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Efficacy of Tacrolimus in Uveitis, and the Usefulness of Serum Tacrolimus Levels in Predicting Disease Control. Results from a Single Large Center

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ABSTRACT

Aims: To evaluate the efficacy of tacrolimus in patients with noninfectious uveitis, as well as the usefulness of serum tacrolimus concentration measurements in predicting disease control.

Methods: A retrospective review was carried out on 71 eligible patients from a single specialist uveitis center for minimum 1-year follow-up. Analysis was carried out on disease activity, visual acuity, and trough serum tacrolimus concentrations (STC).

Results: At 1-year follow-up, disease control was achieved in 49 patients (69.0%), this was significantly more likely in patients with trough STC levels above 5 ng/mL (88% vs 53%, $p = .002$). There was a significant reduction in oral prednisolone (dose ≥7.5 mg, 86% vs 54%, $p < .0001$). Tacrolimus was discontinued in 12 patients (17%) due to side effects.

Discussion: In this study cohort, oral tacrolimus was effective and well tolerated in the treatment of noninfectious uveitis. Trough STC between 5 ng/mL and 10 ng/ml was associated with better disease control at 1-year follow-up.

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In the treatment of noninfectious uveitis, a key aim is to control the degree of inflammation in order to prevent irreversible structural damage and visual loss. To achieve this, ophthalmologists utilize local and systemic corticosteroids, as well as a wide range of immunosuppressive agents. However, the use of these medications must be carefully balanced against the development of any side effects. This management dilemma can often be difficult, owing to the heterogenous nature of different disease etiologies, drug formulations and patients.

The introduction of corticosteroids in the 1950s revolutionized uveitis management. Topical and oral corticosteroid therapy provides rapid control of ocular inflammation, and remains the mainstay of treatment during the acute phase of the majority of noninfectious uveitis.[1] Although doses of oral prednisolone of up to 60 mg/day can generally be prescribed safely in the short term, significant systemic side effects can become problematic with longer treatment. As such, a tapering regime is recommended by most authorities, which in some cases necessitates the addition of an immunosuppressant.

Immunosuppressive agents can be broadly divided into antimetabolites, calcineurin inhibitors, alkylating agents, and biologics. These have been used extensively in bone marrow and solid organ transplantation to reduce the risk of rejection.[2] The efficacy of these agents in the management of uveitis has been demonstrated in numerous previous studies, although the number of randomized clinical trials is limited.[3,4]

Tacrolimus, a calcineurin inhibitor derived from the bacterium *Streptomyces tsukabaensis*, has become a dependable agent in the armamentarium of uveitis specialists. Tacrolimus acts to down-regulate the cytokine interleukin-2, which in turn inhibits the actions of $CD4^+$ T-cells. Its superiority to cyclosporine in preventing solid organ transplants rejection and control of graft vs. host disease has been well established, and the past decade has seen a rise in its use in targeted ophthalmic conditions such as birdshot choroiditis and Behcet's disease.[5–7]

It is well documented that the pharmacokinetic and pharmacodynamic properties of tacrolimus can be highly variable.[8] Tacrolimus is metabolized by CYP3A4 and CYP3A5, which are members of the cytochrome P450 family of enzymes. The activity of these enzymes can be influenced by genetic polymorphisms, dietary intake of inhibitors or inducers, and concurrent medications.[9] As such, therapeutic drug monitoring in the form of trough serum tacrolimus concentration (STC) is recommended to maintain its concentration within a narrow therapeutic range.[10]

Trough STC is generally measured at 12 hours following an oral dose of tacrolimus. In the context of solid organ transplantation, high trough STC was associated with azotemia and increased toxicity, whilst low trough STC was associated with rejection.[11] In the treatment of noninfectious uveitis, a trough STC target of 5–10 ng/dL is commonly adopted.

Despite the widespread use of tacrolimus in uveitis, the impact of trough STC has not been fully explored. As such,

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Synopsis: During the treatment of noninfectious uveitis with oral tacrolimus, trough serum tacrolimus concentration between 5ng/mL and 10ng/ml was associated with better disease control at 1-year follow-up.

the aim of this study was to investigate the efficacy, side effects and steroid sparing properties of tacrolimus, as well as the impact of trough STC on disease control.

Methods

This study was a retrospective case note analysis of patients treated by the uveitis service at Moorfields Eye Hospital, London, between 1st January 2011 and 31st March 2017. The study was performed in accordance with the tenets of the Declaration of Helsinki, and approval from the local Institutional Review Board was obtained.

Patients started on tacrolimus therapy for ocular inflammation during this period were identified through a search of the electronic records and their clinical case notes were retrospectively reviewed. A minimum follow-up of 1 year was required for inclusion. Patients within this study were treated according to existing management strategies utilized at the study center. This included adjustment of systemic immunosuppressant therapies based on disease activity, as well as periocular, orbital floor, or intravitreal forms of local steroid therapy as adjuncts to facilitate disease control.

Baseline characteristics including patient demographics, disease etiology and anatomical location according to SUN classification were recorded.[12] Disease activity was the primary outcome measure, where disease control was defined as quiescent clinical examination at the final visit and no flare-ups during the follow-up period. Other outcome measures included visual acuity, concomitant immunosuppressive therapy and their dosage, and the presence of any side effects.

Following the start of oral tacrolimus therapy, trough serum tacrolimus concentrations (STC) were monitored monthly until stabilization and bimonthly thereafter. Oral tacrolimus dosage was adjusted with a target trough STC of 5–10 ng/dL. Blood samples were taken at 12 hours following the evening dose of tacrolimus, but prior to the subsequent morning dose. In cases where Tacrolimus was stopped before 1 year, the reasons for cessation were recorded. The average trough STC between the final two measurements of the follow-up period or termination of tacrolimus treatment, whichever came sooner, was used for analysis.

Collected data were entered into a spreadsheet created using Microsoft Excel 2016 (Microsoft Corp, Redmond, Washington). Statistical analysis was conducted using IBM SPSS software (version 25, IBM Corp., Armonk, NY). Data normality was assessed using the Shapiro–Wilk test, and non-normally distributed data was compared using the Wilcoxon Signed Rank test. Categorical data were analyzed using the Fisher exact and chi-square tests. Univariate logistic regression was performed to assess potential associations for disease control. Factors with *p*-value below 0.1 were incorporated into a backward stepwise multivariate logistic regression model to calculate likelihood ratios, and the Nagelkerke method was used to calculate R^2 values.

Results

Seventy-one eligible patients were identified between 1st January 2011 and 1st April 2017, and their baseline characteristics are shown in Table 1. Serum tacrolimus levels were not available for five patients, including three patients in whom tacrolimus treatment was stopped within the first month due to significant side-effects, and one patient who developed significant renal impairment within 2 weeks. As such, statistical analysis regarding serum tacrolimus levels included 66 patients.

Disease control, as defined previously, was achieved in 49 patients (69.0%) at the end of the 1-year follow-up period (Table 2). At this time point, disease control was significantly

Table 1. Patient demographics and disease characteristics.

Age		49.06 ± 11.59 years
Gender		
	Female	47 (66%)
	Male	24 (34%)
Ethnicity		
	Caucasian	59 (83%)
	Asian	8 (11%)
	Black African/Caribbean	3 (4%)
	Chinese	1 (1%)
Laterality		
	Bilateral	60 (85%)
	Unilateral	11 (16%)
Anatomical location		
	Posterior uveitis	38 (54%)
	Intermediate uveitis	13 (18%)
	Panuveitis	12 (17%)
	Scleritis	7 (10%)
	Anterior uveitis	1 (1%)
Etiology		
	Birdshot	30 (42%)
	Idiopathic	20 (28%)
	Behcet's	4 (6%)
	Multifocal choroiditis	3 (4%)
	Sarcoidosis	3 (4%)
	VKH	3 (4%)
	Punctate inner choroidopathy	2 (3%)
	Tubercular/serpiginous	2 (3%)
	Granulomatosis with polyangiitis	1 (1%)
	Presumed ocular histoplasmosis syndrome	1 (1%)
	Surgically induced	1 (1%)
	Sympathetic ophthalmia	1 (1%)
Total		71

Table 2. Disease control at 1 year follow-up.

		Disease uncontrolled	Disease controlled
Number		22	49
Tacrolimus therapy	Stopped before 1 yr	16 (73%)	4 (8%)
	Continuing at 1 yr	6 (27%)	45 (92%)
		p < .0001	
Average trough serum tacrolimus concentration	< 5 ng/mL	15 (79%)	17 (36%)
	≥ 5 ng/mL	4 (21%)	30 (64%)
		p = .002	
Local steroid therapy	Not given	19 (86%)	48 (98%)
	Given	3 (14%)	1 (2%)
		p = .085	
Final oral steroid therapy dose	<7.5 mg	13 (59%)	20 (41%)
	≥7.5 mg	9 (41%)	20 (41%)
		p = .15	
Concurrent immunosuppressive agents during treatment period	Decreased by 1	4 (18%)	7 (14%)
	Unchanged	10 (45%)	39 (80%)
	Increased by 1	8 (36%)	3 (3%)
		p = .003	

more likely in patients who remain on tacrolimus treatment as compared to patients in whom tacrolimus was stopped (88% vs 20%, $p < .0001$).

Disease control was also significantly more likely in the average trough STC ≥ 5 ng/mL group as compared to the average trough STC < 5 ng/mL group (88% vs 53%, $p = .002$). Of note, four patients (of 34, 12%) did not achieve disease control despite satisfactory trough STC. Disease diagnosis, sub-categorized into three groups as Birdshot, idiopathic and "miscellaneous" did not influence success of tacrolimus in achieving control.

Median visual acuity significantly improved ($p = .043$) from 0.20 (IQR: 0.00–0.30) at the start of tacrolimus treatment to 0.00 (IQR: 0.00–0.30) at 1 year follow up.

In total, tacrolimus was discontinued in 20 patients (28%) during the first year. Among these, three patients (4%) achieved good disease control, and remained stable after tacrolimus was stopped; five patients (7%) were placed on alternate therapy due to poor disease control; and 12 patients (17%) were intolerant of tacrolimus due to significant side effects (Table 3). The median dose of oral tacrolimus dose used was 3.0 mg (IQR: 2.0–4.0 mg, range: 1.0–8.0 mg). No statistically significant correlation was found between the oral tacrolimus dose and serum tacrolimus level ($p = .77$).

The proportions of patients using concurrent immunosuppressive therapy at the start of tacrolimus therapy and 1-year follow-up is shown in Table 4. A higher proportion of patients with poor disease control required an increase in the number of concurrent systemic immunosuppressive therapies as compared to those with good disease control (36.4% vs 6.1%, $p = .003$, Table 2). In addition, four patients underwent periocular or orbital floor steroid injection, one of whom also underwent intravitreal steroid injection. There were no statistically significant differences in the proportion of patients undergoing local steroid therapy between the groups (2.0% vs 13.6%, $p = .085$).

Overall, there was a statistically significant decrease in the median dose of oral prednisolone by the end of the follow-up period (11.25 mg vs 8.75 mg, $p < .0001$). This was also reflected by a significant decrease in the proportion of patients being treated with a dose of prednisolone ≥7.510 mg (79% vs 34%, $p < .0001$). When comparing groups in reference to disease control, no statistically significant differences were found in the proportion of patients taking oral steroid dose ≥7.5 mg (41% vs 59%, $p = .15$).

Univariate logistic regression of predictive factors associated with disease control was performed; average trough STC showed statistical significance (OR: 1.65, 95% CI: 1.23–2.21, $p < .001$, $R^2 = 0.291$), change in concurrent immunosuppressive therapy showed borderline significance (OR: 0.41, 95% CI: 0.-15–1.09, $p = .072$, $R^2 = 0.068$), and final prednisolone dose did not show significance (OR: 1.024, 95% CI: 0.95–1.11, $p = .565$, $R^2 = 0.007$). The final multivariate logistic regression equation is shown in Table 5 and has an R^2 value of 0.388.

Table 3. Side effects from oral tacrolimus at 1-year follow-up.

Mood and sleep disturbance	6 (9%)
Pain	4 (6%)
Tremors	2 (3%)
Paraesthesia	2 (3%)
Gastrointestinal symptoms	2 (3%)
Hair loss	1 (1%)
Renal impairment and haematuria	1 (1%)
Total discontinuation due to side effects	12 (17%)

Table 5. Multivariate model for disease control.

Factor	Odds ratio	95% CI	P value
Average trough STC	1.67	1.21–2.29	0.002
Change in concurrent immunosuppressive therapy	0.23	0.07–0.84	0.026
		$R^2 = 0.388$	

Discussion

In this cohort of patients with uveitis of heterogeneous etiologies, oral tacrolimus treatment was effective and relatively well tolerated. Disease control, as defined by quiescent clinical examination at 1-year follow-up and no evidence of flare-ups, was achieved in 69% (49/71) of patients. This is comparable to previous studies conducted on tacrolimus in similar patient cohorts, which reported figures of around 68%.[6,13]

Findings from the Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study demonstrated uveitis disease control rates at 12 months of 62–76% for azathioprine, methotrexate, mycophenolate and cyclophosphamide, which are comparable with the findings of this study.[14–17] Notably, cyclosporine appeared to be less efficacious at 52%.[18] Evidence for mycophenolate and methotrexate has been further substantiated by more recent studies.[4]

There has been growing interest in the use of biologic agents in the treatment of noninfectious uveitis, particularly those within the anti-TNFα family such as infliximab and adalimumab.[19] The VISUAL 1 and VISUAL 2 trials established the efficacy of adalimumab in the treatment of both active and

Table 4. Concurrent therapy at the start of tacrolimus therapy and 1-year follow-up.

	Start of tacrolimus		1-year follow-up	
	N (%)	Median dose (mg, IQR)	N (%)	Median dose (mg, IQR)
Prednisolone*	63 (89%)	11.25 (10.00–23.75)	56 (79%)	8.75 (5.00–10.00)
Prednisolone ≥ 7.5 mg*	61 (86%)		38 (54%)	
Mycophenolate	39 (55%)	2000	35 (49%)	2000
Azathioprine	4 (6%)	100	3 (4%)	100
Methotrexate	3 (4%)	17.5	2 (3%)	17.5
Cyclosporine	0 (0%)	-	1 (1%)	200
Anti-TNF	1 (1%)	-	4 (6%)	-

*p < 0.0001; TNF, Tumor necrosis factor; IQR, interquartile range

steroid-controlled inactive uveitis as compared to placebo.[20–22] A recent meta-analysis concluded that adalimumab was effective in achieving disease control in 79% (95% CI: 69%-87%) of patients for follow-up of ≥12 months.[23] Notwithstanding this, conventional immunosuppressive agents are still likely to have a significant role in the management of uveitis for the foreseeable future.

In our study cohort, discontinuation due to significant side effects occurred in 17% (12/71) of patients. In terms of tolerability, tacrolimus was comparable to most other agents such as methotrexate and mycophenolate within SITE and FAST studies.[4,14–16] In contrast, anti-TNFα agents appeared to be much better tolerated, with an overall reported side effect related discontinuation rate of 2.2%.[21,24] However, as the licensing for anti-TNFα agents in uveitis was a relatively recent event, only a small fraction of our study cohort was commenced on anti-TNFα treatment by the end of the follow-up period. It should also be noted that clinical trials designed for head-to-head comparisons between tacrolimus and anti-TNFα agents have not yet been conducted.

This study cohort also demonstrated a significant reduction in oral prednisolone dose after 1 year, reflected by a reduction in the proportion of patients being treated with oral prednisolone dose ≥10 mg (79% vs 34%, $p < .0001$). This appears to be more favorable than the findings of the SITE Cohort Study, which reported figures of 39% - 64% for the aforementioned agents,[8] and comparable to a recent study of methotrexate and mycophenolate mofetil.[25]

A major finding in this study was that an average trough STC ≥ 5 ng/mL was associated with a significantly higher rate of disease control compared to average trough STC < 5 ng/mL (88% vs 53%, $p = .002$). This is in keeping with existing literature in relation to organ transplantation, where higher rates of rejection were found to be associated with low trough STC measurements.[11] To our knowledge, this is the first study to highlight the impact of trough STC on disease control in a cohort of uveitis patients.

In cases where average trough STC measurements were below 5 ng/mL, it is likely that the bioavailability of tacrolimus was subtherapeutic. Whilst this association may not be absolute, the highly statistically significant logistic regression (odds ratio: 1.65, $p < .001$) suggests that trough STC appears to be a valuable predictor of tacrolimus in the treatment of uveitis. The R^2 value of 0.291 indicates that there are additional factors which contribute to the success of tacrolimus therapy.

The use of any concurrent immunomodulatory treatment can influence the treatment of uveitis. In this study, those with good disease control at the end of the follow-up period were significantly associated with an overall reduction of concurrent systemic immunosuppressive therapy ($p = .003$). The use of periocular, orbital floor, and intravitreal steroid therapy were not significantly associated with disease control (2.0% vs 13.6%, $p = .085$), although the sample size was relatively small. Together, these findings suggest that concurrent systemic immunosuppressive therapy was reduced with disease control, and increased as a response to disease activity.

Incorporating average trough STC and concurrent systemic immunosuppressive therapy use into a multivariate model revealed significant contribution of both factors (Table 5). The R^2 value of 0.388 indicates that there are additional factors which contribute to the success of tacrolimus therapy. The influence of concurrent systemic immunosuppressive therapies warrants further investigation, ideally in a prospective study with greater statistical power.

There is some evidence that measuring trough STC alone does not provide sufficient information to effectively adjust oral tacrolimus dose.[26] Furthermore, we found that trough STC measurements did not correlate with oral tacrolimus dose. Incorporating other factors, including CYP3A4/5 genotyping and a record of the presence of any concurrent inducers or inhibitors of cytochrome P450 may help to more accurately predict the effectiveness of tacrolimus. Indeed, it has been suggested that CYP3A5 genotyping should be included routinely as a step in tacrolimus therapy.[27]

Another potential contributor to low trough STC is patient adherence. In clinical practice, it would be of critical importance to explore the possibility of low patient adherence in the event of low trough STC. Patient non-adherence has been shown to be an independent predictor of graft failure in renal transplantation,[28] and its exact role in uveitis warrants further study. It is worth noting that a small proportion (12%) of patients failed to achieve disease control despite adequate trough STC measurements, the reasons behind this finding are currently unclear.

Ophthalmologists are becoming increasingly involved in the initiation and monitoring of immunosuppressive agents in the management of ocular inflammation, as this allows for more precise adjustments to be made based on ocular status. In order to accomplish this, it is important to discover and appreciate the factors which affect the action of drugs such as tacrolimus to maximize their efficacy.[29]

In summary, this study found oral tacrolimus to be well tolerated and effective in achieving disease control in 69% of the patients with a range of etiologies for noninfectious uveitis. Patients in whom therapeutic trough STC ranged between 5 ng/mL and 10 ng/mL were significantly more likely to achieve disease control than those below 5 ng/mL (88% vs 53%, $p = .002$). As such, this study highlights the importance of measuring trough STC during tacrolimus therapy in guiding dose optimization. Further investigations are warranted in determining the therapeutic value of other factors which contribute to tacrolimus efficacy, such as CYP3A5 genotyping.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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