Best Practice & Research Clinical Endocrinology & Metabolism 26 (2012) 313–324

Contents lists available at SciVerse ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

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Treating the thyroid in the presence of Graves' ophthalmopathy

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Keywords:
Graves' ophthalmopathy
hyperthyroidism
hypothyroidism
goiter
antithyroid drugs
radioactive iodine
thyroid surgery
quality of life

The etiology of Graves' orbitopathy (GO) remains enigmatic. Optimal therapeutic choices for the hyperthyroidism associated with Graves' disease (GD) in the presence of GO remain controversial. Whether antithyroid drugs (ATDs), radioiodine (RAI), or thyroidectomy should be favored in such patients remains debated. Pre-therapy variables such as ethnicity, sex, age, thyroid function, level of TSH-receptor antibodies and smoking behavior influence response to therapy. Among the most important management goals are restoring euthyroidism and abstaining from smoking. On average, ATDs and thyroidectomy – independent of extent – do not influence the natural course of GO. RAI can cause *de novo* development or progression of GO, which is largely preventable with oral steroid prophylaxis. In patients with mild

Abbreviations: GD, Graves' disease; GO, Graves' ophthalmopathy or orbitopathy; ATDs, antithyroid drugs; RAI, radioactive iodine; RCT, randomized clinical trial; TRAb, TSH-receptor antibodies; TSAb, thyroid stimulating immunoglobulins; CAS, clinical avtivity score; LT4, Levothyroxine; RTX, rituximab; TTA, total thyroid ablation.

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1521-690X/$ – see front matter
doi:10.1016/j.beem.2011.09.005

GO, the thyroid treatment is largely independent of GO. Moderate to severe GO should be treated promptly. Deciding whether, in the latter, GD is better treated with ATDs, RAI, or surgery, is based more on expert opinion than on evidence. It is clear that in the individual patient a number of factors, not addressed in any trial, influence the final choice of therapy for GD, including concern of developing or negatively affecting pre-existing GO. Evidently, there is room for improving therapy of GO. Progress using novel drugs such as rituximab, which might potentially influence positively both GD and GO, are impatiently awaited.

Introduction

Thyroid disorders affect quality of life, whether related to thyroid dysfunction or due to the goiter causing pressure symptoms and disfiguration of the neck,[1] and whether viewed from the perspective of the physician or the patient.[2] This impairment of everyday life is most pronounced in the minority of patients who have thyroid eye disease (Graves' ophthalmopathy or orbitopathy, GO), and seems independent of type of therapy used to control the hyperthyroidism.[1–4] GO may occur in euthyroid and rarely in hypothyroid individuals but predominantly develops in patients with Graves' hyperthyroidism (GD).[5] Its first manifestations may precede or follow the diagnosis of GD by decades, but the two occur within a few months of each other in around 80% of cases.[5] The natural history, important for the evaluation of the effect of any intervention, is incompletely understood.[6] It is generally thought that rendering, and maintaining, the euthyroid state influences the course of the GO positively.[7] While prevention of GD would most likely eliminate GO, this may not be feasible in the immediate future. This pessimistic view is based on the fact that GD and GO occur in part because of genetic susceptibility.[8–10] These hereditary factors interact with a number of incompletely characterized epigenetic factors[11,12] and environmental triggers, of which cigarette smoking and level of iodine intake are best characterized.[13–15] Most of these etiologic factors are not readily modifiable. Since non-smokers can develop GD and GO, although more rarely, rather it seems imperative to focus attention on potential differences in outcome of GO associated with the therapies for GD.[16] We need to understand with more clarity whether any of these therapies in particular carries more risk of developing *de novo* GO, and whether each alters the course of established GO.

Ideally, a therapy for GD would also reduce, or eliminate, the risk of GO. Availability of a cost-effective, well tolerated, therapy that reduced the rate of disease recurrence would certainly constitute a major advance. Although a therapy provoking remission of both GD and GO does not exist, it is possible that rituximab (RTX), a monoclonal antibody targeting CD20 + B cells (reviewed in ref. 17), might be found to offer these advantages. Awaiting further advances in the prevention and therapy we must understand the advantages and disadvantages of the currently available therapeutic options for GD. These include, antithyroid drugs (ATDs), radioactive iodine (RAI), and thyroid surgery.[18,19]

Pretreatment risk factors for development of Graves' ophthalmopathy

Before examining the importance of therapy choices for GD in the patient at risk of developing or worsening GO, certain pre-treatment variables that might influence this likelihood need to be considered.[5,20]

Gender and ethnic origin

The female to male ratio of GO is approximately 2:1. This is a considerably smaller gender bias than the 5–10:1 ratio seen for GD.[5,18] It follows that males compared to females with GD appear to have a higher risk of developing GO. Furthermore, males develop GO at an older age and in a more severe