EXTENDED REPORT

Use of corticosteroid sparing systemic immunosuppression for treatment of corticosteroid dependent optic neuritis not associated with demyelinating disease

T D Myers, J R Smith, M S Wertheim, R A Egan, W T Shults, J T Rosenbaum

Aim: To describe the authors’ experience and that in the published literature regarding the use of corticosteroid sparing systemic immunosuppression for patients with corticosteroid dependent optic neuritis not associated with demyelinating disease.

Methods: The records of 10 patients from the authors’ clinical database, and 38 patients from the published literature with corticosteroid dependent optic neuritis, were retrospectively reviewed to determine patient demographics, diagnosis, clinical course, and outcomes. These patients had recrudescence of symptoms, such as decreased vision and pain, with attempted taper of corticosteroid. Similarly, patients with evidence of granulomatous disease (for example, cyclophosphamide and chlorambucil) were given to enable taper of corticosteroid while effectively controlling optic neuritis.

Results: The study included 43 women and 5 men: 17 patients with systemic lupus erythematosus, 12 patients with sarcoidosis, 3 with other systemic autoimmune diseases, and 16 with no clinically identifiable systemic condition, including collagen vascular diseases. 79% of all patients benefited from the use of systemic immunosuppression in that they had successful corticosteroid taper, control of inflammation, improvement in symptoms, and/or tolerance of adverse effects. Mild toxicity was common and 19% of patients, most often those taking cyclophosphamide, discontinued medication because of adverse effects. 24 of 28 (86%) patients on alkylators benefited clinically, while 20 of 29 (69%) patients on antimetabolites had clinical benefit.

Conclusion: Systemic immunosuppression may be a safer and more effective treatment alternative to chronic oral corticosteroid use in cases of corticosteroid dependent optic neuritis not associated with demyelinating disease.

Optic neuritis is most often an acute self limited inflammation of the optic nerve that resolves with or without corticosteroid therapy over the course of a few weeks to months. Resolution of inflammation and visual function may be partial or complete. Patients with optic neuritis are usually in their 20s to 50s, more often female, and present with symptoms such as acute visual loss, scotomas, colour vision loss, and pain with eye movement. The vast majority of cases of isolated acute optic neuritis are a manifestation of demyelinating disease, usually multiple sclerosis.

A small percentage of patients have optic neuritis that is not associated with demyelinating disease. In these cases, optic neuritis is often a manifestation of an underlying systemic condition, including collagen vascular diseases, multisystem granulomatous diseases, post-vaccination syndrome, and viral or bacterial infections. In a few cases, the association with systemic disease is less clear. Various names have been given to these unusual cases of optic neuritis to differentiate them from optic neuritis associated with multiple sclerosis. For example, optic neuritis associated with an underlying collagen vascular disease without a systemic diagnosis has been termed “autoimmune optic neuritis”.

Similarly, patients with evidence of granulomatous disease without a systemic diagnosis have been identified as having “chronic relapsing inflammatory optic neuropathy”. Optic neuritis associated with granulomatous or collagen vascular disease is frequently corticosteroid responsive and resistant to drug taper. A smaller number of cases are corticosteroid resistant, requiring large doses of corticosteroid to gain the slightest improvements in visual function. In both examples, patients are often treated chronically with large doses of systemically administered corticosteroid. The morbidity of chronic corticosteroid treatment is well recognised and includes uncontrolled hyperglycaemia, hypertension, weight gain, oedema, osteoporosis, immunosuppression, and mood alteration. Indeed, adverse effects of chronic systemic corticosteroid therapy may contribute more to debility of patients than the underlying disease that the clinician is attempting to treat.

Treatment with corticosteroid sparing systemic immunosuppressive therapy frequently has fewer long term adverse effects than chronic corticosteroid therapy. There are several reports in the published literature regarding corticosteroid sparing immunosuppressive therapy for corticosteroid dependent optic neuritis. However, these reports generally describe a small number of patients treated with a variety of immunosuppressive agents. Consequently, it is difficult to gain an overall impression of the efficacy of such treatment.

We describe the use of corticosteroid sparing systemic immunosuppressive therapy in a cohort of 10 patients with corticosteroid dependent optic neuritis. These patients had been managed with oral prednisone and/or intravenous methylprednisolone over an extended time period before referral, and all had suffered adverse effects as a result of the systemic corticosteroid therapy. In order to provide a more meaningful impression of the efficacy of immunosuppressive therapy we have combined our results with published data from similar cases of corticosteroid dependent optic neuritis that were similarly treated.
<table>
<thead>
<tr>
<th>Patient no</th>
<th>Age/sex/race</th>
<th>Diagnosis</th>
<th>Eye*</th>
<th>Most consistent corticosteroid dose, total duration of corticosteroid treatment at any dose, and indication for corticosteroid sparing agent.</th>
<th>Drug dose and duration</th>
<th>Adverse effects</th>
<th>Corticosteroid dose (final)</th>
<th>Initial visual acuity</th>
<th>Final visual acuity</th>
<th>Comment</th>
</tr>
</thead>
</table>
| 1         | 66/F/W       | Optic neuritis | OD   | 20 mg for 6 years; 25 pound weight gain, mood change, tremor                   | Mycophenylate mofetil 2000 mg daily for 16 months | Anaemia and increased blood urea nitrogen with 3000 mg daily dose | 3–10 mg | 20/25 | 20/25 | Patient reported improved mood, increased energy and improved vision with mycophenylate. 
Optic nerve biopsy pathology showed non-specific inflammation. Continued flares of optic neuritis despite therapy. |
| 2         | 52/F/W       | Optic neuritis | OU   | 15 mg for 18 months; 35 pound weight gain                                   | Cyclophosphamide 125 mg by mouth daily for 13 months | Mild anaemia | 0 mg | OD:HM | OS:20/40 | OD:20/40 |
| 3         | 25/F/W       | Optic neuritis | OU   | 20 mg for 6 months; 25 pound weight gain, labile mood                     | Methotrexate 20 mg weekly for 6 months
Cyclosporine 200 mg daily in combination with methotrexate 20 mg weekly for 1 month
Mycophenylate mofetil 3000 mg daily for 3 months | Headache, fatigue | 17–40 mg | OD:CF | OS:CF | OD:20/20 | OS:20/20 |
| 4         | 62/F/W       | Optic neuritis with hearing loss and cranial neuropathies (VII/V) | OS   | 60 mg for 14 months; 55 pound weight gain, oedema, diabetes, osteoporosis, palpitations, bruising | Azathioprine 200 mg daily for 8 months | None | 0 mg | OD:20/HM | OD:20/HM | OS:20/20 |
| 5         | 29/F/W       | Optic neuritis | OU   | 30 mg for 2 years; 25 pound weight gain, mood changes, oedema, arthralgia | Methotrexate 20 mg weekly for 4 months | None | 0–5 mg | OD:20/20 | OD:20/20 | Patient has severe lung disease. 
Patient has restarted corticosteroid therapy per her internist since her last visit for active lung disease. |
| 6         | 60/F/W       | Sarcoidosis | OD   | 30–60 mg for 35 years; diabetes, weight gain, non-healing wounds 60 mg for at least 4 months; 35 pound weight gain, coughing, weakness, labile mood, decreased energy 40–60 mg for 2 years; 20 pound weight gain, palpitations, sleep disruption, labile mood | Methotrexate 7.5 mg weekly for 7 months
Azathioprine 150 mg daily for 55 months | None | 20 mg | CF | CF | OS:20/40 | OS:20/40 |
| 7         | 56/F/W       | Sarcoidosis | OD   | 60 mg for at least 4 months; 35 pound weight gain, coughing, weakness, labile mood, decreased energy 40–60 mg for 2 years; 20 pound weight gain, palpitations, sleep disruption, labile mood | Methotrexate 20 mg weekly for 42 months | None | 10–20 mg | OD:20/20 | OD:CF | OS:20/40 | OS:20/40 |
| 8         | 55/F/W       | Sarcoidosis | OU   | 60 mg for 10 years intermittently; diabetes, coughing 20 mg for 8 years; 60 pound weight gain, no benefit from corticosteroid | Azathioprine 100 mg daily for 6 weeks
Mycophenylate mofetil 500 mg daily for 3 weeks
Cyclophosphamide 200 mg daily for 42 months | Azathioprine, hypertension, nausea
Mycophenylate, nausea, hoemorrhagic cysts | None | 20 mg | CF | CF | OS:20/40 | OS:20/40 |
| 9         | 53/F/W       | Systemic lupus erythematosus | OU   | 60 mg for 10 years intermittently; diabetes, coughing | Cyclophosphamide 1650 mg IV every six weeks for 12 months | Methotrexate 20 mg daily for 2 months | None | 150 | OD:20/20 | OS:20/20 | Patient has a history of repaired retinal detachment OD and radiation therapy to both orbits. 
Patient has a history of repaired retinal detachment OD and radiation therapy to both orbits. |
| 10        | 50/F/H       | Systemic lupus erythematosus, thyroid related immune orbitopathy | OD   | 60 mg for 10 years intermittently; diabetes, coughing 20 mg for 8 years; 60 pound weight gain | Cyclophosphamide 1650 mg IV every six weeks for 12 months | Methotrexate 2000 mg daily for 3 months | Pneumonitis, nausea | 4 mg | OD:20/HM | OD:20/30 |

F, female; W, white; H, Hispanic; OD, right eye; OS, left eye; OU, both eyes; IV, intravenous; HM, hand motions; CF, counting fingers; LP, light perception; NLP, no light perception.

*Uninvolved eyes are not detailed in this table.
<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Age/sex</th>
<th>Diagnosis</th>
<th>Time and dose of corticosteroid or other therapy</th>
<th>Indication for corticosteroid sparing agent</th>
<th>Drug, dose, and duration (if reported)</th>
<th>Adverse effects</th>
<th>Corticosteroid dose (final)</th>
<th>Initial visual acuity</th>
<th>Final visual acuity</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siatkowski RM</td>
<td>2001</td>
<td>32 F</td>
<td>Systemic lupus</td>
<td>6 months of corticosteroid</td>
<td>3 relapses on corticosteroid</td>
<td>Monthly IV cyclophosphamide for 7 months, no relapses while on therapy</td>
<td>Unknown</td>
<td>Unknown</td>
<td>OD:LP</td>
<td>OS:20/15</td>
<td>Patient discontinued cyclophosphamide because she desired to become pregnant</td>
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<tr>
<td>42 F</td>
<td></td>
<td>OD</td>
<td>Unknown</td>
<td></td>
<td>Unknown</td>
<td>AZathioprine for 16 months, then monthly IV cyclophosphamide</td>
<td>Unknown</td>
<td>20 mg</td>
<td>OD:20/200</td>
<td>OD:20/40</td>
<td></td>
</tr>
<tr>
<td>Frohman LP</td>
<td>2001</td>
<td>51 F</td>
<td>Systemic lupus</td>
<td>100 mg for 2 months</td>
<td>Disease refractory to corticosteroid and/or oral immunosuppression</td>
<td>Cyclophosphamide 0.5-1.0 gm/m² IV on 2 consecutive days monthly, Mean duration 5 months</td>
<td>All patients had side effects: 7 patients with urinary tract infections, 3 patients with upper respiratory infections, 2 patients with herpes zoster infections, 1 patient with pneumonia, 4 patients with oral candidiasis, 5 patients with hair loss, 1 patient with cutaneous abscess</td>
<td>Unknown</td>
<td>OD:20/40</td>
<td>OD:20/30</td>
<td>Only 3 patients discontinued treatment and this was secondary to nausea and vomiting</td>
</tr>
<tr>
<td>Galindo-Rodriguez G</td>
<td>1999</td>
<td>41 F</td>
<td>Systemic lupus</td>
<td>100 mg for 2 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OD:CF</td>
<td>OD:20/50</td>
<td></td>
</tr>
<tr>
<td>35 F</td>
<td></td>
<td>OU</td>
<td>100 mg for 4 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OS:CF</td>
<td>OS:20/100</td>
<td></td>
</tr>
<tr>
<td>36 F</td>
<td></td>
<td>OU</td>
<td>60 mg for 8 months and azathioprine 150 mg for 9 months and cyclophosphamide by mouth for 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OD:CF</td>
<td>OD:20/30</td>
<td></td>
</tr>
<tr>
<td>18 F</td>
<td></td>
<td>OU</td>
<td>60 mg for 24 months and azathioprine 100 mg for 24 months and cyclophosphamide by mouth for 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OD:CF</td>
<td>OS:CF</td>
<td></td>
</tr>
<tr>
<td>44 F</td>
<td></td>
<td>OU</td>
<td>100 mg for 4 months and azathioprine 150 mg for 20 months and cyclophosphamide by mouth for 4 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OD:CF</td>
<td>OD:20/25</td>
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</tr>
<tr>
<td>55 F</td>
<td></td>
<td>OU</td>
<td>100 mg for 2 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OD:20/70</td>
<td>OD:20/20</td>
<td></td>
</tr>
<tr>
<td>43 F</td>
<td></td>
<td>OU</td>
<td>100 mg for 2 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OD:20/70</td>
<td>OD:20/20</td>
<td></td>
</tr>
<tr>
<td>17 F</td>
<td></td>
<td>OU</td>
<td>100 mg for 3 months and azathioprine 100 mg for 2 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OD:CF</td>
<td>OS:20/80</td>
<td></td>
</tr>
<tr>
<td>32 F</td>
<td></td>
<td>OU</td>
<td>150 mg for 4 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OD:CF</td>
<td>OD:20/20</td>
<td></td>
</tr>
<tr>
<td>30 F</td>
<td></td>
<td>OU</td>
<td>60 mg for 1 month</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OD:HM</td>
<td>OD:HM</td>
<td></td>
</tr>
</tbody>
</table>

F, female; M, male; OD, right eye; OS, left eye; OU, both eyes; IV, intravenous; NLP, no light perception; HM, hand motion; CF, count fingers; LP, light perception.

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<th>Drug, dose, and duration (if reported)</th>
<th>Adverse effects</th>
<th>Corticosteroid dose (final)</th>
<th>Initial visual acuity</th>
<th>Final visual acuity</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenbaum JT</td>
<td>1997</td>
<td>32 F</td>
<td>Systemic lupus erythematosus</td>
<td>OS</td>
<td>Unknown doses of corticosteroid and azathioprine</td>
<td>Unknown</td>
<td>IV cyclophosphamide for 28 months, IV cyclophosphamide for 2 months</td>
<td>Unknown</td>
<td>Unknown</td>
<td>OD: HM, OD: 20/20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mount HA</td>
<td>2003</td>
<td>35 F</td>
<td>Sarcoidosis</td>
<td>OU</td>
<td>20–40 mg daily for 5 months</td>
<td>Insomnia, anxiety</td>
<td>Methotrexate 2.5–10 mg weekly for 30 months</td>
<td>0 mg</td>
<td>OD: CF, OD: 20/50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>41 F</td>
<td>OD</td>
<td>10–40 mg daily for 2 months</td>
<td>Hyperglycaemia</td>
<td>Methotrexate 2.5–10 mg weekly for 36 months</td>
<td>18 mg</td>
<td>OD: CF, OD: 20/30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>47 F</td>
<td>OU</td>
<td>10–80 mg daily for 8 months</td>
<td>Mood swings, insomnia, weight gain, depression, alopecia</td>
<td>Methotrexate 7.5–15 mg weekly for 22 months</td>
<td>0 mg</td>
<td>OD: HM, OD: NLP</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bilaley L</td>
<td>1991</td>
<td>48 F</td>
<td>Orbital pseudotumor</td>
<td>OS</td>
<td>Unknown dose</td>
<td>4 patients with weight gain, 2 patients with uncontrolled hyperglycaemia, 2 patients with hypertension</td>
<td>Cyclosporine A 2 mg/kg/day for an average of 16.6 months</td>
<td>Hypercholesterolaemia and hirsutism in unknown number of patients</td>
<td>Unclear</td>
<td>OS: 20/400, OS: 20/20</td>
<td>Weight gain, diabetes and hypertension resolved in all patients after corticosteroid dose was tapered.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>38 M</td>
<td>Sarcoidosis</td>
<td>OU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OD: 20/20</td>
<td>“Normal”</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>56 F</td>
<td>OU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OD: 20/25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25 M</td>
<td>OU</td>
<td></td>
<td></td>
<td>Hypertension and diabetes</td>
<td>4500 cGy of radiation then azathioprine 800 mg daily for 8 months</td>
<td>Unknown</td>
<td>10 mg</td>
<td>OD: 20/40, OD: 20/100, OD: 20/20</td>
<td></td>
<td></td>
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<tr>
<td>Gelwan MJ</td>
<td>1988</td>
<td>45 F</td>
<td>Sarcoidosis</td>
<td>OU</td>
<td>Unknown dose</td>
<td></td>
<td></td>
<td></td>
<td>OD: 20/40, OD: 20/100, OD: 20/20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>32 M</td>
<td>OU</td>
<td>Diabetes, cushingoid, glaucoma</td>
<td>Hypertension and diabetes</td>
<td>Unknown</td>
<td>4500 cGy of radiation then azathioprine 200 mg daily for 5 months</td>
<td>None</td>
<td>10 mg every other day</td>
<td>OD: 20/40, OD: NLP, OD: 20/60</td>
<td>OD: NLP</td>
<td></td>
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<tr>
<td></td>
<td>20 M</td>
<td>OU</td>
<td>Cushingoid</td>
<td>Hypertension and diabetes</td>
<td>Unknown</td>
<td>4880 cGy of radiation then chlorambucil 6 mg daily for 6 months</td>
<td>Unknown</td>
<td>7.5 mg</td>
<td>OD: 20/20, OD: 20/20</td>
<td>Poor compliance</td>
<td></td>
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<tr>
<td>Gressel MG</td>
<td>1983</td>
<td>21 F</td>
<td>Mixed connective tissue disease</td>
<td>OU</td>
<td>40 mg daily</td>
<td>Cushingoid</td>
<td>Azathioprine for 7 months, then oral cyclophosphamide 100 mg daily for 5 months then chlorambucil 4 mg daily</td>
<td>Hemorrhagic cysts and leukopenia on cyclophosphamide</td>
<td>Unknown</td>
<td>OD: 20/40, OD: 20/60</td>
<td>Unknown</td>
<td></td>
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<tr>
<td></td>
<td>1994</td>
<td>32 F</td>
<td>Neuroretinitis</td>
<td>OU</td>
<td>Unknown dose</td>
<td>Inefficacy</td>
<td>Azathioprine for 3 years</td>
<td>Unknown</td>
<td>Unknown</td>
<td>OD: 20/20</td>
<td>Recurrent attacks suppressed with azathioprine</td>
<td></td>
</tr>
</tbody>
</table>

F, female; M, male; OD, right eye; OS, left eye; OU, both eyes; IV, intravenous; NLP, no light perception; HM, hand motion; CF, count fingers; LP, light perception.

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<th>Time and dose of corticosteroid or other therapy</th>
<th>Indication for corticosteroid sparing agent</th>
<th>Drug, dose, and duration (if reported)</th>
<th>Adverse effects</th>
<th>Corticosteroid dose (final)</th>
<th>Initial visual acuity</th>
<th>Final visual acuity</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kupersmith MJ 1988</td>
<td>44 F</td>
<td>Autoimmune optic neuropathy</td>
<td>OD</td>
<td>100 mg daily for 12 months</td>
<td>Corticosteroid intolerance or inefficacy for 6.5 years</td>
<td>Chlorambucil 6 mg daily</td>
<td>None</td>
<td>“lower”</td>
<td>OD: LP</td>
<td>OS: 20/25</td>
<td></td>
</tr>
<tr>
<td>42 F</td>
<td>OU</td>
<td>100 mg daily for 4 months</td>
<td>Chlorambucil 6 mg daily</td>
<td>None</td>
<td>“lower”</td>
<td>OD: NLP</td>
<td>OS: NLP</td>
<td></td>
<td></td>
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<tr>
<td>26 F</td>
<td>OU</td>
<td>100 mg daily for 3 months</td>
<td>Cyclophosphamide 150 mg and Azathioprine 100 mg daily for 5.5 years</td>
<td>None</td>
<td>“reduced”</td>
<td>OD:NLM</td>
<td>OS: 20/25</td>
<td></td>
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<tr>
<td>26 F</td>
<td>OU</td>
<td>100 mg daily for 1.5 months</td>
<td>Chlorambucil 6 mg and Herpetic keratitis Azathioprine 75 mg daily for 6.5 years</td>
<td>None</td>
<td>“lower”</td>
<td>OD: CF</td>
<td>OS: 20/30</td>
<td>OD: 20/25</td>
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<tr>
<td>56 F</td>
<td>OD</td>
<td>Unknown dose</td>
<td>Azathioprine 125 mg daily</td>
<td>None</td>
<td>30 mg</td>
<td>OD: 20/400</td>
<td>OS: 20/30</td>
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<tr>
<td>47 F</td>
<td>OS</td>
<td>20 mg daily for 1 months</td>
<td>Azathioprine 50 mg daily None for 1 week</td>
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<td>60 mg</td>
<td>OD: 20/20</td>
<td>OS: 20/20</td>
<td>Patient refused treatment</td>
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<tr>
<td>45 M</td>
<td>OU</td>
<td>60 mg daily for 1 months</td>
<td>Chlorambucil 8 mg daily None for 18 months</td>
<td>Azathioprine 200 mg daily Chlorambucil 6 mg daily</td>
<td>Chlorambucil 6 mg daily</td>
<td>Agranulocytosis and sepsis for 18 months Azathioprine 200 mg daily</td>
<td>None</td>
<td>OD: 20/60</td>
<td>OS: NLP</td>
<td>OD: 20/20/200 Chlorambucil discontinued because of episode of sepsis.</td>
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<tr>
<td>27 F</td>
<td>OU</td>
<td>80 mg daily for 1 months</td>
<td>Chlorambucil 6 mg daily Unknown for 18 months Azathioprine 200 mg daily</td>
<td>Unknown</td>
<td>0 mg</td>
<td>OD: 20/80</td>
<td>OS: 20/25</td>
<td>OS: 20/20</td>
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<tr>
<td>Dutton JJ 1982</td>
<td>44 F</td>
<td>Autoimmune retrolublar optic neuritis</td>
<td>OU</td>
<td>Unknown dose</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Chlorambucil 6 mg daily</td>
<td>Unknown for 2 years Azathioprine 200 mg daily Chlorambucil 6 mg daily</td>
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<tr>
<td>26 F</td>
<td>OU</td>
<td>Cushingoid, depression</td>
<td>Chlorambucil 6 mg daily and Azathioprine 75 mg daily for 1 year</td>
<td>None</td>
<td>OD: CF</td>
<td>OS: 20/30</td>
<td>OS: 20/30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>42 F</td>
<td>OD</td>
<td>Unknown</td>
<td>Chlorambucil 6 mg daily for 6 months</td>
<td></td>
<td>LP</td>
<td>20/20</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

F, female; M, male; OD, right eye; OS, left eye; OU, both eyes; IV, intravenous; NLP, no light perception; HM, hand motion; CF, count fingers; LP, light perception.*Uninvolved eyes are not detailed in this table.
METHODS

We examined the clinical database of the uveitis service at the Oregon Health & Science University (OHSU) over a 17 year period from September 1985 until December 2002 to identify cases of corticosteroid dependent optic neuritis not associated with demyelinating disease. The OHSU Institutional Review Board gave approval for medical chart review for the purposes of this study. From our records and the published cases, we collected data which included patient demographics, diagnosis, baseline visual acuity, colour vision, presence or absence of an afferent pupillary defect, visual fields, details of corticosteroid use, adverse effects from corticosteroids, details of corticosteroid sparing agent use, adverse effects of corticosteroid sparing agent, and clinical response to therapy including final visual acuity.

A Medline search (keywords: optic neuritis, optic neuropathy AND recurrent, lupus, sarcoidosis, steroid sparing, antimetabolite, methotrexate, azathioprine, mycophenolate, cyclophosphamide, alkylating agent, cyclophosphamide, chlorambucil) was performed to identify published cases of corticosteroid dependent non-demyelinating optic neuritis treated with therapy other than systemic corticosteroid. From these cases we collected data as described above, as far as was possible from the information provided in the published reports. All data were then combined and analysed for evidence of clinical benefit to create an overall impression of the efficacy of corticosteroid sparing therapy.

For an initial analysis including only our patients, three treatment outcomes were defined. A “successful trial” of corticosteroid sparing therapy was strictly defined as: (1) the ability to reduce systemic corticosteroid to a daily dose of 10 mg of oral prednisone or less; (2) clinically reduced inflammation; (3) stabilisation or improvement in visual acuity or symptoms such as pain, and (4) patient tolerance of any drug related side effects. “Clinical benefit” from corticosteroid sparing therapy was defined as satisfaction of at least two, but less than four, of the above criteria. If fewer than two criteria were satisfied, treatment was considered to have “no clinical benefit”. Because of incomplete information from previously published cases, when data relating to our patients were combined with data from the literature, we defined “clinical benefit” as satisfaction of at least two of the above criteria for the entire patient group. If relevant clinical data were not presented, but the authors reported the treatment as beneficial, corticosteroid sparing therapy was also considered to have provided “clinical benefit”.

RESULTS

Ten patients (15 eyes) with corticosteroid dependent optic neuritis not associated with demyelinating disease were identified from our database. One patient (patient 8) is previously described, but is presented here with further follow up data.11 All ten patients were female. Five patients had idiopathic optic neuritis with no clinically identifiable systemic disease (patients 1–5). Three patients had sarcoidosis (patients 6–8), and two patients had systemic lupus erythematosus (patients 9 and 10). In five cases the optic neuritis was retrobulbar, and in five cases there was optic nerve head swelling. A summary of clinical information relating to these patients is found in table 1.

Each of our patients had been given a comprehensive ophthalmic assessment including ocular and systemic history, measurement of visual acuity, colour vision testing, evaluation of the pupils including testing for an afferent pupillary defect, visual field testing, and dilated posterior segment examination. Visual field testing revealed varied patterns of visual field loss from essentially normal to paracentral scotomas and constricted peripheral fields. Additionally, every patient underwent imaging studies including magnetic resonance imaging of the head to rule out white matter lesions consistent with multiple sclerosis. Other imaging studies including chest x ray and, in some cases, computed tomography were performed if indicated to support a diagnosis of sarcoidosis. Diagnostic procedures such as cerebrospinal fluid analysis to identify IgG oligoclonal bands and tissue biopsy with histopathology for non-caseating granulomas were also performed in several patients to assist in the diagnosis of multiple sclerosis or sarcoidosis, respectively. Each patient also had laboratory work including complete blood examination with differential, serum metabolic panel, an erythrocyte sedimentation rate, and where appropriate, testing for autoantibodies.

Optic neuritis was successfully brought into remission (improvement in symptoms, visual acuity, and clinically apparent inflammation) in these 10 patients after systemic
corticosteroid therapy. However, all patients suffered recrudescence of the inflammation when taper was attempted. In addition, each of these 10 patients had experienced adverse effects from systemic corticosteroid therapy.

A trial of corticosteroid sparing therapy was started after unsuccessful attempts to taper systemic corticosteroids, which had been previously administered over a period of 3–72 months. Corticosteroid sparing agents that were used included methotrexate (n = 4), mycophenolate mofetil (n = 5), azathioprine (n = 4), cyclosporine (n = 1), and cyclophosphamide (n = 3). Treatment was selected, prescribed, and monitored in accordance with published guidelines. Patients were followed subsequently for an average of 17.8 months. In some cases it was necessary to change drugs because of lack of effect or drug related complications.

Overall, five of 10 patients (patients 1, 2, 7, 9, and 10) met all of the criteria for a successful trial of corticosteroid sparing therapy. These patients were treated with cyclophosphamide, azathioprine, or mycophenolate mofetil. Three additional patients (patients 4, 5, and 6) showed clinical benefit, but did not meet all four criteria. These patients were treated with one or more of the same three drugs or with methotrexate.

Resolution or improvement of chronic corticosteroid induced adverse effects was reported in all eight patients who had clinical benefit from therapy. Two patients (patients 3 and 8) have not yet responded favourably to initial therapeutic trials with multiple agents and are undergoing trials with other agents.

One patient (patient 5) switched from initial corticosteroid sparing therapy three times either because of intolerable side effects or because of lack of efficacy. Her disease was eventually controlled with cyclophosphamide that was later discontinued because she developed haemorrhagic cystitis.

Another patient (patient 7) was able to discontinue immunosuppressive therapy completely without recurrence of optic neuritis after 55 months of treatment with azathioprine. However, she has subsequently developed active pulmonary sarcoidosis and is currently being treated by her internist with systemic corticosteroids.

Every patient who took mycophenolate mofetil, azathioprine, cyclosporine, or cyclophosphamide reported adverse effects. Three patients had to stop or switch therapy because of adverse effects. One patient (patient 3) developed hypertension after treatment with cyclosporine. Two patients (patients 5 and 9), who both were treated with cyclophosphamide, developed haemorrhagic cystitis and pneumonitis, respectively. Only one patient (patient 3) reported headache and fatigue on methotrexate, whereas other patients using this agent were free of adverse effects.

A Medline search identified 11 papers discussing 38 patients (67 eyes) with corticosteroid dependent optic neuritis not associated with demyelinating disease that was treated with corticosteroid sparing therapy. Thirty three of these 38 patients were female. Fifteen patients had systemic lupus erythematosus, nine had sarcoidosis, and one had mixed connective tissue disease. One had orbital pseudo-tumour associated with optic neuritis, and another had neuroretinitis. In 11 patients there was no clinical diagnosis of a systemic disease associated with the optic neuritis. An additional paper by Kidd et al recently reported at least two patients with “chronic relapsing inflammatory optic neuropathy” managed with corticosteroid sparing immunosuppression, but sufficient detail was not available in the report to merit inclusion in these results. Available clinical data from these cases are presented in table 2.

Thirty of the 38 patients (79%) in the published literature showed clinical benefit from corticosteroid sparing therapy. Five additional patients (14%) had systemic benefit from corticosteroid sparing therapy, but no visual benefit. Three patients (8%) had no benefit. Medications prescribed for these patients included azathioprine (n = 12), methotrexate (n = 4), cyclosporine (n = 4), cyclophosphamide (n = 16), and chlorambucil (n = 10). Mean follow up time on treatment was 21.3 months for patients whose follow up was documented. Five publications reported adverse effects in 15 of 23 (65%) patients. In those reports, four (15%) patients discontinued therapy secondary to adverse effects, including three patients treated with cyclophosphamide and one patient treated with chlorambucil. A sixth paper reported complications, but did not indicate patient numbers and therefore is not represented in these figures.

When data from both groups were combined, 48 patients with an average age of 40.3 years, 43 of whom were women, were identified. Of these 48 individuals, 17 patients had systemic lupus erythematosus, 12 patients had sarcoidosis, and three patients had been given other systemic or ocular diagnoses. Sixteen patients were not clinically diagnosed with systemic disease. During the course of therapy, patients were treated with cyclophosphamide (n = 19), azathioprine (n = 16), chlorambucil (n = 10), cyclosporine (n = 5), methotrexate (n = 8), and mycophenolate mofetil (n = 5).

Thirty eight of 48 patients with optic neuritis (79%) showed clinical benefit from corticosteroid sparing therapy, as illustrated in figure 1. Eleven of 29 patients were able to stop corticosteroid therapy completely. Data on final corticosteroid dosin were not always available. Of these 11 individuals, five patients were treated with alkylating agents, and seven patients were treated with antimetabolites. Twenty two of 38 (58%) of patients had improvement or resolution of corticosteroid induced adverse effects.

Of the 37 cases where data regarding adverse effects from corticosteroid sparing systemic immunosuppression were available, 24 patients experienced adverse effects, as shown in figure 2. However, the majority of these effects were mild, and only seven (19%) patients (five of whom were on cyclophosphamide) ceased therapy because of adverse effects. Ten of 48 patients (21%) stopped or switched therapy because of lack of efficacy. Of those patients, seven individuals were treated with azathioprine. The other three patients were treated at various times with methotrexate, mycophenolate mofetil, and cyclosporine.

DISCUSSION

Treatment of patients with corticosteroid dependent optic neuritis not associated with demyelinating disease is challenging because one must select a treatment that is aggressive enough to minimise visual loss while avoiding adverse effects that may be serious. Clinicians may be reticent to place these frequently young patients on potentially harmful agents such as cyclophosphamide. However, the data presented here offer justification for using such agents not only to treat corticosteroid dependent optic neuritis effectively, but also to avoid the morbidity associated with chronic systemic corticosteroid use. A few patients may experience a relentless progression of their disease despite aggressive treatment; it is likely that these patients are underrepresented in the published literature because of a bias toward publication of cases where treatment was successful.

Many patients with non-demyelinating corticosteroid dependent optic neuritis have an associated underlying systemic disease. Decisions regarding which immunosuppressive agent to use should include consideration of known data regarding the efficacy of certain agents with different systemic diseases. For example, alkylating agents such as cyclophosphamide are known to be particularly effective in treating nephritis associated with systemic lupus erythematosus. Additionally, not all patients may be reasonably expected to discontinue systemic corticosteroid therapy...
neuritis and drug induced lupus.21–23
been associated with induction of demyelinating optic
infliximab and etanercept should probably not be used
routinely to treat inflammatory disease with neurological
manifestations.22 Indeed, treatment with these agents has
been associated with induction of demyelinating optic
neuritis and drug induced lupus.21–23
This study, combining data from our clinical experience
with data from previous publications, may offer some
conclusions about the efficacy of corticosteroid sparing
therapy for optic neuritis not associated with demyelinating
disease. On the surface, the results suggest that alkylating
agents have a higher success rate in treating this challenging
subset of patients. However, when the data are re-examined
from the standpoint of successful treatment based on
diagnosis, the superiority of alkylating agents is not as clear.
Fifteen of 17 (88%) patients diagnosed with systemic lupus
erythematosus were treated with alkylating agents. Two
(13%) of those patients were considered treatment failures.
Only one of the 12 patients diagnosed with sarcoidosis was
treated with alkylating agents; and yet, the treatment failure
rate for this group was similar (8%). This again illustrates the
fact that systemic diagnosis should guide the choice of
corticosteroid sparing therapy. Although alkylating agents
appear to be efficacious in cases of optic neuritis associated
with systemic lupus erythematosus, less potent agents such
as antimetabolites appear to do just as well in cases of
sarcoidosis associated optic neuritis.
Twelve of the 16 patients who were not clinically diagnosed
with a systemic disease were also treated with alkylating
agents. Only one of these 16 cases (6%) was considered a
treatment failure. In those cases, a clearly diagnosed systemic
disease was not available to guide treatment. In four cases,
subtle laboratory or clinical findings suggestive of diseases
such as systemic lupus erythematosus or Wegener’s granu-
latomatisis were used to guide treatment choices. However, in
the majority of cases no diagnostic hints were available.
Combined data for drug efficacy are perhaps most useful in
cases where no systemic disease has been diagnosed.
A favourable treatment response to alkylating agents must
be weighed against the more frequent incidence of adverse
effects that may necessitate discontinuation of these drugs.
Although less often efficacious, antimetabolites offer clinical
benefit to many patients. Antimetabolites are associated with
a lower incidence of adverse effects and these effects tend to
be less severe than those seen with alkylating agents. It
therefore seems reasonable to consider antimetabolites before
alkylating agents for patients whose systemic diagnosis is not
known. Choice of treatment in these cases can also be helped
by published guidelines on corticosteroid sparing immuno-
suppression.18
Without standardised protocols for treatment, monitoring,
follow up, and data reporting, this study, involving retro-
spective data collection from our medical files and review of
cases described in the literature, has obvious limitations. As
mentioned above, there may be a bias toward publication of
cases where treatment with systemic immunosuppression
was successful. However, a clear majority of individuals in
our unselected patient group, as well as those cases published
in the literature, showed clinical benefit from corticosteroid
sparking therapy. Corticosteroid sparing therapy should there-
fore be considered in cases of corticosteroid dependent optic
neuritis not associated with demyelinating disease.

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Use of corticosteroid sparing systemic immunosuppression for treatment of corticosteroid dependent optic neuritis not associated with demyelinating disease

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