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Is radioiodine more likely than antithyroid drugs to worsen ophthalmopathy in patients with Graves disease?

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SUMMARY

This Practice Point commentary discusses the findings and limitations of a systematic review by Acharya *et al.* that assessed the utility of radioiodine to treat Graves hyperthyroidism. The authors examined 10 randomized controlled trials, and focused on the potential causative relationship between radioiodine and Graves ophthalmopathy. They concluded that the risk of Graves ophthalmopathy following radioiodine therapy is higher than that after treatment with antithyroid drugs (relative risk [RR] 4.23). The risk of severe Graves ophthalmopathy was also found to be increased after treatment with radioiodine (RR 4.35). Glucocorticoid prophylaxis was highly effective in preventing disease progression in patients with pre-existing Graves ophthalmopathy (RR 0.03). Here, I highlight the issues to consider when interpreting and generalizing these results, such as the limitations imposed by the inconsistency of disease classification and description in the various trials. Although this systematic review highlighted the small but real risk of Graves ophthalmopathy progression following radioiodine therapy, it could not provide insight into the extent of this progression or identify which patients are at highest risk and so might benefit most from prophylaxis.

Keywords

antithyroid drugs; Graves disease; Graves ophthalmopathy; hyperthyroidism; radioiodine therapy

COMMENTARY

Studies over the past 20 years have identified orbital fibroblasts as the targets of the orbital autoimmune response in Graves ophthalmopathy, and several cellular responses involved in this process have been described.¹ Growing evidence points towards the TSH receptor, which is expressed on orbital fibroblasts, as the primary auto-antigen against which the autoimmune process is directed. In addition, other autoantigens, including the insulin-like growth factor I receptor, may have a role in disease development.² It remains unclear, however, why some patients with Graves disease develop clinically relevant Graves ophthalmopathy, whereas others are unaffected by ocular disease. No unique genetic associations have been identified in patients with severe Graves ophthalmopathy. Environmental factors (such as smoking), variations in orbital anatomy, pressure-related trauma to orbital tissues and post-treatment hypothyroidism seem likely to have a role in disease progression.³ Radioiodine treatment of Graves hyperthyroidism, which might

closely precede the development of eye symptoms, has long been suspected to be a potential risk factor. Proposed sequelae of radioiodine exposure that might explain such an effect include stimulation of the release of autoantigens from the thyroid gland, stimulation of TSH receptor autoantibody production, and destruction of radiosensitive suppressor T cells.

Systematic reviews carry with them limitations, because they have to compare studies that are not uniform in patient population, study design or study end points. In addition, these difficulties are multiplied when few large-scale randomized controlled trials have been performed and approaches to disease classification or description are not standardized. Such limitations are evident in the systematic review by Acharya *et al.*⁴ of 10 randomized controlled trials that described Graves ophthalmopathy outcomes in 1,136 patients. Only six of these trials systematically evaluated eye outcomes as a primary end point, and only two compared radioiodine with antithyroid drugs. Few of the trials specified how many patients had clinical evidence of Graves ophthalmopathy before they received radioiodine, or whether any pre-existing Graves ophthalmopathy was active (defined as a clinical activity score ≥ 3). Description of eye outcomes in the various trials was heterogeneous and included the ophthalmopathy index, clinical activity score, NOSPECS classification, and isolated exophthalmometer readings.

Despite these limitations, however, Acharya *et al.* found that 20 of the 24 patients in these combined trials who developed Graves ophthalmopathy severe enough to require treatment had received radioiodine. Although the absolute risk posed by radioiodine treatment is clearly small, an increased risk seems to be present when radioiodine is compared with antithyroid drugs (RR 4.35). Nevertheless, the very large 95% CI (1.28–14.73) and lack of available clinical data introduce doubt as to whether this finding truly represents an increased risk for the development of severe Graves ophthalmopathy, or whether milder, progressive disease was observed and subsequently treated. The analysis clearly demonstrated that prophylactic treatment with the glucocorticoid prednisolone is effective in preventing disease progression in patients with pre-existing mild to moderate Graves ophthalmopathy. Nonetheless, it must be noted that glucocorticoid treatment is not without its own risks; one hypertensive patient given betamethasone prophylaxis died as a result of cerebral hemorrhage.

The 2008 consensus statement of the European Group on Graves' Orbitopathy (EUGOGO)⁵ on the management of Graves ophthalmopathy recommends offering prophylactic corticosteroids to patients with active Graves ophthalmopathy who are treated with radioiodine. The treatment protocol recommended by EUGOGO is 0.3–0.5 mg oral prednisone per kg bodyweight daily for a period of 1–3 days after radioiodine treatment, followed by gradual tapering of the dose over the next 3 months. By contrast, patients with inactive Graves ophthalmopathy do not require glucocorticoid treatment, provided post-treatment hypothyroidism is avoided.⁴ The lack of detailed clinical data presented in the trials reviewed by Acharya *et al.* precludes estimation of the risk of progression on the basis of disease activity. These trials also did not provide information about the risk for progression in patients with severe Graves ophthalmopathy, as only patients with mild to moderate disease were enrolled. Other studies have shown that patients with uncontrolled thyroid function (both hyperthyroidism and hypothyroidism) are more likely to have severe Graves ophthalmopathy than euthyroid patients.⁶ The EUGOGO consensus statement similarly emphasizes that restoration and maintenance of euthyroidism in patients with Graves ophthalmopathy is more important than the choice of modality used to treat the hyperthyroidism. Use of standardized clinical assessment methods for patients with Graves ophthalmopathy, as developed by EUGOGO and outlined in their consensus statement, will facilitate both multicenter trials and comparisons between single-center trials. The findings in the systematic review by Acharya *et al.* should not be interpreted to suggest that

radioiodine treatment is to be avoided in patients with mild to moderate active Graves ophthalmopathy, as radioiodine is a safe and effective treatment for hyperthyroidism provided post-treatment hypothyroidism is avoided. Whether or not gluco-corticoids are to be given when radioiodine is the treatment of choice is a decision best made in conjunction with the patient and should involve discussion of their risk factors for Graves ophthalmopathy progression, including smoking and high T₃ levels, as well as their risk of complications from glucocorticoids.

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Practice point

Although the absolute risk for progression of Graves ophthalmopathy posed by radioiodine treatment seems to be small, patients with active, mild to moderate Graves ophthalmopathy treated with radioiodine might benefit from glucocorticoid prophylaxis, particularly if they smoke, have high T₃ levels, and are at relatively low risk for complications from treatment with glucocorticoids.