

## SCIENTIFIC REPORT

## The efficacy of sirolimus in the treatment of patients with refractory uveitis

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**Aims:** To determine the efficacy of sirolimus in the treatment of patients with severe non-infectious uveitis.

**Methods:** Eight patients with severe non-infectious uveitis were recruited to an open study. Inclusion criteria were limited to patients whose disease was not controlled with at least two or more separate steroid sparing immunosuppressants (either because of unacceptable side effects or ineffectiveness of the drug) or who required regular doses of corticosteroids either as high dose systemic or orbital floor injections in order to control their disease. Intraocular inflammation, visual acuity, symptoms, corticosteroid burden, drug toxicity, and side effects were monitored.

**Results:** Sirolimus therapy was effective in five of the eight patients, all of whom had their dose of corticosteroids reduced or discontinued. Treatment in three patients was considered a failure as it caused intolerable side effects and/or failed to control the uveitis. Side effects were common and were typically gastrointestinal or cutaneous in nature. The severity of symptoms was dose dependent in most cases and occurred at trough blood levels above 25 ng/ml.

**Conclusion:** Sirolimus is an effective and potent immunosuppressive treatment in the majority of patients with non-infectious uveitis and can reduce the need for long term supplementary corticosteroid therapy. Further studies are required to establish the long term efficacy and safety of sirolimus alone or in combination with other steroid sparing immunosuppressants.

Severe non-infectious uveitis is a serious cause of ocular morbidity<sup>1</sup> and systemic corticosteroids are typically used in the acute stage when local steroid therapy does not control the inflammation. The long term use of systemic corticosteroids to treat chronic disease is problematic because of its adverse side effects<sup>2</sup> but the advent of steroid sparing immunosuppressive agents has greatly improved the treatment options that are available. However, there is still a subgroup of patients with severe disease recalcitrant to established therapies. These patients are dependent on additional high doses of systemic steroids in order to control or treat exacerbations of their disease and we have a cohort of these patients who attend our ocular immunology clinic. The purpose of this study was to assess the efficacy of a novel immunosuppressant sirolimus (Rapamune, Wyeth Pharmaceuticals, Maidenhead, Berks, UK) in these patients with the view not only to control inflammation but to reduce their corticosteroid burden.

## METHODS

Following informed consent patients attending a specialist combined ophthalmology and immunology clinic were recruited into this open study. Inclusion was limited to

patients who had a non-infectious uveitis not controlled with at least two or more separate steroid sparing immunosuppressants (either because of unacceptable side effects or ineffectiveness of the drug) or who required supplementary high dose corticosteroids (systemic or orbital floor injections) in order to control their disease.

Each patient was assessed both ophthalmologically and systemically. Baseline observations included blood pressure, weight, urinalysis, full blood count, urea and electrolytes, liver function tests, C reactive protein, and a fasting cholesterol. On commencement of treatment these parameters were regularly monitored.

Initially a regimen consisting of a single loading dose of 6 mg sirolimus followed by 2 mg daily, rising in increments to achieve satisfactory drug levels was followed. However, this process was too slow in achieving the required levels for our initial patients and so we started with 4 mg daily increasing by increments of 2 mg as determined by disease activity and trough blood levels. Sirolimus trough levels were measured every 4 weeks once stable drug levels were reached.

Success was defined in this study by one or more of the following parameters: an improvement of two or more lines of Snellen visual acuity, symptomatic improvement (that is, reduction subjectively in the number of floaters, pain, or photophobia), reduction in the number of inflammatory cells by binocular indirect ophthalmoscopy (BIO) as graded by two ophthalmologists (VAS and DR) according to an established uveitis scoring system,<sup>3</sup> regression of vasculitis, and a reduction in the amount of corticosteroids required for disease control.

## RESULTS

The patient characteristics, previous immunosuppression, doses of sirolimus used, and clinical outcomes are summarised in tables 1 and 2. A total of eight patients with severe non-infectious uveitis were treated with sirolimus, all of whom had a longstanding history of chronic uveitis with multiple recurrences. Three of these patients had an underlying diagnosis of Behçet's syndrome, one had presumed sarcoidosis, and the other four had idiopathic uveitis. The follow up time ranged from 26 to 60 weeks (median 52 weeks). Three patients were considered to have failed on the treatment. In case 1 there was an initial improvement in ocular inflammation and symptoms but on tapering the dose the disease relapsed. Higher doses of sirolimus did not control the uveitis and the patient experienced significant side effects, notably severe abdominal pains with deranged liver function tests which returned to normal on lowering the dose. Control of the disease has yet to be fully regained and he is currently on combination therapy.

**Abbreviations:** BIO, binocular indirect ophthalmoscopy; CMO, cystoid macular oedema

**Table 1** Clinical details of patients and their treatment

Case No, age, sex	Diagnosis	Relevant history before treatment	Follow up (weeks)	Previous treatment	Maximum/current dose of sirolimus	Side effects of sirolimus therapy
1, 31, M	Anterior and intermediate uveitis	Episodes of CMO treated with orbital floor steroids. History of steroid induced raised intraocular pressure	52	TAC, depomedrone, orbital floor injections	8 mg/4 mg	Acne, abdominal pain, deranged liver function tests
2, 37, M	Panuveitis		52	CYC, MMF, TAC	10 mg/5 mg	Recurrent chest infections
3, 39, F	Panuveitis (unilateral)	Right eye vision reduced as a result of macular scarring secondary to chronic CMO. Repeated episodes of painful uveitis	52	CYC, MMF, TAC, IV MP	8 mg/2 mg	Erythema nodosum
4, 30, M	Sarcoidosis, posterior uveitis	Repeated episodes of vitreous haemorrhage secondary to neovascularisation. Episodes of CMO treated with oral corticosteroids	40	TAC, MMF	4 mg/OARx	Nausea
5, 46, F	Intermediate and posterior uveitis	Right eye vision reduced as a result of macular scarring secondary to chronic CMO. Episodes of CMO in left good eye treated with increased doses of oral corticosteroids. At commencement of trial persisting mild CMO in left eye	60	MMF, TAC, INF	10 mg/0 mg (treatment withdrawn)	Breast oedema and scleroderma-like changes in the feet
6, 44, M	Behçet's syndrome, posterior uveitis and vasculitis		60	CYC, AZA, TAC	5 mg/OARx	Myalgia in legs/painful feet in dorsal region
7, 45, M	Behçet's syndrome. Posterior uveitis and vasculitis	Left optic atrophy secondary to optic nerve ischaemia. Right eye vision reduced because of old maculopathy. Marked systemic symptoms of Behçet's syndrome	52	CYC, TAC	8 mg/6 mg	Seborrheic dermatitis
8, 30, F	Behçet's syndrome, posterior uveitis and vasculitis	Right eye vision lost because of retinal arterial occlusion	26	CYC, Metho, AZA, TAC, INF, IV MP	12 mg/4 mg	Eczematous rash and severe headaches

CMO, cystoid macular oedema; CYC, cyclosporin; TAC, tacrolimus; INF, infliximab; AZA, azathioprine; Metho, methotrexate; IV MP, intravenous methylprednisolone; MMF, mycophenolate mofetil; OARx, off all treatment.

Treatment in case 5 was stopped as soon as the sclerodermatous-like changes in the foot appeared even though there was an improvement in BIO scores. Case 8 continued to have episodic vasculitis which affected the macula and resulted in transient loss of vision. This required "rescue" courses of high dose intravenous methylprednisolone. Full control of these vasculitic episodes was not achieved despite higher doses of sirolimus (12 mg) and were accompanied by unacceptable side effects. In five of the eight patients there was an improvement as adjudged by the above criteria. All of these five patients had their level of corticosteroids reduced to under 10 mg without compromising the control of intraocular inflammation or symptoms.

## DISCUSSION

Sirolimus was originally developed as an antibiotic<sup>4</sup> after being isolated from the fungus *Streptomyces hygroscopicus*. Its potential as an immunomodulatory agent is now established for the prevention of allograft rejection following solid organ transplantation.<sup>5,6</sup> Recently it has been used in sirolimus eluting stents in patients with coronary artery disease,<sup>7</sup> as it has also been shown to possess an antiproliferative effect on smooth muscle cells and on arterial intimal thickening.<sup>8</sup>

Sirolimus is like cyclosporin and tacrolimus as it is an inhibitor of T cell activation—it binds to intracellular receptors known as immunophilins. However, it differs from cyclosporin and tacrolimus in that it targets a unique serine-threonine kinase involved in cell signalling. Hence, it functions as non-calcineurin inhibitor of T cells.<sup>9</sup> It has additional immunomodulatory effects including the

inhibition of IL-2 dependent and independent proliferation of B lymphocytes.<sup>10</sup> Sirolimus has been shown to reduce inflammation in animal models of experimental autoimmune uveitis, albeit in combination with cyclosporin or tacrolimus.<sup>11,12</sup> Hence there were appropriate studies to allow a trial in these patients with treatment resistant uveitis.

Our initial data are promising as five out of the eight patients were deemed to have successful treatment results as determined by our criteria. We were encouraged by the stabilisation of disease and reduction of inflammation without the need for high dose systemic corticosteroids seen in most of our cases. In two patients (cases 4 and 6) the treatment has not only led to a striking improvement in symptoms but the patients have been tapered off all treatment (including sirolimus) and their disease is currently in remission. We speculate that this phenomenon may be related to sirolimus induction of T cell clonal anergy which has been demonstrated *in vivo*.<sup>13</sup> Sirolimus is also likely to be anti-angiogenic. Interestingly, as far back as 1995, Olsen *et al* showed that rats receiving sirolimus following orthotopic allogenic corneal grafts had reduced amounts of corneal neovascularisation.<sup>14</sup> More recently Guba and colleagues have elegantly demonstrated the anti-VEGF (vascular endothelial growth factor) activity of sirolimus in a murine tumour model.<sup>15</sup> This mode of action offers an explanation for the marked clinical improvement in case 4 where there was a dramatic regression of neovascularisation.

The side effects experienced by our patients were mostly dermatological and gastrointestinal in nature. Of the blood tests that were monitored mild increases in serum cholesterol

**Table 2** Clinical outcome of patients treated with sirolimus

Case No	Snellen visual acuity pretreatment	Snellen visual acuity post-treatment	Intraocular inflammation BIO score RE/LE pretreatment	Intraocular inflammation BIO score RE/LE post-treatment	Pretreatment prednisolone dose/current prednisolone dose	Clinical outcome
1	6/6, 6/9	6/5+3, 6/6+3	0 1	1 2	40 mg/10 mg	Treatment failure Initial control of inflammation followed by relapse on tapering treatment requiring higher doses of sirolimus with intolerable side effects Current medication: tacrolimus, prednisolone and sirolimus
2	6/18, 6/12	6/9, 6/9	3 3	0 0	40 mg/6 mg	Symptom improvement: reduction of floaters
3	6/36, 6/4	6/36, 6/4	1 0	0 0	Intermittent IV MP/0 mg	Symptom improvement: reduction in pain and photophobia
4	6/6+1, 6/12	6/5-1, 6/9	1 1	0 0	30 mg/0 mg	Reduction in vasculitis and regression of neovascularisation
5	1/60, 6/18	1/60, 6/9	1 2	0 0	40 mg/15 mg	Treatment failure Despite reduction of inflammation mild CMO persists. Treatment withdrawn due to side effects Current medication: tacrolimus and oral corticosteroids
6	6/5, 6/9	6/5, 6/5	0 2	0 0	50 mg reducing to 20 mg/0 mg	Symptom improvement: reduction in pain
7	6/18, HM	6/18, HM	0 0	0 0	15 mg/7.5 mg	Regression of vasculitis with no further flare ups Marked improvement in systemic symptoms of Behçet's syndrome
8	HM, 6/12	HM, 6/12	2 2	1 1	Intermittent IV MP/6 mg and pulsed IV MP	Regression of vasculitis with no further flare ups Treatment failure Continuing episodes of vasculitis leading to transient vision loss requiring repeated IV MP Currently on tacrolimus, prednisolone, and sirolimus

BIO, binocular indirect score; CMO, cystoid macular oedema; HM, hand movements; IV MP, intravenous methylprednisolone.

were also observed. We noted that these side effects could be eliminated or minimised on dose reduction after the initial loading period. Fortunately we did not observe any of the reported serious adverse effects of sirolimus such as deep vein thrombosis and thrombocytopenia. Nevertheless, in three patients where the treatment was considered a failure also experienced intolerable side effects. The frequency and severity of adverse effects occurred at drug trough levels greater than 25.0 ng/ml and this level remains at the upper end of the therapeutic range. This is 5 ng/ml higher than the upper range suggested for renal transplantation.<sup>16</sup> Thus, close monitoring and awareness of potential side effects are critical for patients to be started on this drug.

The advances in our understanding of the immune system has resulted in an increase in the number of therapeutic options available for the treatment of severe uveitis. The use of newer agents such as mycophenolate mofetil, daclizumab, infliximab, and campath-1-H to treat ocular inflammatory diseases has recently been reported with some success.<sup>17-20</sup> Our experience suggests that sirolimus can be added to this list. However, several key questions remain unanswered: What are the long term effects of these drugs on the immune system? Is there any way to predict which patients are likely to respond to which treatment? Which treatment or combination of treatments is the most effective? The preliminary reports of the newer agents should hopefully be the catalyst for randomised control studies that are needed in order to formulate an evidence base for the best treatment of severe recalcitrant non-infectious uveitis.

We conclude that the management of patients with severe uveitis who do not respond to first line systemic treatment is challenging. Our initial experience with sirolimus demonstrates its effectiveness in the majority of patients with refractory non-infectious uveitis by not only controlling disease activity but also reducing the long term steroid burden.

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