**Novel aspects of immunosuppressive and radiotherapy management of Graves’ ophthalmopathy**

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**ABSTRACT.** Treatment of severe Graves’ ophthalmopathy (GO) is a complex therapeutic challenge and, in spite of any efforts, about one third of patients are disappointed with the outcome of treatment. Glucocorticoids (GC), orbital radiotherapy (RT), or a combination of both, are most frequently used for their immunosuppressive effects. Novel immunosuppressive treatment procedures (or novel modalities of established treatments) are reviewed in the present article. GC has recently been used by the iv route and this treatment modality has been shown to be more effective and better tolerated than the oral route. Promising preliminary results have been reported by some authors with somatostatin analogs, octreotide and lanreotide. The number of patients treated so far is limited, most of the results have been obtained in nonrandomized or uncontrolled studies, and comparison with other validated methods of treatment is also needed. Because of the pathogenic role of cytokines, cytokine antagonists, currently evaluated in other autoimmune diseases, have been tested with positive results also in a small series of GO patients. The use of antioxidants might also be envisioned in the future, since in vitro studies have shown that oxygen free radicals might be involved in GO. Based on the shared antigen(s) theory, total thyroid ablation, by removing the bulk of shared antigens(s), might be beneficial for the course of GO. New data on recently performed placebo-controlled studies on orbital radiotherapy are discussed, together with studies on long-term safety of orbital radiotherapy.

**INTRODUCTION**

Graves’ ophthalmopathy (GO) is an inflammatory process affecting orbital tissues that is strictly associated with autoimmune thyroid diseases, especially Graves’ disease (1). In most instances ocular involvement is minimal, but 3-5% of cases have a severe and progressive disease, resulting in disfiguring and debilitating features that profoundly affect the quality of life (2). Treatment of severe GO is a complex therapeutic challenge and, in spite of any efforts, about one third of patients are disappointed with the outcome of treatment (1). This frequent failure of treatment can, at least in part, be explained by the fact that the pathogenesis of the disease is poorly known. Glucocorticoids (GC), orbital radiotherapy (RT), or a combination of both, are most frequently used for their immunosuppressive effects (1). Novel immunosuppressive treatment procedures (or novel modalities of established treatments) will be reviewed in the present article.

**IVGC**

GC are well established in the management of GO in view of their anti-inflammatory and immunosuppressive actions (3). GC have been used in GO patients since the early 1950s and have been administered either by local (retrobulbar or subconjunctival injection) or systemic (mainly oral up to 15 yr ago) routes (1). Oral GC provide favorable responses in slightly more than 60% of cases, whereas the local route is associated with beneficial effects only in 40% of cases (1). GC are particularly effective on soft tissue changes, recent-onset extraocular muscle involvement and optic neuropathy, whereas proptosis and long-standing eye muscle involvement are poorly responsive. Recurrence of active eye disease is a rather common problem with oral GC therapy, not only when the drug is withdrawn, but also when its dose is tapered down. Other drawbacks of oral GC include the need of high

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doses for a long period, and the frequent and potentially dangerous side effects and complications (1). What is relatively novel regarding GC therapy for GO is the iv route of administration. Iv pulse therapy has been widely used in the management of other autoimmune disorders to avoid complications and side effects due to long-term GC therapy. The rationale for the use of pulse therapy is the observation that GO, unlike other chronic autoimmune diseases, is often characterized by a single flare of the autoimmune process. In addition, there is evidence that in rapidly progressive autoimmune disorders, high-dose iv GC (IVGC) may achieve a more rapid and effective immune suppression. Thus, a short-term series of IVGC pulses may be effective in smoldering the progression and eventually improving the final outcome of the disease. IVGC have been employed in GO since 1987 and an overview of the published data indicates that favorable results can be obtained in about 80% of cases (1). However, in most studies oral GC were also given in the interpulse period or other immunosuppressive agents, or orbital RT were associated with IVGC making it difficult to ascertain the precise role of iv pulse therapy.

We have recently reported the results of a prospective, randomized study in which we compared the effects of oral GC and IVGC (both associated with orbital RT) in patients with severe GO (4). Patients were randomly treated with orbital RT combined with either oral prednisone (100 mg/daily, initial dose, with gradual tapering and withdrawal after 5 months) or iv methylprednisolone (15 mg/kg of body weight for 4 cycles and then 7.5 mg/kg for 4 cycles; each cycle consisted of two infusions on alternate days at 2-week intervals). No oral GC was given in the interpulse period. Each group included 41 patients who were followed-up for 12 months. Both treatment modalities were effective in the majority of patients. Comparison of the iv and oral routes showed an overall greater effectiveness of IVGC, as 83% of patients treated with IVGC had a favorable outcome of therapy compared with 63% in those treated orally (Fig. 1). Optic neuropathy and inflammatory changes were the ocular manifestations that responded to a greater extent to IVGC, even though there was a tendency toward a greater effectiveness also for diplopia. Self-assessment of ocular changes by the patients themselves was in good agreement with the clinical response, pointing to a more favorable outcome of the iv treatment. It cannot be excluded that the difference in efficacy between oral and iv GC might have been due to the higher cumulative dose of GC in the group treated by the iv route (9-12 g vs 6 g).

In spite of a more invasive administration procedure, patients treated with IVGC had a lower rate of side effects, possibly because a continuous and more prolonged administration of GC may have more pronounced untoward metabolic effects. Thus, side effects occurred in 23 (56.1%) IVGC and 35 (85.4%) oral GC patients (Table 1) (p<0.01). In particular, cushingoid features were observed in a very low proportion of IVGC patients, whereas they were present in the vast majority of patients treated with oral GC. One of the patients of the IVGC group developed an asymptomatic, marked increase in serum aminotransferase levels (with no serologic evidence of viral hepatitis) at the end of GC treatment, with spontaneous recovery over the following 2 months.

Weissel and Hauff (5) recently reported the case of a patient who died from acute liver failure, following IVGC pulse therapy for GO. In 1992, we too had observed a case of lethal liver failure following IVGC therapy for severe GO, which had been treated with a higher cumulative dose (18 g methylprednisolone) than that used in the study reported above (4) (un-