

Case Study

Thyroid Orbitopathy, an Overall View of Immunomodulatory Treatment with Special Attention to the Role of the Radiotherapy

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Abstract

Thyroid orbitopathy is the most prevalent non-thyroid symptom in Graves' syndrome. It has a high incidence, especially affecting young women. There is a clear causal relationship between smoking status and the onset, evolution and response to the different treatments. It is an autoimmune process that usually evolves in an independent way from the thyroid status. When it is severe and progressive, it can represent a major therapeutic challenge. Clinical evaluation presents great difficulties in the absence of a truly objective rating scale that is representative of the disease activity. The new molecular and/or inflammatory markers can aid diagnosis and categorization. In this article we review new findings on pathophysiology and describe the different techniques used for treatment of this disease over time. Finally we discuss the immunomodulatory effect of the radiotherapy and the role of corticosteroids.

INTRODUCTION

The Graves or Basedow's syndrome is characterized by the classical triad of goitre, orbitopathy and dermopathy. These symptoms may appear together through the evolution of the disease or develop alone and independently.

Between 25 to 50% of patients with Graves' disease may suffer orbitopathy. There is a wide spectrum of presentation, from low degree to severe symptoms. Only 5% of the patients affected by orbitopathy will receive any kind of more intensive treatments surgery, radiotherapy or corticosteroids. The incidence of any orbitopathy due to Graves'disease is around 16 women and 3 men per 100,000 inhabitants. The ratio of female: male is 5:1 [1,2]. The onset is usually during the third or fourth decade of life. The clinical onset can be more aggressive in the elderly and male populations whilst it can be less severe in persons of Asian origin [2,3].

There is a clear relationship with tobacco and disease origin, evolution, response to therapies and recurrence after treatments [4-6]. This observation has been well observed since the first description of this entity and is more important in women. The link could be explained due to tissue hypoxia, the modulation of the cytokines and the over-expression of HLA-DR from the

fibroblasts. Discontinuation of tobacco is one of the mainstays of treatment [7].

Genetics factors are evident in determining disease predisposition, an increase in the frequency of HLA B8, DRw3, Bw36, Bw46 has been noted. Furthermore the polymorphism of a single nucleotide (PSN), rs179247, has been observed [8].

The thyroid orbitopathy (TO) may involve one or both orbits but more commonly is of bilateral affection. However the severity of disease on one side can be independent of the other side. The evolution is usually steadily progressive with some soft correlation with the thyroid status. 80-90% of the patients may present with hyperthyroidism at the onset [2]. 50-64 % of patients may see an improvement or stability in 22-33 % [9,10]. Compared with hyperthyroidism, hypothyroidism is much less in TO. Always other intra orbitary/cranial pathologies need to be excluded. The differential diagnoses include: cavernous sinus thrombosis, transfenoidal wing meningioma, retrobulbar tumours/ intracranial tumours (including orbitary lymphomas), essential orbitary inflammatory disease or pseudotumour ocular, lymphoid hyperplasia, uraemia, malignant hypertension, over use of alcohol, COPD, high mediastinum obstruction, carotid-cavernous fistula and Cushing syndrome.

In case of doubt, detection of thyroid stimulating immunoglobulins (TSI), TSH-binding inhibitor immunoglobulin (TBI), antiperoxidase antibodies, thyrotropin-releasing hormone (TRH) abnormal stimulation or thyroid suppression tests suggest that the origin could be a TO. It is important to note some cases of TO have a normal thyroid status or is even hypothyroid [2].

When TO is severe and progressive, this is a truly challenge for treatment. The majority of these patients develop a benign disease independent from the thyroid status. Even in moderate to severe cases, the disease may decrease over time resulting in only a low degree of exophthalmos and/or ophthalmoplegia [2,9].

Consideration of treatment should be taking into account due to the largest peak of activity is recorded between 13 to 24 months after onset. Subsequently, most patients (up to 80-90%) will have improvement or stable disease [11]. On the other hand, in up to 5% of cases there is late recurrence [2].

There is no evidence that total thyroid ablation with surgery or Iodine-131 is more beneficial for the TO than anti-thyroid drugs. Nevertheless a consensus exists about the necessity to control thyroid function [7,12].

Pathophysiology

Recent findings are aiding better understanding of the pathophysiology of this auto-immune disease.

Initially there lacks a control of the immune system that allows auto-immunity against the thyrotropin receptor or Thyroid Stimulating Hormone Receptor (TSH-R). In keeping with this, a SNP (Single Nucleotide Polymorphism) has been discovered, rs179247, in the intron 1 of the genes of TSH-R [8]. At the thymus, one develops tolerance through the elimination of reactive lymphocytes against self-antigens (95% of all lymphocytes T), including the TSH-R. The presence of the rs179247 SNP induces low expression of the TSH-R which inhibits the antigenic recognition and the subsequent destruction of the reactive lymphocytes against TSH-R [8]. The immune response will continue with a complex network of intercellular connections that culminate with the development of the Graves' disease symptoms including TO. Further publications deal with this topic and so has not been included at this stage [13-15].

Signs and symptoms

Which are due to the inflammatory/infiltrative process with congestive phenomena:

Signs:

Palpebral retraction

Slowed down palpebral movements

Superior vision limitation plus insufficiency of the convergence

Palpebral and conjunctival hyperemia

Palpebral oedema

Caruncle/conjunctival chemosis

Proptosis/exophthalmus

Ptosis

Corneal opacity

Papilledema

Lagophthalmus

Corneal ulcers

Symptoms:

Visual deficits

Color perception impairment

Diplopia (initially intermittent)

Blurry vision

Hypersensitivity to the light

Pain with ocular movements

Ocular or retro-ocular pain resting

Ophthalmic assessment

There are a multitude of assessment scores which take into account for the different aspects of pathology. However, the degree of activity is often not well reflected in these scores. The lack of an objective assessment score may influence the contradictory results published so far. Moreover this entity may suffer clinical variability, with a trend to improve; this along with several confounding factors makes an objective assessment more difficult. Confounding factors such as smoking, age, sex, diabetes mellitus, thyroid status, previous treatments or long term disease [15].

Adequate and agreed assessment scores are needed by a correct interpretation of the effectiveness of therapies. Currently there are no objectives or reproducible methods for that. New biological or inflammatory markers or even the use of the MRI may aid in the diagnosis and scoring of this difficult pathology [16-18].

The scales used include:

NOSPECS: Most commonly used in the US, divided into classes and grades. It is subjective, difficult to complete, and requires training prior to use [19].

CAS (Clinical Activity Score): Most commonly used in Europe. Evaluates pain and inflammatory findings involving soft tissues. This scale has demonstrated its effectiveness in assessing the response to treatment (steroids or Radiotherapy) [20]. According to Gorman, some of their items are hard to define because the cause could be congestive or non-inflammatory (periorbital or caruncle and chemosis), with both being an intimately related process [1,11]. Despite being more objective this continues to have uncertainty in patients with grade 2-3 regarding treatment decisions.

Other score scales: VISA, EUGOGO, OI, STI, EMR, GAG, MRI, Octreoscan [21,22].

Quality of life assessment scores [23]:

Generals: MOS SF-24 y SF-36.

Specific: GO-QoL.

Therapeutic approaches

- Symptomatic measures are advised at the initial stage of the disease such as: ocular lubrication, luminic protection, cold pads, rising of the head of the bed, palpebral occlusion at night, botulinum toxin in the case of superior palpebral retraction and finally prisms in case of diplopia [15,24].

- Smoking cessation needs to be a priority in the management of this pathology [4-7].

- A consensus has been agreed about the importance of controlling the hyperthyroidism, using drugs or thyroid ablation [15]. However it is to be noted that antithyroid drugs or thyroidectomy do not affect the natural evolution of the disease and treatment with iodo-131 may worsen the status of disease [25]. A low dose of corticosteroids after ablation with iodo-131 is advised, especially in an active smoker, in an attempt to prevent the progression of TO [7,25,26].

- For a long time, corticosteroid therapy has been used to treat the TO, including different regimes and routes of administration. They have been used in the moderate or severe degree of disease alone or in conjunction with radiotherapy and surgery. The aim is to decrease the inflammatory-infiltrative component, with outcomes rates in controlling symptoms of about 65-85% [27,28]. Currently the most commonly used route is intravenous bolus with methylprednisolone and prednisone [27-29]. Starting with a high dose and steadily tapering until the minimum effective dose is reached.

The most frequent regime used in the USA and Europe is weekly methylprednisolone 500 mg intravenous during 6 weeks, followed by another weekly 250 mg intravenous dose for extra 6 weeks. If after that, the patient does not respond then alternative therapies should be considered. Trials of higher doses of steroid only showed a slight increase in short term response but with an increase in the toxicity profile [30]. Patient selection is important before starting corticosteroids in terms of background and adequate liver function tests [27]. In the absence of compressive neuropathy at the optical nerve it is advised not to surpass the cumulative dose of 8 g [27,31].

It has been observed that systemic administration of steroids have greater efficacy than retrobulbar injection [32]. Evidence from a randomized clinical trials (RCTs) and two different meta-analysis showed better outcomes and less iatrogenic disease when administered by iv bolus versus high dose oral corticosteroid with maintenance treatment [27,28,33-35]. After withdrawal of corticosteroids, reactivation of TO may occur in a high number of patients [30,36]. In a study from the European Group of Graves' Orbitopathy (EUGOGO), 3 different regimes of iv methylprednisolone were trialed, the percentage of relapse at 24 weeks was 33%, 21% and 40%, respectively with doses of 7.47, 4.98 and 2.25g [30] (Figure 1). Finally, it is important to remember the side effects of long-term corticosteroid therapy: hyperglycaemia, hypertension, immunological compromise, proximal myopathy, capillary fragility, redistribution of body adipose tissue, rash, psychosis, osteoporosis, liver function impairment, etc, including fatal events [27,31].

- Surgical decompression should be reserved for rapidly



Figure 1 Example of response to RT after failure of 2 cycles of intravenous corticosteroids at high dose. (a) August 2006 (before corticosteroid and RT), (b) August 2007 (6 months after RT).

progressive compressive neuropathy not responding to corticosteroids or radiotherapy [37]. Furthermore surgery is advised in patients without activity, no thyroid function alterations and with functional sequela. In that case, surgery needs to be performed after a reasonable gap of 6-12 months since last treatment [24,37]. The procedure comprises of the extraction, through different anatomical approaches, of part of the orbital osseous component to relieve the intraorbital pressure. The most commonly used approaches are the transpalpebral and transconjunctival [37,38]. Removing only the orbital fat has been less effective and with a higher rate of relapse [39]. In the inactive phase of the disease, surgery has achieved a significant reduction of exophthalmus/proptosis. Surgery is efficacious and safe when used following progressions in spite of corticosteroids and/or radiotherapy, or to solve the strabismus due to established muscle fibrosis [37,40]. However, it should be noted that it may worsen previous strabismus.

- Other therapies have been used such as azathioprine and metronidazole but not with satisfactory results. Topical guanethidine sulphate 5-10% has been used with low efficacy and undesirable side effects in the form of keratitis at the site of instillation [41]. Recent RCTs using placebo versus octreotide have been performed due to its effect of suppression of the proliferation and lymphocytic activation but not with positive results [21,42].

- New drugs are being studied in relation to the better knowledge of the pathophysiology in the recent years [15]. They act against several different targets. Especially good results have been obtained with tocilizumab and rituximab [43,44].

- A recent double blind randomized study using supplements of selenium (100g BD) versus pentoxifylline (600mg BD) versus placebo (BD) during 6 months in low degree TO, has showed an increase in the quality of life, less ocular involvement and with minor rates of progression in the selenium group [45]. The preventive effect persisted during the 6-12 months of follow-up. No adverse effects were described with the use of selenium but gastrointestinal symptoms were noted in the pentoxifylline group. That said, the prolonged use of selenium leading to type 2 diabetes mellitus has been described (200g a day) along with cardiovascular disease (CVD), glaucoma or mortality for any reason. Furthermore it may interact with anticoagulants [46,47]. Therefore selenium should not be used beyond 6 months. Interestingly, an Australian study showed a lower serum concentration of selenium in patients with TO [48].

Radiotherapy

Radiotherapy (RT) has been in use since the 1940s. The first published paper is from 191349, but it was not until Donaldson in 1973, with the generalization of the megavoltage (LINACs and cobalt bombs), when the current approach was implemented [49,50]. This regime supplies a total dose of 20Gy in 2 Gy fractions (five days a week) during 2 weeks (normo-fractionation). The initial prescription of radiotherapy was empirical as many actions in medicine [32,36,51-53]. It was not until 1993 when the first randomized trial appears [54]. Nowadays we have meta-analysis confirming RT's efficacy [55-58]. Levels of evidence and grades of recommendation used to describe their effectiveness are based on the criteria of the U.S. Preventive Services Task Force (USPSTF) updated in 2001 [59].

Radiotherapy indications:

1. RT has no place in the purely aesthetic treatment of TO [11].
2. RT is not indicated in low activity disease.
3. RT is advised for the treatment of the moderate-severe degree of activity in TO [32,34,55-58].
4. To treat compressive neuropathy of the optic nerve, it is recommended to start with high dose corticosteroids followed by RT due to complexity/high risk of surgery [60]. If in spite of this, if neural compression is not resolved then surgery is indicated [15].
5. RT is also advised after surgery in the case of partial resolution of symptoms [16].

-Radiotherapy contraindications:

1. Previous retinopathy [61].
2. Poorly controlled diabetes mellitus.

Efficacy

1. In retrospective studies and meta-analysis RT has been shown effective in the control of the inflammatory signs of the soft tissues (erythema, chemosis, periorbital oedema), with responses around 80%. Furthermore it is effective in recovering the vision from the compressive neuropathy in the active phase of the disease (41-71%). RT aids recovery of the mobility of the involved extraocular muscles (61%). Unfortunately, remission of proptosis is rare (23-51%) with a few millimetres of response and with minimal or doubtful aesthetic repercussion [6,36,52,53,55,57,58,62-65].

Evidence Level I, Grade of Recommendation B.

2. In an important retrospective study, it was observed that joint use of corticosteroids and RT obtained a significant decrease in the risk of developing optic neuropathy compared to the use of corticosteroids alone [62]. Recent meta-analysis supported the joint efficacy [55,57].

Evidence Level I, Grade of Recommendation B.

3. There have been at least 5 systemic revisions regarding the efficacy of RT in the treatment of TO, including the Cochrane Collaboration [55-58]. Many of the randomized trials suffer

from methodological problems that may confer some bias to the final conclusions. The evolution of the disease, patient's selection criteria, measurement of the different objectives focused on activity rather than on quality of life measurements. This emphasises the difficulty in classification of the disease and in obtaining clear recommendations. Review of all the data has resulted in the following conclusions in relation to the efficacy of RT:

- Increased efficacy with RT 20 Gy plus oral corticosteroid compared with oral corticosteroid alone.
- More effective with RT 20 Gy compared with sham RT.
- More effective with RT 20 Gy plus intravenous corticosteroid compared with RT plus oral corticosteroid.
- No observed differences between RT 20 Gy compared with corticosteroid alone.
- There is no evidence that RT plus intravenous corticosteroids is more effective than single intravenous corticosteroids.
- Finally, there is no difference in terms of quality of life, intraocular pressure or RT costs compared to corticosteroid.

Evidence Level I, Grade of Recommendation B.

4. Taking into account the published series, after completion of the concurrent treatment of corticosteroid plus RT, it is possible to discontinue the corticosteroid in a high percentage of patients (71-91%) [51-53].

Evidence Level II-III, Grade of Recommendation B.

5. Around 20% of the patients may require salvage decompressive surgery after RT, plus/minus corticosteroid. Most of them due to the persistence of smoking [6,37].

Evidence Level III, Grade of Recommendation B.

6. The more established and developed the inflammatory-fibrotic orbital process is, then the lower the efficacy of RT [11,57,58].

Evidence Level I, Grade of Recommendation B.

7. The improvement with the RT may occur later than 6 months after completion of treatment [50].

Evidence Level II-III, Grade of Recommendation B

8. Finally, re-irradiation after 2 months at least, could be helpful with high rates of response in spite of the initial resistance or after relapse of the symptoms, with no increase in toxicity [53].

Evidence Level II-III, Grade of Recommendation B

Regimens of radiotherapy

There have been no differences noted between 20 or 30Gy with 2 Gy per fraction in retrospective studies [51]. There are only 2 RCTs comparing total dose (TD). One compares 2.4 versus 16 Gy in 0.3 and 2 Gy per fraction respectively, with no significant differences between schedules [66]. The second study compares 3 arms: 20 Gy (1 Gy/week), 10 Gy (1 Gy/day) and 20 Gy (2 Gy/day), last 2 arms in 2 weeks. The first arm obtains a statistically significant improvement in relation to the other two in keeping

with ocular symptoms, palpebral fissure, intraocular pressure, proptosis, visual acuity, ocular motility, muscle thickening and in NOSPECS scale parameters. Moreover, a lesser degree of toxicity and better degrees of satisfaction were obtained with the first arm [60]. However, in spite of being a good balanced study, it suffers bias due to the small cohort of patients. In keeping with a current meta-analysis no difference has been observed between 20 Gy and other regimens of RT [55].

Side effects

No severe side effects have been described in relation with RT, except visual alterations or blindness in the context of previous retinopathy. Thus RT is contraindicated in cases of previous retinopathy or poorly controlled Diabetes Mellitus [61]. The most frequent side effects are cataracts which could also be as a result of high dose corticosteroids [6,63]. Some patients may suffer alopecia of the lateral aspects of the eyebrows due to the RT fields, usually with complete recovery. In a minimal percentage, patients may suffer from dry eyes [6,53,63]. In long-term follow-up no important secondary tumours have been reported in keeping with the RT [1,67]. There has been description of rare cases of pigmented basal carcinoma [68]. The theoretical risk of developing a secondary cancer after the irradiation of the orbit with 20 Gy is 0.3-1.2% [69]. For this reason some authors will not prescribe RT to young people (<35 years) [24]. A minimum of a 3 year follow up period is advised after radiation, although there are some controlled series with more extensive follow-up but with no significant complications observed [6,36,53,61,63,67]. It is common to undergo corrective surgery after RT to fix the diplopia or the effects on the muscle and lids due to either the disease or treatment [24,37,53]. This usually occurs after a short period following RT. For all these reasons, it is highly advised that a multidisciplinary approach should be adapted for this complex entity.

Radiotherapy technique

Usually radiation is supplied with high energy level photons (4-6 MV). A thermoplastic shell is used to keep the patient immobile during the treatment. We use points on the shell as a reference point to allow reproducibility of the setup of the patient in each session (Figure 2).

Nowadays, there are more accurate and conformed techniques of localization and administration of the radiation. There are different systems to deliver the radiation including stereotactic fractionated radiotherapy, intensity modulated radiotherapy, guided image radiotherapy, volumetric arch therapy techniques and so on. All of them are different systems of localization of the target, administration of the radiation or more sophisticated in terms of calculation of the dose. All allow improved conformation of the target and preserve the organs at risk (in this case the lids, lens, retina and hypophysis) (Figure 3).

SUMMARY

In conclusion, RT with or without corticosteroid, significantly improves TO of moderate or severe degree. RT improves diplopia, visual acuity, optic neuropathy, palpebral thickening and ocular motility. Its efficacy is increased with the concurrent use of corticosteroid. However this has not shown any advantage



Figure 2 Thermoplastic shell with metallic marks over the laser reference points (laterals and nasion).

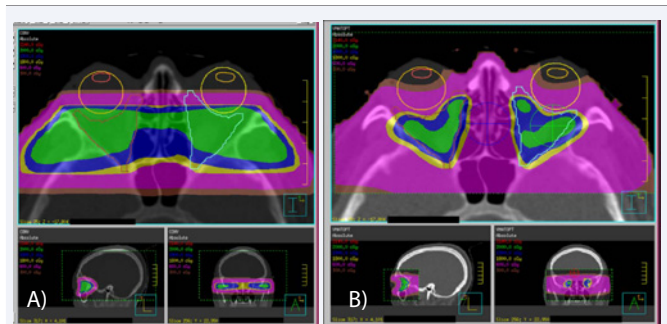


Figure 3 Examples of radiotherapy planning and dose distribution using external beam conventional 3D radiotherapy (using two lateral and opposed fields) (a) versus Volumetric modulate arch therapy (VMAT) (b) Observe the increase in conformation of the retrobulbar area of irradiation with VMAT.

in comparison to alternative therapies in keeping with cost, decrease of the intraocular pressure or quality of life [55-58].

Evidence Level I, Grade of Recommendation B.

DISCUSSION

Taking into account all the contradictory results from several publications in relation to the different therapies used in TO, it is important to consider whether the studied cohorts are representative of patients with moderate or severe activity due to their TO. This is because only in this setting immune-suppressant measures are effective. It should be noted that both RT and corticosteroid therapy as new therapeutic approaches base their performance on the immunosuppressant effect. Joint use of corticosteroid plus radiotherapy has an important advantage as corticosteroids control the inflammation due to the TO and also the radio-induce oedema [11,65]. If low dose radiation (≤ 1 Gy / session) is used repeatedly, concurrent corticosteroid therapy could be avoided. It has been described that low doses are enough to control and relieve the inflammatory symptoms due to the inhibition of the nitric oxide pathway present in that process. This pathway is activated by the normo-fractionated radiotherapy that uses 2 Gy per fraction and is the reason for radio-induce oedema [60,70]. In many institutions they have used regimes with lower doses per session and an extension of the total treatment time, with greater efficacy in clinical control and lower toxicity compared to normo-fractionation [66,71,72]. In summary, patients with TO of moderate or severe activity for a short time are likely to benefit most from the use of RT

[55,60,64]. RT could be used as first line treatment with or without corticosteroid, or after failure, rejection or intolerance to the intravenous corticosteroid. We have enough evidence to suggest against other alternatives, with similar or lower costs and equal quality of life measurements. The side effects derived from the radiation are local and of low-intermediate degree, with non-fatal events. Secondary tumours are exceptional, and the low number of reports of retinopathy or optic neuropathy is in keeping with previously poorly controlled Diabetes, or with compressive phenomena due to the intra-orbital pressure increase. Even so, it is good practice to provide prolonged and close monitoring.

There is no reliable method for measuring disease activity and all attempts to quantify seem to bring more confusion, especially when taking into account the inter-observer differences. The use of new molecular or inflammatory markers, and/or MRI could represent progress in this issue. The other question is the appropriate time to initiate treatment, because in patients with a long history, without inflammatory activity and fibrosis then unsatisfactory results may be achieved. In front of this complex entity, a multidisciplinary approach to manage the patient is highly recommended to achieve the best care. Finally expectations of the patient and the doctors may be different. For this reason quality of life assessment should be a tool in the management of these patients. With this information, it is possible to have objective information about efficacy of the treatment over symptoms and not only over signs.

CONCLUSIONS

The conclusions that we may obtain about the management of this entity after the current review are:

- New diagnostic tests are needed that truly reflect disease activity.
- At the early stage of disease only symptomatic measures and selenium supplements are advised.
- Smoking cessation is paramount in the control of the orbitopathy.
- Control of the thyroid function is considered necessary by most of the specialists involved in the management of this disease.
- Corticosteroid and radiotherapy, concurrent or not, are advised in low-moderate degree TO.
- Decompressive surgery is advised in steroid (+/- radiotherapy) resistant optic neuropathy or to reduce local symptoms.
- Furthermore surgery should be used to repair strabismus and severe palpebral affectation. In terms of aesthetics then cosmetic surgery may be adopted.
- The multidisciplinary approach to manage this complex entity is highly advised.
- The quality of life assessment should be included as a common tool in the management of TO.

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