

Cyclosporin A therapy in refractory non-infectious childhood uveitis

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Abstract

Aims—To assess the immunosuppressive efficacy, steroid sparing effect and adverse effects of cyclosporin A (CsA) therapy in refractory non-infectious childhood uveitis.

Methods—A retrospective case series review of the medical records of children on CsA therapy attending a tertiary referral centre for refractory endogenous uveitis was performed. Low dose (≤ 5.0 mg/kg/day) CsA therapy was started either as monotherapy or in combination with other agents. The CsA immunosuppressive efficacy was assessed by visual acuity and binocular indirect ophthalmoscopy (BIO) score outcomes and steroid sparing effect by growth charts and ability to withdraw or maintain a low steroid dose. Possible CsA adverse effects were monitored by routine biochemistry (including serum creatinine) and haematological tests, blood pressure recordings, and symptoms.

Results—14 patients (25 eyes, 10 males, four females) were recruited with steroid failure as the most common CsA indication. Age (mean (SD)) at start of CsA therapy was 8.7 (4.1) years with a duration of CsA therapy of 20.9 (range 3.5–88.3) months at a maintenance CsA dose of 4.0 (1.0) mg/kg/day. From baseline, visual acuity improved or was maintained in 23 (92%) eyes and BIO score improved in 19 (76%) eyes. Height centiles were preserved and the maintenance prednisolone dose was 6.3 (3.3) mg/day, where required, in 10 (71%) patients. Nephrotoxicity was not observed, with transient systemic hypertension developing in one patient. Minor adverse effects were more common but were well tolerated.

Conclusions—Cyclosporin A therapy is effective and safe in the medium term, if closely monitored, in refractory non-infectious childhood uveitis.

(Br J Ophthalmol 1998;82:737–742)

Childhood uveitis, while uncommon, may present with sight threatening intraocular inflammation which poses distinct management problems as to whether long term immunosuppression should be instituted.¹ The proportion of patients with uveitis beginning before the age of 16 years is reported to range between 5.2% and 10.6%.^{2–5} Presentation is often delayed with advanced disease,^{1 6–8} with a recent study reporting 26% of eyes having a visual acuity of less than 20/200 at first

referral,¹ possibly due to asymptomatic insidious onset or uveitis in a preverbal child. Corticosteroids have traditionally formed the mainstay of systemic immunosuppression in childhood uveitis.^{1 9–11} However, the well described adverse effects of systemic corticosteroids on the immature immune, metabolic, and skeletal systems,^{12–18} which may result in permanent disability including growth retardation,^{15–18} restrict their long term use in children. Although alternative immunosuppressive agents, such as cyclosporin A (CsA), antimetabolites, and alkylating agents, when carefully administered and monitored, have relatively few permanent adverse effects in the therapy of adult ocular inflammatory disease,^{12 19–24} there are additional concerns which restrict their use in childhood uveitis. These include the potential long term risks of neoplasia, myelosuppression, nephrotoxicity, or hypertension.^{12 22 26 27} It has therefore, not surprisingly been reported that the potential benefit of cytotoxic agents in the treatment of intractable childhood uveitis is outweighed by the risk of serious adverse effects.¹¹

Cyclosporin A is a powerful steroid sparing immunosuppressive agent which has been shown to be both effective and relatively safe in low doses in the treatment of refractory endogenous posterior uveitis in adults.^{20–24} There are, however, few reports which examine the efficacy of CsA therapy in refractory non-infectious childhood uveitis.^{1 28 29} One of the main concerns with CsA therapy is nephropathy but a large review in patients treated for a range of autoimmune diseases found CsA less nephrotoxic in children compared with adults,²⁷ possibly because of greater CsA clearance in children.³⁰ The maximal degree of CsA induced renal dysfunction can be measured by the percentage increase in serum creatinine above the patient's baseline value which is reported to be the best predictor of CsA induced nephropathy.²⁷ To minimise dose dependent CsA induced nephropathy, many reports propose maintaining a CsA dose of 5 mg/kg per day or less and then titrating the dose to keep within a 30% increase in serum creatinine over the baseline value.^{27 31 32}

The efficacy of CsA as a steroid sparing immunosuppressant is highlighted within other branches of paediatric medicine where growth is preserved after renal^{18 30 33–36} and cardiac³⁷ transplantation in children, controlling nephrotic syndrome,^{38 39} and treating recent onset type I insulin dependent diabetes mellitus.⁴⁰ Therefore, the aims of this study were to examine the immunosuppressive efficacy, steroid sparing effect, and adverse effects

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Accepted for publication
29 January 1998

Table 1 Patient diagnosis and duration of cyclosporin A therapy

Patient No/sex/age at onset of uveitis (years)	Diagnosis	Classification (IUSG*)/uni/bilaterality	Duration CsA therapy (months)
1/F/3.9	JCA	Panuveitis/both eyes	88.3
2/M/9.2	Pars planitis	Intermediate uveitis/both eyes	52.2
3/M/3.9	Idiopathic	Intermediate uveitis/both eyes	28.3
4/M/3.8	Sympathetic ophthalmia	Posterior uveitis/both eyes	25.0
5/M/5.8	Pars planitis	Intermediate uveitis/both eyes	24.9
6/M/6.7	Sympathetic ophthalmia	Posterior uveitis/both eyes	14.3
7/M/3.0	Idiopathic	Intermediate uveitis/both eyes	14.1
8/M/5.6	Pars planitis	Intermediate uveitis/both eyes	11.7
9/F/2.3	JCA	Panuveitis/both eyes	10.6
10/F/11.4	JCA	Intermediate uveitis/right eye	6.5
11/M/8.6	Idiopathic	Panuveitis/right eye	5.1
12/M/9.3	Pars planitis	Intermediate uveitis/both eyes	4.5
13/F/6.0	Idiopathic	Posterior uveitis/right eye	3.8
14/M/15.2	Pars planitis	Intermediate uveitis/both eyes	3.5

*IUSG = International Uveitis Study Group; CsA = cyclosporin A; JCA = juvenile chronic arthritis.

of CsA therapy in refractory endogenous childhood uveitis.

Methods

PATIENTS AND CLINICAL MONITORING

From the uveitis database of patients attending the uveitis clinics at Aberdeen Royal Hospitals NHS Trust (ARHT), a tertiary referral centre, a consecutive series was collected and medical records reviewed of patients under the age of 16 years who received systemic CsA for refractory non-infectious uveitis. Patients received CsA monotherapy or in combination with systemic low dose steroids and/or other immunosuppressives. Previous history and follow up data were collected from the referring physician when indicated. Clinical data collected included age, uveitis diagnosis, uni/bilaterality of uveitis, sex, prior/current periocular or systemic steroid treatment including dosage and duration, indication for CsA treatment, CsA dosage variables, duration of therapy, and adverse effects. Uveitis was classified both anatomically, following the International Uveitis Study Group classification system,⁴¹ and also by systemic disease associations or as isolated defined uveitis entities, such as pars planitis or sympathetic ophthalmia. Infectious aetiology was excluded clinically and/or by associated negative serology for *Toxoplasma*, *Toxocara*, herpes simplex and zoster viruses, cytomegalovirus, Epstein-Barr virus, *Treponema*, *Borrelia*, and negative skin tuberculin test when indicated. Visual function was assessed by recording the best corrected visual acuity (BCVA), using Kay's pictures, Sheridan-Gardiner test types, or the Snellen chart (depending on the age and comprehension of the patient), before CsA therapy and at the last clinic visit. Amblyopia was deemed to contribute to

Table 2 Indications for cyclosporin A therapy

Indication	No of patients*	Percentage*
Failure of systemic steroids/ persistent severe IOI	6	43
Chronic systemic steroid sparing therapy	6	43
Toxicity of systemic steroids	3	21
Specific CsA therapy indication	2	14

*Total number of patients and percentages exceed 14 patients and 100% respectively as some patients had more than one indication. IOI = intraocular inflammation; CsA = cyclosporin A.

reduced final BCVA when age at first presentation was under 8 years. The anti-inflammatory efficacy of CsA therapy was assessed by measuring the binocular indirect ophthalmoscopy (BIO) score.⁴² All patients were examined at each visit by the same ophthalmologist (JVF) to achieve standardisation. All adverse effects related to prior high dose and/or chronic systemic steroid therapy, such as cushingoid features and growth retardation were recorded. Heights and weights were recorded on age and sex matched charts⁴³ for the duration of therapy where data were available. Similarly, adverse effects of CsA therapy, especially renal dysfunction and systemic hypertension, were closely monitored. Renal function was assessed by baseline isotope glomerular filtration rate, and in some cases by baseline creatinine/lithium clearance,⁴⁴ with serial assessments of serum creatinine at each follow up visit. The full blood count, electrolytes including magnesium, blood glucose, total cholesterol levels, serum uric acid, and CsA levels were measured at each visit.

INDICATIONS FOR AND OPTIMISING CSA THERAPY

Indications for starting low dose CsA therapy included one or more of the following: (1) steroid dependency; (2) toxicity from previous steroid/immunosuppressive therapy; (3) a specific indication for CsA therapy (such as sympathetic ophthalmia); (4) failure/inadequate response with steroid/other immunosuppressive therapy. Contraindications to CsA therapy included abnormal baseline renal/liver function tests or uncontrolled systemic hypertension. Detailed informed consent, involving an explanation of the potential risks and benefits of CsA therapy, was obtained from both patient, if possible, and parents. Cyclosporin A therapy was commenced at 5.0 mg/kg daily in two divided doses. Follow up outpatient assessments occurred at 2 weeks, 1 month, and then on a monthly basis for the first year with subsequent visits every 2–3 months or sooner if clinically indicated. Subsequent CsA dosage adjustments and/or the addition of other steroid sparing agents or steroid dosage adjustments, as in other reports,^{21 24 45–47} were titrated according to the degree of vitreous and retinal inflammation, rather than the visual acuity, aiming to achieve the lowest possible dosage that maintained adequate inflammatory control yet minimised adverse effects. If an inadequate response to CsA therapy at the maximal dose occurred, azathioprine (1.5–2.0 mg/kg daily) was added to the regimen. If an insufficient anti-inflammatory response persisted, the CsA dose was increased to slightly exceed the usual upper limit of 5 mg/kg daily in order to achieve adequate immunosuppression. If intraocular inflammation was clinically controlled, a slow reduction of CsA dosage was attempted. Any subsequent recurrences or rebound increase in intraocular inflammation during steroid or CsA dose reduction was managed by a compensatory increase in steroid and/or CsA dosage. Long term remission of intraocular inflammation was confirmed when CsA could

Table 3 Renal responses to cyclosporin A therapy

Patient No	Maint* CsA dose (mg/kg)	Max CsA dose (mg/kg)	End serum creatinine ($\mu\text{mol/l}$) (End % from baseline)	Normal serum creatinine for age! (% above upper limit)
1	3.3	5.0	53 (2)	30–76 (0)
2	4.2	5.3	89 (98)	29–85 (5)
3	4.8	5.0	41 (–16)	23–73 (0)
4	1.4	5.0	61 (3)	15–93 (0)
5	3.0	3.0	79 (119)	25–75 (5)
6	4.3	5.1	70 (32)	24–80 (0)
7	5.0	7.5	25 (14)	23–63 (0)
8	4.0	5.5	75 (42)	23–73 (3)
9	3.6	6.0	88 (24)	20–98 (0)
10	3.5	5.0	80 (13)	27–97 (0)
11	4.7	5.0	80 (14)	24–80 (0)
12	4.7	5.0	79 (5)	30–80 (0)
13	4.8	5.1	78 (8)	30–80 (0)
14	4.2	5.5	89 (6)	21–109 (0)

* Maint = maintenance; Max = maximum; CsA = cyclosporin A. Figures are outlined in bold if the serum creatinine at the time of last visit had risen more than 30% from baseline.

Table 4 Minor cyclosporin A induced adverse effects

Adverse effect	No of patients*	Percentage*
Hypertrichosis	4	29
Fatigue/lethargy	3	21
Malaise	2	14
Gastrointestinal cramps	2	14
Nausea/vomiting	2	14
Hypomagnesaemia	2	14
Diarrhoea	1	7
Paraesthesia	1	7
Gingival hyperplasia	1	7

* Total number of patients and percentages exceed 14 patients and 100% respectively as some patients had more than one adverse effect.

is represented in Figure 2 which shows the BIO score pre CsA and post CsA therapy. BIO score improved in 19 eyes (76%), remained unchanged in four eyes (16%) and worsened in two eyes (8%) at the end of follow up. The two eyes with worsened BCVA and BIO score (due to more severe vitritis) occurred in the same patient with pars planitis who received triple therapy of CsA, prednisolone, and azathioprine.

Although CsA therapy was not withdrawn in any patient because of adverse effects, dose reductions were made in four patients because of rises in serum creatinine and in one patient because of the development of systemic hypertension. Table 3 outlines the maintenance and maximum doses of CsA and corresponding maximum and sustained serum creatinine responses. A transient rise in serum creatinine was seen in nine (64%) patients after starting CsA therapy. Serum creatinine, at the last visit, ranged from 25 to 89 (mean 69 (19)) $\mu\text{mol/l}$ and this corresponded with a sustained rise of more than 30% from baseline creatinine in four patients (32%, 42%, 98%, and 119%). However, when corrected for age at the end of follow up, these elevated serum creatinine levels were marginally above the upper limit of the normal age corrected range (0%, 3%, 5%, and 5% respectively). Both creatinine and lithium clearance were assessed in four patients, with a further four patients having creatinine clearance alone measured, and all were within normal limits. Transient systemic hypertension requiring treatment developed in one patient who had received a maximum daily CsA dose of 6.0 mg/kg but serum creatinine remained within normal age corrected limits and the

blood pressure returned to normal on CsA dose reduction. One patient inadvertently received a maximum CsA dose of 7.5 mg/kg/day for a period of 1 month, but this was well tolerated with no adverse renal effects and the CsA dose was reduced to a daily maintenance of 5.0 mg/kg. Table 4 outlines other minor CsA induced adverse effects. The most common were hypertrichosis in four patients (29%) and fatigue in three patients (21%). Hypomagnesaemia occurred in two patients (14%), with associated gastrointestinal cramps, requiring magnesium supplementation. Two patients (14%) required CsA dose reductions because of malaise which resolved at a lower CsA dose. No patient developed anaemia, abnormal liver function tests, hypercholesterolaemia, fasting hyperglycaemia, or hyperuricaemia. With respect to systemic steroid adverse effects, five patients (36%) developed cushingoid facies but only two (14%) had excess weight gain (>90th centile), and all had preserved height centiles.

Discussion

The most important finding of this study is that the data suggest that CsA therapy is effective in refractory non-infectious childhood uveitis, yet is well tolerated. Most eyes (23, 92%) had either improved or maintained best corrected visual acuity and 19 eyes (76%) had an improved inflammatory (BIO) score with a mean follow up of 26.8 months. No patient required discontinuation of CsA therapy due to adverse effects. Nephrotoxicity did not occur but one patient developed transient systemic hypertension which resolved after CsA dose reduction. Minor adverse effects were more common yet were surprisingly well tolerated and mild in severity. One of the most positive effects of CsA therapy was to allow steroid sparing anti-inflammatory efficacy, with four patients on CsA monotherapy alone and reduction to a mean prednisolone dose of 6.3 mg/kg/day in the other patients, and preservation of height centiles in all patients. Most patients (64%) were treated de novo with Neoral, which is reported to have a 20% greater bioavailability than Sandimmun,³² which may have contributed to the efficacy of low dose CsA therapy in this childhood uveitis cohort. However, no specific CsA dose reduction pattern was noted in those patients who had been previously treated with Sandimmun.

To our knowledge, this is the largest reported cohort of children on CsA therapy for refractory uveitis. The number of patients in this study, however, is still small, owing to the infrequent nature of these challenging cases, even in a tertiary referral setting. One study of 60 children with intermediate uveitis reported a positive response in three of five patients treated with "immunosuppressive agents" but no comment was made on the nature of immunosuppressive therapy.⁹ Tugal-Tutkun and colleagues, in a recent study of 130 patients with childhood uveitis, reported therapeutic failure in three of six patients who received CsA therapy but made no comment on CsA related adverse effects.¹ Both studies favoured steroid

therapy, with 62 patients (44%) in the latter study receiving systemic steroids.¹ Immunosuppressive therapy was required most frequently in JCA, with all CsA therapeutic failures occurring in JCA.¹ On this basis, one would expect a disproportionately higher frequency of JCA in our group with refractory childhood uveitis but this has not been seen. The most common diagnosis in our group was pars planitis (36%), with CsA therapeutic failure occurring in only one patient, who had pars planitis. A recent Italian study²⁹ on 16 children with Behçet's disease, found that 56.3% cases required immunosuppressive therapy, with similar indications to our group, such as uncontrolled intraocular inflammation on high dose steroid therapy or the development of steroid related side effects. Cyclosporin A was used in only four cases, however, and their approach was to delay immunosuppressive therapy (mean age at commencement was 15.7 years compared with 8.4 years in our study) for as long as possible so that treatment outcomes were assessed in a much older paediatric cohort. If sight threatening intraocular inflammation is present, we recommend prompt institution of adequate systemic immunosuppression, even in very young children where the potential for amblyopia associated with aggressive uveitis is great. Similar to a previous report,¹ the most common cause of reduced visual acuity was maculopathy in our group, with amblyopia probably contributing in most eyes (six of seven) with maculopathy, compared with only two of 18 eyes with maculopathy previously reported. In common with Pivetti-Pezzi and colleagues,²⁹ we regard CsA as the immunosuppressive agent of choice, compared with potentially more toxic immunosuppressive agents such as alkylating agents or antimetabolites, in refractory paediatric uveitis.

Our approach in paediatric sight threatening intraocular inflammation is to institute short term high dose oral steroid therapy initially, to control active inflammation, and monitor the clinical response, with appropriate reductions in steroid dosage over 4–6 weeks. Depending on the adequacy of inflammatory control, a decision is made on the requirement for immunosuppressive therapy and CsA therapy is instituted (as discussed in Methods). Systemic steroid dose reduction can then be achieved, without compromising inflammatory control, and in some cases systemic steroid therapy can be eliminated, as seen in four patients in our cohort. While the majority of patients in this study still required steroids or other immunosuppressive agents, the aim of this study was not to assess CsA monotherapy alone, but to show that CsA, alone or in low dose combination therapy, was effective and safe in childhood uveitis. In particular, the addition of CsA allowed the dose reduction or elimination of other, potentially more toxic, immunosuppressive agents.

Although 50% of the patients required initial CsA dose reduction, by careful monitoring, patients avoided CsA major adverse effects (apart from one patient with transient systemic

hypertension) and one of the major adverse effects of chronic systemic steroids in children, growth retardation. Cyclosporin A is being increasingly used other branches of paediatric medicine as a steroid sparing immunosuppressive agent^{17 18 30 36–39} but, as in this study, the long term effects, particularly any possible increased risk of neoplasia, are relatively unknown and these should be considered before commencing CsA therapy. One study of 32 children¹⁸ found CsA therapy after renal transplantation to be very effective, over a mean of 6.5 years, and while the CsA doses were higher at 5–7 mg/kg/day, there were no malignancies. While Lane *et al* did not show an increased risk of malignancy in patients with severe ocular inflammatory disease treated with systemic immunosuppression,²⁶ their cyclosporin treated group had a mean duration of therapy of only 15.4 months, with a median follow up of 1.34 years, precluding any conclusions about the long term risks of neoplasia.

Previous reports have favoured the use of periocular steroids for intraocular inflammatory recurrences in an effort to reduce systemic side effects.^{9 11 46} Giles reported the use of periocular steroids in 52 (87%) children with intermediate uveitis,⁹ many requiring general anaesthesia for administration, while a review of 315 children with uveitis, mostly with JCA, found periocular steroids of considerable value in refractory cases.¹¹ It has been recently shown, however, that periocular steroids have significant systemic absorption, with a periocular injection of 5 mg dexamethasone achieving serum levels equivalent to 50 mg oral prednisolone.⁵² While no patient received periocular steroids for inflammatory recurrences in our group, as the risk of systemic adverse effects is not avoided and systemic steroids are easier to administer with a more titratable dosage, periocular steroids may be useful in inflammatory recurrences that are unilateral or predominantly anterior.^{11 46}

A potential criticism of this study is that only 44% eyes had a significant improvement in BCVA, but this was accompanied by 48% eyes preserving the pre CsA BCVA, which is itself an important therapeutic goal in refractory endogenous posterior uveitis (EPU), and amblyopia must also be considered as a cause of irreversible acuity loss in childhood uveitis. A potential limitation of the acuity measurements is that different methods of acuity assessment were used, particularly in the three patients with uveitis onset before the age of 5 years with more than 2 years of follow up, but this is relatively unavoidable in longitudinal childhood acuity recordings. The degree of intraocular inflammation can be reliably assessed by the BIO score^{42 53} and is widely accepted as a reliable method of determining treatment efficacy in EPU.^{47 54} Although BIO scores were reviewed retrospectively, and so may be relatively subjective, reproducibility was enhanced by the same experienced observer assessing the BIO score at each visit.

In conclusion, CsA is effective in refractory non-infectious childhood uveitis and relatively safe in low doses, if closely monitored, when

compared with traditional chronic steroid therapy or potentially more toxic alternative immunosuppressive agents. The alternatives to systemic immunosuppression, however, are the immediate and long term consequences of persistent sight threatening intraocular inflammation, often with adverse effects of chronic steroid therapy, in childhood. Medium term inflammatory control may be all that is necessary in some children, as seen in this study, until disease remission takes place.

Presented as a poster at the Oxford Ophthalmological Congress, Oxford, UK, July 1997.

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