Azathioprine in the treatment of thyroid-associated ophthalmopathy

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Abstract. Azathioprine is used in the treatment of thyroid-associated ophthalmopathy, but its effectiveness has not been evaluated. In the present study 20 patients with moderately severe ophthalmopathy were recruited; 10 patients received azathioprine and the other 10 matched patients served as controls. During the treatment period (lasting 1 year) and 1 year later, no changes were detected in exophthalmometer readings, visual acuity or measurement of palpebral aperture. Differential intraocular pressure fell with time in both groups. Azathioprine treatment did not significantly influence these parameters, although it did induce significant decrease in thyroid microsomal antibodies and in thyroid-stimulating hormone binding inhibiting immunoglobulin index. The study demonstrates that thyroid-associated ophthalmopathy of moderate severity, often improves with time without treatment. Azathioprine is not an effective treatment for patients with moderately severe thyroid-associated ophthalmopathy. The study emphasises the necessity for an adequately matched control population in the evaluation of therapy.

We report the results of a prospective controlled study of azathioprine therapy in patients with moderately severe ophthalmopathy.

Patients and Methods

Twenty consecutive patients with thyroid-associated ophthalmopathy, American Thyroid Association grade 2-4 (6), were recruited. Eighteen patients had Graves' hyperthyroidism, one patient had primary myxedema and one patient had no associated thyroid dysfunction (ophthalmic Graves' disease). Thyroid status was assessed by clinical examination, and estimation of serum T₄, T₃ and TSH. Informed consent was obtained from all patients. Ten patients were given azathioprine 150 mg orally per day, and 10 patients served as controls. The two groups were matched for age, sex, clinical grade, and concurrent treatment with carbimazole (Table 1). The duration of eye

Thyroid-associated ophthalmopathy, is probably an autoimmune disease (1) and immunosuppression is a desirable objective in management. The drug treatment of the disease is not very satisfactory, high dose steroids being the most effective agents (2).

Azathioprine has been used in thyroid-associated ophthalmopathy (3,4) but its efficacy has not been evaluated in a controlled fashion; a previous retrospective, report (5) claimed that azathioprine was beneficial in the prevention of thyroid-associated ophthalmopathy when given to patients with Graves' disease.

<table>
<thead>
<tr>
<th>Table 1.</th>
<th>Matching of patients in the treatment and control groups.</th>
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<tbody>
<tr>
<td></td>
<td>Treatment group</td>
</tr>
<tr>
<td>Females</td>
<td>8</td>
</tr>
<tr>
<td>Males</td>
<td>2</td>
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<tr>
<td>Mean age (years)</td>
<td>48.5</td>
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<tr>
<td>Clinical grade</td>
<td>II</td>
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<tr>
<td></td>
<td>III</td>
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<td></td>
<td>IV</td>
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<td>On carbimazole</td>
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disease varied between two months and 28 months, with the exception of one patient in the treatment group who had the disease for 18 years. All patients were euthyroid throughout the study. Azathioprine was administered for one year and had to be withdrawn in one patient because of leukopenia. No other undesirable adverse effects were noted. The control group received no specific treatment for their ophthalmopathy medical, surgical or otherwise.

Patients were assessed clinically and by ophthalmometry, before treatment, 3-monthly during the treatment year, and 1 year after treatment. Patients were seen jointly on each visit by a thyroidologist and an ophthalmologist.

Exophthalmos was measured by a Hertel exophthalmometer. The palpebral apertures were measured in the midline. Intraocular pressure was measured with an applanation tonometer by the same observer (ALC); differential intraocular pressure was defined as the difference in intraocular pressure measured in the primary position and on upward gaze (or attempted upgaze). Visual acuity was assessed with a Snellen chart.

Thyroid-stimulating hormone binding inhibiting immunoglobulin index (TBII) was measured as described (7) and expressed as a percentage ratio of TSH specifically bound in the presence of the test immunoglobulin, to TSH specifically bound in the presence of pooled normal immunoglobulin. Eye muscle antibodies (EM-ab) were measured by enzyme linked immunosassay (ELISA), (8) and expressed as optical density at 492 nm (OD 492). Microsomal antibodies were measured by an ELISA kit provided by Pharmacia.

The data were analysed using Wilcoxon’s rank sum test.

Results

Most patients remained clinically stable both with regard to thyroid status and ophthalmopathy during the study; two patients receiving azathioprine improved in their clinical grade in the post-treatment period, as did one control patient.

Visual acuity was not impaired in any patient and did not change during the period of observation. Similarly, no significant differences could be detected in exophthalmometer readings (Fig. 1 upper panel) or palpebral aperture (Fig. 1 middle panel) between the two groups, or within each group at different stages of follow-up.

The differential intraocular pressure fell, significantly both at the end of the treatment period and 1 year later (Fig. 1 lower panel); comparison between the azathioprine-treated group and controls, however showed that the two groups were not significantly different.

There was an overall significant fall in TBII in the azathioprine-treated group at the end of treatment. (Fig. 2 upper panel). Microsomal antibody levels also fell significantly in the azathioprine group; no such trend was observed in the controls (Fig. 2 middle panel). No significant changes were observed in EM-ab in either group; (Fig. 2 lower panel).

Discussion

Thyroid-associated ophthalmopathy is widely accepted to be an autoimmune disease (1,9). Abnormal cellular and humoral immune responses have been described (10,11), although the precise role of these in the pathogenesis is unknown. Many immunosuppressive regimes have been tried, but most are only partially effective and give rise to significant adverse effects (12-14). Winand & Mahieu (5), advocated that azathioprine should be used in patients with Graves’ disease to prevent the development of ophthalmopathy, based on their observation that the incidence of malignant exophthalmos declined sharply after adopting the policy of treating all Graves’ disease patients with azathioprine. However their study was retrospective and many factors could have contributed towards the change in the pattern of the disease.

In the present study, treatment and control groups were carefully matched. The effect of azathioprine on disease activity was assessed prospectively, both clinically and by detailed ophthalmometric measurements. The results indicate that there was little change in any of the parameters measured except for differential intraocular pressure which declined with time in both groups. Differential intraocular pressure reflects extraocular muscle compliance and therefore the degree of involvement of muscles by the disease (15), it would appear that there was an improvement in both groups (without any significant advantage in azathioprine-treated patients), which is probably attributable to the natural history of the disease.

The autoantibody measurements showed a drop in TBII and microsomal antibodies in the azathioprine-treated patients. This could be a result of the immunosuppression induced by the drug. However, the groups are too small to ascertain this possibility. While the significance of EM-ab in the pathogenesis of the disease is not known, it is noteworthy that azathioprine produced no change in disease activity and no change in EM-ab levels.
This study demonstrates that patients with moderate ophthalmopathy frequently, though not always, improve without any treatment; a practical approach in the management of these patients would be to repeat their measurements at regular intervals and if deteriorating consider treatment.

Fig. 1.
Exophthalmometer readings (upper panel), palpebral apertures (middle panel), and differential intraocular pressures (IOP) (lower panel), of patients on azathioprine (left) and controls (right), before treatment (1), at the end of treatment (2), and 1 year later (3).
Fig. 2.
Thyroid stimulating hormone binding inhibiting immunoglobulin index (TBII) (upper panel), microsomal antibodies (middle panel), and eye muscle antibodies (EM-ab) (lower panel) in patients treated with azathioprine (left) and controls (right) at the beginning (1) and end (2) of treatment. TBII fell in 9 and remained stable in 1 treated patient, whereas it rose in 3, declined in 6, and remained unchanged in 1 of the control patients. Microsomal antibodies fell in 9 and did not change in 1 treated patient, but increased in 2, remained unchanged in 4, and decreased in 2 control patients.
The need for controlled studies in therapeutic trials for thyroid-associated ophthalmopathy is emphasized. The data presented show that azathioprine used alone has no role as a therapeutic agent in the management of established, moderately severe thyroid-associated ophthalmopathy. This does not exclude a use for the drug as a steroid-sparing agent in patients with more severe disease, though this has not been well demonstrated.

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References

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