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Long-term follow-up of tacrolimus treatment in immune posterior uveitis

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PURPOSE. *To study the efficacy of tacrolimus in immune posterior uveitis.*
METHODS. *Twenty-one eyes of 11 patients with immune posterior uveitis under tacrolimus treatment were prospectively followed for 1 to 5 years. Tacrolimus dosage was adjusted to maintain blood levels in the range of 7 to 10 ng/mL. Systemic and ophthalmic evaluations were performed at baseline and during follow-up.*
RESULTS. *After a mean follow-up of 45 months, no treatment other than tacrolimus was necessary to control the inflammation in 6 cases (54.5%). The number of annual recurrences decreased from 3.2 to 1.29 during tacrolimus treatment (p=0.021). In four patients, tacrolimus was suspended after a treatment period of 27±3.5 months and a follow-up period of 12 months free of uveitis relapses. All four were free from relapses following tacrolimus withdrawal. Visual acuity remained unchanged in 16/21 (76%) eyes, deteriorated in 4/21 (19%), and improved in 1/21 (5%). Renal function transiently deteriorated in four patients from basal serum creatinine levels of 0.84, 1.1, 0.88, and 0.78 mg/dL to maximum levels of 1.33, 2.48, 1.38, and 1.39 mg/dL, respectively. This deterioration was directly related with elevated tacrolimus serum levels, returning to normal when doses were reduced. During the overall controlled evolution period, a slight increase of serum creatinine from a basal value of 0.89±0.2 mg/dL to a final of 1±0.19 mg/dL was detected, which was not statistically significant. All secondary effects were mild, transient, and did not require interruption of long-term treatment to be controlled.*
CONCLUSIONS. *Tacrolimus was well tolerated and useful in controlling posterior immune uveitis. Tacrolimus could be considered a real alternative to cyclosporine, and not only in cases of cyclosporine resistance or toxicity. (Eur J Ophthalmol 2007; 17: 69-74)*

KEY WORDS. *Immune uveitis, Posterior uveitis, Tacrolimus*

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INTRODUCTION

Immune posterior uveitis is a group of diseases of unknown origin, with a recurrent and chronic evolution and a poor response to treatment. It can severely affect visual outcome, even if anti-inflammatory or immunosuppressive treatment is administered. Corticosteroids are used as first-line treatment for many ocular inflammatory conditions, but the risk of adverse effects requires conversion to combination drug treatments with immunomodulatory agents such as antimetabolites (azathioprine, methotrexate, mycophenolate mofetil), alkylating agents (cyclophosphamide, chlorambucil), or T-cell inhibitors (cyclosporine, tacrolimus). To date, cyclosporine A has been the most effective method of controlling these diseases. However, a certain percentage of patients do not respond

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to this treatment, or they do so only partially or temporarily. The drug also has a number of severe secondary effects. Furthermore, cyclosporine A is not recommended for long-term use, particularly because of its capacity to induce nephrotoxicity in prolonged treatment regimes. For this latter group of patients, an alternative immunosuppressive therapy would be necessary.

FK506 (tacrolimus), in contrast to cyclosporine, is a macrolide antibiotic produced by fungi, yet its powerful immunosuppressive effects on T cells are similar to those of cyclosporine (1). The similar immunosuppressive properties of the two drugs are attributable to the fact that both agents inhibit the phosphatase activity of calcineurin, a common final pathway (2). FK506 directly inhibits the transduction signal mediated by the T-cell receptors necessary for the transcription of interleukin-2 and other lymphokines, and indirectly inhibits T-cell proliferation (1). It yields good results in the immunosuppressive treatment of kidney and liver transplants, and although nephrotoxic, it is better tolerated than cyclosporine A at the same levels of efficacy (3, 4). Decreased serum creatinine levels, increased creatinine clearance, and a lowering of lipid metabolism were noted in renal transplant patients converted from cyclosporine to tacrolimus, without increasing the rate of rejection (5).

In a multicenter study, Mochizuki et al showed for the first time the efficacy of tacrolimus in the treatment of refractory Behçet disease and in other types of immune endogenous uveitis. He reported an improvement or stabilization of visual acuity in 73% of the patients after 12 weeks of follow-up (4). Among the secondary effects described were the following: kidney function deterioration in 28.3%, neurologic symptoms in 18.9%, gastrointestinal symptoms in 20.8%, and hyperglycemia in 13.2%. As these secondary effects were mild, transitory, and dose-dependent, the authors recommended strict control of the therapeutic range by monitoring tacrolimus levels in total blood.

Subsequently, in another multicenter study, Ishioka et al also reported that tacrolimus was effective in the treatment of autoimmune uveitis, and not only for refractory cases (6). Sloper et al recently reported the efficacy of FK506 in the treatment of immune posterior uveitis in cases that were either refractory to cyclosporine A or those that had developed secondary effects to the latter drug (7). With the study by Murphy and colleagues (11), we now have good-quality evidence to show a superior safety profile at equivalent levels of immunosuppressive efficacy for tacrolimus over cyclosporine in patients with an autoimmune disease process such as uveitis.

In this article, we describe our experience with tacrolimus for the treatment of immune posterior uveitis in a study that included at least 1 year of follow-up for all patients.

METHODS

During a period from November 2000 to November 2005, 11 patients under tacrolimus treatment for at least 12 months were included in this uncontrolled treatment study. Informed consent was obtained from all patients before the start of tacrolimus treatment.

Inclusion criteria were as follows: patients above the age of 18 years with immune posterior active uveitis either refractory (4 patients) or intolerant (3 patients) to cyclosporine A, and cases of immune posterior uveitis not previously treated with any other immunosuppressive agent (4 patients).

Exclusion criteria were infectious uveitis, a medical history of arterial hypertension, basal renal function impairment (i.e., creatinine levels above 1.5 mg/dL, proteinuria or changes in urinary sediment, or abnormalities in echographic images), liver dysfunction, uncontrolled diabetes mellitus, active systemic infection, or cancer of any kind.

Treatment with tacrolimus was undertaken with an initial dose of 0.1 mg/kg body weight/day, orally administered bid. During follow-up, tacrolimus dosage was adjusted in order to maintain tacrolimus whole blood levels in the range of 7 to 10 ng/mL. Tacrolimus levels were measured by the enzyme-linked immunosorbent assay. Tacrolimus levels in blood were checked on an initial weekly basis until they were stable, which occurred approximately 1 month after inclusion in the study. Thereafter, tacrolimus levels were monitored bimonthly.

To rule out possible secondary effects, a clinical symptoms evaluation, blood pressure, weight, and a number of laboratory tests were performed at baseline, in each visit during follow-up, and 3 months after suppression of treatment. Laboratory tests performed were complete peripheral blood cell counts, glucose, urate, serum lipids, biochemical kidney glomerular and tubular function, and biochemical liver function tests. Renal function toxicity was defined as a rise in creatinine level greater than 30% above baseline value.

The ophthalmologic study included the following evalu-

ations:

• Snellen best-corrected visual acuity, in which a gain of two or more lines of vision was considered an improvement and a loss of two or more lines was considered deterioration.

• Inflammation in the anterior and posterior segment. The degree of inflammation was evaluated according to the Uveitis Scoring System of Ben Erza and Forrester (Complete Uveitis Scoring System [CUSS]) (8).

• Intraocular pressure.

The Wilcoxon paired test was used for statistical analysis. Statistical significance was stablized at 0.05. Analyses were carried out using the Statistical Package for the Social Sciences (SPSS 10.0).

RESULTS

A total of 21 eyes of 11 patients (10 female and 1 male) with an average age of 40.6±14.7 years (range: 32–59) were included in the study. Patients' clinical data are described in Table I. The autoimmune diseases included were idiopathic intermediate uveitis (3/11), idiopathic pars planitis (2/11), birdshot retinopathy (1/11), idiopathic panuveitis (1/11), Behcet disease (2/11), idiopathic vasculitis in young adults (1/11), and acute zonal outer retinopathy (1/11).

After a mean follow-up of 45 months (range: 15–60 months), no treatment other than tacrolimus was necessary in 6 cases (54.5%). In five other cases, tacrolimus had to be combined with oral corticoids in low doses (2.5–5 mg/24 h), and two of these patients required azathioprine and azathioprine plus mycophenolate mofetil, respectively. The average number of annual uveitis relapses prior to tacrolimus treatment was 3.2/year. Inflammatory recurrences decreased significantly with the start of treatment to 1.29/year (p=0.013; Wilcoxon test). In four patients, tacrolimus was suspended after a treatment period of 27±3.5 months (range: 23–30) and a follow-up period of 12 months free of uveitis relapses. In these patients, tacrolimus doses were tapered over a period of 6 months to 1 year until suppression. All of them were free of relapses after a follow-up period of 17.7±12.9 months (range: 8–38) following tacrolimus withdrawal.

Although tacrolimus treatment decreased uveitis relapses by the end of follow-up, visual acuity remained unchanged in 16/21 (76%) eyes, deteriorated in 4/21 (19%), and improved in 1/21 (5 %) (Tab. II). During follow-up, cataracts progressed in 7 of 21 eyes. In five of these cases, surgery was performed with no complications, owing to the good control of the inflammatory disease. In two cases, surgery was not indicated due to the poor visual prognosis associated with the lesions in the posterior segment.

Adverse side effects were observed in 9 of 11 patients treated. All secondary effects were mild, transient, related to highest serum tacrolimus levels, and did not require interruption of long-term treatment to be controlled. The following systemic adverse effects were found during the treatment period: distal hand tremor in 8/11 patients, headache in 6/11, dyspepsia in 3/11, subjective mammary turgidity in 2/11, acne in 1/11, and hair fragility with slight loss in 1/11. One patient with a family history of arterial hypertension had a slight increase of blood pressure to 142/94 mmHg that needed association of low dose diuretic and beta blocker.

TABLE I - CLINICAL DATA OF PATIENTS UNDER TACROLIMUS THERAPY

Patient no.	Diagnosis	Indication	Treatment before tacrolimus	Associated treatment
1	Behçet	No response	Pred+CsA+Aza	Pred
2	Panuveitis	CsA intolerance	CsA	none
3	Pars planitis	De novo	Pred	none
4	AZOOR	CsA intolerance	Pred+CsA+Aza	Pred+Aza+MM
5	Birdshot	De novo	none	none
6	Intermediate uveitis	No response	Pred+CsA+Aza	Pred+Aza
7	Intermediate uveitis	No response	Pred+CsA	Pred
8	Vasculitis	No response	CsA	None
9	Pars planitis	De novo	Pred	Pred
10	Behçet	De novo	None	None
11	Intermediate uveitis	CsA intolerance	Pred+CsA	None

Pred = Prednisone; CsA = Cyclosporin A; Aza = Azathioprine; MM = Mycophenolate mofetil

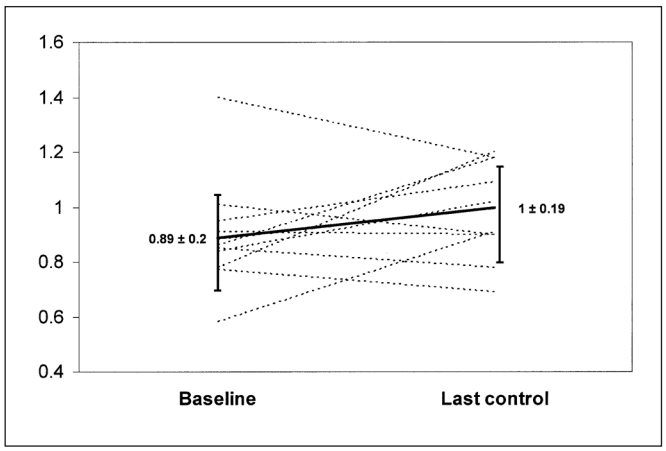

Fig. 1 - *Serum creatinine levels at baseline and in last analytical control. Changes were not statistically significant. Values in mg/dL.*

The time of appearance of these side effects differs from one patient to another, but in most they appeared in the initial treatment phase when tacrolimus doses were adjusted and the highest levels were reached. Light frontal headaches appeared at the start of treatment, but they were transitory in all but one patient. Self-treatment with paracetamol was necessary in some cases. The mild hand tremor was unrelated to tacrolimus blood levels.

Renal function transiently deteriorated in four female patients from basal serum creatinine levels of 0.84, 1.1, 0.88, and 0.78 mg/dL to maximum levels of 1.33, 2.48, 1.38, and 1.39 mg/dL, respectively. This deterioration was directly related to elevated tacrolimus serum levels to 15.1 and 20.1 ng/mL. In all these patients, renal function returned to previous normal levels when doses were reduced and reached optimal therapeutic tacrolimus levels. During the overall controlled evolution period, we found a slight increase of serum creatinine from a basal value of 0.89±0.2 mg/dL to a final of 1±0.19 mg/dL, which was not statistically significant (Fig. 1).

All four patients who completed tacrolimus treatment had serum creatinine levels that were similar to basal values 3 months later.

We found no cases of hyperglycemia, hematologic, or any other biochemical changes.

DISCUSSION

Tacrolimus is an effective treatment of refractory autoimmune uveitis, where patients develop cyclosporine toxicity or resistance. Strictly speaking, FK506 cannot be considered a new immunosuppressive agent, since the mode of action of cyclosporine and FK 506 is essentially identical (9). However, tacrolimus seems to have a high capacity for suppressing T-cells and T-cell-mediated inflammation in both animals and humans, possibly playing an important role in the good therapeutic results of tacrolimus on cyclosporin-resistant patients. Tacrolimus suppresses the induction of messenger RNA for interleukin-2 of CD4+ lymphocytes at dosages 100 times lower than cyclosporine (1).

Visual acuity was stable in most of our cases (76 %), decreased in four eyes (19%), and improved in one (5%) after a follow-up of 45 months. Sloper et al (7), Kilmartin et al (3), and Ishioka et al (6) had similar results after a follow-up of 4, 8.7, and 13.7 months, respectively. Sloper et al reported vision improvement in 2 of the 12 eyes (17.7%) and stabilization in 10 (83.3%). Of the 11 patients

TABLE II - VISUAL ACUITIES

Patient number	Initial VA RE	Final VA RE	Initial VA LE	Final VA LE
1	1	1	CF	CF
2	0.9	1	0.9	0.9
3	0.2	0.2	1	1
4	0.9	0.4	0.4	CF
5	1	1	1	1
6	0.2	0.1	0.1	0.2
7	0.8	0.7	0.3	0.7
8	0.9	0.9	NLP	NLP
9	0.5	0.6	0.4	0.5
10	1	1	1	1
11	1	0.6	0.7	0.5

VA = Visual acuity; CF = Count fingers; NLP = No light perception

in the Kilmartin et al study, vision stabilized in 9 (81.8%), improved in 1 (9.1%), and deteriorated in 1 (9.1%). Ishioka et al found that vision stabilized in 60.7% of the cases, improved in 25%, and deteriorated in 14.3%. Mochizuki et al, however, had better results. They found that vision improved in 55.2% of the eyes, remained unchanged in 17.7%, and deteriorated in 27.1% (4).

However, we believe that visual acuity is not the best measure of the efficacy of treatment. Indeed, an assessment of inflammatory activity is a more reliable and objective measurement of response to tacrolimus therapy. As we have seen, the number of annual recurrences decreased from 3.2 to 1.29 per year, and the median from 4 to 1.25 ($p=0.021$; Wilcoxon test). Analysis shows that the rate of inflammatory recurrences decreased in 9 of the 11 cases, while it increased in one and remained the same in the other case. These results are consistent with those reported by Mochizuki et al, who compared the rate of recurrence 12 weeks prior to treatment with the rate during 12 weeks of treatment, finding that it decreased from 3.6±2.5 to 2.7±2 ($p<0.05$) (4).

Tacrolimus not only reduced the rate of inflammatory recurrence in our patients, but it also allowed us to cancel other systemic drugs in six patients. In the remaining five cases, tacrolimus had to be combined with oral prednisone at low doses (<10 mg) to control the disease. Tacrolimus is therefore a valuable corticosteroid-sparing agent. After 27±3.5 months of treatment, tacrolimus treatment was discontinued in four patients. There were no recurrences in either of them after a follow-up period of 17.7±12.9 months. This protective effect following the end of treatment has also been reported by Mochizuki et al (10) and Ishioka et al (6). The latter author reported a patient who ended medication owing to drug intolerance, and no recurrence of inflammation was found in nine months of follow-up. Good control of inflammation with tacrolimus also allowed us to perform cataract surgery in five eyes with no postoperative complications.

In a recent controlled study, Murphy et al observed that tacrolimus and cyclosporine had comparable efficacy (response rates of 67% and 68% with cyclosporine and tacrolimus, respectively) in the treatment of posterior and intermediate uveitis but that tacrolimus had a superior adverse event profile (11). Tacrolimus may cause fewer adverse effects when compared with cyclosporine, in part due to its greater immunosuppressive potency and the lower dose consequently required to control uveitis. In our study, the mean dose required to maintain blood levels of tacrolimus in the range of 7–10 ng/mL was 0.12±0.03 mg/kg body weight/day (range 0.09–0.2), which is similar to that previously reported.

Tacrolimus should therefore be considered a real alternative to cyclosporine and not only an alternative in cases of cyclosporine resistance or toxicity. In the four cases where tacrolimus was administered as the first therapeutic option, the response was excellent. These results require a larger controlled study with more patients to be confirmed.

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