ORIGINAL ARTICLE

Safety and efficacy of combined immunosuppression and orbital radiotherapy in thyroid-related restrictive myopathy: two-center experience

Nikolaos T. Chalvatzis[1,2], Argyrios K. Tzamalis[1], Georgios K. Kalantzis[2,3], Nabil El-Hindy[3], Stavros A. Dimitrakos[1], Michael J. Potts[2]

[1] 2nd Department of Ophthalmology, Aristotle University of Thessaloniki - Greece
[2] Bristol Eye Hospital, Bristol - UK
[3] Ophthalmology Department, St James Hospital, Leeds - UK

Purpose: *To evaluate the safety and efficacy of oral steroids when combined with long-term oral azathioprine (AZA) and orbital radiotherapy in patients with active thyroid-related restrictive myopathy.*
Methods: *A total of 88 patients from adnexal outpatient clinics of Bristol Eye Hospital, UK, and 2nd Department of Ophthalmology at Aristotle University of Thessaloniki, Greece, were enrolled in a retrospective, twin-center study. All patients were diagnosed with active thyroid eye disease and concomitant restrictive myopathy. Treatment included oral AZA, low-dose steroids, and orbital radiotherapy (20 Gy). Clinical activity scores as well as orthoptic assessments were consistently evaluated. Clinical activity scores, improved levels of diplopia, and single muscle excursions were considered major criteria for treatment success.*
Results: *Clinical success was achieved in 54 (61.4%), 57 (64.8%), and 61 (69.3%) patients at 3-, 6-, and 12-month time points, respectively, after the initiation of the combined treatment. At 18 months following initiation of treatment, the percentage of treatment success reached 73.9% (n = 65). Nine patients developed AZA-related side effects. In 4 patients the drug had to be discontinued.*
Conclusions: *Combined immunosuppression with orbital radiotherapy appears to reduce morbidity in patients with marked restrictive myopathy by improving major motility parameters such as diplopia and duction amplitude.*

Keywords: *Azathioprine, Diplopia, Immunosuppression, Orbital radiotherapy, Thyroid eye disease*

Accepted: February 27, 2014

INTRODUCTION

Thyroid eye disease (TED) is an autoimmune disorder strongly related to Graves disease. Thyroid-derived antigens are found in orbital tissues and trigger a cell-mediated immune response. Orbital lymphocyte infiltration as well as fibroblast proliferation and adipogenesis seems to play a major part in pathogenesis and clinical severity of TED (1, 2). Locally produced cytokines amplify the immune response while high glycosaminoglycan levels contribute to interstitial edema and enlargement of extraocular muscles (3-6). There are several classifications of severity and activity. The recently revised consensus of the European Group on Graves' Orbitopathy (EUGOGO) (7-10) seems to ensure an accurate and reproducible assessment of TED patients.

Ocular restrictive myopathy is considered one of the severe morbidities that patients may experience during the course of the disease. It is either due to inflammatory involvement and enlargement of extraocular muscles in the active phase of TED or to fibrosis, usually observed during the burnt-out

phase of TED. Inferior rectus is most frequently affected, with medial and superior rectus following (10, 11). As a result, this group of patients complains predominantly of intermittent or, less frequently, constant diplopia in either primary or extreme positions of gaze.

Steroids represent the mainstay in management of TED (1-2, 8). Other therapeutic options such as orbital radiotherapy and second-line immunosuppressants (12, 13) such as azathioprine (AZA) and cyclosporine, nonsteroidal anti-inflammatory drugs, and, more recently, biological agents (14, 15) have been proposed with success rates that vary according to different studies. Combined regimens have often been tried aiming to achieve better efficacy while reducing steroid-related adverse effects (16, 17). We have routinely used combined treatment protocols for 10 consecutive years in patients with severe, active, noncompressive TED using the onset of motility restriction as indication for treatment. Anecdotal evidence has risen over this period of time that such patients may benefit significantly by using oral steroids when combined with orbital radiotherapy and AZA. This study investigates this hypothesis by analyzing essential parameters concerning ocular motility and clinical activity scores.

MATERIALS AND METHODS

This is a retrospective, record-based study conducted by 2 tertiary centers specializing in management of TED. Bristol Eye Hospital, Bristol, UK (center 1), and 2nd Department of Ophthalmology at Aristotle University of Thessaloniki, Greece (center 2), shared therapeutic protocols for patients with marked disease and thyroid-related restrictive myopathy. Both centers facilitate joined TED outpatient clinics run by expert ophthalmologists and endocrinologists. Data collected from both centers came from patients treated between 2000 and 2011.

The medical records of 88 patients were studied in total. This series was extracted from a total of 142 patients treated for TED in the same period. Fifty-four patients were not found eligible for the study, with decisions based on inclusion and/or exclusion criteria outlined in Tables I and II. A total of 65 were seen in center 1 in 2000-2009 and 23 in center 2 in 2005-2011.

The therapeutic treatment protocol consisted of an initial intravenous pulse of methylprednisolone 10 mg/kg no later than 7 days from the diagnosis followed by oral prednisolone 0.5 mg/kg/day, for at least 2 weeks, tapered gradually to 0.2 mg/kg/day and discontinued when clinical activity score (CAS) was ≤3 for more than 4 weeks. The AZA was also administered from week 1 after initial diagnosis, at doses of 200 mg/day reduced gradually to 50 mg/day and discontinued at 6 months after withdrawal of steroids (stable CAS ≤3). Standard guidelines and precautions regarding administration of steroids were also followed (i.e., blood pressure measurements, glucose levels, body weight). Patients were advised to take AZA at night, before sleep, to avoid any drug-related sickness. All patients underwent focused orbital radiotherapy of 20 Gy in total (6 MV photons from a linear accelerator; Mevatron MD2 and Primus, Siemens Medical Solutions, Erlangen, Germany). Radiotherapy was started within the first 2 weeks after the initial visit given in 10 fractions of 200 cGy for 10 consecutive days.

TABLE I - INCLUSION CRITERIA FOR STUDY CANDIDATES

Definitive criteria for study candidates	• Recently diagnosed marked TED (the time of first TED diagnosis should not exceed 2 months from presentation) • EUGOGO clinical activity score (8) of 5 or higher on 2 clinical visits 8 weeks apart • Enlargement of at least one extraocular muscle confirmed by MRI-STIR sequences
Relative criteria for study candidates	• Diplopia in primary position of gaze • Stable euthyroidism assessed by means of normal thyroid function tests for a minimum 3-month period

All definite criteria represented prerequisites for patient selection.
EUGOGO = European Group on Graves' Orbitopathy; STIR = short T1 inversion recovery; TED = thyroid eye disease.

TABLE II - EXCLUSION CRITERIA FOR STUDY CANDIDATES

Tobacco smoking
Thiopurine methyltransferase enzyme deficiency
Known malignancies
Age younger than 20 years
Diabetic retinopathy or other retinal vasculopathies (potential exacerbation during radiotherapy)
Drugs with known interaction with azathioprine (e.g., allopurinol)
Burnt-out disease
History of strabismus or other ocular conditions that may interfere with ocular motility variables
Previous steroid treatment was an exclusion criterion

Hematologic tests was requested at every follow-up and included full blood count, liver function parameters (SGOT, SGPT, γGT, bilirubin, albumin), urea and electrolytes, and blood glucose.

Azathioprine-related side effects were closely monitored and considered to be a strict indication for drug discontinuation in cases where abnormal hepatic enzymes (SGOT and/or SGPT >80 IU/L and/or γGT >60 IU/L), leukopenia (<4000/mL), low mononuclear count (<1%), pancreatitis, or persistent vomiting were apparent.

Clinical assessment and orthoptic examination based on Hess chart, field binocular single vision (BSV test), as well as uniocular fields of fixation (UFF) were performed at baseline and on regular follow-up usually arranged bimonthly, and at 6 months following withdrawal of treatment. The BSV and Hess chart interpretation was mainly based on 3 restriction zones assessment: inside the central 30° zone (zone 1: severe restriction) or outside the central 30° zone (zone 2: moderate/mild restriction) and no detectable restriction (zone 3). Uniocular fields of fixation has been suggested as a more accurate test in quantification of muscle restriction in TED patients (18). Although less than 5° changes may be recognizable with this technique, we decided to apply a simpler evaluation that conforms to our BSV and Hess chart measurements. Thus, restriction of at least one single muscle excursion within the central 30° was considered to be severe impairment, while restriction outside 30° was considered as moderate to mild. However, changes of 5° in motility were still applicable for CAS assessment purposes. Parameters for treatment success were defined as CAS ≤3 and concomitant improvement in diplopia and muscle excursions by at least one zone of restriction, as stated above.

Signal intensity ratio (SIR) in short T1 inversion recovery (STIR)–MRI sequences was also assessed in all patients prior to and after therapy. Signal intensity ratio represents the ratio of signal brightness between the examined extraocular muscle and the ipsilateral temporalis muscle. As Mayer and colleagues (19) proposed, the higher the ratio, the more active the disease.

Statistical analysis was performed by the use of Medcalc statistical software (version 9.3.0.0, Medcalc, Mariakerke, Belgium) and SPSS (v. 17.0 for Windows, SPSS Inc., Chicago, Illinois, USA). The data are given as mean ± standard deviation. Both parametric and nonparametric statistical tests were used for the analysis according to the existence of normal distributed data per case. All p values were 2-sided, and considered statistically significant when less than 0.05.

RESULTS

Demographic and clinical characteristics of the study are presented in Table III. A total of 88 patients (61 female and 19 male), mean age 52.3 years, were found eligible for the study. Signs and symptoms of TED were recognized and recorded bilaterally in 30 subjects, while 58 patients were unilaterally affected (27 right eyes and 31 left eyes) at the beginning of treatment. Total duration of follow-up ranged between 24 and 77 weeks.

Mean duration of combined treatment was 44.8 ± 4.25 weeks. Azathioprine administration ranged from 1 to 55 weeks (38.4 ± 2.6). Nine patients (10.2%) developed AZA-related side effects during treatment. Of the above patients, 4 experienced nausea to a variable degree, 2 had mildly elevated SGOT (55-70 IU), and 3 patients developed leukopenia (leukocytes <3500 cells/mcL and monocytes <1%). In 4 cases the drug had to be discontinued due to leukopenia (n = 3) and persistent nausea (n = 1). Prednisolone tapering ranged from 4 to 25 weeks (11.4 ± 2.3). Exacerbation of TED was diagnosed in 11 patients over the tapering phase of immunosuppression and treated with higher doses until reduced activity was diagnosed.

TABLE III - MAIN DEMOGRAPHIC AND CLINICAL CHARACTERISTICS DATA OF STUDY POPULATION

	Mean	Median	Range
Age, y	52.3 ± 10.8	56	23-71
Follow-up, wk	64.4 ± 11.5	62	24-77
Azathioprine administration, wk	38.4 ± 2.6	38	1-55
Prednisolone administration, wk	11.4 ± 2.3	12	4-25
Free T3, pmol/L	5.2 ± 1.7	5.1	2.3-7.2
Free T4, pmol/L	14.9 ± 2.1	15.2	12.9-17.3
TSH, mU/L	0.37 ± 0.12	0.34	0.05-0.54
TSI, SRR%	187.26 ± 31.43	176.2	135.7-243.2

T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; TSI = thyroid-stimulating immunoglobulin; SRR = specimen-to-reference ratio.

Forty patients (45.5%) had previously undergone radioactive iodine ablation for hyperthyroidism and developed flare-up shortly thereafter. On initial examination, 29 patients (33%) experienced diplopia in primary position of gaze, within the central 30° of field, confirmed by BSV test, while 59 patients (67%) were diagnosed with diplopia on extremes of gaze outside the central 30° of field. Hess charts and UFF tests showed severe restriction in single ductions, of at least one muscle, in 35 patients (39.8%) and mild to moderate restriction in 53 patients (60.2%) outside central 30° of excursion.

Orthoptic assessment at the end of treatment revealed an overall improvement in both diplopia and single muscle ductions. More specifically, 10 patients (11.4%) had residual diplopia in primary position. A total of 39 patients (44.3%) experienced diplopia only in extreme gaze, while 39 patients (44.3%) experienced complete relief from double vision ($p<0.001$, chi-square test). With respect to ductions, only patients with severe restriction of at least one muscle benefited significantly from the regimen ($p = 0.023$, McNemar test for paired proportions).

Mean CAS, calculated at final follow-up, was 1.91 ± 1.02 (median 2, range 0-6), and had significantly improved compared to mean CAS before treatment, which was 5.97 ± 0.78 (median 6, range 4-7, $p<0.001$, Mann-Whitney test).

Further subgroup analysis of the study population (n = 88) was undertaken according to CAS score after completion of treatment. This is detailed in Table IV.

Group A (CAS 0-3) included 64 patients (72.7%), group B (CAS 4-5) 23 patients (26.1%), and group C (CAS ≥6) 1 patient (1.2%). The latter patient was reported to show poor compliance to treatment. Compared to baseline data, a clinical improvement was noted in diplopia, CAS, and SIR ($p<0.001$, chi-square test).

TABLE IV - DIPLOPIA, CLINICAL ACTIVITY SCORE, AND SIGNAL INTENSITY RATIO AT BASELINE AND 6 MONTHS POSTTREATMENT WITH RESPECTIVE P VALUES

	Baseline	6 months posttreatment	p Value
Diplopia			
None	0	39	<0.001
Extremes	59	39	
Primary position	29	10	
CAS, median (range) and frequency	6 (4-7)	2 (0-6)	<0.001
0-3	0	64	<0.001
4-5	12	23	
6-7	76	1	
SIR, mean ± SD	2.16 ± 0.58	1.63 ± 0.53	<0.001

p Values using Mann-Whitney nonparametric test for median comparison in clinical activity score (CAS), Student *t* test for mean comparison in signal intensity ratio (SIR), chi-square test for frequencies comparison of diplopia and CAS, and Fisher exact test for frequencies comparison of SIR.

Signal intensity ratio comparison before and after treatment

A total of 35 patients had shown a ratio less than 2 in at least one muscle and 53 patients ≥2. At the last follow-up review, 67 patients were found with ratio 1-2, while only 21 patients had ratio of 2 or more ($p<0.001$, Fisher exact test). The SIR indicated a statistically significant reduction from 2.16 ± 0.58 to 1.63 ± 0.53 ($p<0.0001$, paired *t* test).

Out of the study population of 88 cases, clinical success was achieved in 54 (61.4%), 57 (64.8%), and 61 (69.3%) at 3-, 6-, and 12-month time points, respectively, after the initiation of the combined treatment. All patients were evaluated 6 months following withdrawal of treatment. At 18 months following initiation of treatment, the percentage of treatment success reached 73.9% (n = 65).

With respect to surgical procedures required during the course of treatment or following remission of disease, 8 patients underwent strabismus surgery for correction of persistent diplopia. Three patients underwent orbital decompression for cosmetic reasons and 10 patients had correction of eyelid malposition in the burnt-out phase of TED.

DISCUSSION

The concept of 2-agent medical immunosuppression combined with orbital radiotherapy derived from the notion that other combinations such as steroids and second-line immunosuppressant (AZA or cyclosporine) or steroids and orbital radiotherapy are more efficacious than use of either treatment alone (20). It is recommended that orbital radiotherapy is avoided in ages younger than 35; however, there are studies comprising patients as young as 17 years who received irradiation of 20 Gy without showing higher incidence of extraocular or radiation-related morbidities compared to older age groups (21). We included one man

under the age of 35 (23 years old) in our study, who had severe, persistent diplopia in primary position of gaze, previously unresponsive to steroid treatment alone. Long-term immunosuppression based on AZA and low-dose steroids was subsequently administered in patients whose disease remained active.

It is encouraging to observe that there was a sustained positive clinical improvement at 3-, 6-, and 12-month time points equating to 61.4%, 64.8%, and 69.3%, respectively, after the initiation of the combined treatment. At 18 months following initiation of treatment, the percentage of treatment success reached 73.9% (n = 65).

Diplopia, particularly in the primary position of gaze, represents one of the most disabling morbidities related to TED. Driving, reading, and working, either in office or industry environment, become difficult or impossible for affected patients. As shown in Table III, diplopia improved significantly with our combined treatment, resulting in complete cure in almost half of the patients enrolled in the study (44.3%). Additionally, primary gaze diplopia improved in 65.5% of cases in this subgroup. It is also notable that only 10 patients experienced persistent, posttreatment diplopia and among those 8 (9.1%) required strabismus surgery while 2 were satisfied with prism prescription. As Prummel and colleagues (22) reported, squint or decompression surgery was required in over 70% of their series of patients following treatment with either orbital radiotherapy or standard dose steroids. However, patients with inactive and irreversible disease were not excluded from the above study and this might be related to high demand for rehabilitative surgery.

Direct comparison of TED studies is notoriously difficult due to differences in study designs and variable outcome measures. The current consensus treatment for active TED remains high-dose intravenous steroids. However, in our study, we tried to combine an initial intravenous pulse with lower oral dosages since at the time the particular treatment protocol was conducted no prospective randomized studies were available comparing intravenous to oral steroids in TED. A regimen commonly used is outlined in Kahaly et al (23). In this study, patients received either once weekly intravenous methylprednisolone (0.5 g, then 0.25 g, 6 weeks each) or oral prednisolone starting with 0.1 g/day, then tapering the dose by 0.01 g/wk. At 6 months follow-up, there was a positive clinical improvement in TED in 77% of the intravenous glucocorticoid group compared to 51% in the oral glucocorticoid group. In our study, the overall improvement at 6 months was 61.4%, improving to 69.3% at 18 months. Our study shows a lesser degree of clinical improvement in TED in comparison to Kahaly et al. However, when specifically looking at the motility deficit subgroup (constant diplopia), we note an improvement in 33.3% in the oral glucocorticoid group and an improvement of 56.5% in the intravenous glucocorticoid subgroup at 12 weeks. In this respect, our study shows a more favorable improvement in this subgroup of 65.5%.

Although alterations in ocular motility were our primary concern, CAS as well as SIR was also assessed in all patients pretreatment and posttreatment and this may represent the first attempt in the literature to apply a modern assessment consensus in combined treatment regimens for TED. Overall improvement in CAS was found to be statistically significant and positively comparable to recent studies that involve pulse steroid treatment alone (17). Improvement in TED-related myopathy correlates to low CAS scores after treatment in this series of patients.

The use of AZA, as a steroid-sparing agent, significantly reduced the total prednisolone intake on a long-term basis since the vast majority of patients did not exceed 25 mg/day. Azathioprine-related adverse effects have been extensively studied because of its broad use in many other autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, myasthenia gravis, and ocular pemphigoid (24). In our series, 4 patients (4.5%) required withdrawal of AZA due to adverse effects. These effects were reversible after discontinuation of treatment.

Over the last 4-5 years, a multicenter prospective, controlled, randomized study between tertiary centers specializing in management of TED, the Combined Immunosuppression and Radiotherapy in Thyroid Eye Disease (CIRTED) study, has been undertaken (25). Patients enrolled in this study were initially put on oral steroids and subsequently randomized to 4 groups including possible combinations with radiotherapy, sham radiotherapy, AZA and placebo, and AZA. Results are expected shortly.

In conclusion, combined immunosuppression with orbital radiotherapy appears to reduce morbidity in patients with active disease and specifically the subgroup with marked restrictive myopathy by improving major motility parameters such as diplopia and duction amplitude and decreases the need for rehabilitative surgery. In this study, AZA appeared to be well-tolerated. Azathioprine used as a steroid-sparing agent may reduce the total cumulative steroid dose and the related adverse effects. Although the present

study has some limitations due to its retrospective nature and the difficulty in distinguishing cases whose improvement was a result of the natural course of the disease, it provides useful clinical evidence to support the efficacy of combined regimens in management of active thyroid-related myopathy.

ACKNOWLEDGEMENT

The authors thank the Medical Records Department of Bristol Eye Hospital, UK, for help in data collection; Ann Starbuck, Senior Orthoptist at Bristol Eye Hospital, UK, and the orthoptic staff for patient assessment and care; and the staff of the Radiotherapy Department at the Papageorgiou General Hospital, Thessaloniki, Greece, for their collaboration in management of the above series of patients and for state-of-the-art treatments.

Financial Support: No financial support was received for this submission.

Conflict of Interest Statement: None of the authors has conflict of interest with this submission.

Address for correspondence:
Argyrios Tzamalis, MD, PhD, FEBO
2nd Department of Ophthalmology
Aristotle University of Thessaloniki
Faculty of Medicine
"Papageorgiou" General Hospital
GR-56429, Thessaloniki
Greece
argyriostzamalis@yahoo.com

REFERENCES

1. Perros P, Krassas GE. Graves orbitopathy: a perspective. Nat Rev Endocrinol 2009;5:312-8.
2. Durairaj VD. Clinical perspectives of thyroid eye disease. Am J Med 2006;119:1027-8.
3. Lehmann G, Feldon S, Smith T, et al. Immune mechanism in thyroid eye disease. Thyroid 2008;18:959-65.
4. Burch HB, Wartofsky L. Graves' ophthalmopathy: current concept regarding pathogenesis and management. Endocr Rev 1993;14:747-93. [QUERY: Please verify or correct reference 4.]
5. Wiersinga WM. Graves' ophthalmopathy. Thyroid Int 1997; 3:1-15.
6. Bahn RS, Heufelder AE. Pathogenesis of Graves' ophthalmopathy. N Engl J Med 1993;329:1468-75.
7. Dickinson AJ, Perros P. Controversies in the clinical evaluation of active thyroid-associated orbitopathy: use of a detailed protocol with comparative photographs for objective assessment. Endocrinol Metab Clin North Am 2001;55: 283-303. [QUERY: Please verify or correct reference 7.]
8. Bartalena L, Baldeschi L, Dickinson AJ, et al. Consensus statement of the European Group on Graves' Orbitopathy (EUGOGO) on management of Graves' orbitopathy. Thyroid 2008;18:333-46.
9. Wiersinga WM, Perros P, Kahaly GJ, et al; European Group on Graves' Orbitopathy (EUGOGO). Clinical assessment of patients with Graves' orbitopathy: the European Group on Graves' Orbitopathy recommendations to generalists, specialists and clinical researchers. Eur J Endocrinol 2006;155: 387-9.
10. Rundle FF, Wilson CW. Development and course of exophthalmos and ophthalmoplegia in Graves' disease with special reference to the effect of thyroidectomy. Clin Sci 1945;5: 177-94.
11. Steel DHW, Hoh HB, Potts MJ, Harrad RA. Uniocular fields of fixation in thyroid eye disease. Eye 1995;9:348-51.
12. Prummel MF, Mourits MP, Berghout A, et al. Prednisone and cyclosporine in the treatment of severe Graves' ophthalmopathy. N Engl J Med 1989;321:1353-9.
13. Claridge KG, Ghabrial R, Davis G, et al. Combined radiotherapy and medical immunosuppression in the management of thyroid eye disease. Eye 1997;11:717-22.
14. Salvi M, Vannucchi G, Campi I, et al. Rituximab treatment in a patient with severe thyroid-associated ophthalmopathy: effects on orbital lymphocytic infiltrates. Clin Immunol 2009;131:360-5.
15. Naik V, Khadavi N, Naik M, et al. Biologic therapeutics in thyroid-associated ophthalmopathy: Translating disease mechanism into therapy. Thyroid 2008;18:967-71.
16. Bartalena L, Marcocci C, Chiovato L, et al. Orbital cobalt irradiation combined with systemic corticosteroids for Graves' ophthalmopathy: comparison with systemic corticosteroids alone. J Clin Endocrinol Metab 1983;56:1139-44.
17. Sterker I, Tegetmeyer H, Papsdorf K, Führer-Sakel D. Effect of combined intravenous glucocorticoids and orbital radiotherapy in restoring driving competency in patients with Graves' orbitopathy. Horm Metab Res 2009;41:391-6.
18. Haggerty H, Richardson S, Mitchell KW, Dickinson AJ. A modified method for measuring uniocular fields of fixation: reliability in healthy subjects and in patients with Graves orbitopathy. Arch Ophthalmol 2005;123:356-62.

19. Mayer E, Herdman G, Burnett C, Kabala J, Goddard P, Potts MJ. Serial STIR magnetic resonance imaging correlates with clinical score of activity in thyroid disease. Eye 2001;15: 313-8.
20. Bradley EA, Gower EW, Bradley DJ, et al. Orbital radiation for graves ophthalmopathy: a report by the American Academy of Ophthalmology. Ophthalmology 2008;115:398-409.
21. Marcocci C, Bartalena L, Rocchi R, et al. Long-term safety of orbital radiotherapy for Graves' ophthalmopathy. J Clin Endocrinol Metab 2003;88:3561-6.
22. Prummel MF, Mourits MP, Blank L, Berghout A, Koornneef L, Wiersinga WM. Randomized double-blind trial of prednisone versus radiotherapy in Graves' ophthalmopathy. Lancet 1993;342:949-54.
23. Kahaly GJ, Pitz S, Hommel G, Dittmar M. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. J Clin Endocrinol Metab 2005;90: 5234-40.
24. ABPI Data Sheet Compendium. London: Data-pharm Publications; 1995:1929-32.
25. Rajendram R, Lee RW, Potts MJ, et al. Protocol for the Combined Immunosuppression and Radiotherapy in Thyroid Eye Disease (CIRTED) trial: a multi-centre, double-masked, factorial randomised controlled trial. Trials 2008;9:6.