Immunosuppressive Treatment of Choroidal Neovascularization Associated With Endogenous Posterior Uveitis

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Objective: To determine whether resolution of choroidal neovascularization (CNV), a recognized sight-threatening complication of endogenous posterior uveitis, and maintenance of vision could be achieved with immunosuppression.

Patients and Methods: Fourteen patients (17 eyes) with CNV associated with endogenous posterior uveitis were enrolled in an open study. Ages ranged from 5 to 51 years. Three eyes had extrafoveal CNV, 6 juxtafoveal, and 8 subfoveal. Three patients were treated with a single course of oral corticosteroids, 2 had additional cyclosporine for up to 2 years, and 9 continued to receive a low-dose regimen of a combination of immunosuppressive drugs.

Results: After a median follow-up of 15 months (range, 7 months to 6½ years), 9 of 17 eyes had an improvement in visual acuity; 6 remained within 1 Snellen line of initial visual acuity, and 2 had lost 2 Snellen lines. Angiographically, CNV resolved in 13 eyes, resolved then recurred in 3, and improved but persisted in 4.

Conclusion: These results support a role for immunosuppressive therapy in the treatment of CNV associated with endogenous posterior uveitis.


There is a spectrum of clinical manifestations of chronic noninfectious posterior uveitis, or endogenous posterior uveitis (EPU), which parallels the pathological changes seen in the animal model, experimental autoimmune uveitis. This includes vitritis, chorioretinal infiltrates, retinal vasculitis, and macular edema.1 In addition, however, choroidal neovascularization (CNV) occurs in chronic low-grade inflammatory disorders such as multifocal choroiditis,2 birdshot chorioretinopathy,3 and sympathetic ophthalmia,4 as well as during the late phases of experimental autoimmune uveitis.5 Although the exact pathogenesis remains unknown, both proangiogenic growth factors and cytokines released during chronic inflammation are thought to contribute significantly to CNV formation.6

Presumed ocular histoplasmosis syndrome (POHS)6 and other similar clinical entities of EPU7-9 have been well documented as being associated with low-grade posterior segment inflammation and sight-threatening CNV. Typically, although there is little or no vitritis, the multifocal choroidal lesions show the hallmarks of chorioretinal infiltrates during their evolution10 and, occasionally, CNV cannot be distinguished from a choroidal microgranuloma until excision.11 The choroidal neovascular membrane has been shown to contain inflammatory cells, typically macrophages and lymphocytes,12 with the latter in significantly higher numbers than in age-related CNV. In addition, Suttorp-Schulten et al13 propose that idiopathic CNV and CNV in association with POHS and other EPU's should be regarded as a spectrum of neovascular responses to low-grade chronic intraocular inflammation when there is no other degenerative condition of the retinal pigment epithelium. Patients younger than 50 years seen with idiopathic CNV have a clinical course similar to patients with CNV in association with POHS or EPU.13

Documented experimental and clinical evidence of EPU as outlined earlier suggests that CNV develops in direct response to low-grade chronic intraocular inflammation and, therefore, may respond to immunosuppressive therapy. This study shows that immunosuppressive induction of regression of CNV with improvement or maintenance of vision.
PATIENTS AND METHODS

PATIENT DATA AND DIAGNOSIS

In this open study, 14 patients (17 eyes) who were seen at the Uveitis Unit at the Eye Department of the Aberdeen Royal Infirmary, Aberdeen, Scotland, between 1990 and 1997 for CNV associated with EPU underwent immunosuppression after informed consent was obtained. Patients were classified according to International Uveitis Study Group guidelines.14 Patients who had idiopathic CNV had no evidence of other conditions known to be associated with CNV (including age-related macular degeneration and pathologic myopia). All patients underwent full ophthalmic examination including best-corrected Snellen visual acuity (VA) and fundus biomicroscopy. Color fundus photography and fluorescein angiography were performed in all cases except in the case of a 3-year-old boy (case 1 in the Table) with sympathetic ophthalmia. Diagnosis of CNV was based on fundus biomicroscopy (presence of serous retinal detachment with or without retinal hemorrhages and exudates) and fluorescein angiography (the presence of early-phase hyperfluorescence with late leakage). Except for patient 1, all patients demonstrated classic components of CNV with angiography, and could be further classified as extrafoveal, juxtafoveal, or subfoveal as defined by the Macular Photocoagulation Study Group.15

IMMUNOSUPPRESSION AND MONITORING

Three immunosuppressive regimens were employed: (1) a single course of prednisolone acetate; (2) combined low-dose immunosuppression with prednisolone and cyclosporine16; (3) triple therapy with prednisolone, cyclosporine, and azathioprine. The clinical decision to give medium or long-term combined therapy was taken if any of the following factors applied: (1) concurrently active EPU, (2) bilateral disease, (3) recurrence of CNV after favorable response to steroid course, and (4) incomplete resolution of CNV following steroid course.

The single steroid course (regimen 1) comprised the following: oral prednisolone was started at 1 mg/kg of body weight per day, was then gradually reduced to 15 mg/d over the course of a few weeks, and was eventually withdrawn over a period of a few months. If long-term immunosuppression with combination low-dose steroid and cyclosporine was required (regimen 2), the following regimen was adopted: prednisolone (0.05-0.15 mg/kg per day) and cyclosporine (3-5 mg/kg per day). The cyclosporine dose was reduced from 5 to 4 or 3 mg/kg per day if the serum creatinine level rose more than 30% above baseline levels17 or if other side effects occurred. If additional immunosuppression was required to preserve vision (regimen 3), the following triple therapy regimen was used: azathioprine BP, 1 to 1.5 mg/kg per day in addition to steroids and cyclosporine as described earlier. The general approach to management of patients with EPU has been described previously in greater detail.18

In addition to immunosuppression, 2 patients underwent argon green laser photoablation. One patient (case 6 in the Table), who had an extrafoveal CNV in the diseased eye and a disciform scar in the fellow eye and who had initially refused laser treatment, was treated with laser photocoagulation when 2 months of combined immunosuppressive therapy failed to produce a favorable response. Another patient (case 14 in the Table) who was successfully immunosuppressed for juxtafoveal CNV in the affected eye developed an extrafoveal CNV in the fellow eye that was treated with laser photocoagulation.

Follow-up was done on all patients at intervals of 2 to 4 weeks while either the CNV or the EPU was active, and thereafter 4 times per year. Treatment outcome was assessed by VA, fundoscopy, and fluorescein angiography. Blood pressure, weight, and serum electrolyte levels were checked and complete blood cell count and urinalysis were performed at each follow-up visit. In addition, the serum creatinine level and liver function parameters of cyclosporine-treated patients were checked at each visit and the glomerular filtration rate at baseline was checked once per year or if the serum creatinine level rose more than 30% above baseline value and did not return to baseline on reduction of the cyclosporine dose.19 Cyclosporine blood levels were also obtained to ensure patient compliance and to correlate with possible drug interactions.

RESULTS

All patients’ clinical data are summarized in the Table. The study group included 17 eyes of 14 patients. There were 5 men and 9 women; the median age was 36 years (range, 5-51 years). Choroidal neovascularization was defined as extrafoveal in 3 eyes, juxtafoveal in 6 eyes, and subfoveal in 8 eyes. Four patients had concurrently active EPU (1 sympathetic ophthalmia, 2 multifocal choroiditis, and 1 serpiginous choroiditis), 6 had POHS (CNV and ≥2 atrophic peripheral choroiditis scars), and 4 had idiopathic CNV.

Best-corrected Snellen VA at the time of CNV diagnosis ranged from 20/30 (near acuity, 5) to counting fingers (N48), median 20/80 (near acuity, 24). Patient data, management, and outcome are given in the Table. Except for patient 1, all patients had CNV and posterior uveitis, and therefore were not taking immunosuppressants prior to enrollment in the study.

After a median follow-up of 15 months (range, 7 months to 6½ years), 9 (53%) of 17 eyes had a VA of 2 or more Snellen lines better than when patients were initially seen; 6 (35%) remained within 1 Snellen line of initial VA, and 2 (12%) had lost 2 Snellen lines of VA (1 due to recurrent CNV and 1 due to cystoid macular edema and optic disc vasculitis related to multifocal choroiditis [MFC]) (Figure 1). Besides the patient with MFC who was also seen initially with vitritis (binocular indirect ophthalmoscopy score of 2), the other patients did not have cystoid macular edema (clinically or angiographically) or media opacities (eg, cataracts) that might influence visual outcome. Patient 2 developed cystoid macular edema after resolution of CNV, which resulted in reduced vision (Table). Thirteen of 17 eyes showed resolution of CNV during the course of treatment, as evidenced by resolution of serous retinal detachment on fundus biomicroscopy and absence of dye leakage on fundus fluorescein angiography. In 3 eyes (cases 11, 13, and...
Details of 14 Patients (17 Eyes) With Choroidal Neovascularization as a Complication of Endogenous Posterior Uveitis, Treated With Immunosuppression

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age at Onset, y</th>
<th>Visual Activity</th>
<th>Location of CNV</th>
<th>Diagnosis</th>
<th>Treatment, Dose/Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/5</td>
<td>20/200 OD</td>
<td>JF</td>
<td>SO (Inciting)</td>
<td>5.5 g/4 y NT 47.4 g in 28 mo</td>
</tr>
<tr>
<td>L 40/80</td>
<td>L 20/30</td>
<td>SF</td>
<td>SO (Sympathizing)</td>
<td>5.5 g/4 y NT 47.4 g in 28 mo</td>
</tr>
<tr>
<td>2/F/44</td>
<td>R 20/40 N5</td>
<td>R 20/20 N5</td>
<td>JF</td>
<td>15.6 g/8/5 y 22.5 g in 9 mo 136 g in 18 mo</td>
</tr>
<tr>
<td>L 20/60</td>
<td>L 20/100 N18</td>
<td>JP</td>
<td>MFC</td>
<td>15.6 g/6/5 y 22.5 g in 9 mo 136 g in 18 mo</td>
</tr>
<tr>
<td>3/F/20</td>
<td>R CF N48</td>
<td>R 20/200 N36</td>
<td>SF</td>
<td>MFC 420 mg in 1 wk 6.0 g in 4 mo 60 g in 20 mo</td>
</tr>
<tr>
<td>L 20/80 N24</td>
<td>L 20/40 N8</td>
<td>JF</td>
<td>MFC</td>
<td>420 mg in 1 wk 6.0 g in 4 mo 60 g in 20 mo</td>
</tr>
<tr>
<td>4/M/44</td>
<td>L 20/200 N48</td>
<td>L 20/200 N48</td>
<td>SF</td>
<td>SC 3.4 g in 7 mo NT 72 g in 7 mo</td>
</tr>
<tr>
<td>5/F/28</td>
<td>L 20/60 N10</td>
<td>L 20/100 N24</td>
<td>JF, later SF</td>
<td>POHS 16.2 g in 3 y 9.1 g in 6 mo 270 g in 3 y</td>
</tr>
<tr>
<td>6/M/40</td>
<td>L 20/30 N5</td>
<td>L 20/30 N5</td>
<td>EF</td>
<td>POHS 5.2 g in 12 mo 13.8 g in 5/2 mo 142 g in 12 mo</td>
</tr>
<tr>
<td>7/F/51</td>
<td>L 20/100 N36</td>
<td>L 20/60 N24</td>
<td>SF</td>
<td>POHS 4.3 g in 12 mo NT 109.5 g in 12 mo</td>
</tr>
<tr>
<td>8/F/44</td>
<td>R 20/30 N24</td>
<td>R 20/100 N36</td>
<td>SF</td>
<td>I 3.0 g in 9 mo NT 81.4 g in 9 mo</td>
</tr>
<tr>
<td>9/M/30</td>
<td>R CF N48</td>
<td>R 20/60 N24</td>
<td>SF</td>
<td>I 3.4 g in 7 mo NT 84.8 g in 7 mo</td>
</tr>
<tr>
<td>10/F/34</td>
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<td>L 20/100 N48</td>
<td>SF</td>
<td>POHS 3.8 g in 11 mo NT Nil</td>
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<tr>
<td>11/F/38</td>
<td>R 20/30 N5</td>
<td>R 20/15 N5</td>
<td>EF, JF</td>
<td>POHS 6.4 g in 20 mo NT 45.6 g in 5 mo</td>
</tr>
<tr>
<td>12/F/48</td>
<td>R 20/60</td>
<td>R 20/30</td>
<td>JF</td>
<td>I 1.3 g in 7 wk NT Nil</td>
</tr>
<tr>
<td>13/F/19</td>
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<td>R 20/30 N5</td>
<td>JF</td>
<td>I 2.7 g in 10 mo NT Nil</td>
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<tr>
<td>14/M/34</td>
<td>R 20/200</td>
<td>R 20/30</td>
<td>SF</td>
<td>POHS 4.1 g in 8 mo NT 85 g in 8 mo</td>
</tr>
</tbody>
</table>

*MJ indicates juxtafoveal; SO, sympathetic ophthalmia; NT, no treatment; NA, not applicable; RNT, receiving no treatment; SF, subfoveal CNV; JP, juxtapapillary; MFC, multifocal choroiditis; VA, visual acuity; CF, counting fingers; SC, serpiginous choroiditis; POHS, presumed ocular histoplasmosis syndrome; EF, extrafoveal; CNV, choroidal neovascularization; and I, idiopathic. Patients 1 to 4 had CNV with active posterior uveitis. Patients 5 to 10 had persistent or recurrent CNV. Patients 11 to 14 had a simple CNV that was resolved. Total doses and duration of treatment are given for each immunosuppressant. No patient was treated with more than 5 mg/kg of cyclosporin or 2 mg/kg of azathioprine at a given daily dose.

As shown in Figure 2 (patient 13), which demonstrates the angiographic appearances when CNV has resolved following immunosuppression. In 4 eyes, the CNV persisted despite combination immunosuppression. Patient 6 (Table) underwent laser ablation for persistent extrafoveal CNV 8 weeks. Patient 9, who had an extensive juxtapapillary CNV extending subfoveally, showed partial resolution with a decrease in the area of active CNV and increasing fibrosis. Similarly, patients 9 and 10 showed a decrease in the area of leakage on fluorescein angiography, and improved vision (Figure 3: patient 9). Recurrence of CNV occurred in 3 eyes of 3 patients. Patient 5 (Table), initially diagnosed and treated for Toxoplasma chorioretinitis prior to referral to the Uveitis Clinic, had 3 recurrences over a 2½-year period: at 4, 15, and 26 months after the initial visit, respectively. Patient 7, with subfoveal CNV that was resolved with combination therapy, had a persistent recurrence at 7 months that was eventually managed with surgical removal. Patient 2, seen with bilateral juxtapapillary CNV that initially resolved, had ongoing active MFC requiring maintenance immunosuppression. A further active juxtapapillary CNV developed in 1 eye at 5 years, and again resolved on further immunosuppressive therapy. Of the remaining 8 patients (10 eyes) with resolution of CNV and no recurrence after follow-up of 8 months to 6½ years, 4 (cases 1, 11, 12, and 13) are presently receiving no treatment, while 4 (cases 2, 3, 4, and 14) continue on combination immunosuppression. In this cohort, POHS/idiopathic CNV had a higher incidence of either persistent (although decreased leakage) or recurrent (yet still responsive to therapy) CNV, although the number of patients is too small to make any significant distinction. In addition, response was not related to inflammatory activity at the time of the initial visit.

Side effects of treatment occurred in 3 patients: 2 developed systemic hypertension (cases 2 and 8), which was managed by lowering the cyclosporin dose and commencing treatment with amiodipine besylate, a calcium
Figure 2. Patient 13. Fundus fluorescein angiogram of right eye (Table) before and after treatment with systemic steroids. Visual acuity improved from 20/100 to 20/30. A, Before treatment, early phase of angiogram. B, Before treatment, late phase of angiogram. C, After treatment, early phase of angiogram. D, After treatment, late phase of angiogram. Angiograms C and D demonstrate the ring of hypofluorescence associated with resolved choroidal neovascularization, with no leakage and only window defects associated with scarring and secondary pigment epithelial disease.
channel antagonist; 1 patient (case 11) developed gastritis and liver enzyme levels rose. She was seronegative for hepatitis virus A, B, and C, but she did have a *Heli-
cobacter pylori* infection diagnosed by carbon 13 (13C) breath testing, for which she was treated with eradica-
tion antibiotic therapy. Her cyclosporine treatment was
stopped, after which her liver enzyme levels returned to
normal and her gastric symptoms improved. No patient
had a significant (30%) rise of serum creatinine level above
baseline.

**COMMENT**

Although the visual outcome of idiopathic CNV and CNV
in association with POHS and other types of EPU are gen-
erally better than that in age-related CNV, there is still a
significant visual morbidity. For example, the natural his-
tory of CNV in POHS is not favorable: a visual acuity of
20/200 or worse at 3-year follow-up in 65% of juxtafoveal
CNV (38% at 5 years in the Macular Photocoagulation Study
Group20) and in 76% of subfoveal CNV have been re-
ported.21 Present treatment options (laser photocoagula-
tion and surgical excision) have their limitations. They are
aimed at eliminating the subretinal membrane and do not
address an underlying inflammatory disease process. They
are destructive to neurosensory retina and retinal pig-
ment epithelium. Laser photocoagulation is of proven ben-
etit20 with severe visual loss in 8% in treated vs 33% in un-
treated eyes with juxtafoveal CNV in POHS at 5-year follow-
up. However, if the foveal side of a juxtafoveal membrane
is either undertreated or overtreated, severe visual loss oc-
curs 25% of the time.22 The authors of that article con-
clude that “the required accuracy of treatment is difficult
to achieve.”22 Persistent and recurrent neovascularization
following laser treatment (reported) occurred in 22% and
10% of eyes, respectively,23 and was associated with se-

Figure 3. Patient 9. Fundus fluorescein angiogram of the right eye (Table), with choroidal neovascularization (CNV) active and resolving on receipt of
immunosuppression therapy, demonstrating partial resolution of CNV with concomitant improvement in visual acuity. A, Early phase of angiogram (active CNV).
B, Late phase of angiogram (active CNV). Early (C) and late (D) phases of angiogram during immunosuppressive therapy showing partial resolution of CNV.
Subfoveal CNV can be treated by surgical excision, in some instances with remarkable restoration of vision. A report of surgical excision for subfoveal CNV in POHS in 117 eyes, however, shows that VA improved in 40%, remained the same in 41%, and was worse in 19% following surgery. In addition, 14% had complications, which included retinal detachment, cataract, macular pucker, and macular hole formation. Moreover, despite surgical excision, postoperative recurrence of CNV is very common, as much as 44% in one series. The rationale behind treatment of selected cases of CNV with immunosuppression includes (1) treatment of underlying inflammatory response and (2) offering a therapeutic modality, as many of the patients in our series do not meet Macular Photocoagulation Study Group criteria for laser photocoagulation treatment: for example, 5 eyes had subfoveal CNV, and 4 patients had active posterior uveitis rather than POHS. Furthermore, 1 had multiple areas of CNV, 1 refused laser treatment, and 2 had CNV of several disc diameter in size. With regard to immunosuppressive therapy for 17 eyes with CNV in our series, the results are encouraging in that CNV completely resolved in 13 eyes, partially resolved in 4 eyes (with improved VA), and recurred in only 3 eyes. We acknowledge that recurrence rates from these data can of course only be interpreted in the context to duration of follow-up, which in some cases is as short as 7 months. Resolution of CNV is paralleled by improved VA (Table). These results suggest that there is a place for immunosuppressive therapy in the treatment of idiopathic CNV and CNV in association with POHS and other types of EPU, either as an alternative to existing treatments or in combination with them. These patients comprise a heterogeneous diagnostic group within the spectrum of uveitis syndromes initially seen with CNV, which all possess common underlying immunologic mechanisms.

Considering the variability of time of onset and duration, we are not attempting to recommend particular therapeutic strategies, but simply stress the positive therapeutic role of immunosuppression we found in this cohort. Further studies are therefore warranted, first to confirm the efficacy of immunosuppression therapy by itself, and second to determine its place among other treatments. For instance, it may well be that the prognosis of laser treatment or surgery is better after first initiating immunosuppression, or that continued immunosuppression therapy reduces the number of recurrences. Furthermore, although this study shows potential therapeutic benefit, there is no control group to assess for possible spontaneous resolution rates or compare treatment modalities, and ultimately a randomized control trial is necessary.

Many other questions remain unanswered, such as how long treatment should continue and at what dosage. For example, at present, treatment time is largely empirical, based purely on patient response and the presence or absence of active EPU. Last, a better understanding is needed of which cytokines and growth factors play a role in the evolution of CNV in inflammatory eye disease. This may then allow the development of more specific treatment strategies by modifying the proangiogenic environment within the inflamed chorioid.

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