Combination of Azathioprine and Corticosteroids in the Treatment of Serpiginous Choroiditis

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Abstract

Purpose: To evaluate the role and efficacy of combination of azathioprine and corticosteroids in the treatment of serpiginous choroiditis. Methods: Medical records of all patients with serpiginous choroiditis those were treated with a combination regimen of azathioprine 2.5 mg/kg/body weight in 3 divided doses and prednisolone 1 mg/ kg body weight for at least 6 months were reviewed. The patients were followed up every month for atleast 6 months or till the lesions showed clinical and angiographic signs of inactivity. Doses of both azathioprine (50 mg/ month) and prednisolone (10 mg/ week) were tapered as and when the lesions became inactive. On subsequent follow-up visits, any episode of relapse was treated by resuming the therapy with both agents in the doses described above with a more prolonged tapering. Blood counts were monitored every 15 days and liver function tests every month. Sight threatening serpiginous choroiditis was initially treated with 1 gram/day of intravenous methyl prednisolone for 3 days, followed by the above mentioned regimen. Wilcoxon sign rank test was done to obtain the p value for comparison of pretreatment and post treatment visual acuity. Results: Medical records of 30 eyes of 19 patients were evaluated. All patients showed disease regression having inactive lesion at the time of last follow-up. Only four out of the thirty eyes showed deterioration of visual acuity. Thirteen (43%) out of the thirty eyes maintained their pretreatment visual acuity and another thirteen (43%) eyes had improvement in visual acuity. (p = 0.023). Conclusion: Combination therapy of azathioprine and corticosteroids is an effective regimen for treatment of serpiginous choroiditis.

Key words: azathioprine, corticosteroids, immunosuppressive agents, intravenous methyl prednisolone, serpiginous choroiditis.

Serpiginous choroiditis is a chronic, visually debilitating, progressive condition of undetermined etiology. The disease shows recurrent episodes of choroiditis involving both eyes primarily affecting the retinal pigment epithelium (RPE), the choriocapillaris and the choroid. Apart from the typical peripapillary form of the disease, many different forms have been described like macular serpiginous choroiditis (predominantly involving the macular area) and ampigenous choroiditis (which combines the signs of serpiginous choroiditis and APMPE) wherein the fundus lesions involve the disc and the macula in a multifocal pattern.

Many systemic diseases are reported to be associated with serpiginous choroiditis, but they are, merely an association rather than the cause of the disease. Infections such as tuberculosis and herpes have been associated with serpiginous choroiditis in India. Approximately 25% of the patients may develop choroidal neovascular membrane (CNVM) that leads to loss of central vision late in the course of disease. The visual implications of serpiginous choroiditis are, therefore, quite serious and about 75% of patients have a final visual acuity of less than or equal to 6/60. The therapeutic options available for treatment are systemic corticosteroids, antimetabolites and immunosuppressive agents. A number of studies have been done to find the optimum therapeutic regimen for serpiginous choroiditis. Hooper and Kaplan have described triple agent therapy for serpiginous choroiditis consisting of corticosteroids, azathioprine and cyclosporine. However this therapeutic regimen exposes the patient to serious side effects of two immunosuppressive agents and corticosteroids. Therefore, in the present study, we have tried to explore the efficacy of treatment using a single immunosuppressive agent (azathioprine) along with systemic corticosteroids.

Materials and Methods:
The medical records of all patients diagnosed as...
Serpiginous choroiditis and treated with combination therapy of Azathioprine and Corticosteroids, in a tertiary care centre in southern India between January 2000 to December 2008 were reviewed. Patients on any other immunosuppressive regimen were excluded from the study. The study was approved by the Institutional Review Board and a written consent taken as per Helsinki Declaration. All patients received oral azathioprine 2.5 mg/kg body weight/day in three divided doses. Systemic corticosteroids were given in a dose of 1 mg/ kg body weight/day orally with 10 mg/ week tapering for a minimum period of 6 months. Sight-threatening disease was treated initially with intravenous methyl prednisolone (IVMP) 1 gm/day for 3 consecutive days followed by azathioprine and oral corticosteroids10. Azathioprine was continued for at least 6 months along with corticosteroids and the patients were reviewed every month for first 6 months.

A detailed ophthalmic examination including best-corrected visual acuity (BCVA), applanation tonometry, slit-lamp biomicroscopy, fundus examination by noncontact +78D lens and indirect ophthalmoscopy were performed at each visit. Fundus fluorescein angiogram was done as and when felt necessary. During each review, activity of the lesion, any drop in vision from the previous visit and side effects of azathioprine and corticosteroids were noted. Azathioprine and corticosteroids were continued till the lesions showed clinical signs of regression. If required, fundus fluorescein angio-graphy was performed during follow up and the absence of late phase leakage from the margins of active lesions was considered as the evidence of regression. If the lesions were found to be active, therapy was further continued till they became inactive. Corticosteroids were tapered at the first sign of inactivity at a rate of 10 mg per week and azathioprine in a dose of 50 mg per month.

During follow up visits, development of new lesions and / or appearance of lesions adjacent to the previously inactive lesions were taken as signs of relapse, that were treated by resuming the therapy with a more prolonged tapering. Total leukocyte count and total platelet count were monitored every fortnight and liver function test was repeated at monthly interval.

Statistical analysis was performed using SPSS for Windows (version 14; SPSS, Inc., Chicago, IL). Disease activity at final follow-up, visual acuity outcome, duration of azathioprine therapy and number of relapses were recorded. Vision was recorded in Snellen's and converted into logMAR for statistical analysis. Pre and post treatment visual acuity were compared by Wilcoxon sign rank test. Significance was assessed at p 0.05 level for all parameters.

Results:

Thirty eyes of 19 patients were analyzed. Six (31.5%) were females and 13 (68.5%) were males. The mean age was 36.16 years (range 16-63 years). Eleven (58%) patients had bilateral disease. Mean duration of follow-up was 32.9 months (range 6 to 79 months, S.D.18.15) and mean duration of azathioprine therapy was 6.5 months (range 3 to 20 months, S.D. 5.7). All patients showed disease regression in the form of inactive lesion at the time of last follow-up. But three patients (5 eyes, 16.6 %) developed recurrence once and one (2 eyes, 6.6 %) had two episodes of recurrence which were managed by increasing the doses of oral corticosteroids and azathioprine. The mean initial BCVA was 0.33 LogMAR units. The mean final BCVA was 0.15 LogMAR units (Mean visual acuity cannot be calculated in snellen as it is a non continuous parameter hence we have provided the mean logMAR value- Please mention snellen's VA) The improvement in the visual acuity before and after institution of combination therapy was statistically significant (p = 0.023, Wilcoxon sign rank test). Thirteen (43.3%) eyes had improvement in visual acuity, 13 (43.3%) maintained the pretreatment visual acuity. Four (13.4%) eyes showed deterioration of visual acuity in spite of disease remission clinically as a result of involvement of the center of fovea.

Discussion:

The pathogenesis of serpiginous choroiditis remains unknown despite various studies done in the past to identify the infectious, the immunological, and the vascular etiology of the disease. Various infections such as tuberculosis and herpes virus have also been implicated in the pathogenesis2,10. The inflammatory nature of the disease is supported by histopathological findings such as lymphocytic infiltrates in the choroid and the vessel wall11. A large number of immunosuppressive agents have been tried either alone or in combination to treat serpiginous choroiditis (Table 1). Corticosteroids have both anti-inflammatory and immuno-suppressive actions. The difficulty with corticosteroid therapy alone is that it has no effect on prevention of recurrences. Recurrences are common while tapering the dose or shortly after discontinuation of the treatment. Gupta et al treated
patients of serpiginous choroiditis with corticosteroids\textsuperscript{12}. Sixty five percent of their patients achieved visual acuity of 20/40 or better, while only one patient developed CNVM. However the study reported very high rates of recurrence in their cohort (92%).

Azathioprine is a prodrug that gets metabolized to the active agent, 6-mercaptopurine. It affects the DNA and the RNA metabolism on getting converted to 6-thioinosine -5-phosphate (T-IMP) by the enzyme hypoxanthine guanine phosphoribosyltransferase. T-IMP is probably incorporated into the nucleic acids leading to false codes being generated. The adverse effects of azathioprine are leucopenia, thrombocytopenia, and gastrointestinal disturbances. The long term concern is the increased risk of neoplasia on chronic immunosuppression. Andrasch and colleagues have used the combination of azathioprine with low dose corticosteroids in the treatment of uveitis\textsuperscript{13}. Half of their patients showed a positive therapeutic response and the other half had either no response or developed severe adverse effects. Raul et al were the first to describe the efficacy of this regimen (azathioprine + corticosteroids) in 5 eyes of 4 patients of serpiginous choroiditis\textsuperscript{14}. They were able to achieve disease inactivity in all the eyes within the first month of therapy, but two patients had relapses which were treated by adding methotrexate and mycophenolate mofetil. In our study the relapses could be managed only with increasing the dose of immunosuppressives without adding another medication.

Akpek et al treated 9 patients with alkylating agents (Cyclophosphamide or Chlorambucil) for triple therapy-resistant cases\textsuperscript{7}. Six patients (9 eyes) had improvement in visual acuity by 1 to 5 Snellen's lines and seven patients had long term drug-free remission. Only one patient developed CNVM. Unfortunately, all patients had bone marrow suppression as a short term side effect and one patient developed carcinoma bladder as a long term complication. Alkylating agents are relatively toxic drugs. In addition to reversible bone marrow suppression, cyclophosphamide causes hemorrhagic cystitis, alopecia, and sterility. Chlorambucil causes bone marrow suppression and sterility. Moreover, increased risk of malignancies with alkylating agent therapy is a matter of great concern. In our opinion, this regimen should be reserved for those rare cases of serpiginous choroiditis that are resistant to all other available therapeutic options.

Cyclosporine is an immunomodulatory agent which acts by inhibiting activation of T-lymphocytes\textsuperscript{15}. Although cyclosporine theoretically would affect any cell with its binding protein, but its major clinical effect is directed against the factors that promote T-cell activation and

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Treatment</th>
<th>Complications</th>
<th>Follow-up</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akpek et al (2002)</td>
<td>9</td>
<td>CYCLO / Chloram</td>
<td>CNVM</td>
<td>1-8 years</td>
<td>Nil</td>
</tr>
<tr>
<td>Christmas et al (2002)</td>
<td>6</td>
<td>Ster+CSA/AZA/MC</td>
<td>CNVM (12)</td>
<td>1-9 years</td>
<td>2 pts (33%)</td>
</tr>
<tr>
<td>Akpek et al (2001)</td>
<td>6</td>
<td>CSA+AZA+CYCLO</td>
<td>NIL</td>
<td>1-9 years</td>
<td>2 pts (33%)</td>
</tr>
<tr>
<td>Raul et al (2006)</td>
<td>4</td>
<td>Ster+ AZA</td>
<td>NIL</td>
<td>1-9 years</td>
<td>1 pt (25%)</td>
</tr>
<tr>
<td>Present study (2009)</td>
<td>19</td>
<td>Ster+AZA</td>
<td>NIL</td>
<td>1-7 years</td>
<td>3 pts (16%)</td>
</tr>
</tbody>
</table>

N=number of patients, Ster=corticosteroids, AZA=azathioprine, CSA=cyclosporine, CYCLO=cyclophosphamide, Chloram=chlorambucil, MC=mycophenolate mofetil, CNVM=Choroidal neovascular membrane, VA=Visual acuity, pts=patients.
recruitment. Its common side effects are nephrotoxicity, hypertension, and myelosuppression. Hooper and Kaplan have reported triple agent immunosuppression\(^9\) (combination of azathioprine, corticosteroids and cyclosporine) in the treatment of serpiginous choroiditis. They treated five patients of bilateral disease where three patients had remission while being maintained on low dose triple therapy and two had relapses. Christmas et al treated 34 eyes of 17 patients with corticosteroids and various immunosuppressive agents\(^{10}\). Only 23-26% of their patients had a final visual acuity of less than 20/200, but they had a higher rate of CNVM development (35%). Akpek et al treated 6 patients with different combinations of immunosuppressive agents, cyclosporine and azathioprine in 3 patients, cyclophosphamide in 2 patients and cyclosporine in 1 patient\(^{15}\). They reported visual improvement in 10 eyes and recurrences in two. Araujo et al treated 14 eyes of 7 patients with corticosteroids and cyclosporine\(^17\). In addition, two patients received azathioprine and one had mycophenolate mofetil. Vision was maintained in 10 eyes, 3 had improvement and one had deterioration due to the formation of cataract. Laatikainen et al treated 15 patients with antitubercular drugs or corticosteroids\(^{18}\). They reported development of CNVM in 2 eyes and their series did not report any favorable outcome at all. All these studies employing different regimens did not show convincing evidence to prove one’s superiority over another. Till date, ours is the largest case series evaluating the efficacy of combination therapy of azathioprine and oral corticosteroids in the treatment of serpiginous choroiditis.

In the present series, the patients in whom the final BCVA in the affected eye showed deterioration had involvement of fovea by the disease process. In fact the lesions became inactive with the treatment and all the patients showed resolution of the disease. None of the patients reported major side effects of either azathioprine or oral corticosteroids. Two patients had one episode of relapse and one had two episodes of relapse that were managed by increasing the dose of immunosuppressive and by more prolonged tapering of corticosteroids. The outcome of this study as determined on analysis of 19 eyes of 30 patients was that an improvement in visual acuity does occur with treatment with azathioprine and corticosteroids. We report stabilization or improvement in around 86% of the eyes and minimal recurrence. Limitations of this study are inherent to its retrospective, cross-sectional design and that it lacked a comparator group. As a retrospective review, the sample size and selection bias are likely significant factors. Furthermore, the patients in this study were not a homogenous group, and represent serpiginous choroiditis in various stages of disease. We recognize that there are subjective limitations to fundus picture and angiogram interpretation. We suggest further prospective studies to optimize treatment protocols.

We conclude that combination therapy employing azathioprine and corticosteroids is an equally effective alternative to triple agent therapy in the treatment of serpiginous choroiditis.

References:


