An update on medical management of Graves’ ophthalmopathy

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ABSTRACT. Graves’ ophthalmopathy (GO), the most frequent extrathyroidal manifestation of Graves’ disease, is a disorder of autoimmune origin, the pathogenic mechanisms of which are still incompletely understood. Although GO is severe in only 3-5% of affected individuals, quality of life is severely impaired even in patients with mild GO. Management of severe GO can be either medical or surgical (orbital decompression, eye muscle or lid surgery). Medical management relies on the use of high-dose systemic glucocorticoids or orbital radiotherapy, either alone or in combination. Studies carried out in the last 5 yr have shown that glucocorticoids are more effective through the iv route than through the oral route. However, particular attention should be paid to possible liver toxicity of iv glucocorticoids. Recent randomized clinical trials have, with one exception, confirmed that orbital radiotherapy is an effective and safe therapeutic procedure for GO. At variance with previous encouraging data, recent randomized clinical trials have shown that currently available SS analogs are not very effective in the management of GO. Antioxidants might have a role, at least in mild forms of GO. Particular attention should be paid to correction of risk factors (cigarette smoking, thyroid dysfunction, radioiodine therapy) involved in GO progression.

INTRODUCTION

Graves’ ophthalmopathy (GO), also known as thyroid-associated orbitopathy or thyroid-eye disease, is the main extrathyroidal expression of Graves’ disease, even though it may occasionally be observed in patients with chronic autoimmune (Hashimoto’s) thyroiditis or in patients without clinically evident thyroid abnormalities (euthyroid Graves’ disease) (1). In most instances, Graves’ patients apparently have no ocular involvement or show modest (often self-limiting) eye signs and symptoms requiring no treatment besides local measures and prompt control of thyroid dysfunction (1). It is worth mentioning, however, that even in its mild expressions GO has a profound negative impact on the quality of life of affected individuals (2). Pathogenesis of GO is complex and incompletely understood (3). It is commonly believed that eye disease may be triggered by autoimmune reactions directed against antigen(s) shared by thyroid and orbit: this would explain the close link between ocular and thyroidal disease. However, the search for autoantigen(s) involved has not yet provided definitive results (4). Once eye disease has been triggered, proliferation of orbital...
fibroblasts and adipocytes occurs. This causes an increased secretion of cytokines, involved in maintenance of ongoing reactions, and of glycosaminoglycans (3). The latter, hydrophilic in nature, attract water and are ultimately responsible for many manifestations of the disease (peri-orbital edema, extraocular muscle swelling and dysfunction, proptosis) (1). A minority of patients (approximately 3-5%) have severe GO which warrants aggressive treatments in order to arrest further progression to sight-threatening conditions and to achieve, if possible, regression of existing ocular signs and symptoms (1). Severe GO constitutes a major therapeutic challenge, because available treatments provide unsatisfactory results in about one third of cases (5). Management of severe and active GO can be either medical or surgical. Surgical approach is represented by orbital decompression consisting in the removal of one or more orbital walls: this expands the space available to the high-volume orbital content (swollen extraocular muscles, increased fibro-adipose tissue), making it possible to reduce proptosis and compression on the optic nerve (1). Surgical approach probably does not influence the autoimmune pathogenic mechanisms of GO, although it has been suggested that it might favor the efflux of inflammatory mediators from the orbit. Orbital decompression is considered the first-line treatment when optic neuropathy not responding promptly to high-dose glucocorticoids is present, but, with the improvement of surgical techniques, it is currently performed also to solve cosmetic problems (particularly related to residual proptosis) when the disease is burnt out (1). Other surgical procedures, such as rehabilitative eye muscle or lid surgery, are often required and should be performed in the inactive phase of the disease (1).

Medical management of GO classically relies on the use of glucocorticoids and orbital radiotherapy, but other treatments have recently been proposed (6). The aim of this article is to review recent information on the use of classical treatments, preliminary results reported using novel treatments, as well as future directions in the management of this disease.

**GLUCOCORTICOIDS**

Glucocorticoids have been used for several decades in the management of GO in view of their antiinflammatory actions, but also because they might exert immunosuppressive effects useful to control the course of the ophthalmopathy (7). The latter include interference with the function of T and B lymphocytes, decreased recruitment of neutrophils and macrophages to the inflamed area, and inhibition of cytokine release (1). Furthermore, they reduce glycosaminoglycan secretion from orbital fibroblasts (5). The effectiveness of glucocorticoids depends on the activity of GO: eye disease goes through an initial phase of high activity (inflammation) associated with the appearance and progression of ocular signs and symptoms; then it stabilizes and, finally, tends to improve and to become inactive (fibrotic), although spontaneous regression of ocular manifestations is often incomplete (1). These different phases last for a variable period of time, but it is commonly believed that GO is usually burnt out in a couple of years (1). Glucocorticoids are effective only when GO is active, i.e., of short duration, progressive and with relevant flogistic manifestations, while minor improvements observed when steroids are given during the inactive stage (long-lasting and/or stable disease) are likely to be ascribed to the natural history of the ophthalmopathy (1).

Glucocorticoids have been used through different routes of administration. Locally administered (subconjunctival or retrobulbar injections) glucocorticoids are in general less effective than systemically given steroids (8). However, in a recent randomized clinical trial peribulbar injections of 20 mg triamcinolone acetate (4 injections at weekly intervals) were associated with a substantial improvement in diplopia and reduction in extraocular muscle dysfunction (9). Although steroid injections around the eye bear the risk of side effects and complications (10), published series support the idea that this procedure is substantially safe (1, 9, 10). Thus, this route of administration might be reconsidered, but, in our view, only when absolute contraindications to the oral or iv administration of glucocorticoids exist. Oral glucocorticoids have been for a long time the mainstay in the management of GO (1). High doses of the drug are required, treatment lasts for several months, recurrence of eye disease is common following drug tapering or withdrawal, and side effects are frequent (8). Among the latter, iatrogenic Cushing’s syndrome and prolonged suppression of the hypothalamus-pituitary-adrenal gland axis are particularly relevant (1). These considerations led to the use of iv glucocorticoids, as done for other autoimmune disorders. After the first report by Kendall-Taylor et al. (11), several small and uncontrolled studies docu-