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The use of corticosteroids for choroidal neovascularisation in young patients

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Abstract

Purpose **To investigate the role of systemic corticosteroids in the treatment of sight-threatening choroidal neovascularisation (CNV) in patients with punctate inner choroidopathy (PIC) and multifocal inner choroiditis (MIC).**

Methods **Twelve eyes of 10 patients with evidence of PIC or MIC with recent visual symptoms were identified. All eyes had CNV within the foveal avascular zone on fundus fluorescein angiography (FFA). Systemic oral prednisolone at an initial dose of 1 mg/kg (60–80 mg) was given for 3–5 days and the dose was subsequently tapered. Changes in best corrected visual acuity and leakage on FFA were recorded during follow-up. Systemic side-effects of the corticosteroids were monitored.**

Results **In 10 of 12 eyes vision improved or stabilised. Leakage on FFA resolved in 9 eyes and was reduced in 3. Four patients required more than one course of oral corticosteroids. One patient was maintained on low-dose oral corticosteroids for recurrent CNV activity. No systemic complications from the treatment were observed.**

Conclusion **A course of oral corticosteroids in healthy young patients with subfoveal CNV in PIC or MIC may reduce subretinal vascular leakage and stabilise vision when no other proven treatment option is available.**

Key words Choroidal neovascularisation (CNV), Chorioretinal scarring, Punctate inner choroidopathy (PIC), Multifocal inner choroiditis (MIC), Corticosteroid therapy

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Choroidal neovascularisation (CNV) is a common cause of visual loss in a wide variety of disorders affecting the choriocapillaris–Bruch's membrane–retinal pigment epithelial (RPE) complex, with age-related macular degeneration (ARMD) being the most common. Inflammatory conditions associated with disseminated chorioretinal scars can also predispose to macular CNV, including punctate inner choroidopathy (PIC), multifocal inner choroiditis (MIC) and presumed ocular histoplasmosis syndrome (POHS).

PIC is characteristically seen in young myopic women. There are multiple yellow opacities at the level of the inner choroid at the posterior pole and in the mid-periphery without other evidence of ocular inflammation. In the late stages, these lesions become variably pigmented or atrophic chorioretinal scars.[1,2] In contrast, MIC is associated with recurrent intraocular inflammation, but the retinal findings have many similarities with PIC. The prognosis for vision is good in both PIC and MIC unless CNV or cystoid macular oedema occur, which may happen in 40–50% of cases.[3,4] POHS comprises a triad of punched-out chorioretinal scars, peripapillary atrophy and submacular CNV without any observable intraocular inflammation.[5,6]

Young patients with extrafoveal CNV associated with chorioretinal scars due to PIC or MIC have a relatively good visual prognosis and require no active treatment.[1] However, once CNV has grown into the fovea, the visual outlook is generally poor regardless of the underlying process. This has been shown in prior studies for ARMD, where 70% of patients with juxtafoveal or subfoveal CNV suffer visual reduction to 6/36 or less within 2 years,[7] and for POHS, where 86% of patients have vision reduced to 6/18 or less within 3 years.[5] A recent natural history study of PIC and MIC showed that 32% of patients with MIC and 40% with PIC developed CNV over 3 years and that significant visual loss in their series was usually due to CNV.[4]

Patients with early subfoveal CNV may present with a relatively good visual acuity and can pose a therapeutic dilemma. The only proven treatment in POHS shown by a randomised trial is laser photocoagulation for patients with well-defined extrafoveal and juxtafoveal CNV.[8–13] Foveal photocoagulation has been studied in ARMD, but these results do not necessarily apply to inflammatory disorders.[14,15] The results of surgical extraction of subfoveal CNV are encouraging[16,17] but no

results from a randomised trial exist. The use of radiation[18] and anti-proliferative[19–21] or anti-angiogenic agents[22–24] has been suggested in order to decrease CNV activity, but these treatment modalities are still considered experimental.

Oral corticosteroids may be a viable treatment option when no other treatment is possible, and we have attempted to study the role for steroid treatment in this group of patients. In this communication, we present the results of a cohort of patients with PIC or MIC and subfoveal CNV in whom we prospectively evaluated the effect of oral corticosteroids on their clinical course and final visual outcome.

Subjects and methods

We studied 12 eyes of 10 patients with MIC or PIC from the Medical Retinal Clinics at Moorfields Eye Hospital who presented with recent onset of symptomatic CNV. In all cases the CNV was either under the centre of the fovea, or there was blood and/or pigment obscuring the details of the fovea on fundus fluorescein angiography (FFA). They were not suitable for laser photocoagulation as extrapolated from Macular Photocoagulation Study (MPS) guidelines.[8–13] In the absence of other treatment options, a course of oral corticosteroids was offered. All patients had a chest radiograph to rule out tuberculosis prior to initiating corticosteroids, a full blood count, and measurement of electrolytes, blood pressure and blood sugar. No women were pregnant or contemplating pregnancy.

An initial dose of 60–80 mg (approximately 1 mg/kg) or oral prednisolone was given for 3–5 days; the dose was then reduced by 10 mg every 3–5 days over a 1–2 week period and tapered altogether by 6–8 weeks. If retreatment became necessary it was carried out in the same manner as the initial corticosteroid course. Patients were followed with slit-lamp examinations of the fundus using a non-contact 78 dioptre lens and with serial colour fundus photographs beginning 1 week after initiation of corticosteroid therapy and then at 2 week intervals until the CNV and/or vision had stabilised. FFA was performed prior to treatment and additionally during the course of treatment and follow-up if best corrected visual acuity decreased or if the patient reported a change in vision and/or on amsler grid monitoring. During corticosteroid treatment we monitored blood pressure, patient weight and blood sugar measurements for evidence of adverse corticosteroid effects. Best corrected Snellen visual acuities were measured at each examination prior to dilation. Improved visual acuity during review was defined as two lines or better than baseline on the Snellen chart over the previous two follow-up evaluations. We recorded subjective visual improvement, reduction or resolution of distortion, changes in the amount of subretinal fluid and/or haemorrhages, and the development of fibrosis and changes in pigmentation associated with the CNV. The FFAs were reviewed by two independent observers looking specifically for a decrease in hyperfluorescence in the late arteriovenous phase when compared with the baseline FFA.

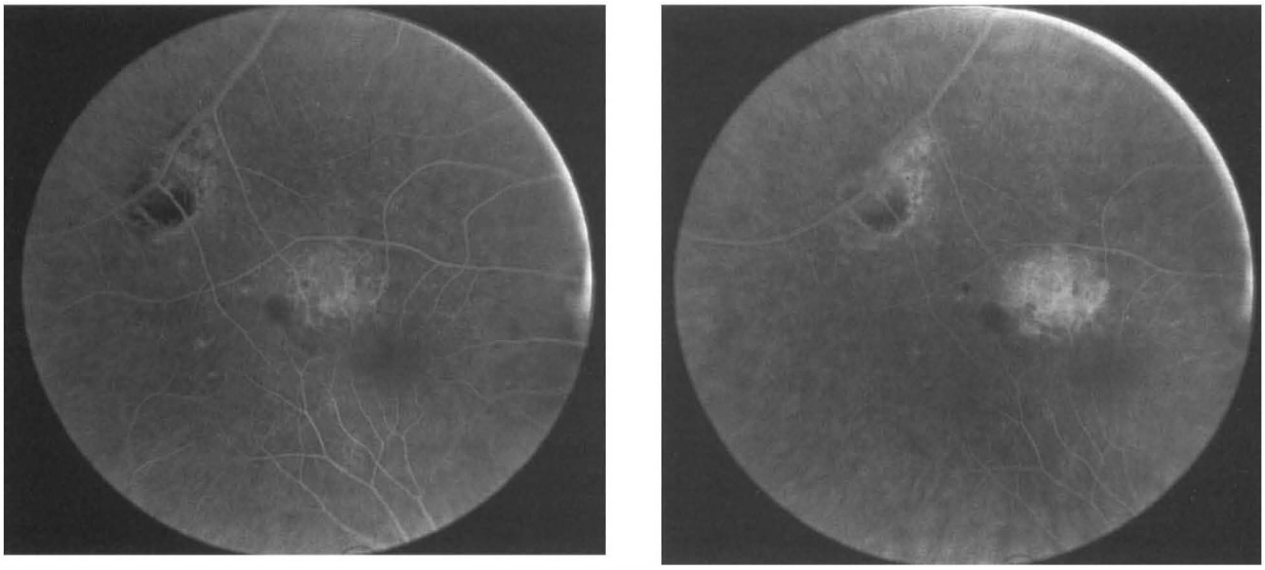
Results

Results are summarised in Table 1. Ten patients with CNV were identified: 2 men and 8 women with a mean age of 31 years (range 24–41 years). Eight patients (all

Table 1. *Patient details*

Eye no.	1st or 2nd eye	Refractive error	Age (years)	Eye	Diagnosis	VA acuity before steroids	FFA leakage before steroids (leakage + to +++)	No. of steroid courses [length] (weeks between courses)	Final VA	FFA leakage after steroids (leakage 0 to ++)	Length of follow-up (months)
1	2nd	Emmetrope	41	LE	MIC	6/12	SRP; +	2[6], [12](8)	6/12	chronic SRF 0	12
2	2nd	−9	31	RE	PIC	6/9	+	3[6], [12], [6](4) (24)	6/9	0	18
3	1st	−14	31	LE	PIC	6/9	++	2[6], [6] (3)	6/18[a] (1/60)[b]	0	24
4	2nd	−7	25	LE	PIC	6/18	+++	1	6/9	0	14
5	1st	−0.5	24	LE	PIC	2/60	+++	1	6/9	0	12
6	2nd	Emmetrope	24	RE	PIC	6/12	+++	1	6/9	0	18
7	1st	Emmetrope	24	LE	PIC	6/60	++	1	6/12	+	18
8	1st	Emmetrope	36	RE	PIC	1/60	+	2 (no interval)[c]	6/60	0	8
9	2nd	Emmetrope	36	LE	PIC	6/5	+++	2 (no interval)[c]	6/9	++	8
10	2nd	−2	38	RE	MIC	6/9	+++	1	6/9	+	12
11	2nd	−2	26	RE	PIC	6/60	+++	2[6], [8](16)	6/9	0	8
12	1st	−2	21	RE	PIC	2/60	+++	1	6/60	0	4

VA, visual acuity; FFA, fundus fluorescein angiogram; LE, left eye; RE, right eye; MIC, multifocal inner choroiditis; PIC, punctate inner choroidopathy; SRF, subretinal fluid.
[a]Vision after second course of steroids.
[b]Vision after surgical CNV extraction.
[c]Reactivation occurred during each attempted steroid taper.



(a) (b)

Fig. 1. *(a), (b) Early and late phases of the fluorescein angiogram of eye 2 before treatment.*

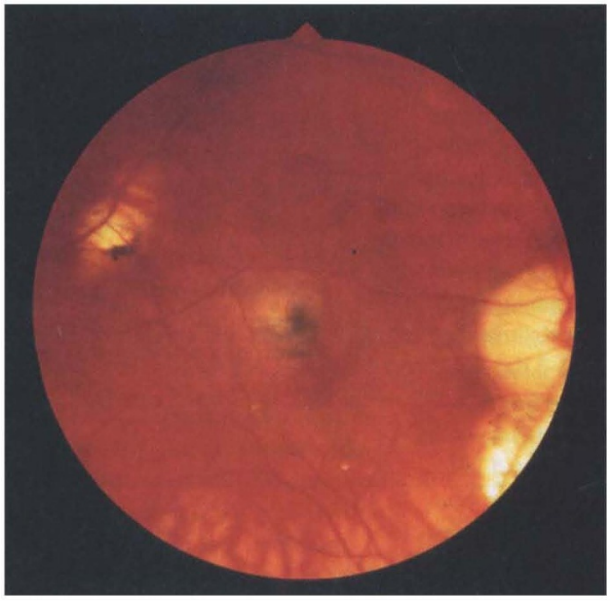
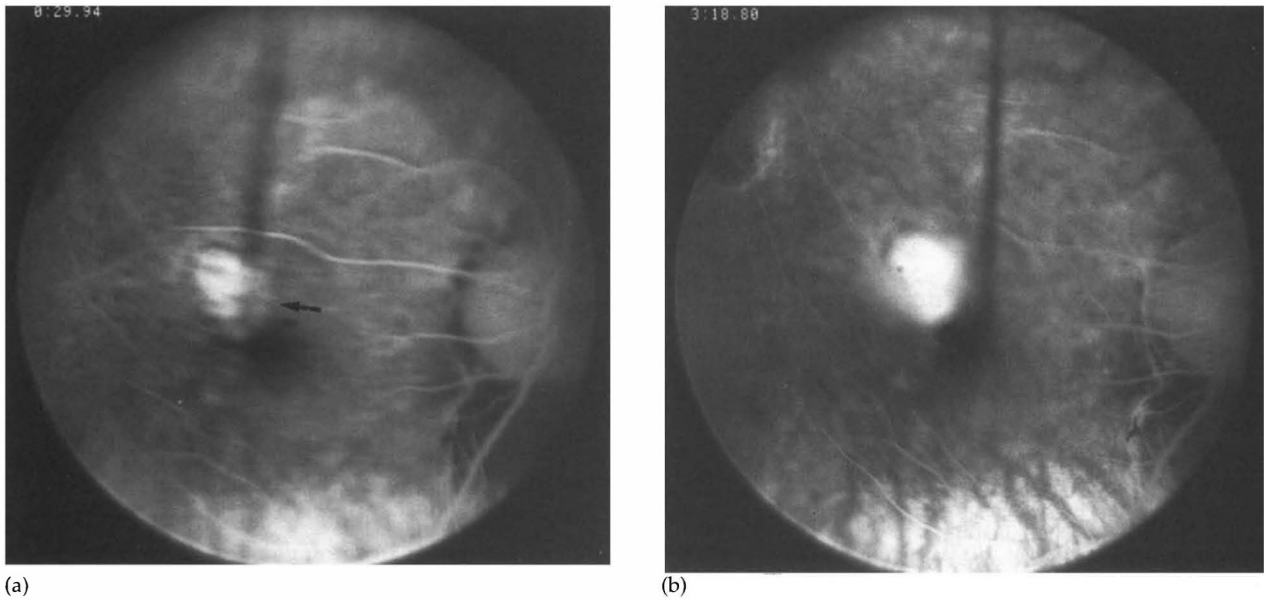
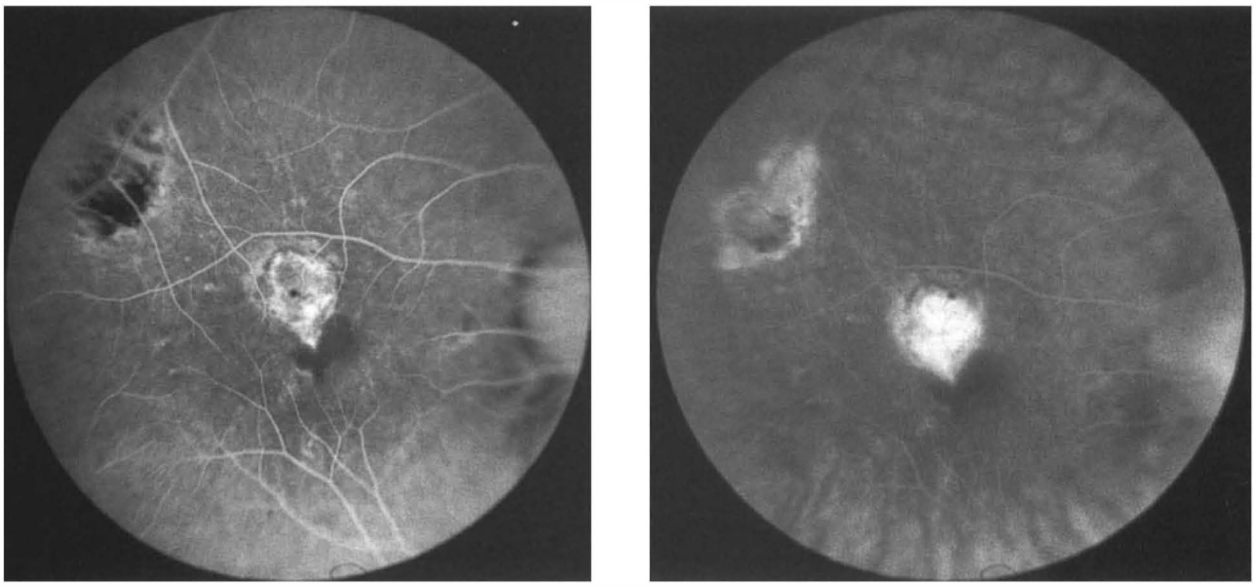


Fig. 2. *Eye 2 after the first steroid course.*



(a) (b)

Fig. 3. *(a), (b) Early and late phases of the fluorescein angiogram of eye 2 showing reactivation after steroid withdrawal.*



(a) (b)

Fig. 4. *(a), (b) Early and late phases of the fluorescein angiogram of eye 2, 2 weeks after the second steroid course without leakage.*

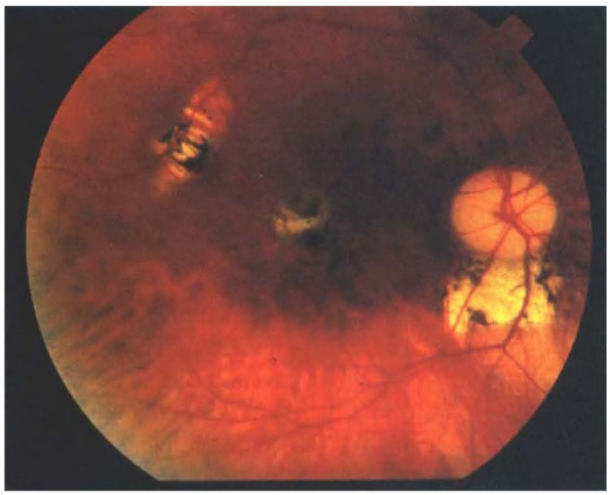


Fig. 5. *Eye 2, 2 years after steroid withdrawal.*

female) had a diagnosis of PIC and 2 patients had MIC (both male). All patients presented with recent (1 day to 2 weeks) decreased central vision and metamorphopsia. The average review period was 13 months (range 4 months to 2 years). All patients were Caucasian and all were from Britain. No patient had a history of trauma. In 5 of 12 cases, extensive medical evaluation was undertaken to identify treatable causes of inflammation such as tuberculosis, syphilis, sarcoidosis and toxoplasmosis that could lead to chorioretinal scars (eyes 1, 2, 8, 10, 11). These tests included a full blood count, erythrocyte sedimentation rate, chest radiograph, syphilis serology, angiotensin converting enzyme, and toxoplasmosis titre; all results were normal.

Initial visual acuity ranged from 6/5 to 1/60 (average visual acuity 6/18). Six of 12 eyes had vision of 6/12 or better – too good to consider surgical excision at our institution at that time. Vision was 6/18 to 1/60 in 6 eyes; these patients declined surgical intervention.

With corticosteroid treatment, 10 of 12 eyes showed either improvement in Snellen visual acuity or stabilisation of vision, with final visual acuities ranging from 6/6 to 6/60 (average final visual acuity 6/12) (Fig. 6). Subjectively, all patients noted either improvement or stabilisation of visual symptoms including distortion. One eye had final acuity of 1/60 following surgical removal of the subfoveal CNV (eye 3), although the pre-operative acuity immediately following corticosteroid withdrawal was 6/18. The other eye that deteriorated was eye 9, which had decreased leakage from CNV after a second course of corticosteroids with final vision of 6/9.

Seven of 10 patients had bilateral CNV and presented only when they became symptomatic in their second eye. Five of these 7 were found to have inactive fibrotic subfoveal disciform scars in the fellow eye, and 2 had bilateral active CNV. Patient 1 initially presented in 1991 with a CNV in the left eye (LE) and multiple pale choroidal lesions in both eyes. The patient developed

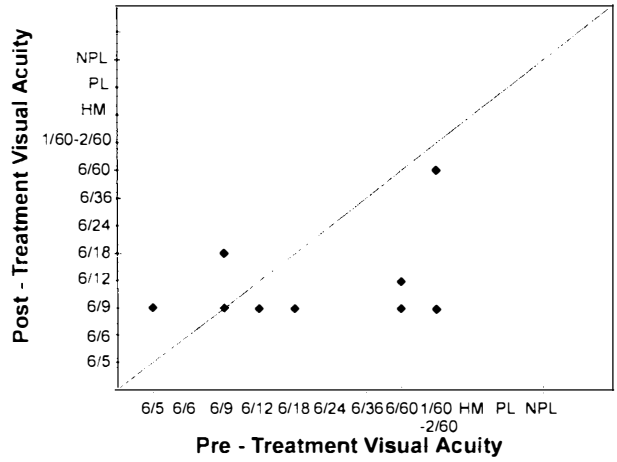


Fig. 6. *Scattergram of pre-steroid visual acuity versus post-steroid visual acuity.*

subretinal fibrosis with best corrected vision of 6/18 in this eye. She presented again in 1993 with metamorphopsia of the right eye (RE). FFA demonstrated an active CNV adjacent to the fovea emanating from a small choroidal scar with haemorrhage into the foveola (Fig. 1). Visual acuity at this time was 6/12 RE and 6/18 LE. As the lesion in the RE was not treatable by MPS standards[10] the patient was offered a course of oral corticosteroid therapy, and was treated with oral prednisolone in our standard fashion with a rapid taper over 6 weeks. Vision stabilised at 6/9 RE with continued fibroses of the subfoveal CNV and no leakage on FFA (Fig. 2). One month after corticosteroids were discontinued, the FFA showed active leakage along the edge of the CNV (Fig. 3). Corticosteroids were recommenced in the standard fashion and again rapidly tapered. The patient's vision stabilised and repeat FFA 2 weeks after corticosteroids were discontinued showed no evidence of leakage (Fig. 4). She has required no further treatment during the 2 year review period. Her vision remains 6/9 RE and has decreased to 6/36 LE due to extensive subretinal fibrosis. The most recent examination demonstrated a pigmented and fibrotic CNV RE (Fig. 5).

At the time of presentation, 4 study eyes had significant subretinal fluid involving the fovea. Six of 12 eyes had submacular haemorrhage associated with the CNV but only 2 had haemorrhage extending beneath the fovea. Nine eyes had pigment hyperplasia at the fovea. Eleven of 12 eyes had angiographic evidence of classic CNV as indicated by leakage of fluorescein dye in the arteriovenous phase and persistent hyperfluorescence in the late stages of the angiogram. Those lesions associated with haemorrhage, pigment, or both, showed blockage of fluorescence throughout the study. An atypical FFA appearance was seen in 1 eye (eye 1) showing slow choroidal filling with delayed fluorescence of CNV.

When we applied the laser treatment criteria from the MPS-krypton laser for ocular histoplasmosis trial,[12] 2 eyes were ineligible for laser by these standards due to haemorrhage within 200 μm of the foveal avascular zone and CNV within the same region, 5 eyes were ineligible due to the presence of both haemorrhage and pigment at the fovea, and 4 eyes were ineligible due to the presence of pigment only at the fovea. One patient had neither haemorrhage nor pigment within the foveal avascular zone but she had a peripapillary lesion that was deemed ineligible for laser. After corticosteroids were discontinued, 8 eyes showed no leakage on FFA and 3 of these had fibrotic scars in the fovea. Two eyes showed persistent, minimal leakage on FFA but no evidence of recurrent CNV (eyes 7 and 10). One eye showed decreased leakage until the corticosteroids were tapered below 10 mg and then the leakage increased. Corticosteroids are currently being very gradually weaned (eye 9). One eye had chronic subretinal fluid but no leakage on FFA; the fluid did not resolve after a second course of corticosteroids (eye 1).

Four eyes required a repeat course of oral corticosteroids when CNV activity recurred. Vision and leakage stabilised in all these eyes after a repeat course of corticosteroids with no systemic side-effects. The length of time for vision to stabilise after corticosteroids were restarted was 1 week in all patients. Only eye 9 required continuous oral corticosteroid therapy.

Only 2 of the 12 eyes showed a loss of vision following corticosteroid taper; thus 83% of the eyes in this study retained their pre-treatment vision (average vision after corticosteroids 6/12).

Discussion

Young patients with subfoveal CNV and PIC or MIC pose a difficult management problem. They present with sudden and dramatic decreased vision often with bilateral involvement. The natural history of these lesions is generally unfavourable.[4,6,7] We acknowledge that some CNV in young patients may regress even without treatment.[4,6,25] Natural history studies of subfoveal CNV in POHS suggest that the final vision in 86% is 6/18 or less[6] and a recent report of subfoveal CNV in eyes with PIC and MIC showed similar results.[4] With such poor visual outcome it would be helpful to establish clinical signs indicative of better visual prognosis, but no studies

have evaluated these factors in conditions other than ARMD. In their large natural history study in ARMD, Teeters and Bird[26] found that patients with best visual outcome had initially small neovascular complexes with minimal subretinal fluid and little or no cystoid macular oedema. They also noted that the prognosis was better for eyes with the shortest duration of symptoms whose CNV became pigmented and/or fibrotic leading to the resolution of subretinal fluid. Though we cannot extrapolate directly from this study to our current series of young patients, it seems reasonable that some of their observations hold true in our series.

The search for better treatment options for CNV continues to be an active area of research, but the research protocols are focused on ARMD. Current treatment modalities of CNV include its destruction by laser photocoagulation, surgical removal of the CNV, and other treatment modalities to encourage rapid involution of the CNV such as radiation therapy (teletherapy) or drug treatment.[14–25,27–30] Only laser photocoagulation[11,12] has been proved to be effective in the treatment of extrafoveal CNV due to POHS and none of the current treatment methods has been found to be effective in CNV due to inflammatory disorders such as PIC or MIC. Surgical extraction shows promising early results in patients with POHS though there is a high rate of CNV recurrence post-operatively.[16,17,22]

Other treatment options are currently being evaluated in ARMD, and may be considered in other cases of CNV if promising results are shown. Laser treatment of subfoveal CNV had been shown to be effective but only in certain cases of ARMD.[14,15] Teletherapy is a new potential treatment for subfoveal CNV in ARMD, and randomised trials are in progress.[18,22] Early encouraging results using alpha-interferon had been reported in ARMD,[19] but more recent studies[20] have failed to show a benefit in patients with exudative ARMD. The results of efficacy and toxicity studies have also caused some concern amongst clinicians regarding systemic side-effects of alpha-interferon.[21] Local administration of a slow-release anti-angiogenic agent has been suggested, such as a Lincoff balloon-type device,[31] but research is still in its early stages.

Use of corticosteroids in the management of CNV associated with PIC, MIC and POHS has been previously described in the literature.[2,4,6,25,27,32–36] These series were not all collected prospectively, and the visual results were variable. While it is difficult to compare individual series, the final visual acuities in our patients were better than those reported previously. This may be due to a number of factors such as patient selection, corticosteroid dosage and duration. In our study, treatment was initiated only when the patient's symptoms indicated threat to central vision and FFA demonstrated active leakage from submacular CNV. The dose of systemic corticosteroids we used was generally higher than in other reports and we did not use peri-ocular corticosteroids.

Seven of our 10 patients had bilateral CNV at the time of presentation. Five of these had established inactive subfoveal disciform scars in their fellow eyes. The 2 patients with bilateral active CNV were initially placed on corticosteroids primarily for the active CNV in the better eye, but in fact the visual acuity improved in both eyes. The fellow eyes of the other 5 patients showed no change in the visual acuity and/or in the appearance of the CNV on FFA. This would imply that steroids have a greater effect on actively proliferating CNV, though the exact mechanism of action remains speculative.[23,26–28] Steroids have been shown to prevent growth of new blood vessels and cause existing vessels to regress.[22–24] They may be acting to reduce the active inflammatory component,[29] which may in turn decrease the stimulus to endothelial proliferation. They also decrease vascular permeability by stabilising the basement membrane of the CNV and thus reducing oedema, and encouraging more rapid involution of CNV.[29] Schlaegel has previously reported the use of steroids in the treatment of CNV in POHS before laser photocoagulation was available.[25] He suggested that corticosteroids reduce capillary permeability and oedema in inflammation and interfere with passage of immune complex across basement membranes.[25]

Histopathological examination of surgically excised CNV has demonstrated inflammatory cells associated with the fibrovascular complex.[26,27,30] A recent report describes evidence of granulomatous inflammation in a surgically excised CNV in a patient with POHS.[28] This patient had recurrent CNV post-operatively and was treated with systemic steroids with improvement in vision. This scenario implicates inflammation as a mediator in this particular disease process and the authors advocate corticosteroids as a possible treatment in some CNV.[28] In the absence of any other proven treatment modality for foveal CNV in young individuals, it is reasonable to try to suppress the CNV growth and abnormal vascular permeability as well as to modify the inflammatory process.[27] Corticosteroids are widely used in many inflammatory conditions of unknown aetiology and the method of their administration and potential side-effects are well documented. Systemic corticosteroids are well tolerated in otherwise healthy young adults. Unlike other anti-angiogenic agents such as alpha-interferon, they are relatively safe over a short period of time with very few side-effects. None of our patients required more than three courses of steroids, though one patient needed a slower taper over 4 months. We realise that small numbers and lack of a control group make it difficult to formulate conclusions, but in comparison with historic controls, the visual outcome in our patients was reasonably good.

In this study, we used a uniform protocol for administration of corticosteroids in all patients, with an overall favourable response. It appears that although the visual acuity may not recover completely, limiting the new vessel growth may result in a more favourable visual outcome. Stabilisation of visual acuity is especially beneficial in patients with second eye involvement.

Conclusion

A course of oral systemic corticosteroids is a reasonable option for healthy young patients with active subfoveal CNV in the setting of PIC or MIC, since no other proven treatment options are available. A course of 1 mg/kg (approximately 60–80 mg) per day of oral prednisolone is started for 3–5 days, then tapered over 6–8 weeks. More than one course of corticosteroids may be required if CNV reactivates after corticosteroid taper. In unusual cases a prolonged corticosteroid course may be necessary with a very slow taper based on CNV activity on FFA and visual acuity.

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