Saudi Journal of Ophthalmology (2017) xxx, xxx–xxx

Review article

Review of the treatment of Graves' ophthalmopathy. The role of the new radiation techniques

Iñigo San Miguel [a]; Meritxell Arenas [b,*]; Ruth Carmona [a]; Joaquin Rutllan [c]; Francisco Medina-Rivero [c]; Pedro Lara [a]

Abstract

Graves ophthalmopathy (GO) is an autoimmune disorder and the most frequent extrathyroidal manifestation of Graves' disease. GO is an inflammatory process leading to an increased volume of the extraocular muscles and orbital connective and adipose tissues associated with multiple histopathological changes. Despite recent progress in the understanding of its pathogenesis, GO often remains a major diagnostic and therapeutic challenge. It has become increasingly important to classify patients into categories based on disease severity and activity. Low doses of radiotherapy (RT) have demonstrated a benefit in the treatment of moderate-to-severe GO with very few side effects. New RT techniques deliver a more conformal dose distribution to the target and decrease the dose to normal healthy tissue minimizing the risk of side effects. In this review we briefly analyzed the pathogenesis of GO and discussed the most relevant therapeutic approaches, with particular emphasis in the new RT technics. Appropriately designed and powered clinical studies are necessary to determine the most effective treatment with the lowest risk of side effects.

Keywords: Graves' opthalmopathy, Radiotherapy, Toxicity

https://doi.org/10.1016/j.sjopt.2017.09.003

Introduction

Graves' disease (GD) is an autoimmune disorder involving the thyroid gland. GO is an autoimmune condition of the orbit that occurs in 25–50% of patients with GD. GO is the most prevalent extra-thyroidal manifestation and may develop regardless of the presence of hyperthyroidism. In 3–5% of patients, GO evolves into a severe form, significantly impairing the quality of life of the patients [1].

GO is associated with multiple histopathological changes which induce inflammatory process leading to an increased volume of the extraocular muscles and orbital connective and adipose tissues [2]. Pathogenesis is related to the activation of T lymphocytes (mostly CD4+) that invade the orbit and release cytokines, usually as a response to the presence of circulating autoantibodies that bind to and stimulate the thyroid hormone receptor (TSHR). These cytokines act in a paracrine manner and induce the activation of fibroblasts due to an increase in the production of the hydrophilic glycosaminoglycans (GAGs) in the orbital tissue. This excessive secretion of GAGs together with the lymphocyte infiltration

Received 1 August 2016; accepted 12 September 2017; available online xxxx.

[a] Radiation Oncology Department, Hospital Dr. Negrin, Las Palmas de Gran Canaria 35070, Spain
[b] Radiation Oncology Department, Hospital Universitari Sant Joan de Reus, Reus 43201, Tarragona, Spain
[c] Ophthalmology Department, Hospital Dr. Negrin, Las Palmas de Gran Canaria 35070, Spain

* Corresponding author at: Radiation Oncology Dept, Hospital Universitari Sant Joan de Reus, Tarragona, Spain, C/Sant Joan, s/n, 43201 Reus, Tarragona, Spain.
e-mail addresses: isanmiguela@gmail.com (I. San Miguel), marenas@grupsagessa.com, meritxell.arenas@gmail.com (M. Arenas), rcarmona@ulpgc.es (R. Carmona), jrutllan@ulpgc.es (J. Rutllan), fmedina@ulpgc.es (F. Medina-Rivero), pedrocarlos.lara@ulpgc.es (P. Lara).

Peer review under responsibility of Saudi Ophthalmological Society, King Saud University

Production and hosting by Elsevier

Access this article online: www.saudiophthaljournal.com www.sciencedirect.com

Please cite this article in press as: San Miguel I., et al. Review of the treatment of Graves' ophthalmopathy. The role of the new radiation techniques. *Saudi J Ophthalmol* (2017), https://doi.org/10.1016/j.sjopt.2017.09.003

results in an osmotic pressure increase, significant tissue oedema, and the clinical ophthalmopathy [3,4].

Classification is based on severity and activity and determines the therapeutic approach [5], but activity and severity are not synonymous.

Severity is defined by the degree of functional deficit at any stage of the disease. The European Group of Graves' Orbitopathy (EUGOGO) suggests classifying severity into three categories, based on the subjective symptoms and objective signs [6]:

1. Mild: minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. Patients have one or more of the following signs/symptoms: minor lid retraction (<2 mm), mild soft tissue involvement, exophthalmos > 3 mm above normal for race and gender, transient or no diplopia, corneal exposure responsive to lubricants.
2. Moderate-to-severe: Not sight-threatening but sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Patients have one or more of the following signs: lid retraction $\geq$ 2 mm, moderate or severe soft tissue involvement, exophthalmos $\geq$ 3 mm above normal for race and gender, inconstant or constant diplopia.
3. Sight-threatening: patients with dysthyroid optic neuropathy and/or corneal breakdown. This category warrants immediate intervention.

Activity refers to the presence of inflammatory signs and is measured using the Clinical Activity Score (CAS) based on the classical features of inflammation. To be classified as active, at least 6 of 10 items (Table 1) should be present [6].

Treatment

Treatment is based on the severity and activity of GO. The approach is suggested by the EUGOGO consensus statement [5].

Mild forms of GO may improve spontaneously and simple follow up and symptom management is usually sufficient. Lubricants and ointments are recommended to help symptoms. Glucocorticoids and radiotherapy (RT) are usually not recommended. In a multicenter, randomized, double blind, placebo-controlled trial performed by EUGOGO, it was reported that a 6-month course of selenium (sodium selenite 100 mg twice daily) is associated with a significant improvement in quality of life and GO symptoms, and a lower rate of progression to more severe forms without adverse effects [4].

The therapeutic approach in patients with moderate-to-severe GO depends on whether the disease is ''active'' or ''inactive''. In patients with active disease an immunosuppressive or anti-inflammatory treatment, either systemic therapy and/or RT should be offered. In contrast, in patients with inactive GO rehabilitative surgery should be considered.

Finally, in patients with sight threatening GO, first line treatment is based on immunosuppressive or anti-inflammatory therapy but if there is a poor response or the disease is inactive, immediate surgical intervention is warranted.

Table 1. Items of the clinical activity score.

Clinical activity score items
Painful, oppressive feeling on or behind the globe, during the last 4 weeks
Pain on attempted up, side or down gaze, during the last 4 weeks
Redness of the eyelid
Diffuse redness of the conjunctiva, covering at least one quadrant
Swelling of the eyelid
Chemosis
Swollen caruncle
Increase of proptosis of $\geq$2 mm during a period of 1–3 months
Decrease in eye movements in any direction $\geq$5o during a period of 1–3 months
Decrease of visual acuity of $\geq$1 line on the Snellen chart during a period of 1–3 months

Surgery

There are two surgical options, orbital decompression and corrective surgery for eyelid retraction and restrictive myopathy. Actual indications for surgical treatment are optic neuropathy, persistent inflammation or congestion refractory to steroid treatment, desire to reduce excess proptosis and cosmetic discomfort. Surgeons must decide whether or not to remove orbital bony walls and fat, as well as the amount and location to be removed [4].

Systemic therapy

First line treatment of active moderate to severe GO is systemic glucocorticoids, based on their anti-inflammatory and immunosuppressive effects. Intravenous glucocorticoids (ivGC) have a higher response rate and are better tolerated than oral. Glucocorticoids, however, are not devoid of adverse events (Cushingoid features, weight gain, hypertension, diabetes, etc) and in patients with planned glucocorticoids treatment longer than three months, antiosteoporotic therapy should be considered.

Other medical options that have a proven benefit include Cyclosporine, the most widely immunosuppressant drug used, that combined with oral prednisone was more effective than oral GC alone in a clinical trial conducted by Kahaly [4]. Also other drugs such as Etanercept, a TNF-a inhibitor, used in the treatment of autoinmune diseases, based on the capacity to regulate the immune-inflammatory response of many organ systems, has shown some activity in a small-uncontrolled study [1]. Rituximab, a chimeric monoclonal antibody against the CD 20 antigen, is under evaluation but in some studies shows a similar benefit to ivGC[4]. Other agents such as Somatostatin, a peptide hormone that regulates the endocrine system and inhibits numerous secondary hormones, had no proven benefit in randomized clinical trials [1].

Radiotherapy

Rationale: anti-Inflammatory and Inmunosupresor effect of RT

The rationale for using RT in GO is based on its modulating role of inflammatory response in irradiated tissues. Therefore this could be considering an alternative to systemic anti-inflammatory therapies [7]. Although RT induces the production of pro-inflammatory cytokines and leads to an inflamma-

Please cite this article in press as: San Miguel I., et al. Review of the treatment of Graves' ophthalmopathy. The role of the new radiation techniques. *Saudi J Ophthalmol* (2017), https://doi.org/10.1016/j.sjopt.2017.09.003