THE EFFICACY OF SYSTEMIC CORTICOSTEROIDS IN SIGHT-THREATENING RETINAL VASCULITIS

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SUMMARY

This study was undertaken to assess the efficacy of a standard regime of high-dose systemic oral corticosteroids in the management of retinal vasculitis. The study was performed because the single most common reason for referral to our specialist clinic is the apparent failure of patients to respond to a course of systemic steroids, which in most cases appeared to be due to an inadequate initial dose. A retrospective study of 29 patients (30 treatment episodes) with sight-threatening retinal vasculitis managed initially with high-dose systemic steroids was evaluated 1 year after treatment. Patients included in the study all started treatment with ≥1 mg/kg prednisolone and remained on a high steroid dose (≥40 mg prednisolone) for at least 5 weeks. No patient was on any other immunosuppressive agent at the start of the study. Therapeutic success for this regime, as judged by improvement in visual acuity, was 60%, improving to 77% with addition of other immunosuppressive agents. Eight patients required additional immunosuppressives. Although documented side-effects of steroids were common (50% of cases managed on steroids alone), in only 5 patients were they therapeutically important. Twelve of the 22 patients managed on high-dose steroids alone were off treatment at 12 months. There was no correlation at any stage between visual acuity, activity index or relapses and the final visual outcome at 12 months. Seven cases had a poor visual outcome and the causes for this included relapse in the twelfth month of follow-up, persistent cystoid macular oedema and lens opacity. These results suggest that high-dose oral steroids should be tried in the initial management of such patients before contemplating other more complicated regimes or accepting a poor visual outcome.

Corticosteroids were first introduced for the management of sight-threatening retinal vasculitis in the 1950s.[1,2] An improved understanding of the pathological mechanisms underlying this blinding disease[3] has led to the utilisation of other immunosuppressive agents,[4] but systemic steroids remain the mainstay of treatment. A wealth of information exists in the literature on these other, newer immunosuppressives, but there is a surprising paucity of data evaluating steroid regimes. Corticosteroid treatment regimes tend to be empirical, and advocate starting with a high dose of steroids (1–2 mg/kg) and reducing the dose according to the patient's response.[5–7]

The most common reason for patients to be referred to our specialist retinal vasculitis clinic is failure of response to a course of systemic steroids. On each occasion this appeared to be an inadequate course of steroids beginning with 40 mg prednisolone daily or less. Our practice is to employ a high-dose steroid regime (80 mg prednisolone for 4 days, 60 mg prednisolone for 4 days, 40 mg prednisolone for 1 month, reducing thereafter) in all such patients. This retrospective study was carried out to evaluate the therapeutic efficacy of our regime; if a simple oral regime is effective, then there is no need to resort to intravenous treatment or newer immunosuppressives with all the attendant sophisticated medical back-up often not practical in eye units.

PATIENTS AND METHODS

All case notes of patients attending the Medical Eye Unit, St Thomas' Hospital, with retinal vasculitis in the past 10 years were examined. Patients included in the study received a course of high-dose systemic steroids for active retinal vasculitis, were on no other immunosuppressive agents at the start of the study period, and had complete follow-up records for 1 year. Patients were excluded if they had undergone any form of ocular surgery or laser therapy during the follow-up period, and if they were started on any immunosuppressive agents other than azathioprine or cyclosporin A after the high-dose steroids (this was to exclude patients who had received immunosuppressives now not routinely employed at St Thomas'). A treatment episode was defined as a course of high-dose systemic steroids administered for active retinal vasculitis with complete follow-up for 1 year. A course of high-dose

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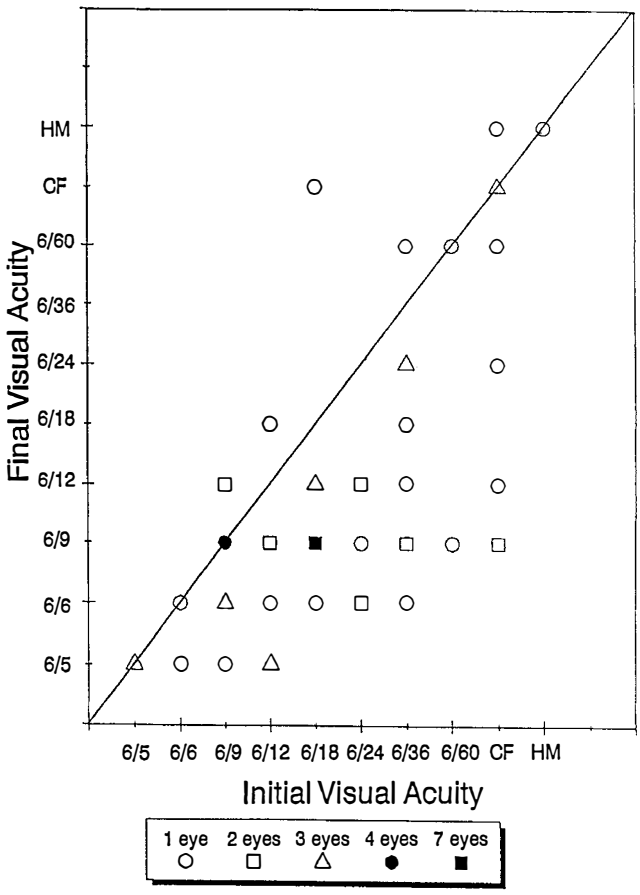

Fig. 1. *Scattergram to illustrate initial and final Snellen visual acuities of all cases (60 eyes).*

steroids was defined as 80 mg prednisolone for 4 days, 60 mg prednisolone for 4 days, 40 mg prednisolone for 1 month, reducing thereafter. Indications for treatment were a marked increase in activity of retinal vasculitis alone or increased activity associated with a drop in visual acuity.

Case notes were assessed at minus 1 month, zero, 1 month, 3 months, 6 months and 12 months, and details of treatment, disease activity, Snellen visual acuity, side-effects of the drugs and results of fluorescein angiography recorded. Disease activity was assessed using a weighted visual morbidity scale.[8]

Outcome was assessed in terms of changes in visual acuity by the end of the study period. Visual acuity was graded as follows: grade 1, 6/6 or better; grade II, 6/9 or 6/12; grade III, 6/18 to 6/36; and grade IV, 6/60 or worse. A successful visual outcome was defined as either (1) maintenance of visual acuity of 6/12 or better, or (2) improvement of one or more grades by the end of the study period. Patients who did not fulfil either of these criteria were considered to have a poor visual outcome. A relapse was defined as an increase in visual symptoms (blurred vision, floaters) associated with an increase in vitreous cellularity,[9] and did not necessarily involve a drop in visual acuity.

RESULTS

Patients' Characteristics

Two hundred and fifty case notes were examined of patients who had had systemic immunosuppressives for retinal vasculitis. Twenty-nine patients were found to fit the inclusion criteria and had undergone 30 treatment episodes. Eight patients had associated pathology: 3 sarcoidosis, 3 birdshot chorioretinopathy, and 2 Behçet's disease. The remaining 21 patients had isolated retinal vasculitis. One of the patients with isolated disease qualified for two treatment episodes. Five of the 30 cases had treatment for unilateral disease, although in only 1 of these (with idiopathic retinal vasculitis) the other eye had never been involved. At minus 1 month, 8 patients were on no treatment, 3 were on topical steroid and the remaining 19 were on systemic steroid with doses ranging from 2.5 mg to 30 mg prednisolone. Although the activity index at zero time, i.e. at initiation of high-dose steroids, was variable (6–34, with a mean of 12), patients fell into two groups: those with marked disease activity associated with a high activity score (21/30) and those with persistent grumbling activity unresponsive to low-dose systemic steroids

Table I. Patients requiring additional immunosuppressive therapy

Patient	Aetiology	Time at which immunosuppressive added (months)	Immunosuppressive added	Reason added	Dose of prednisolone at time of relapse (mg)	Visual outcome
PH	Isolated retinal vasculitis	1	Azathioprine	Poorly controlled disease activity	20	Success
CA	Isolated retinal vasculitis	4	Azathioprine	Relapse when off all treatment	Nil	Success
AW	Isolated retinal vasculitis	3	Cyclosporin A	Poorly controlled disease activity	20	Success
RS	Sarcoidosis	1	Azathioprine	Side-effects of prednisolone	40	Success
NW	Behçet's disease	8	Azathioprine	Side-effects of prednisolone	15	Success
PG	Isolated retinal vasculitis	2	Azathioprine	Side-effects of prednisolone	25	Failure
SS	Isolated retinal vasculitis	3	Cyclosporin A	Poorly controlled disease activity	20	Failure
ET	Behçet's disease	7	Azathioprine	Poorly controlled disease activity	10	Failure

Table II. Documented side-effects of treatment of patients managed on steroids alone

Side-effect	No. of cases	Therapeutic intervention
Diabetes mellitus	1	Oral hypoglycaemics
Hypertension	1	Oral hypotensives
Weight gain	10	
Reduced renal threshold to glucose	3	
Cushingoid facies	3	
Malaise	3	
Acne	2	
Sweating	1	
Snoring	1	
Bruising	1	

(9/30). Initial and final Snellen visual acuities of all cases (60 eyes) are illustrated in Fig. 1. None of the cases had their initial visual acuity reduced secondary to macular ischaemia.

Twenty-two of the 30 treatment episodes (73%) were managed with steroids alone throughout the year. This group consisted of 17 cases of isolated vasculitis, 3 of birdshot chorioretinopathy and 2 of sarcoidosis. The remaining 8 treatment episodes required additional immunosuppressive therapy (Table I): 6 (20%) with azathioprine (3 isolated vasculitis, 2 Behçet's disease, 1 sarcoidosis) and 2 (6%) with cyclosporin A (2 isolated vasculitis). The time at which these drugs was added was variable, but tended to be in the first 4 months.

Twelve of the 22 treatment episodes managed on steroids alone were off treatment by 12 months. Six of the remaining 10 patients still on prednisolone at 12 months were on 10 mg prednisolone per day or less; the highest maintenance dose of the remaining patients was 20 mg/day.

Side-effects of steroids were common (Table II). Twelve of the 22 (54%) treatment episodes managed on steroids alone resulted in documented side-effects. Two of these cases required therapeutic intervention: 1 patient developed diabetes mellitus requiring oral hypoglycaemics, while the other became hypertensive requiring hypotensives. In 3 further cases hyperglycaemia or marked weight increase required additional immunosuppressive therapy (azathioprine in all 3 cases) to enable the prednisolone dose to be reduced.

Disease Course and Outcome

Nine cases in all suffered a relapse during the 12 month period (Table III). Two cases had two relapses. Seven of the total 11 relapses occurred between 5 and 7 months.

Twenty-three (77%) of the 30 treatment episodes resulted in a successful visual outcome at 12 months (see Fig. 1). Eighteen (60%) patients with a successful visual outcome were managed on steroids alone, and of these 10 were off treatment at 12 months; 4 (13%) were managed on steroids and azathioprine, and of these, 1 was off treatment at 12 months. One was managed on prednisolone and cyclosporin A, and remained on this treatment at 12 months. There was no correlation at any stage between either visual acuity or activity index and good visual outcome at 12 months. Furthermore, there did not appear to be any relationship between relapses and final visual outcome.

Seven (23%) patients had a poor visual outcome, for a variety of reasons (Table IV). It should be noted that patient MA who had a poor visual outcome at 12 months due to increasing lens opacity, had good visual function restored after cataract surgery performed outside the study period. Two of the 9 patients who at inclusion in the study had persistent grumbling disease activity despite low-dose systemic steroids, had a poor visual outcome (patients PS and SP).

Table III. Patients relapsing during the 12 month follow-up period

Patient	Aetiology	Time of relapse (months)	Treatment at time of relapse	Change in treatment	Visual outcome at 12 months
DF	Isolated retinal vasculitis	5	Prednisolone 2 mg	Increase in dose	Good
RK	Isolated retinal vasculitis	6	Prednisolone 16 mg	Increase in dose	Good
NW	Behçet's disease	6	Prednisolone 10 mg	Increase in dose	Good
FL	Isolated retinal vasculitis	7	Prednisolone 5 mg alt. die	Increase in dose	Good
PH	Isolated retinal vasculitis	3	Prednisolone 10 mg and azathioprine	Increase in steroid dose	Good
CA	Isolated retinal vasculitis	3	No treatment	Addition of azathioprine	Good
MA	Isolated retinal vasculitis	6	Prednisolone 5 mg	Increase in dose	Failure (due to increasing lens opacity)
PS	Isolated retinal vasculitis	6	Prednisolone 15 mg	Increase in dose	Failure (relapse at 12 month follow-up)
		12	Prednisolone 10 mg	Addition of cyclosporin outside follow-up	
ET	Behçet's disease	7	Prednisolone 10 mg	Addition of azathioprine	Failure (relapse at 12 month follow-up due to poor treatment compliance)
		12	Nil (discontinued by patient)	Recommencement prednisolone and azathioprine	

Table IV. Details of cases with poor visual outcome

Patient	Aetiology	Treatment	Initial visual acuity		Visual acuity at 12 months		Reason for poor visual outcome
			Right	Left	Right	Left	
MM	Isolated retinal vasculitis	Prednisolone	6/36	6/36	6/24	6/24	Band keratopathy, some lens opacity, retinal damage
PS	Isolated retinal vasculitis	Prednisolone	6/12	6/36	6/18	6/60	Relapse at 12 months
MA	Isolated retinal vasculitis	Prednisolone	6/18	6/18	6/9	CF	Increasing left lens opacity
SP	Isolated retinal vasculitis	Prednisolone	6/9	CF	6/9	CF	Left persistent cystoid macular oedema
SS	Isolated retinal vasculitis	Prednisolone and cyclosporin A added at 3 months	6/36	6/60	6/24	6/60	Persistent cystoid macular oedema
PG	Isolated retinal vasculitis	Prednisolone and azathioprine added at 2 months	CF	6/9	HM	6/6	Right optic neuropathy
ET	Behçet's disease	Prednisolone and azathioprine added at 7 months	CF	6/9	CF	6/9	Poor treatment compliance

CF, counting fingers.

DISCUSSION

This paper presents 29 patients with retinal vasculitis managed with a course of high-dose steroids and followed up for 1 year. The study was carried out to assess our current treatment regime and to evaluate a number of factors including efficacy, side-effects and optimum length of treatment. Only 2 patients had Behçet's disease, which is known to have a poor visual prognosis, but a successful visual outcome was achieved at the 12 month follow-up in a total of 77% cases, a third of whom were off all treatment. Those receiving steroids only achieved a 60% visual success. The fact that 7 patients who had previously failed to respond to a lower dose of systemic steroids and now had a favourable outcome supports our clinical impression that the initial dose of steroids must be high (−1 mg/kg) for at least 1 week and that patients must then take at least 0.5 mg/kg for a further month to optimise the chance of success.

Surprisingly, there is little published in the literature on the efficacy of high-dose steroid regimes for comparison with our success rates, but Nussenblatt *et al.*[7] carried out a double-masked study on 56 patients with idiopathic intermediate and posterior uveitis randomising them to high-dose oral prednisolone (80–60 mg starting dose, depending on body weight) versus cyclosporin A. It is not clear for how long the prednisolone was maintained above or equal to 40 mg prednisolone as in our study, but at the 3 month follow-up 13 of 28 (46%) cases were deemed a success (improvement in visual acuity by 3 lines or more in at least one eye, or improvement of at least two increments on their vitreous haze scoring).

Our study was retrospective and thereby limited in a number of respects. It would be of interest to carry out a prospective study randomising suitable patients with retinal vasculitis to compare directly this high-dose steroid regime (with maintenance of 40 mg prednisolone for at least 5 weeks) with a regime in which steroid dose is titrated to patient response. Studying the 9 of 30 cases with grumbling disease unresponsive to low-dose steroids does support the proposition that a course of high-dose steroids can be effective in controlling disease. Although the numbers are small and it is therefore difficult to draw firm conclusions, 7 of these 9 cases (77%) had a successful visual outcome – interestingly in exact proportion to the success rate overall.

All the systemic drugs currently in clinical use for treatment of posterior uveitis have serious side-effects.[4,13] Side-effects of steroids are common and well documented,[10] and just over half of our patients managed on steroids alone experienced them. Only 2 required therapeutic intervention for hyperglycaemia and hypertension, while a further 3 required addition of azathioprine to allow reduction in the steroid dose (total 5/30 = 16%). Half the patients managed on steroid alone were off treatment at 12 months, while three-quarters of those still on prednisolone were on a maintenance dose of 10 mg or less. The use of immunosuppressive agents for life-threatening conditions is well established,[11,12] but their use in the management of disorders such as uveitis must necessarily be more circumspect. Currently cyclosporin A and azathioprine are the immunosuppressive agents most commonly used in the management of uveitis. Bone marrow suppression and gastrointestinal upset are the side-effects of azathioprine that most commonly limit its clinical role.[13,14] This was illustrated in our study, as 1 of the 2 patients who had their azathioprine discontinued did so due to gastrointestinal upset (patient RS), while in the second it was stopped due to abnormal liver function tests (patient NW). A third patient on azathioprine (PH) developed a transient lymphopenia which did not warrant discontinuing the drug: The major side-effects of cyclosporin that limit its use are nephrotoxicity and hypertension. These have been widely reported in both transplant

patients[15] and uveitis patients.[16–18] The changes in renal function appear to be largely reversible,[12] but more worrying are the seemingly non-reversible histological changes on renal biopsy in both transplant patients[19] and uveitis patients.[20,21]

In conclusion, our study showed a 60% success rate in visual outcome at 1 year in posterior uveitis patients managed on steroids alone, improving to 77% with the addition of other immunosuppressive agents. We feel this good result may well be due to the unique feature of this regime in that patients are kept on a high initial dose of systemic steroid for at least 5 weeks. This study illustrates that oral steroids still have a key role to play in the management of posterior uveitis, especially as both our understanding and experience with them is much greater than with the newer immunosuppressive agents.

This study will provide a useful standard with which to compare the results of more sophisticated regimes of intravenous therapy or modern immunomodulators.

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