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ORIGINAL PAPER

Long-term control of cystoid macular oedema in noninfectious uveitis with Mycophenolate Mofetil

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Abstract *Purpose* To evaluate the long-term safety and efficacy of Mycophenolate Mofetil (MMF) for the control of cystoid macular oedema (CMO) secondary to noninfectious uveitis (NU). *Methods* The medical records of 19 consecutive patients with inflammatory CMO treated with MMF were retrospectively reviewed. Patient demographics, best corrected visual acuity (BCVA), fluorescein angiography (FA), and optical coherence tomography (OCT) findings were evaluated. *Results* There were eight females and 11 males with a mean age of 32.9 ± 8.9 years. After a 1-year follow-up, 18/19 patients (31 eyes, 96.9%, $P < 0.05$) no longer had signs of CMO, as per their FA and OCT findings; the mean central foveal thickness (CFT) was 167.2 ± 12.8 μm. At the last follow-up, only 3/19 patients, all affected by Behçet panuveitis, had recurrences of CMO. Mean BCVA improved from 0.34 ± 0.14 SD at baseline to 0.65 ± 0.2 SD at last follow-up. *Conclusions* MMF was safe and effective in controlling CMO and in reducing the uveitis relapse rate in patients not responding to traditional immunosuppressants. Further case–controlled studies are mandatory to validate those preliminary results.

Keywords Cystoid macular oedema · Immunosuppression · Mycophenolate Mofetil · Uveitis

Abbreviations

AZA	Azathioprine
BPU	Behçet panuveitis
BS	Birdshot
CSA	Cyclosporine A
IIU	Idiopathic intermediate uveitis
IRV	Idiopathic retinal vasculitis
IVT	Intravitreal triamcinolone
STT	Sub-Tenon triamcinolone
MCP	Multifocal choroiditis with panuveitis
MMF	Mycophenolate mofetil
MTX	Methotrexate
ASAU	Ankylosing spondylitis associated uveitis
PIA	Previous immunosuppressive agents
Sarc	Sarcoidosis

Introduction

Uveitis is one of the leading causes of visual impairment in ophthalmology; one of its most

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dangerous sequela is the cystoid macular oedema (CMO) [1]. The prevalence of CMO is estimated in 28–64% of patients with uveitis and leads to permanent visual impairment in 8.5% of the cases [2]. Fluorescein angiography (FA) and, more recently, optical coherence tomography (OCT) [3–5] are used to detect it. Persistent or recurrent CMO could be due to an insufficient control of the inflammation and could be interpreted as a dangerous manifestation of the inflammation itself [6].

Steroids, both local [7] and systemic [8], are the first line of treatment for the control of CMO secondary to uveitis. On the other hand, long-term therapy with steroids could lead to complications such as high blood sugar level, osteoporosis, blood cell abnormalities, cataract, and glaucoma [9].

When the inflammation appears to be steroid dependent, immunosuppression is considered [10].

Several immunosuppressants have been proposed for the control of sight-threatening uveitis. Some of the drugs used are azathioprine [11], methotrexate [12], cyclosporine A [13], and, more recently, FK506 [14]. Considering the role of certain cytokines [15], such as transforming growth factor-β [16], on CMO pathophysiology, and the effect of some drugs on the production of those cytokines [17], other immunosuppressive agents could be considered for the management of uveitic CMO. Mycophenolate mofetil (MMF), another drug recently used for the control of uveitis, has shown promising results in downregulating those cytokines [18] that lead to the oedema.

MMF is a reversible, noncompetitive, selective inhibitor of the de novo pathway of purine synthesis, successfully used in the treatment of rheumatoid arthritis [19], pemphigus vugaris [20], and psoriasis [21]. Several reports have been published on its use for the control of uveitis: in 1998, Kilmartin and coworkers [22] reported a case series of patients, unresponsive to traditional immunosuppressants, successfully treated with MMF. More recently, a larger number of cases has been presented in a retrospective study by Thorne et al. [23] and Siepmann et al. [24], confirming the results previously published.

However, the reports mentioned above did not provide data regarding patients with CMO, and no statistical analyses have been carried out. In addition, we are unaware of any publication on the long-term control of inflammatory CMO using steroid-sparing drugs.

The purpose of this report is to assess the efficacy of MMF in controlling uveitic CMO.

Patients and methods

The study was designed as a retrospective case series.

We reviewed 19 notes of 19 patients affected by noninfectious uveitic (NU) CMO, unresponsive to traditional immunosuppressants, and treated with MMF. Patients have been examined at The Eye Clinic of the Polytechnic University of Marche in Ancona between 2003 and 2007. All patients were examined by one of the authors (PN).

Demographic and clinical variables were collected. Data was entered into an SPSS database (SPSS version 11.0.1, SPSS Inc., Chicago, IL) for the statistical analysis.

International Uveitis Study Group (IUSG) guidelines [25] and the standardization of uveitis nomenclature (SUN) working group [26] were used for the inflammatory scores and uveitis classifications.

An associated systemic disease was diagnosed based on the results of compatible historical, clinical, and/or laboratory data by the appropriate specialist such as a rheumatologist or a dermatologist.

All patients underwent a fluorescein angiography (FA; TRC-50 IX fundus camera, Topcon Corporation, Tokyo, Japan) and an optical coherence tomography (OCT; STRATUS OCT^{TM} Carl Zeiss Meditec Inc., Jena, Germany).

Full blood cell count, liver function, and renal function were tested every 4–6 weeks during the MMF treatment.

Decrease or improvement in visual acuity was defined as a reduction or increase of two or more lines from the initial best corrected visual acuity (BCVA), presented as mean $\pm$ standard deviation (SD). An early treatment diabetic retinopathy study (ETDRS) chart was used for the examination.

The uveitis and CMO relapse rates are presented as frequency (number of relapses in a period of 1 year).

The Kaplan–Meyer life-table analysis was used to describe the incidence of CMO resolution and steroid tapering.

The linear correlation between different variables was studied.

The primary end point was the long-term control of CMO secondary to NU with MMF with a dose of

steroids <10 mg/day, without OCT signs of intraretinal cysts and/or increase of central foveal thickness, and without FA evidence of CMO. Secondary end points were a reduction in the uveitis relapse rate during the MMF treatment and improvement in BCVA.

Results

The patients had the following diseases (Table 1): idiopathic retinal vascualitis 26.3% ($n = 5$), Behçet-disease-associated panuveitis 15.8% ($n = 3$), idiopathic intermediate uveitis 21% ($n = 4$), sarcoidosis 10.5% ($n = 2$), birdshot retinochoroidopathy 5.3% ($n = 1$), ankylosing spondylitis associated uveitis 10.5% ($n = 2$), and multifocal choroiditis with panuveitis 10.5% ($n = 2$); 32 eyes were considered. There were eight females and 11 males with a mean age of 32.9 ± 8.9 years.

Thirteen patients (68.4%) had bilateral chronic uveitis with associated CMO; six patients (31.6%) had unilateral chronic uveitis with secondary CMO. All patients changed therapy because of the persistency of CMO. At the beginning of their previous therapy, 17/19 patients (89.5%) received intravenous methylprednisolone followed by oral steroids at the starting dose of 1 mg/kg with an immunosuppressant; 2/19 patients (10.5%) had only oral steroids at the starting dose of 1 mg/kg coupled with an immunosuppressant. The mean duration of previous immunosuppressant was 9.6 ± 2.1 months. Before the introduction of MMF, the mean dose of systemic steroids was 31 ± 8.4 mg/day. All patients with unilateral affection had been treated at least one time with both sub-Tenon and intravitreal injections of triamcinolone acetonide (Kenacort™, Squibb pharma).

Before the introduction of MMF, all patients discontinued previous steroid-sparing drug treatments.

Table 1 Patient data

No./age/sex	Affection	PIA	Previous IVT	Previous STT	Follow-up (months)	BCVA RE			BCVA LE		
						Baseline	1 year	Last follow-up	Baseline	1 year	Last follow-up
1/45/M	IRV	CSA	No	No	27	0.32	0.63	0.63	0.1	0.32	0.32
2/18/M	IIU	CSA	No	No	33	0.2	0.5	0.5	0.32	0.63	0.5
3/42/F	MCP	AZA	No	No	25	0.5	0.8	0.8	0.5	0.8	1
4/38/M	IRV	CSA	No	No	21	0.32	0.63	0.63	0.32	0.63	0.63
5/23/F	ASAU	CSA	Yes	Yes	22	0.4	0.8	0.8			
6/51/M	Sarc	AZA	Yes	Yes	19	0.5	0.8	0.8	0.32	0.63	0.63
7/29/F	BPU	MTX	Yes	Yes	34				0.1	0.1	0.1
8/25/F	IIU	CSA	No	No	38	0.5	0.8	0.63	0.32	0.8	0.8
9/31/M	MCP	MTX	No	No	29	0.32	0.63	0.8	0.5	0.8	0.8
10/42/M	IRV	AZA	No	No	25	0.5	0.8	0.8	0.1	0.5	0.4
11/33/F	IRV	CSA	No	No	38	0.2	0.5	0.5	0.2	0.63	0.63
12/28/F	IRV	CSA	No	No	36	0.32	0.8	0.8	0.2	0.5	0.5
13/35/M	BS	AZA	No	No	28	0.5	1	1	0.32	0.63	0.5
14/21/M	IIU	CSA + MTX	Yes	Yes	34	0.32	0.8	1			
15/25/F	IIU	MTX	Yes	Yes	28				0.5	0.8	0.63
16/31/M	ASAU	CSA	No	No	31	0.2	0.5	0.4	0.5	0.8	0.8
17/28/M	BPU	CSA + MTX	Yes	Yes	27	0.32	0.63	0.63			
18/39/F	BPU	CSA + MTX	No	Yes	37	0.63	1	0.8	0.2	0.5	0.4
19/42/M	Sarc	CSA	Yes	Yes	38	0.2	0.63	0.5			

AZA, azathioprine; BPU, Behçet panuveitis; BS, birdshot; CSA, cyclosporine A, IIU, idiopathic intermediate uveitis, IRV, idiopathic retinal vasculitis, IVT, intravitreal triamcinolone; STT, sub-Tenon triamcinolone; MCP, multifocal choroiditis with panuveitis; MTX, metotrexate; ASAU, ankylosing spondylitis associated uveitis; PIA, previous immunosuppressive agents; Sarc, sarcoidosis

Table 2 Mean central foveal thickness at different times

CFT (μm)	Baseline	3 months	12 months	Last follow-up
Mean	441.3	167.4	167.2	162.7
SD	48.6	12.8	14.3	5.6

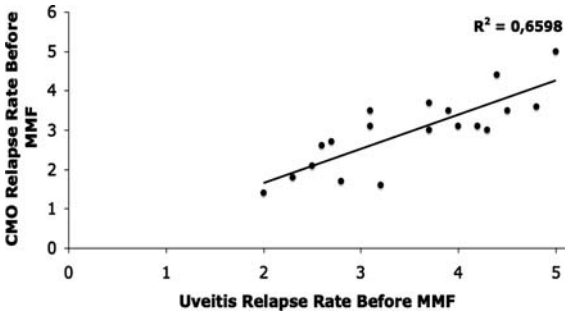

Fig. 1 Linear correlation between CMO relapse rate and uveitis relapse rate before MMF introduction

At baseline, mean BCVA was 0.34 ± 0.14 (range: 0.1–0.63); mean follow-up time was 30 ± 6 months (range: 19–38 months). Mean baseline central foveal thickness (CFT) was 441.3 ± 48.6 μm (Table 2).

The uveitis relapse rate (Fig. 1) had a strong correlation with the CMO relapse rate before MMF introduction ($R = 0.8123, R^2 = 0.6598, P < 0.0001$).

All patients were treated with intravenous methylprednisolone (1 g/day) for 3 days, followed by oral prednisone (1 mg/kg/day) coupled with MMF (1 g twice/day).

At 1-year follow-up, 18/19 patients (31 eyes, 96.9%, $P < 0.05$) had no signs of CMO, both verified by FA and OCT; the mean CFT was 167.2 ± 12.8 μm (Table 2). After 1 year of follow-up, 18/19 patients (94.7%) had no signs of uveal inflammation and CMO ($P < 0.05$). At last follow-up, 16/19 patients (28 eyes, 87.5%, $P < 0.05$) did not experience a CMO relapse, using MMF with a dose of steroid <10 mg/day. After 37 days, the probability of having a regression of OCT and FA signs of CMO was 98.2% (Fig. 2).

The probability of reducing the dose of steroids <10 mg/day was 97% after 25 weeks (Fig. 3); the median time observed for the tapering of oral prednisone <10 mg/day was 19 weeks (range: 9–35 weeks).

Patients 17/28/M and 18/39/F had a CMO relapse after 18 and 16 months, respectively; oral prednisone

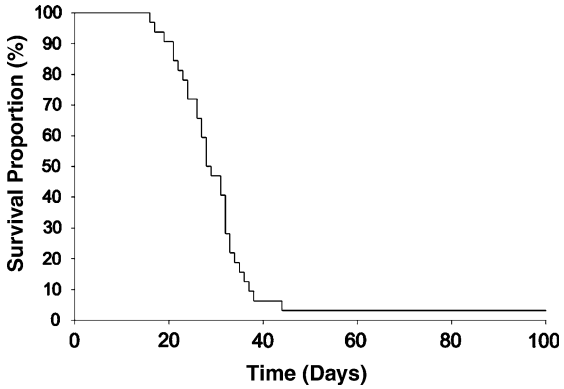

Fig. 2 Survival curve of patients with signs of CMO; *y*-axis: probability of having CMO, *x*-axis: days of follow-up time

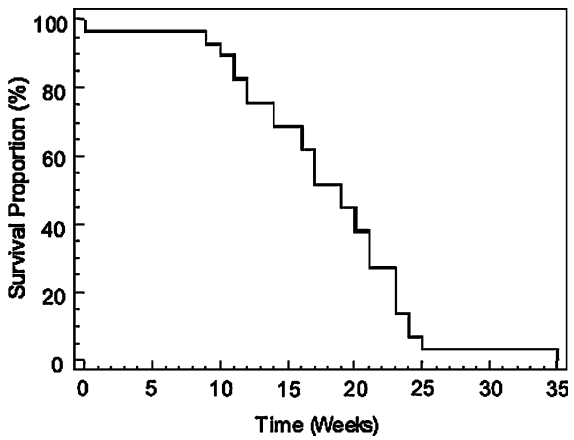

Fig. 3 Survival curve of patients undergoing steroid therapy. *y*-axis: probability of having the dose of steroids >10 mg/day, *x*-axis: weeks of follow-up

was increased to 25 mg, and FK506 was then introduced to achieve good control of the inflammation.

In patient 7/29/F, MMF exhibited no control of both uveitis and CMO: uveitis scores were not under control and signs of CMO did not resolve after MMF introduction; MMF was stopped and, after 2 weeks, interferon α 2a (Intron A, Schering-Plough Pharma) was introduced. All patients (3/3) were affected by Behçet panuveitis.

At 1-year follow-up, BCVA improved in 18/19 patients (31 eyes, 96.9%, $P < 0.05$); the mean BCVA was 0.67 ± 0.18 (range: 0.1–1). There was a strong inverse linear correlation (Fig. 4) between baseline CFT and BCVA after 1 year ($R = -0.829$,

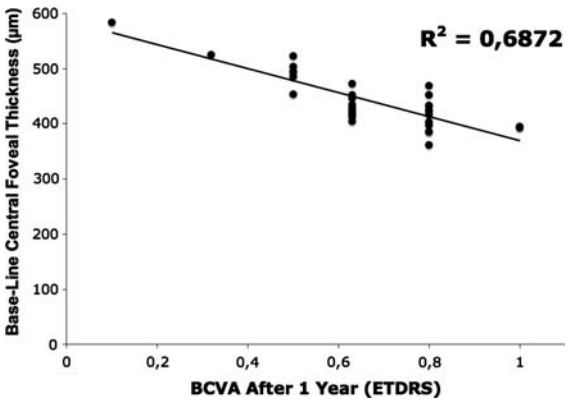

Fig. 4 Linear correlation between baseline central foveal thickness and BCVA at 1-year follow-up

Table 3 Side effects

Side effects	Total (%)
Tiredness	26.3
Headache	21
Dizziness	15.8
Anorexia	21
Dyspepsia	31.6
Raised cholesterol	5.3

$R^2 = 0.6872$, $P < 0.0001$.) At last follow-up, the mean BCVA was 0.65 ± 0.2 (range: 0.1–1).

After 1 year of treatment, 17/19 (89,5%) of patients did not experience uveitis relapse.

The mean uveitis relapse rate decreased from 3.5 ± 0.9/year at baseline to 0.4 ± 0.5/year at last follow-up.

Up to the last follow-up, no severe side effects were recorded during treatment with MMF (Table 3).

Discussion

Cystoid macular oedema is one of the leading causes of visual impairment in patients with uveitis. Steroids are the first step for the control of noninfectious ocular inflammation and for the reduction of associated CMO; knowing their side effects, such as cataract, ocular hypertension. and glaucoma [9], steroid-sparing drugs are mandatory in steroid-dependent inflammations.

Although the role of immunosuppression in ophthalmology has been established [27], there are several unsolved points: the main difficulty probably lies in choosing the right steroid-sparing drug. There is no data regarding CMO control in active uveitis; recently, Deuter and co-workers described the safety and efficacy of interferon-α in patients with quiet uveitis and persistent CMO [28], but no other papers have been published.

Mycophenolate Mofetil is a relatively new immunosuppressive drug, successfully used after solid-organ transplants [29–31]. Recent studies have proven its efficacy with a long-lasting remission in patients affected by Crohn's disease [32], severe atopic dermatitis [33], Wegener's granulomatosis, and microscopic polyangioitis [34].

Thorne et al. [23] and Siepman et al. [24] have recently confirmed the satisfactory control of uveitis with MMF in a large cohort of patients.

To our knowledge, there are no studies on MMF for the control of CMO associated with noninfectious uveitis.

Patients treated in our study showed a good response to MMF: 87.5% of eyes treated ($P < 0.05$) had no recurrence of CMO during the treatment with MMF; the mean BCVA at last follow-up was substantially better than at baseline: 0.67 ± 0.18 at 1-year versus 0.34 ± 0.14 at baseline ($P < 0.05$).

It is important to stress that, before the treatment, there was a strong linear correlation between the uveitis and CMO relapse rates ($R = 0.8123$, $R^2 = 0.6598$, $P < 0.0001$) meaning that the CMO could be interpreted as the expression of uveitis severity. After MMF introduction, no correlation was observed and the uveitis relapse rate decreased from 3.5 ± 0.9/year at baseline to 0.4 ± 0.5/year at last follow-up; in addition, a strong inverse linear correlation was observed between baseline CFT and last follow-up BCVA ($R = -0.829$, $R^2 = 0.6872$, $P < 0.0001$), meaning that the BCVA outcome would be worse in those patients with a thicker baseline CFT. This correlation could justify an aggressive treatment at the beginning of the protocol to achieve a better BCVA outcome.

The apparently better efficacy of MMF in controlling CMO can be interpreted on the basis of some evidence found in literature: some immunosuppressive drugs, such as cyclosporine A [17], FK506, and sirolimus [35], are known to produce nephrotoxicity [17], inducing the overexpression of soluble mediators that have an important role in CMO pathogenesis

[15]. MMF has proven to be effective in reducing such biomechanisms [18], improving arteriolopathy and decreasing the amount of soluble mediators involved in CMO pathophysiology.

In addition, it is important to stress the treatment strategy used to control CMO: the initial high dose of steroids acted to control the inflammation as much as possible, preparing a favorable background for MMF action.

Another key point shown in our study is the reduction of steroids: the probability of reducing the dose of steroids <10 mg/day was 97% after 25 weeks, according to data published previously [23]. In addition, after 1 year, 18/19 patients (31 eyes, 96.9%, $P < 0.05$) had no recurrence of CMO and 17/19 patients (89.5%) did not have a uveitis relapse.

It is important to stress that patients who had insufficient control of inflammation and CMO were all affected by Behçet panuveitis, thus likely confirming the data published by Adler et al. [36].

The data obtained in our study reflects promising results on the control of both inflammation and associated CMO, supported by evidence of good tolerance of the drug.

It is well known that the balance between the traditional drugs' efficacy and their side effects can be quite unstable, and MMF has a better profile [37, 38]. The good tolerance to MMF probably derives from its pharmacodynamics: mycophenolic acid has a strong effect on the type II isoform of inosine monophosphate dehydrogenase enzyme, with minor action on the type I expressed in most other cell types, warranting a more potent cytostatic effect on lymphocytes than on other cell types [38]. In addition, another recent publication has highlighted the safety and efficacy of MMF, describing its use in paediatric patients [39]. Our study confirms its good tolerability, emphasizing the need to pay attention to its minor and reversible side effects to the stomach.

In conclusion, the data obtained from this study suggests that MMF is a safe and effective corticosteroid-sparing drug for a substantial portion of patients with uveitic CMO unresponsive to treatment with other immunosuppressants.

This study, however, should be interpreted with the limitations of a retrospective case series. Moreover, due to the difficulty in recruiting large numbers of patients for trials on immunosuppression, multicentric trials are suggested for a larger recruitment, possibly prospective, randomised, and controlled.

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