</tr>
<tr>
<td>TNF-α activated, %</td>
<td>70.8 (55.3–74.3)</td>
<td>74.9 (60.2–89.0)</td>
<td>.38</td>
</tr>
<tr>
<td>Week 2</td>
<td>48.7 (41.9–80.0)*</td>
<td>61.5 (50.3–73.3)</td>
<td>.63</td>
</tr>
<tr>
<td>Week 4</td>
<td>52.3 (35.1–68.6)</td>
<td>67.8 (65.7–78.3)</td>
<td>.17</td>
</tr>
<tr>
<td>Week 12</td>
<td>52.2 (43.2–67.4)</td>
<td>51.8 (43.7–84.1)</td>
<td>.61</td>
</tr>
<tr>
<td>IFN-γ activated, %</td>
<td>15.8 (9.3–21.9)</td>
<td>19.0 (7.2–25.7)</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Week 2</td>
<td>19.4 (12.4–28.6)</td>
<td>14.1 (5.3–27.0)</td>
<td>.40</td>
</tr>
<tr>
<td>Week 4</td>
<td>20.8 (10.2–27.9)</td>
<td>28.1 (10.4–33.7)</td>
<td>.81</td>
</tr>
<tr>
<td>Week 12</td>
<td>14.6 (10.1–27.4)</td>
<td>24.3 (5.2–26.2)</td>
<td>.69</td>
</tr>
</tbody>
</table>

Abbreviations: IFN-γ, interferon-γ; IL-10, interleukin 10; IQR, interquartile range; and TNF-α, tumor necrosis factor α.

*P = .03 compared with baseline for the cyclosporine group.

Figure 3: CD4⁺ T-cell expression of tumor necrosis factor α (TNF-α) before and after treatment with cyclosporine or tacrolimus therapy, showing a significantly lower TNF-α expression 2 and 4 weeks after commencing treatment in responders (n = 13) compared with nonresponders (n = 8). The horizontal lines represent the median value for each data set.
The inclusion of the patient with presumed ocular histoplasmosis in this study reflects our approach to the treatment of patients with inflammatory choroidal neovascular membranes in the clinic. The improvement of visual acuity from 0.88 to 0.44 logMAR within 3 months of commencing cyclosporine and prednisolone therapy supports the use of immunosuppression for inflammatory choroidal neovascular membranes, as we have reported previously. Because this was an intent-to-treat study, we did not exclude the patient with intraocular lymphoma from the analysis because this origin was not recognized until after recruitment to the study. Excluding this patient from the analysis would alter the number of treatment failures in the tacrolimus therapy group from 6 (32%) to 5 (26%).

The results of this study should be interpreted with several limitations in mind. First, since an insufficient number of patients were recruited based on the power calculation, the lack of difference between the 2 treatment groups with regard to efficacy may represent a type 2 error (false negative). However, an interim analysis of the data indicated that although the response rates for cyclosporine and tacrolimus were similar, significant differences in adverse-effect profile were apparent. Second, this was not a study of a single uveitis entity but a heterogeneous collection of PSII disorders that may differ with regard to clinical manifestations, severity, prognosis, and treatment response. Compensating for this heterogeneity would require the recruitment of large patient numbers, which is an impractical task given the rarity of these diseases. Finally, visual acuity is not an ideal outcome measure of treatment for uveitis, as recently highlighted by Rosenbaum et al. Thus, in patients with macular disruption, cataract, or glaucoma, the visual acuity may not improve despite the resolution of ocular inflammation.

Using multiple outcome measures such as visual acuity, BIO score, and resolution of cystoid macular edema or fluorescein angiographic evidence of retinal vasculitis, for example, would allow the detection of all treatment responders but would also introduce significant bias because in some cases 1 or more of these outcome measures might be achieved spontaneously. As a compromise, we chose visual acuity and the BIO score as the 2 outcome measures for efficacy.

The principal cell driving the efferent arm of the immune response in noninfectious PSII is the CD4+ T cell. We studied the effect of tacrolimus and cyclosporine therapy on CD4+ T-cell activation status by measuring CD69. We also investigated whether immunosuppression modulates CD4+ T-cell phenotype by measuring its effect on chemokine receptor and intracellular cytokine expression (T<sub>1</sub>17-associated CXCR3, TNF-α, and IFN-γ and T<sub>1</sub>R2-associated CCR4, CCR5, and IL-10). We found that CD69 expression was not useful as a surrogate marker of ocular inflammation because it did not decrease in parallel with the improvement in uveitis activity with tacrolimus or cyclosporine therapy, in contrast to a previous study. However, the greater reduction in CD4+ T-cell expression of TNF-α in patients who responded to tacrolimus or cyclosporine therapy compared with patients who were refractory to treatment suggests that CD4+ T-cell TNF-α may be a surrogate marker of treatment response. This finding and the significant decrease in TNF-α-positive CD4+ T-cell expression in the cyclosporine group provide a rationale for the use of anti–TNF-α therapy in PSII when other immunosuppressants have failed.

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REFERENCES


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**January 2005 Web Quiz Winner**

Congratulations to the winner of our January quiz, Salim Ben Yahia, MD, Fattouma Bourguiba University Hospital, Monastir, Tunisia. The correct answer to our January challenge was Coats disease. For a complete discussion of this case, see the Clinicopathologic Reports, Case Reports, and Small Case Series section in the February ARCHIVES (Lim WK, Nussenblatt RB, Chan CC. Immunopathologic features of inflammatory Coats disease. *Arch Ophthalmol.* 2005;123:279-281).

Be sure to visit the Archives of Ophthalmology Web site (http://www.archophthalmol.com) and try your hand at our Clinical Challenge Interactive Quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the ARCHIVES. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site and will also be able to choose one of the following books published by AMA Press: *Clinical Eye Atlas, Clinical Retina, or Users’ Guides to the Medical Literature.*