COMBINED RADIOTHERAPY AND MEDICAL IMMUNOSUPPRESSION IN THE MANAGEMENT OF THYROID EYE DISEASE

K. G. CLARIDGE[1], R. GHABRIAL[1], G. DAVIS[1], M. TOMLINSON[2], S. GOODMAN[2], R. A. HARRAD[1] and M. J. POTTS[1]

Bristol

SUMMARY

Although systemic steroids or orbital radiotherapy are effective in limiting the inflammatory response in thyroid eye disease (TED), there are reports of over 70% of treated patients requiring subsequent rehabilitative surgery: either orbital decompression or strabismus correction. This study investigated whether combined immunosuppression with primary orbital radiotherapy together with azathioprine and low-dose prednisolone, applied early in the active disease state, was more effective in treating TED. Forty consecutive patients with active TED were recruited. Orbital MRI (STIR sequence) was used to assess disease activity. Median duration of symptoms was 1.0 year. Subjects were treated with bilateral orbital radiotherapy (20 Gy in 10 fractions) and oral prednisolone and azathioprine. Pre- and post-treatment activity was measured clinically, including uniocular field of fixation, Mourits score and total eye score, until TED became inactive off all treatment. Before treatment, 15 subjects had signs of dysthyroid optic neuropathy, 35 had significant motility restriction and 38 had marked soft tissue signs. On average TED became inactive after 1.2 years (SD 0.7) of immunosuppression, and treatment was well tolerated. One patient required subsequent cosmetic orbital decompression, 6 had successful strabismus surgery and 13 required minor cosmetic lid surgery. Compared with previously reported treatment regimes we think that combined orbital radiotherapy and medical immunosuppression is far more effective than either treatment alone in the management of active TED, and led to fewer side effects of high-dose steroids. In particular there was more than a four-fold reduction in the requirement for orbital decompression and strabismus surgery.

From: [1]Bristol Eye Hospital; [2]Bristol Oncology Centre, United Bristol Hospital Trust, Bristol, UK.
Correspondence to: M.J. Potts, PhD, FRCOphth, Bristol Eye Hospital, UBHT, Lower Maudlin Street, Bristol BS1 2LX, UK.

Thyroid eye disease (TED) is an autoimmune phenomenon. Although in most cases the ophthalmopathy is mild and resolves within 3 years leaving no long-term sequelae, in 5–10% of patients long-term diplopia (50%), proptosis (70%) and lid retraction (50%) may result.[1,2] These patients may require multiple rehabilitative surgical procedures, i.e. the classical four-stage management described by Shorr and Seiff,[3] which is often only partially successful. In 2–7% of patients congestive optic neuropathy[4] may require urgent orbital decompression, after which a third of patients can develop new post-operative motility defects.[5,6]

In order to prevent long-term morbidity several immunosuppressive regimes have been tried with varying degrees of success. High-dose (60–80 mg/day) systemic steroids can be effective in up to two-thirds of patients,[7] but recovery may be transient and the doses used are associated with serious steroid-related side-effects.[1] The effect of corticosteroids has been improved by co-administration of cyclosporine, but if used alone cyclosporine was less effective than prednisolone.[7] Results with azathioprine[8] and exchange plasmapheresis[9,10] have been variable. Several studies have reported good results with orbital radiotherapy with few if any permanent sequelae.[11–18] However, in most of these studies radiotherapy did not reverse ophthalmoplegia or proptosis and recurrence of symptoms occurred in 14–28% of cases.[12,15] Whereas some reports found radiotherapy was superior to high-dose systemic steroids in reversing TED,[18] Prummel *et al.*[19] found radiotherapy was no more effective than systemic steroids in a double-masked randomised trial and over 70% of patients eventually required surgical procedures other than minor lid surgery. The combination of orbital radiotherapy and high-dose systemic methyl prednisolone has been shown to be

more effective than steroids alone, but patients still developed significant steroid-related side-effects.[20] Our methodology developed as an extension of this, and azathioprine was added as a steroid-sparing agent to reduce the steroid side-effects. Furthermore we have concentrated on applying this regime in the early 'active' phase of the disease, usually using the onset of motility disorder as an indication for treatment.

In 1944 Rundle first described the pattern of TED activity.[21] He originally divided the disease into two phases. The first was the dynamic phase, which he subdivided into the ingravescence or active period, during which symptoms and signs increased to a maximum, and the remission, or regression, period in which there was some natural though incomplete resolution of the disease. This was followed by the static or inactive phase when the disease became burnt out and signs remained stable. Rehabilitative surgical intervention is contraindicated until the final inactive phase is reached. The speed and magnitude of deterioration and extent of recovery differ for each patient. Fig. 1 illustrates four idealised schematic 'Rundle's curves' covering the spectrum of TED from (a) mild transitory TED often undetected and with no sequelae, (b) moderate TED with only lid retraction and mild proptosis sequelae, (c) marked TED with lid, proptosis and diplopia sequelae, to (d) severe TED with optic nerve compression in addition to the above sequelae. Patients presenting with clinical signs typical of advanced curve (b), (c) or (d) are considered serious enough to benefit from orbital immunosuppression.

The initiating autoimmune trigger for TED is unknown, and possible candidates have been recently reviewed by Char.[2] Cellular studies have indicated that circulating T lymphocytes are sensitised to orbital fibroblasts and stimulate an infiltrative cellular immune response during which the activated orbital fibroblasts lay down new collagen leading to fibrotic contraction before the final inactive disease state is reached.[22] The phases of Rundle's curve can therefore be linked to this cellular response. The initial wet phase (Fig. 1) occurs with cellular infiltration and proliferation which is followed by the contractile fibrotic response of the regression phase (Fig. 1), which leads into the final inactive/burnt-out phase when the immune trigger has ceased and permanent fibrosis occurred. Immunosuppressive treatment is effective only during the dynamic period of the disease[23] and should be initiated before significant fibrosis occurs as indicated by the dotted 'treatment box' in Fig. 1; this is consistent with clinical studies which found that orbital radiotherapy was more effective if TED had been present for less than 6 months.[15,16] Furthermore immunosuppression should be maintained for as long as the initial immune trigger exists, which may require months of treatment. However, since radiotherapy is not repeatable and long-term high-dose steroids have unacceptable side-effects, neither treatment is suitable for extended immunosuppression.

In 1992 this department started using orbital radiotherapy to suppress the immune response of active TED. In patients whose disease remained active, long-term immunosuppression was then continued with the steroid-sparing antimetabolite azathioprine, and/or low-dose steroids. More recently, due to the succcess of this approach azathioprine and low-dose steroids have been used in all patients from the outset of treatment.
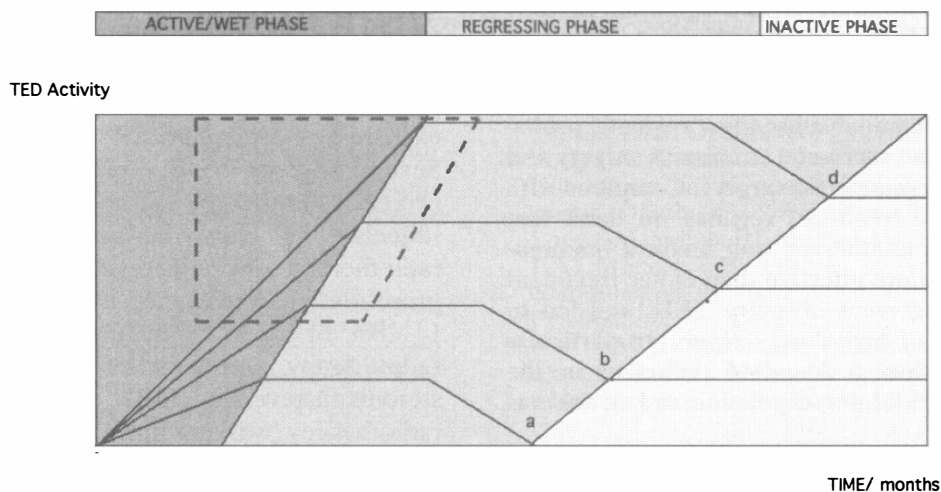

Fig. 1. Four idealised Rundle's curves profiling active thyroid eye disease (TED). Curve **a**, mild transitory TED with no sequelae; curve **b**, moderate TED with lid retraction; curve **c**, the above + proptosis + diplopia; curve **d**, the above + optic neuropathy + corneal exposure. The dotted box indicates the clinical stage at which patients best respond to immunosuppression treatment.

PATIENTS AND METHODS

Forty consecutive patients referred to the orbital/ adnexal clinic at BEH with active TED were recruited between 1992 and 1994. Current disease activity was judged by clinical examination using a pro forma which included Snellen acuity, Ishihara pseudoisochromic colour testing, presence of relative afferent pupil defect, lid or conjunctival oedema and/ or inflammation, keratitis, intraocular pressures (Goldmann tonometry), proptosis (Hertel exophthalmometer) and fundal examination. All patients had a full orthoptic assessment with uni-ocular fields of fixation (UFOF), which have been shown to be the most useful parameter for assessing motility dysfunction in active TED.[24] UFOF were quantified by adding the vertical and horizontal meridians, measured in degrees from primary position, and this method has been closely correlated with the actual area of field (D.H.W. Steel, personal communication).

TED was quantified by both an activity score devised by Mourits et al.[25] and the total eye score.[7] The former evaluates those signs and symptoms indicative of active, and therefore reversible, ophthalmopathy whereas the latter is based on the NO SPECS classification of the American Graves' Disease Classification System[26,27] and includes signs of both active and inactive disease. All but one patient underwent MRI using the Short Tau Inversion Recovery (STIR) sequence. High signal in the extraocular muscles using this technique has been shown to correlate with disease activity.[28]

Patients with active disease and moderate TED signs (NO SPECS score at least 2b) were referred for orbital radiotherapy and in most cases medical immunosuppression with combined oral steroid and azathioprine. Only 3 of the 40 patients had isolated soft tissue signs (i.e. NOSPECS = 2b) as their indication for treatment.

Radiotherapy Technique

The radiotherapy treatment was adapted from the method described by Olivotto et al.[12] Patients were treated on a 6 MV linear accelerator and the treatment volume encompassed the posterior 0.5 cm of the globe of both eyes and the entire retro-orbital tissue, but excluded the pituitary fossa posteriorly. Asymmetric jaws were used to limit forward beam divergence, with the anterior margin of the treatment volume being on the central axis of the beam, thus ensuring minimal lens exposure. Beam position was checked daily and altered if proptosis regressed. Snellen acuity and conjunctival oedema were assessed daily and if either worsened systemic prednisolone (usually 20 mg/day) was started during radiotherapy. All but one patient was given a total midplane dose of 20 Gy divided into 10 fractions over 12 days. One patient with unilateral proptosis was given a reduced midplane dose of 12 Gy.

Some patients had already either received systemic steroids or undergone corrective surgery prior to referral. Four patients had had orbital decompressive surgery, but despite this 3 of these still had progressive proptosis, one with optic nerve dysfunction; the fourth had compressive optic neuropathy. Sixteen patients had received systemic steroids for an average duration of 0.9 years, yet all had signs of deteriorating active TED on recruitment.

Medical Immunosuppression

After radiotherapy, disease activity was reassessed and systemic prednisolone, maximum dose 40 mg/ day, and/or azathioprine, up to 3 mg/kg per day, were started if disease activity persisted. Patients were re-examined at a minimum of 3 monthly intervals during which medical immunosuppression was tailored until TED was inactive and medication was stopped. Systemic blood pressure, urinalysis and the full blood count were checked at each visit to ensure there were no drug-related side-effects.

Once TED had become inactive patients were listed for surgery as necessary. Pre- and post-treatment comparison of parameters was performed by paired t-test and Spearman rank correlation.

RESULTS

The 40 patients comprised 23 women and 17 men and the average age at onset of TED was 52.8 years (range 19.1–75.7 years). Thirty-four had been hyperthyroid, 2 had had hypothyroidism and 4 have remained euthyroid. Eighteen of the 34 hyperthyroid patients had been treated with radio-iodine and there was on average 1.1 years (SD 2.4, range −2.2 to 7.0 years) between treatment with iodine-131 and the development of TED. Six hyperthyroid patients developed TED prior to receiving radio-iodine. All patients were euthyroid when given orbital radiotherapy, though 2 developed recurrent thyroid dysfunction whilst on medical immunosuppression. The median duration of TED prior to orbital radiotherapy was 1.0 year (range 0.3–17.7 years).

Fig. 2 illustrates the clinical signs present prior to immunosuppression. If the two eyes differed in severity of disease, the clinical signs of the worse eye have been presented. The group mean pre-treatment Mourits score was 5.4 (SD 1.7, range 9–1) and the group mean total eye score was 15.5 (SD 7.0, range 32–4). The STIR sequence of the pre-treatment MRI scans showed the characteristic high signal in the retro-orbital muscles indicating high water content within the tissues, typical of inflammatory oedema. Quantitative analysis of the muscle signal was not performed routinely.
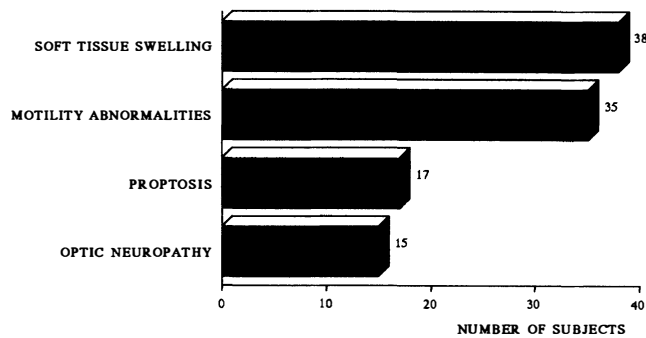
Fig. 2. *Clinical signs of thyroid eye disease in 40 patients prior to treatment.*

After orbital radiotherapy 9 patients had no further treatment, 10 received oral prednisolone alone, 18 had prednisolone and azathioprine, and 3 were started on azathioprine alone as the patients preferred to avoid steroids. Medical treatment was withdrawn gradually as disease activity regressed. On average TED became inactive off all treatment 1.2 years (SD 0.7, range 0.2–3.0 years) after orbital radiotherapy. The group mean changes in the Mourits score, total eye score, proptosis and uni-ocular fields of fixation are shown in Table I.

Prior to treatment all patients with optic neuro-pathy had reduced acuity; in addition 12 had an abnormal Ishihara colour vision test, 9 had a relative afferent pupil defect and 6 had distinct optic disc swelling. After treatment all had improved acuity, 2 still had reduced colour vision but none had a pupillary defect or residual disc swelling.

Treatment was well tolerated with no side-effects requiring a change in management. One patient had diabetes, but as she had no signs of coexistent retinopathy orbital radiotherapy was given. Over 3 years of follow-up she has shown no signs of developing retinopathy. A few patients developed mild weight gain whilst on steroids but none developed hypertension or diabetes. None of the patients showed disturbance of their haematological profile, indicating no drug-induced bone marrow suppression. Three patients have undergone success-ful cataract extraction following immunotherapy. In all patients lens opacification had been noted before orbital radiotherapy and may have been age-related or steroid dependent.

Table I. Group mean (SD) values before and after immunosuppression

	Before immuno-suppression	After immuno-suppression	*p* value (Student's *t*-test)
Mourits score	5.4 (1.7)	0	*p* < 0.0001
Total eye score	15.5 (7.0)	3.7 (3.8)	*p* < 0.0001
Proptosis (mm)	23.6 (2.7)	20.7 (2.5)	*p* = 0.0004
UFOF (deg)	115 (39)	153 (30)	*p* < 0.0001

UFOF, uniocular fields of fixation.

Fig. 3 illustrates the corrective surgical procedures required after TED had become inactive. In particular 52.5% of patients required no surgery. Six of the 35 patients with pre-treatment motility abnormalities had successful strabismus surgery; 1 patient required two-muscle surgery whereas the others underwent reces-sion of a single muscle. Only 1 of the 15 patients presenting with signs of optic neuropathy required an orbital decompression and this was for cosmetic asymmetry as the patient had had a similar procedure performed on the other eye prior to radiotherapy. This patient was also one of those requiring strabis-mus surgery. The 2 patients who developed recurrent thyroid dysfunction during immunosuppression did not require rehabilitative surgery.

There was no correlation between the duration of TED prior to radiotherapy and the duration after immunosuppression, or the final total eye score (*p*>0.1 for both comparisons). Similarly there was no differ-ence in the duration of active TED prior to treatment in the patients requiring corrective surgery and those who did not (*p*>0.5, unpaired *t*-test). The average follow-up time after TED had become inactive was 1.7 years (SD 0.9, range 0.1–3.6 years) and no patient has presented with signs of recurrent active disease.

In our sample of 40 patients 3 are still tailing off medical immunosuppression. It is clear from their recent examination that 2 will require no corrective surgery and 1 may choose to have a cosmetic blepharoplasty. As all 3 now have full ocular motility and no proptosis none will need strabismus or orbital surgery. The data from these patients have been included in all the results except in the average time for TED to become inactive after radiotherapy and the average follow-up time after TED became inactive.

DISCUSSION

Our results show that the early application of the combined regime of orbital radiotherapy and medical immunosuppression is effective in the treatment of active thyroid eye disease and dramatically reduces the requirement for corrective surgery. Prummel *et al.*[19] found that over 70% of patients treated with either orbital radiotherapy or a standard dose of
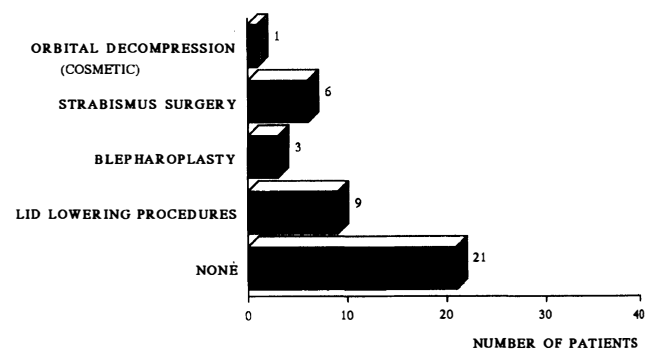

Fig. 3. *Final surgical outcome of all patients.*

systemic steroids required rehabilitative surgery excluding lid procedures. Despite the mean total eye score of our group of patients being higher than that in Prummel's series (15.5 vs. 9.1), the requirement for corrective strabismus or orbital decompressive surgery was 4 times lower in our series. The reason for the difference in our results might be that our patients were selected on the basis of having active and therefore reversible TED and were treated early in the active phase of the disease. Alternatively the difference may also arise from the fact that in the present series medical immunosuppression was continued as long as TED remained active, which in one case was 3 years. In Prummel's series systemic steroids were administered according to a protocol and not titrated to the patients' disease.

Our results are consistent with those of Kazim et al.[18] who found that only 1 of 29 patients with compressive optic neuropathy required surgical decompression after orbital radiotherapy. However, they found that ocular motility dysfunction and proptosis were relatively insensitive to orbital radiotherapy, both of which responded well to our combined regime.

TED is an autoimmune phenomenon and should therefore be treated medically before irreversible fibrosis occurs. The aim of our technique is first to bring the immune response rapidly under control with orbital radiotherapy and, secondly, to continue medical immunosuppression until the immune trigger wanes. Interestingly radiotherapy has been used to reduce drainage bleb fibrosis after trabeculectomy surgery and an identical dose of 20 Gy has successfully suppressed fibroblast proliferation (P. Khaw, personal communication). With our regime of a fractionated dose using asymmetric jaws, the radiation exposure to the lens is no more than 17% and that to the retina no more than 30% of the maximum tolerated dose and the theoretical long-term risk to neighbouring tissues is considered

minimal. Petersen et al.[14] have up to 21 years follow-up on 311 patients treated with orbital radiotherapy for TED and found none developed radiation-induced cataract or retinopathy or indeed secondary orbital tumours, despite some patients having received 30 Gy. Yet side-effects relating to high-dose systemic steroids are well documented. Azathioprine is an imidazole derivative of 6-mercaptopurine and has been used as a steroid-sparing immunosuppressant in rheumatoid arthritis, systemic lupus erythematosus and myasthenia gravis.[29] Its exact mechanism of action is unclear but probably involves inhibition of many pathways in nucleic acid biosynthesis necessary for lymphocyte and fibroblast proliferation. Although not seen in our series, azathioprine may cause bone marrow depression, and regular blood counts should be performed. Its effect is potentiated in the presence of renal or hepatic impairment and by co-administration of allopurinol, and the dose should be altered accordingly. Animal studies have indicated teratogenicity and azathioprine should be avoided in pregnancy. With the use of azathioprine it is possible to maintain immunosuppression with a low dose of prednisolone and so prevent unwanted side-effects. More recently adequate control of active TED has been gained using an initial prednisolone dose of 30 mg/day.

We feel that patients with active TED showing at least motility disturbances or profound soft tissue signs will gain maximum benefit from combined orbital immunosuppression in the early active phase of the disease as outlined by the 'treatment box' in Fig. 1. Our present treatment regime is illustrated in Fig. 4. Orbital radiotherapy is given as a standard dose of 20 Gy in 10 fractions over 12 days. Azathioprine is started on referral to the radiotherapist at a dose of 3 mg/kg per day as its immune effect takes between 3 and 4 weeks to become fully established.[29] Prednisolone, typically 30 mg/day, is added during the second week of orbital radio-
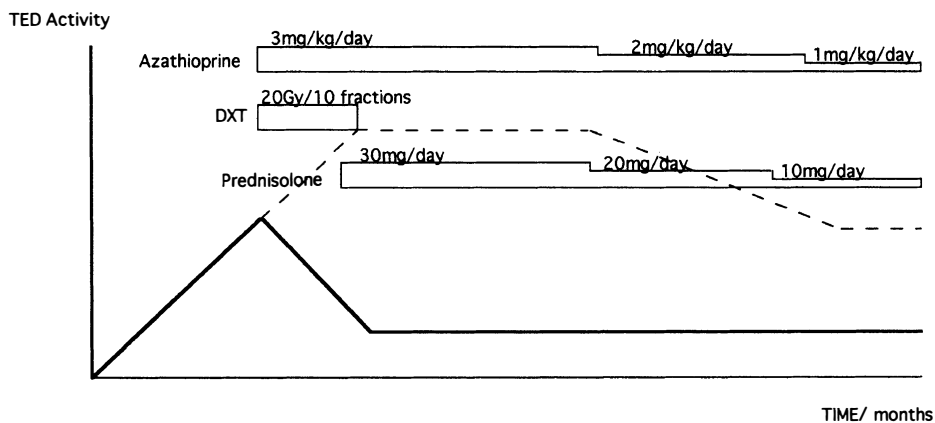

Fig. 4. *Diagram to illustrate suggested treatment regime now practised in our department. The continuous Rundle's curve indicates schematically how treatment can alter the profile of the original dashed Rundle's curve. DXT, orbital radiotherapy.*

therapy to counter any inflammatory post-radiation effects. The azathioprine and steroid dose are reduced progressively in stepwise fashion, depending on disease activity; this is most readily assessed by UFOF and Mourits score. The precise time over which a given patient will be weaned off medical immunosuppression is entirely dependent on their disease activity, i.e. Rundle's curve profile. Whilst reducing the dose some patients have developed a flare-up in disease activity requiring an increase in medical immunosuppression and subsequently a slower tailing off period. We feel that adequate immunosuppression initiated early enough in the disease course gives the best chance of complete reversal of the physical signs, thus avoiding rehabilitative surgery. As our results have shown, no patient required decompressive surgery for dysthyroid optic neuropathy during or following immunosuppression, the quality of motility recovery was good, with most patients achieving normal UFOF and Hess charts, and residual proptosis was almost always correctable by minor lid procedures rather than major orbital surgery with its high complication rate.

This paper describes our experiences in developing a more effective 'combined' immunosuppressive treatment regime for active TED which has been highly successful in our hands. A controlled trial is now needed to prove its effectiveness matched against other established treatment regimes.

Key words: Thyroid eye disease, Graves' ophthalmopathy, Orbital radiation, Azathioprine, Immunosuppression.

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