CONTROVERSY IN CLINICAL ENDOCRINOLOGY: GRAVES' OPHTHALMOPATHY

Claudio Marcocci

Department of Endocrinology and Metabolism, University of Pisa, Pisa, Italy

Graves' ophthalmopathy (GO) is present in about 50% of patients with Graves' hyperthyroidism. It may range from mild to moderately severe to (rarely) sight-threatening. It is commonly believed that an autoimmune response against antigen(s) shared by the thyroid and the orbit is responsible for GO, the TSH receptor being the most likely culprit.
From a clinical point of view two aspects are still debated: i) how to manage Graves' hyperthyroidism in patients with associated GO; 2) which is the more appropriate medial management of active GO.

Prompt restoration and stable maintenance of euthyroidism should be obtained in all patients. Antithyroid drugs and thyroidectomy *per se* do not influence the natural course of GO On the other hand radioiodine therapy can be associated with progression of *de novo* appearance of GO, particularly in smokers. This can be presented by oral glucocorticoids administration. In patients with mild GO, the choice of thyroid treatment is largely independent of GO. Moderate-to-severe and active GO should be treated without delay. In these patients the choice between conservative (antithyroid drugs) or ablative (radioiodine, thyroidectomy or both) treatment is presently expert-opinion rather than evidence-based. The potential use of biological agents, such rituximab, which counteracts pathogenetic mechanism of both hyperthyroidism and GO, requires further evaluation in randomized clinical trials.

Glucocorticoids (GC) are used in the management of GO in view of their anti-inflammatory and immunosuppressive effects. GC have been employed either locally or systemically, the latter route being less effective, but may be considered in patients with absolute contraindications to systemic use of GC. Oral GC have an overall favourable response rate in about 60% of GO patients, but recurrence of eye disease is not uncommon and side effects are frequent, especially iatrogenic Cushing's. These considerations led to the use of intravenous (iv) GC pulse therapy. ivGC pulse therapy is widely employed with many differences in regimen of administration, total dose, interpulse interval and duration of the treatment and there is no evidence for the superiority of any of these schedules. Recent randomized clinical trials have shown that the iv route is more effective and better tolerated than the oral route. A favourable response is observed in ~80% of cases, with low prevalence of Cushingoid features. However particular attention should be paid to possible liver toxicity of ivGC. GC can used either alone or associated with orbital radiotherapy. The combined regimen has been shown to more effective than either treatment used alone. GC are effective only when GO is active, i.e. of short duration, progressive and with significant phlogistic manifestations.

In patients in whom GC therapy fails the medical armamentarium is rather limited. Orbital radiotherapy can be considered in those patients who did nor received it in association with GC. Indeed, recent randomized clinical trials have confirmed that orbital radiotherapy is an effective as safe therapeutic procedure. Somatostatin analogs have been extensively investigated, based on the observation that somatostatin receptors are expressed in orbital tissues of GO patients. Four well-designed randomized clinical trials have shown that either octreotide LAR or slow-release lanreotide have no role (apart from marginal and questionable eye changes) in the management of GO. Novel somatostatin analogs, such as SOM230, with different receptor specificity, should be evaluated. Finally, interesting results have been recently reported using rituximab, a chimeric-murine monoclonal antibody targeting the CD-20 antigen. A randomized clinical trial using rituximab will be started shortly.