

EDITORIAL

Radioiodine and Graves' ophthalmopathy reconsidered

The principal features of Graves' disease are hyperthyroidism and ophthalmopathy, but the pathophysiological link between the two remains unclear. The hyperthyroidism can be successfully treated by either radioactive iodine or antithyroid drugs but there are concerns about the effect these have on the ophthalmopathy. This controversial subject has been widely discussed but recently the debate has slowed, largely due to the publication of a large prospective randomized controlled trial by Bartalena *et al.* [1].

The trial recruited 450 patients with Graves' hyperthyroidism and mild or no ophthalmopathy. Surprisingly, only seven were lost to follow-up. The patients were rendered euthyroid with 3–4 months of methimazole and were then randomly assigned to receive either radioiodine at 120–150 μ Ci (150 patients); radioiodine with a 3 month course of adjuvant prednisolone (145 patients) or to continue on methimazole for a further 18 months (148 patients). The groups were matched demographically, for smoking and for both thyroid status and ophthalmopathy at baseline. Patients were evaluated for changes in thyroid status and progression of ophthalmopathy at 1–2 month intervals over 12 months. Hypothyroidism and persistent hyperthyroidism were treated medically within 2–3 weeks of their diagnosis.

The study showed that 23 of the 150 patients treated with radioiodine alone developed or had worsening of their ophthalmopathy within 6 months. This was most prevalent amongst smokers. No radioiodine patients with ophthalmopathy at baseline improved. The changes were generally transient, lasting for 2–3 months, but persisted in eight patients. All but one of these had ophthalmopathy at baseline. These eight patients required further orbital therapy (radiotherapy, high-dose steroid). In contrast, only four of the 148 patients treated with methimazole had worsening of their ophthalmopathy and only one of these required orbital intervention. Three showed an improvement in baseline ophthalmopathy. Amongst the 150 treated with steroids and radioiodine none progressed and 50 of the 75 with ophthalmopathy at baseline improved.

The conclusions drawn from the study were that

... radioiodine for Graves' hyperthyroidism is followed by the appearance or worsening of ophthalmopathy more often than treatment with methimazole. Worsening of ophthalmopathy after radioiodine therapy is often transient and can be prevented by the administration of prednisolone.

In addressing these conclusions one needs to reconsider the natural history and pathophysiology of Graves' disease which, unfortunately, is poorly understood. Even the definition of the disease poses difficulty and is usually given as a collection of associated signs [2]. Concepts like 'euthyroid Graves' and 'Graves' hyperthyroidism without ophthalmopathy' suggest an element of independence of these two main features [3]. Furthermore, the clinical time course of ophthalmopathy and hyperthyroidism can be independent, with ophthalmopathy preceding hyperthyroidism in 45% of cases [4]. This implies that 'Graves' disease' may cover a range of conditions and that certain factors may exist to predispose Graves' patients to clinical ophthalmopathy. In the absence of true randomization (e.g. sample size less than infinity) these factors will act as confounding variables. Some such confounders have been identified already and Bartalena's group addressed many in their paper. The first and most dramatic is smoking [5] and, interestingly, the study found that patients in whom ophthalmopathy developed or worsened were much more likely to be smokers ($P < 0.001$).

The second potential confounding factor is that of pre-existing disease activity at the point of entry into the trial, and can be difficult to determine [6–8]. The study controlled for pre-existing orbitopathy (by clinical ocular examination) and rendered all patients euthyroid prior to the trial, matching free tri-iodothyronine (T3) and thyroid-stimulating hormone (TSH) levels. However, better markers of overall disease activity may have existed which were not controlled for, e.g. the dose of methimazole needed to render a patient euthyroid, or the maximum uncontrolled T3 levels. These may have given a more accurate picture of the severity of the patient's underlying disease and enabled more accurate control of groups.

A third recently identified and potentially confounding variable is treatment-induced hypothyroidism [9]. This issue fuelled most of the criticism for the other large prospective randomized trial addressing ophthalmopathy and treatment of Graves' disease [10]. The authors of this later study confirmed that post-radioiodine hypothyroidism exacerbated ophthalmopathy [11]. In the study by Bartalena *et al.* [1]

... the percentages of patients in each group who were euthyroid, hyperthyroid and hypothyroid at various times did not alter significantly, except that more patients in the methimazole group were euthyroid during the follow-up period.

The actual data given showed that following treatment 20–29 of the 150 patients in the radioiodine group were hypothyroid compared with none in the methimazole group. Despite this, the authors claimed that there was no relation between the thyroid status and the development or progression of ophthalmopathy as most radioiodine patients who developed ophthalmopathy were in the euthyroid group. However, this latter group included treated hypothyroid patients and patients with sub-clinical disease who had elevated TSH but normal T3. The biochemical results were given in 3-monthly intervals despite the data being collected monthly. Interestingly, a recent prospective controlled study involving non-smoking patients who did not develop hypothyroidism or elevated TSH levels following intervention showed no exacerbation in ophthalmopathy with radioiodine [12].

A final confounding factor to consider in the pathophysiology of Graves' disease is the prognosis of the condition. Both the hyperthyroidism and the ophthalmopathy show a 'Rundle's curve' pattern of activity with burn out after approximately 2 years [13]. This suggests that the duration of the disease prior to treatment is an important factor. Thus patients who have had hyperthyroidism for more than 12 months without ophthalmopathy may be less likely to develop ophthalmopathy in the future. Whilst a range of 3–15 months was given in the study for this duration, there were no mean values for each group and it is possible that in one cohort most subjects lay at an extreme end of the scale.

Having reviewed the natural history, randomization and control of the study one can reconsider the conclusions and their clinical relevance. Bartalena's group claimed a statistically significant deterioration in ophthalmopathy in the group treated with radioiodine only ($P > 0.001$). However, most of these changes were transient, lasting for 2–3 months, and required no treatment. This is highlighted by the group's argument that previous studies in which radioiodine was not

shown to affect ophthalmopathy may not have been following the patients closely enough immediately post-operatively and may therefore have missed such small changes. It is possible that such transient changes may cause patients some limited distress. However, when considering prophylaxis, the important cohort is actually those patients whose ophthalmopathy persisted and required significant intervention (described in the study as radiotherapy and high-dose glucocorticoids). This involved eight of the 150 patients treated with radioiodine, one of the 145 treated with methimazole and none in the group on prophylactic prednisolone. This result is far less significant than when transient effects are included and, based on the entry criteria used in the trial, 150 patients would require prophylaxis to prevent eight such cases. Furthermore, seven of the eight radioiodine patients needing orbital treatment had pre-existing ophthalmopathy, which suggests the possibility of an identifiable sub-group.

Of key importance is the ophthalmic assessment criteria used to determine the threshold for intervention in these 'severe' cases, which is not given in the study. There is only a subjective approach relating to

... an overall evaluation that took into account the degree of inflammatory changes and related symptoms, the extent of proptosis and extra ocular muscle dysfunction and optic nerve involvement and the degree of interference to the patient's daily activities.

The management of this kind of severe active dysthyroid ophthalmopathy is a very controversial topic, with little consensus regarding the need for timing and type of intervention [14–17]. Accordingly, until this question is settled, decisions about the role of prophylaxis to prevent the development of such pathology cannot be made.

Even accepting the existence of a group of patients with significant ophthalmopathy that is directly attributable to radioiodine treatment, one must consider the risks of prophylaxis. The study used 0.4–0.5 mg of prednisolone/kg body weight/day starting 2–3 days after radioiodine therapy and continuing for 3 months (tapering off over the last two). Steroids have long been associated with a multitude of significant side effects [18], none of which are given as outcome measures in the treated group. Furthermore, if transient ophthalmopathy forms part of the group justifying the prophylaxis, even minor side effects of prophylaxis need to be considered in a quality of life assessment. Alternative prophylactic drug and dose regimes may also warrant analysis.

In conclusion, there is no doubt that the paper by Bartalena *et al.* [1] is the largest source of data we have regarding the effects of anti-thyroid treatment on ophthalmopathy. However, questions still arise regard-

ing the natural history of Graves' disease and uncontrolled confounding variables. In addition, the clinical relevance of worsening thyroid ophthalmopathy is uncertain, especially considering it is often transient. The benefit of long-term biochemical thyroid control achieved with radioiodine will ensure its continued use despite allegations of increased ophthalmopathy. Ophthalmological problems may be minimized by stricter thyroxine substitution following radioiodine treatment or by identification of high-risk patients prior to its use. The use of prophylactic steroid treatment to prevent radioiodine related ophthalmopathy requires further study, particularly in relation to the risk/benefit ratio. At present it may be more appropriate to use steroids as a treatment option in those 'severe' cases of active eye disease only.

Finally, the short-term changes in ophthalmopathy observed by the study group may reflect a greater difficulty in post-radioiodine thyroid control compared to those observed with the use of methimazole. In the overall analysis, this is compensated for by better long-term control with radioiodine. It may therefore be that improved thyroid control and aggressive treatment of active thyroid ophthalmopathy hold the key to successful radioiodine use.

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