DOI: 10.5603/OJ.2022.0015

Treatment of moderate to severe and active thyroid orbitopathy during SARS-CoV-2 pandemic

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ABSTRACT

Thyroid orbitopathy (TO) is the most common non-thyroid manifestation of Graves' and Basedow disease. Assessment of the inflammatory activity of TO can be performed using the clinical activity score (CAS) and using imaging methods — mainly magnetic resonance imaging (MRI). The severity of TO is assessed using a seven-grade NOSPECS classification and a three-grade scale proposed by the European Group on Graves' Orbitopathy (EUGOGO). In moderate to severe and active TO, the recommended standard as first-line treatment is the combined use of methylprednisolone intravenously (*i.v.*) with concurrent oral (*p.o.*) administration of mycophenolate sodium. Second-line treatment options are orbital radiotherapy with or without oral or *i.v.* systemic glucocorticosteroid therapy, cyclosporine, or azathioprine in combination with *p.o.* glucocorticosteroid, methotrexate monotherapy, and a group of biologic drugs (riuximad, tocilizumab, teprotumumab). All recommended therapies for moderate to severe and active TO involve immunosuppressive and immunomodulatory drugs, which are a risk for the unfavorable course of COVID-19. There are no available recommendations for treating TO in Graves' and Basedow disease patients during the SARS-CoV-2 pandemic. Moderate to severe and active TO patients present a serious dilemma during SARS-CoV-2 pandemic. It seems reasonable that in patients with moderate to severe TO, who are not at risk of sight deterioration, *i.v.* glucocorticosteroids should be avoided, and an observational strategy should be used, whereas in patients with more severe TO and at risk of sight worsening, i.v. glucocorticosteroids are the therapeutic choice regardless of SARS-CoV-2 infection or clinical signs of COVID-19

KEY WORDS: Graves' and Basedow's disease; thyroid orbitopathy; glucocorticosteroid treatment; SARS-CoV-2 infection; ocular manifestations of SARS-CoV-2

Ophthalmol J 2022; Vol. 7, 94–102

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INTRODUCTION

In December 2019, a new type of coronavirus family that causes severe acute respiratory syndrome (SARS) was identified. The World Health Organization (WHO) has named the disease it causes coronavirus disease 2019 (COVID-19) and the pathogen as severe respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. On January 30, 2020, WHO proclaimed a global health emergency and then on February 11, 2020, WHO officially introduced the name coronavirus disease 2019 (COVID-19) [2].

SARS-CoV-2 is an enveloped RNA virus and belongs to the beta-coronavirus family [3, 4]. It has been isolated from nasopharyngeal secretions, sputum, and feces but also from the tear film of infected individuals [5]. It is transmitted mainly by the droplet route and by direct contact of the virus with mucous membranes containing angiotensin II-converting enzyme (ACE2), which acts as a cellular receptor for SARS-CoV-2. The virus binds its spikes to ACE2 as a cellular receptor to obtain entrance into the cell. The receptor for transmembrane serine protease 2 (TMPRSS2) also plays an important role in cell infection [6]. This protein facilitates viral entry into host cells by proteolytically cleaving and activating viral envelope glycoproteins. Viruses that use these receptors to enter the cell include influenza viruses and the human coronaviruses Middle East respiratory syndrome virus (MERS-CoV), severe acute respiratory syndrome virus (SARS-CoV), and SARS-CoV-2 [6].

SARS-CoV, MERS-CoV, and SARS-CoV-2 viruses also induce symptoms beyond the respiratory system, including ocular tissues, the gastrointestinal tract, and the endocrine system [7, 8], with possible short- and long-term health consequences [9].

Ocular symptoms of COVID-19 are not very common, which may be due to the low amount of ACE2 in ocular surface tissues [10]. In retrospective studies, the prevalence of ocular symptoms in SARS-CoV-2 infected patients ranged from less than 1% to more than 60%, with an average prevalence in more than 5% of patients, and symptoms were often associated with disease severity [11].

ACE2 and TMPRSS2 receptors have been shown to be expressed in conjunctival and corneal cells [6]. Follicular cells of the thyroid also show expression of ACE2; therefore, this gland is susceptible to damage by SARS-CoV-2 when infected [12–15].

Both hyperthyroidism and hypothyroidism are often caused by an autoimmune process. A genetic factor is thought to be responsible for about 80% of the pathogenesis of Graves' and Basedow disease (GBD) and Hashimoto thyroiditis, and environmental factors (infections, smoking, stress) are responsible for about 20%. Viral infections (parvo, Epstein Barr virus, hepatitis C virus) are among the environmental factors included in the pathogenesis of autoimmune thyroid diseases [16, 17]. Lanzolla et al. and Jiménez-Blanco et al. presented reports of patients in whom GBD and thyroid orbitopathy (TO) developed after infection with SARS-CoV-2, suggesting that it may have played a role as an environmental factor in its pathogenesis [18, 19].

Patients with existing autoimmune thyroid diseases have not been shown to be more susceptible to viral diseases, including SARS-CoV-2 infection, and that they are to be at risk for more severe course of COVID-19. A group of patients with autoimmune thyroid disease who develop TO and are treated with intensive immunosuppression are at increased risk of developing severe SARS-CoV-2 infection [20].

An association between the severity of systemic inflammation, especially IL-6 levels, and hyperthyroidism has been demonstrated. Patients with hyperthyroidism, thyrotoxicosis, and COVID-19 had a worse prognosis and longer hospitalization than euthyroid patients [21]. IL-6 can induce the onset or recurrence of hyperthyroidism in GBD [22], and cases of recurrent GBD have also been described in patients in recovery after COVID-19 [19]. Although GBD per se does not increase the risk of COVID-19, SARS-CoV-2 infection in patients with GBD can lead to hyperthyroidism which requires prompt diagnosis and treatment to reduce the risk of more severe infection [23]. Unregulated hyperthyroidism will lead to cardiovascular events, including cardiac arrhythmias, hemodynamic instability, and myocardial ischemia [24], increase oxidative stress [25], and impair coagulation-fibrinolytic balance [26].

The aim of this paper is an attempt to present the ocular manifestations and recommended treatments of TO according to the European Group on Graves' Orbitopathy (EUGOGO) guidelines and to respond to these recommendations in relation to the SARS-CoV-2 epidemic period.

DIAGNOSIS AND TREATMENT OPTIONS FOR HYPERTHYROIDISM IN GBD WITH THE LIMITATIONS OF THE SARS-COV-2 PANDEMIC

Control of thyroid function has a significant impact on the course and effectiveness of TO treatment. Both hyperthyroidism and hypothyroidism adversely affect its course [27].

In TO patients, it is essential to quickly restore and stably maintain euthyreosis. Importantly, in moderate to severe and active TO, the priority is to treat TO, and euthyreosis should be restored with antithyroid drugs (ATD) and stably maintained if possible.

Diagnosis and treatment of hyperthyroidism, as well as hypothyroidism during the SARS-CoV-2 pandemic, are carried out according to practice but with reduced frequency of follow-up visits and laboratory tests in patients with the previously well-controlled disease. Good-controlled hypothyroidism and hyperthyroidism are not related to an increased risk of SARS-CoV-2 infection or its severity.

There are three methods used to treat hyperthyroidism:

- pharmacological, using ATD;
- isotopic, using radioactive iodine ^{131}I (RAI);
- surgical, using sub-total, near-total, or total thyroidectomy [28, 29].

ATD and thyroidectomy *per se* do not seem to have a negative impact on the natural course of TO, whereas treatment with RAI is associated with a small but certain risk of exacerbation or *de novo* development of TO, especially in smokers [30].

Newly diagnosed hyperthyroidism during the SARS-CoV-2 pandemic should be treated with ATD, keeping in mind the potential for adverse effects of these drugs. Treatment with ATD carries a risk of neutropenia (neutrophil count < 1.0×10^9/L) or agranulocytosis (neutrophil count < 0.5×10^9/L), which occurs in 0.2–0.5% of patients, especially during the first months of treatment [28, 29]. The symptoms of neutropenia (sore throat, mouth ulceration, fever, and flu-like illness) may overlap with those of COVID-19 (fever, new continuous cough, and flu-like illness). Differentiating between these two diagnoses is difficult, if not impossible. Because the neutropenia caused by ATD is associated with an elevated risk of infection, it is likely that this uncommon adverse effect of ATD promotes SARS-CoV-2 infection and progression to COVID-19 [31, 32].

Approximately 50% of patients who died from COVID-19 had coexisting secondary bacterial infections. The presence of neutropenia increases the risk of such co-infections and thus affects the severity of the disease course [32].

The use of radioactive iodine ^{131}I (RAI) for the treatment of hyperthyroidism has been limited as a result of healthcare priorities, including the relocation of medical staff. RAI treatment is contraindicated in patients with moderate to severe and active TO. RAI is allowed in mild and active TO or with existing risk factors for developing TO, under the condition of glucocorticosteroid prophylaxis [30, 31].

Selected surgical treatments also have been limited. Thyroid surgery may be required in individual cases of patients with uncontrolled thyrotoxicosis who have significant side effects from ATD [31].

OCULAR MANIFESTATIONS IN SARS-COV-2 INFECTION

Serous conjunctivitis is the most common ocular manifestation in patients with COVID-19, and its prevalence has been reported to range from 0.8% [33] to as high as 64% [34]. Most authors reported the incidence of ocular symptoms between 3% and 8%, and interestingly, investigators have reported a much lower incidence of keratitis than conjunctivitis [35–37]. In a study conducted on a group of 74 patients, Polish authors demonstrated the presence of ocular symptoms in almost half of the subjects (n = 35), but only 7 patients showed advanced conjunctivitis [36].

Conjunctivitis in COVID-19 may be unilateral or bilateral. It has not been shown to be associated with gender or age, and there is no correlation between the severity of SARS-CoV-2 infection and the severity of ocular symptoms [38].

Subjective and objective symptoms of acute conjunctivitis in COVID-19 range from mild (foreign body sensation, conjunctival hyperemia, and lacrimation) to more severe (severe photophobia, eyelid swelling, mucous secretion in the conjunctival sac, dry eye syndrome, conjunctival chemosis often with nodular reaction in the conjunctival sac), which may mask TO symptoms [39, 40].

OCULAR MANIFESTATIONS AND CLASSIFICATIONS OF TO

Ocular symptoms associated with hyperthyroidism were first described in 1840 [41], but the pathogenesis of TO is still not fully understood [42].

TO is a combination of symptoms resulting from inflammation of the orbital soft tissues, less commonly pathology of the eyeball itself, which occurs mainly in patients with GBD but also in patients with thyroiditis in the course of Hashimoto's disease and even more rarely without thyroid disease [42].

The receptor for thyroid-stimulating hormone (TSH) (TSH-R), located mainly on thyrocytes but also on orbital fibroblasts, is the autoantigen responsible for hyperthyroidism in GBD and is considered the main pathogenetic factor of TO. Antibodies against the TSH-R (TRAb) are present in all GBD patients, and the severity and activity of TO correlate positively with blood TRAb levels [43]. Another potential target autoantigen in TO is the insulin-like growth factor (IGF-1) receptor (IGF-1R) [44], and it seems that the interaction between TSH-R and IGF-1R is more important than the action of individual molecules [45, 46].

It has been suggested that disturbances of the oxidation-reduction system and angiogenesis play a role in the pathogenesis of GBD and probably also TO, although results are inconclusive and often contradictory [47–49].

Assessment of TO inflammatory activity can be performed using the clinical activity score (CAS) [50] and with imaging techniques — mainly magnetic resonance imaging (MRI) [51, 52].

The severity of TO is assessed using several classifications, the most popular and recommended being the NOSPECS classification [53] and the severity scale proposed by the European Group on Graves' Orbitopathy (EUGOGO) [54].

The severity classification of TO according to EUGOGO guidelines includes three grades:

- 1 — mild TO — TO symptoms have little impact on daily life; retraction < 2 mm, mild soft-tissue inflammation, exophthalmos < 3 mm above normal, no or only intermittent diplopia, corneal symptoms resolving after moisturizers;
- 2 — moderate to severe TO — without sight-threatening TO symptoms but with the presence of symptoms that make daily life difficult: eyelid retraction > 2 mm, moderate to severe soft tissue symptoms, exophthalmos > 3 mm above normal, intermittent or persistent diplopia;
- 3 — sight-threatening TO (very severe) — optic nerve neuropathy and/or corneal abnormality up to corneal rupture (ulceration/perforation) [54].

THE ROLE OF AN OPHTHALMOLOGIST IN THE DIAGNOSTIC AND THERAPEUTIC PROCESS OF TO

Evaluating of the presence and severity of ocular symptoms of TO and its differential diagnosis of other causes of eyelid and conjunctival edema and hyperemia.

Evaluation of the inflammatory activity of TO using the CAS scale and assessment of the severity of the disease based on the available classification scales and a joint decision on the form of therapeutic management (observation or initiation of first-line treatment). Rehabilitative surgical treatment of strabismus in clinically inactive TO cases with diplopia in primary gaze position and eyelid plastic surgery.

Thyroid orbitopathy is not an additional risk factor for infection or severity of SARS-CoV-2 infection. However, ocular manifestations associated with COVID-19 in patients with GBD, especially conjunctivitis, may lead to delayed TO diagnosis but may also be misdiagnosed as mild TO [55].

There are no recommendations available from national or European societies for the treatment of TO in GBD patients during the SARS-CoV-2 pandemic. The implementation of basic science knowledge and current epidemiologic and pathogenetic knowledge of both TO and SARS-CoV-2, as well as the clinicians' own experience, is important in this regard.

Management of TO depends on the severity and activity of the disease. Moderate to severe and active TO patients present a serious dilemma during the SARS-CoV-2 pandemic.

Mild TO does not require active treatment with immunosuppressive drugs. Thus, the management of mild TO during the SARS-CoV-2 pandemic does not differ from the recommendations published by EUGOGO expert group [54]. As spontaneous regression of ocular symptoms can occur in most patients (up to 60%) with mild TO, up to one year after normalization of thyroid function, observation and local treatment seem to be sufficient [54, 56]. We try to reduce or eliminate such symptoms as photophobia by recommending dark glasses and foreign body sensations through "artificial tears" solutions. In case of increased intraocular pressure, we recommend topical drops of β-blockers and in case of exophthalmos and related lagophthalmos, a wet chamber and "artificial tears", in case of double vision, alternate covering of the eyes or, if possible, prism glasses.

We always recommend avoiding smoking and selenium supplementation [54, 56].

TREATMENT OF MODERATE-TO-SEVERE TO WITH RESPECT TO THE LIMITATIONS OF THE SARS-COV-2 PANDEMIC

In moderate to severe and active TO, the standard (according to EUGOGO) as first-line treatment is the combined use of methylprednisolone *i.v.* (cumulative dose of 4.5 g over 12 weeks) with concomitant administration of mycophenolate sodium (0.72 g per day for 24 weeks) [54].

It seems reasonable that in patients with moderate to severe TO, who are not at risk of sight deterioration, *i.v.* glucocorticosteroids should be avoided, and an observational strategy should be used, whereas in patients with more severe TO and at risk of sight worsening, *i.v.* glucocorticoids are the therapeutic choice regardless of SARS-CoV-2 infection or clinical signs of COVID -19 [20, 57]. It is necessary to keep in mind the increased risk of SARS-CoV-2 infection and other potential adverse effects of intensive *i.v.* glucocorticosteroids therapy. Very rarely acute liver failure can occur, even leading to death [58]. Cases of myocardial failure and acute coronary syndromes in patients without previous cardiac disorders, hypertension leading to myocardial infarction, ischemic stroke, and pulmonary embolism after treatment with intravenous methylprednisolone pulses have been documented [59, 60].

Patients with viral hepatitis, impaired liver function, severe cardiovascular disease, and psychiatric illness should not be qualified for high-dose *i.v.* methylprednisolone treatment regardless of the risk of SARS-CoV-2 infection.

All recommended therapies for moderate to severe and active TO involve immunosuppressive and immunomodulatory drugs, which are a risk factor for an unfavorable course of COVID-19.

Mycophenolate is a first-line treatment for moderate to severe and active inflammatory TO. It competitively and reversibly inhibits inosine monophosphate dehydrogenase, resulting in decreased antibody production by B lymphocytes and a dual antiproliferative effect on both B and T lymphocytes which may increase the risk of SARS-CoV-2 infection or severe course of COVID-19 [61].

Despite the lower efficacy and worse tolerability of *p.o.* steroids demonstrated in clinical trials during the pandemic period of SARS-CoV-2, *p.o.* prednisone administered at home may be a good compromise in patients with moderate to severe and active TO reserving *i.v.* methylprednisolone administration for severe forms of TO, especially those sight-threatening [54, 62]. Oral prednisone treatment can be administered at home with strict adherence to social distancing and hygiene.

Very high doses of steroids used to treat COVID-19 have been shown not to cause adrenal suppression, and normal adrenal function has been observed in patients who have survived COVID-19 infection [63]. Sudden stop of long-term glucocorticosteroid treatment can lead to adrenal insufficiency, increasing the risk of infections and associated mortality, including COVID-19 [64]. Ambroziak et al. demonstrated that treatment of TO patients with i.v. glucocorticosteroids according to the standard of administration recommended by EUGOGO (12-week cumulative dose of 4.5 g), does not lead to secondary adrenal insufficiency. On the other hand, supplementing the treatment at the end of intravenous therapy with low doses of oral glucocorticosteroids (prednisone in a gradually decreasing dose from 30 mg/day for 3 months) may lead to secondary adrenal insufficiency in some patients [65].

If TO is in moderate to severe and active stage and we decide to start immunosuppressive treatment, both the patient and the physician should be aware that treatment with immunosuppressive drugs is a risk factor of severe COVID-19. Self-isolation should be recommended for the duration of treatment (at least 12 weeks) [20,30]. This applies to patients taking glucocorticosteroids at immunosuppressive doses, as well as patients taking other immunosuppressive drugs such as mycophenolate, azathioprine, and biologic drugs, including teprotumumab, rituximab, and tocilizumab used to treat TO [66].

It is important for the treated person to strictly follow the general rules regarding isolation and quarantine, hand and surface hygiene, and masks even when patients go outside [20].

Orbital radiotherapy (ORT) with low doses of radiation shows immunosuppressive effects mainly by decreasing leukocyte adhesion to the endothelium, stimulating apoptosis of immune cells involved in inflammation, increasing the expression of anti-inflammatory cytokines, and decreasing the secretion of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), and nitric oxide (NO) and reactive oxygen species (ROS) [67].

Prummel et al. demonstrated that ORT is as effective as oral prednisone [68], and other studies have shown that ORT synergistically amplifies the effects of oral glucocorticosteroids [69].

A cumulative dose of 20 Gy to the orbit given over 2 weeks as ten daily fractions of 2 Gy each is recommended [54, 70]. Also, a regimen of 1 Gy per week for 20 weeks has been shown to be effective [71].

Treatment with ORT is a local treatment with no effect on overall immune status. In this sense, it is a safe alternative during the period of the increased epidemic risk of SARS-CoV-2 for the treatment of moderate to severe TO. Still, it should be kept in mind that the beneficial effect of ORT is remote and will probably occur 6 to 12 months after its application. At the same time, this treatment is associated with an epidemic risk due to the 2-week duration of inpatient treatment.

On the other hand, severe, sight-threatening forms of TO require aggressive immunosuppressive treatment to avoid irreversible sight loss. There are no guidelines available for the treatment of these patients during the COVID-19 pandemic. Severe sight-threatening TO, whether due to dysthyroid optic nerve neuropathy (DON) or corneal complications, must be treated as a priority condition, a vision-threatening condition, and we mandatorily administer treatment according to the EUGOGO standard regardless of the SARS-CoV-2 pandemic [20].

In a complete sanitary regimen, the treatment of choice in DON is the urgent inclusion of large *i.v.* doses of methylprednisolone (500–1000 mg) for three consecutive days of the week or on alternate days with constant local monitoring [54]. When symptoms stabilize or improve, which is usually observed, we continue this regimen the following week. In the event of symptom progression despite the regimen mentioned above, the patient should be referred for urgent orbital decompression - vision at risk. During the SARS-CoV-2 pandemic, orbital decompressions performed for medical or cosmetic indications in non-active TO should be delayed. Similarly, rehabilitative surgeries (strabismus and eyelid surgeries) should also be delayed.

In patients with DON, immediate decompression has not resulted in better outcomes than *i.v.* glucocorticosteroids as first-line treatment [72]. In the active phase of OT, decompression surgery is indicated in patients with severe exposure keratopathy and, as second-line treatment, in patients with DON unresponsive to *i.v.* glucocorticosteroids [20, 73].

As SARS-CoV-2 virus mRNA has been detected in the tear film [74], patients with TO who develop COVID-19 may represent an essential source of spreading infection, especially if they have marked periorbital soft tissue involvement. Patients with TO are recommended to avoid touching their eyes, and health care staff involved in their treatment are advised to follow strictly personal protective equipment guidelines during the SARS-CoV-2 pandemic.

With ongoing vaccination of the population, the risks associated with immunosuppression will gradually decrease. Although the effect of immunomodulatory/immunosuppressive agents on the efficacy of COVID vaccination is unknown, because we know that steroids and other immunosuppressive agents reduce the efficacy of other vaccines, it seems reasonable to suggest that patients already treated should continue *i.v.* glucocorticosteroids or other immunosuppressive therapy, under careful monitoring, and to recommend that vaccination or the next dose of vaccine should be administered at least 2 to 4 weeks after the end of immunosuppression [20].

CONCLUSIONS

No studies are available on the use of *i.v.* glucocorticosteroids or other immunosuppressive agents for TO during the current SARS-CoV-2 pandemic.

Treatment of mild TO during the SARS-CoV-2 pandemic does not differ from the recommendations published by EUGOGO, and observation and local treatment seem to be sufficient. It seems reasonable that in patients with moderate to severe TO, who are not at risk of sight deterioration, *i.v.* glucocorticosteroids should be avoided, and an observational strategy should also be used, whereas in patients with severe TO and at risk of sight loss, *i.v.* glucocorticosteroids are the therapeutic choice regardless of SARS-CoV-2 infection or clinical signs of COVID -19.

Conflict of interest

The authors declares that there is no conflict of interest.

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