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Tocilizumab Plus Methotrexate as Effective Rescue Therapy in Dysthyroid Optic Neuropathy Relapsing after Surgical Orbital Decompression

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Abstract

Background: The treatment of Dysthyroid Optic Neuropathy (DON) relapsing after surgical orbital decompression has not been established. Both radiotherapy and corticosteroids frequently fail. Novel immunosuppressive drugs have been used in limited series or case reports. The association of tocilizumab (TCZ), a monoclonal antibody directed against the IL-6 receptor, and methotrexate (MTX) has reasonable pharmacological and pathophysiological bases.

Material and Methods: A patient with steroid-resistant DON relapsed four weeks after three-wall orbital decompression surgery. She was treated with a combination of TCZ (8mg/kg; four administrations four weeks apart) and MTX (10mg s.c/week for 24 weeks, then 7.5mg/week for 6 weeks).

Results: A complete and long-lasting recovery of visual acuity associated to marked reduction of the thickness of extraocular muscles and followed by inactivation of orbitopathy was observed with combined immunosuppressive therapy.

Conclusions: The combination of TCZ and MTX may be an effective option for treating steroid-resistant DON.

Keywords: Graves'orbitopathy; Dysthyroid optic neuropathy; Orbital decompression; Tocilizumab; Methotrexate

Introduction

Dysthyroid optic neuropathy (DON) is the most severe complication of Graves' orbitopathy (GO), and is characterized by impaired vision due to compression of the optic nerve by enlarged extraocular muscles at the orbital apex [1]. DON must be promptly treated to prevent permanent nerve damage and loss of visual function. High-dose intravenous corticosteroids have been shown to be effective in recovering visual function in up to 40% of patients, but urgent surgical decompression of the bony orbit is necessary in more than half of the cases [2]. Relapse of DON after orbital decompression is a rather uncommon event, but it may occur a few weeks after surgery especially when orbitopathy remains active [3]. This was reported by Dolman et al. in 15% of the patients who in fact had visual improvement following decompression [1].

Treatment of relapsing DON may be challenging. Retrobulbar radiotherapy was reported to improve visual function, while corticosteroids may not be effective [4]. The use of biologics, which are proposed as second-line treatment in moderate to severe orbitopathy [5], has been reported only in anecdotal cases or in small series of patients with relapsing DON [6,7]. Here we report on a woman with DON, relapsing after three-wall surgical orbital decompression and resistant to iv. corticosteroids, who responded to combined therapy of tocilizumab (TCZ), a monoclonal antibody directed against the IL-6 receptor which blocks the effects of IL-6, a cytokine involved in the mechanisms of orbital inflammation [8], with methotrexate (MTX), showing rapid recovery of visual function and improvement of orbitopathy.

Case Report

In July 2020 a 50 yr woman affected with moderate to severe Graves' orbitopathy (GO) was seen in our tertiary referral Center for Thyroid Diseases. On admission, the patient was euthyroid on methimazole therapy and remained so throughout the observation period. Serum TRAb were consistently elevated (25 mU/L; n.v.<2.9). Ophtalmological examination showed bilateral proptosis (Hertel exophtalmometry 115/25-27 mm) and symmetric orbital involvement. Visual acuity was 8/10, the optic disc was normal as well as color vision and ocular motility (Gorman score 0). The Clinical activity score (CAS) was 4/7, and NOSPECS classification was 2b 3b 40 50 60. Orbital MRI showed bilateral and moderately increased thickness of the extraocular muscles. Intravenous methylprednisolone (MPN) was started (500 mg weekly), but during treatment the patient began to complain of visual impairment. Her visual acuity decreased to 2/10 and therefore the dosage of MPN was increased to 750 mg every other day for two weeks, but any significant improvement in orbital inflammation or in visual acuity was seen. Therefore, orbital surgery was promptly carried out (three-wall orbital decompression). After a transient improvement (5/10), the patient's visual acuity rapidly deteriorated again (2/10 bilaterally). Second line immunosuppression with three 1000 mg methylprednisolone infusions on alternate days, and subsequently 500 mg rituximab (November 2020), was carried out without significant visual improvement.

On December 30th the patient underwent total thyroidectomy; LT4 therapy was started and euthyroidism was consistently maintained.

In January 2021 (six months after initial assessment and about three months after orbital decompression) visual acuity was still 2/10 in both eyes, the CAS was 6/10 and NOSPECS was 2b 3a 5a 6b; class 4 was not assessable due to severe visual defect (Figure 1a). Orbital MRI showed marked enlargement of orbital muscles (Figure 1: a1-a3), when compared to their size before surgical decompression. The patient's serum TRAb titers had risen to > 60 mU/L.

At that point, we sought to try a combined therapy with TCZ and MTX as a rescue for this relapsing and treatment resistant form of DON. The first of four monthly intravenous infusion of TCZ (8 mg/kg administered over 60 min) was carried out on February 18th and was well tolerated. MTX (10 mg s.c.) was also started at the same time (with supplementation of folic acid). At week 1 after therapy with TCZ+MTX, orbital inflammation and visual acuity began to improve. Four weeks later (March 2021), visual acuity was 4/10 in the right eye and 8/10 in the left eye, inflammatory signs significantly improved (CAS dropped from 6 to 3). Three additional monthly TCZ infusions were subsequently administered and MTX was continued (10 mg/week for 24 weeks and then 7.5/week for 6 weeks). Three months after the start of TCZ+MTX therapy, we observed an almost complete recovery of vision (9/10 right and 8/10 left eye), and disease inactivation (CAS 2). The patient's exophthalmometry was 23-20 mm and constant diplopia was present.

MRI imaging performed one month after the end of TCZ therapy, showed significant reduction of extraocular muscles thickness in both eyes and of the apical crowding (Figure 1: b1-b3). In July 2021 the patient only had mild palpebral edema (Figure: 1b), fully recovered normal visual acuity and color vision. Diplopia was corrected by prisms.

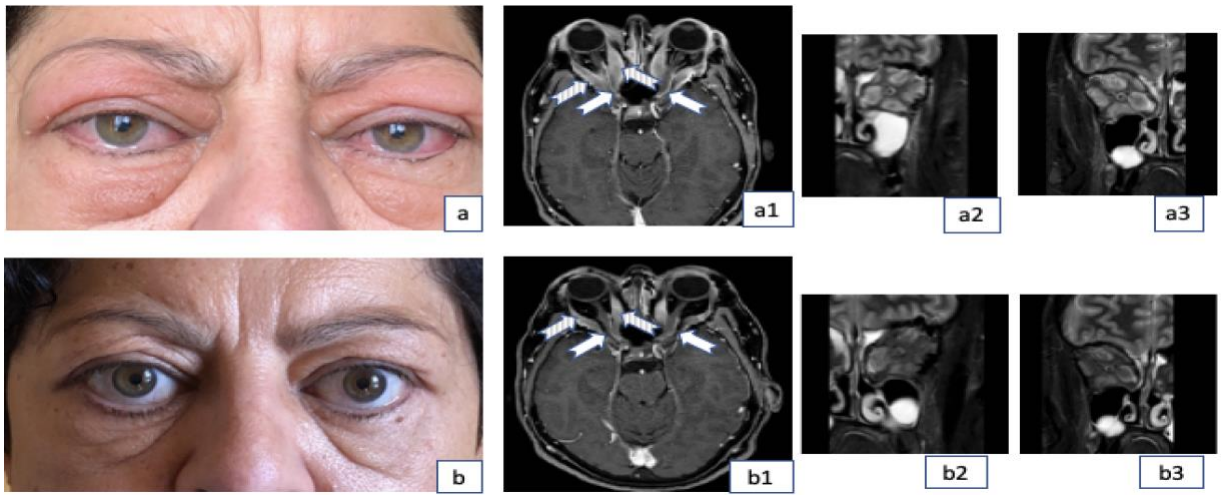

Figure 1a: Picture of the patient taken in February 2021, before the start of tocilizumab and methotrexate therapy. **(a1):** Axial T1 weighted RMN images with contrast before the start of the therapy. Enlarged bodies of extraocular muscles (dotted arrows) and optic nerve compression with the absence of a cleavage between the nerve and the muscles (white arrows) are evident; (**a2** and **a3):** Coronal RMN STIR sections (which are useful to detect intramuscular oedema) showing the enlargement of extraocular muscles before therapy.

Figure 1b: Picture of the patient taken in July 2021 (two months after the last tocilizumab administration and ongoing methotrexate). **(b1):** Axial T1 weighted RMN images with contrast recorded in June: dotted arrows indicate the bodies of the muscles, shranked after therapy; white arrows indicate the evident cleavage between the muscles and the optic nerve; **(b2** and **b3):** Coronal RMN STIR sections showing the reduction of the thickness of extraocular muscles due to improvement of the oedema. The diameters of the muscles after therapy were the following: **right eye:** medial rectus 8mm vs 11.3mm before therapy, superior rectus 7mm vs 14.5mm, lateral rectus 8 mm vs 14.7mm, inferior rectus 7mm vs 15mm; **left eye:** medial rectus 8mm vs 13mm before therapy, superior rectus 8mm vs 13mm, lateral rectus 11mm vs 14mm, inferior rectus 8mm vs 14mm).

Combined TCZ and MTX therapy was well tolerated, with no observed adverse events. Even after discontinuing MTX, GO remained inactive, with persistent normal visual acuity and exophtalmometry 23-20mm. Serum TRAb were 8.6 mU/L. CAS score and visual acuity recorded during observation period and the therapeutic interventions carried out are shown in Figure 2. Follow-up at 14 months after the end of MTX confirmed inactive GO and normal visual acuity, along with normalization of TRAb titer.

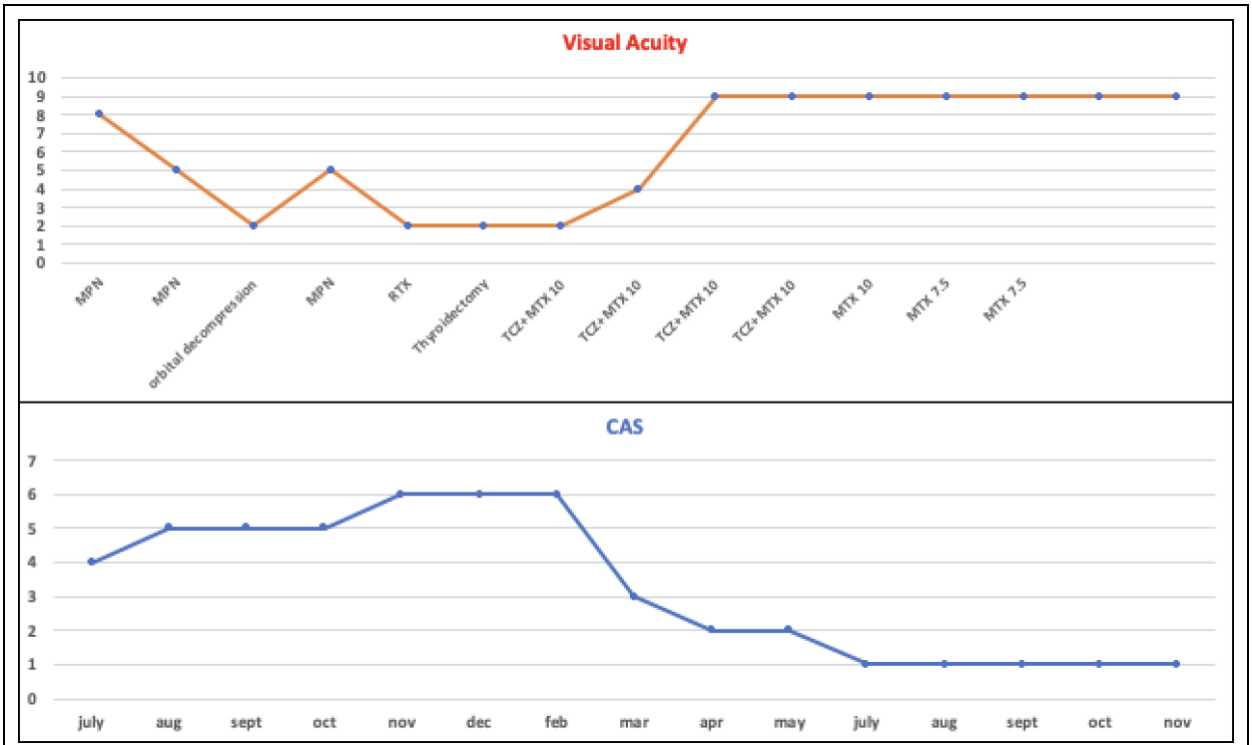

Figure 2: Visual acuity and Clinical Activity Score (CAS) from 2020 July to 2021 November. The therapeutic interventions are reported in the middle of the figure. MPN: methylprednisolone. TCZ: tocilizumab. MTX: methotrexate.

Discussion

Recurrence of DON after surgical orbital decompression occurs rarely, usually in association to reactivation of orbitopathy [1-3]. Therefore, the treatment of relapsing DON is not established and has not been standardized. Currently available guidelines do not provide suggestions for this peculiar condition and its clinical management relies on the experience of the clinician and on few literature reports.

Dolman et al. reported improvement of visual acuity after external radiotherapy [4], when corticosteroids are not effective [1]. This patient, clearly had steroid-resistant DON, that relapsed despite prompt three-wall orbital decompression. Medical treatment was sought as rescue therapy, as the patient refused radiotherapy.

Several novel immunosuppressive agents have been shown to be effective in GO. Rituximab (RTX) is recommended as second line therapy in moderate to severe GO [5], as it has been proven to work in steroid-resistant patients [10,11]. RTX has been reported to increase the risk of worsening of DON, due to possible release of cytokines causing acute swelling of orbital tissues [11], although in some reports DON has improved following RTX administration [6,10,12]. Unfortunately, when used in our patient, RTX did not improve inflammation, nor visual acuity. Thyroidectomy also did not have a favorable effect on GO, despite having maintained the patient persistently euthyroid.

We, therefore, sought other options of immunosuppression with the specific aim of reducing the size of extraocular muscles and their impact on the apical crowding that was causing the compression of the optic nerve and the persistent severe visual defect. We thought that the association of TCZ with MTX may be beneficial because TCZ has a rapid anti-inflammatory activity, and MTX may act as adjuvant because of its nonspecific immunosuppressive effect. Such combination therapy may target different pathophysiological pathways in GO and may exert additive anti-inflammatory effects especially on the volume of eye muscles which compress the optic nerve and cause loss of vision, thus providing a more aggressive approach in those cases carrying a high risk of permanent optic nerve damage.

Some studies, carried out in moderate to severe GO, have demonstrated efficacy of TCZ [13], which has been shown to induce a significant reduction of the thickness of extraocular muscles [14] and has been successfully used in patients with DON [15], even in the disease relapsing after orbital decompression [16]. As shown in a randomized trial in patients with moderate to severe GO, TCZ has a rather rapid effect [13], and this finding may suggest its usefulness in situations where a rapid anti-inflammatory action is required, as in the case of our patient.

MTX is a disease modifying drug with immunomodulating and anti-inflammatory activity which is currently used as first line therapy in inflammatory arthritis and also in other autoimmune conditions involving inflammation of soft tissues, such as inflammatory and autoimmune eye diseases [17]. MTX is known as a non-specific immunosuppressor, as it inhibits tetrahydrofolate reductase, leading to enhanced extracellular release of adenosine, which in turn decreases the production of inflammatory cytokines [17]. MTX was reported to be effective as a steroid sparing (adjuvant) agent in moderate to severe GO and was shown to improve visual acuity and orbital inflammation in severe sight-threatening GO, thus allowing earlier rehabilitative surgery [18,19]. It is known that the onset of anti-inflammatory and immunosuppressive effects of MTX is seen at least six to eight weeks after the beginning of therapy, and in moderate to severe GO, three to six months are required to appreciate a significant clinical improvement [19].

The fast and dramatic improvement observed in this patient started one week after the administration of TCZ and continued with progressive inactivation of GO, associated with a marked reduction of the size of extraocular muscles, yielding to recovery of visual acuity and of color vision. This is likely to be attributed to the anti-IL6 blockade, although MTX may have played a role as an adjuvant. Indeed, while it is conceivable that the resolution of DON is due to the rapid effects of TCZ, it is difficult to ascribe the inactivation of the disease to one drug instead of the other.

However, despite some cases are reported in whom inactivation of orbitopathy was obtained by TCZ alone, it is reasonable that the combination of the mechanisms of action of both drugs may have resulted in an additive anti-inflammatory effect which, in turn, lead to a pronounced, long-lasting inactivation of the orbitopathy. Furthermore, it is worth noting that Graves' orbitopathy is a disease with a heterogeneous pathogenesis, making difficult to predict what drug will be effective in any single patient; for this reason, in more complex situations, as in the present case having a high risk of permanent vision loss, combined therapies targeting different pathophysiological mechanisms may be warranted.

To our knowledge, this is the first report on the efficacy of TCZ plus MTX in rescuing visual loss in DON and inactivating GO after surgical orbital decompression.

We are aware of the limitations of this study. Indeed, in our patient anti-inflammatory therapies were administered sequentially: we cannot exclude that the improvement observed in our patient may be due to a late effect of such previous therapies or to a spontaneous favorable evolution of the disease. However, no clear benefit had been observed in this patient until combined TCZ and MTX therapy was started, about five months after the end of steroids and three months after RTX, when efficacy of these such therapies would be expected. The decrease of the size of extraocular muscles on MRI and the decrease of serum TRAb levels observed especially after TCZ, is suggestive of a direct effect of such pharmacologic approach.

Based on this observation, we suggest the potential usefulness of TCZ, also in combination with MTX, in DON especially after surgical decompression in patients who require additional therapy to achieve normal vision. Prospective studies specifically addressing this condition are mandatory.

Disclosures

Paolo Piero Limone have contributed to the present study and does not have any conflict of interest to declare.

Maurilio Deandrea have contributed to the present study and does not have any conflict of interest to declare.

Claudia Lomater have contributed to the present study and not have any conflict of interest to declare.

Annalisa Macera have contributed to the present study and does not have any conflict of interest to declare.

Vittorio Ferrero has contributed to the present study and does not have any conflict of interest to declare.

Stefano Sellari Franceschini has contributed to the present study and does not have any conflict of interest to declare.

Eleonora Cerutti has contributed to the present study and does not have any conflict of interest to declare.

Mario Salvi has contributed to the present study and does not have any conflict of interest to declare.

Marco Mellano has contributed to the present study and does not have any conflict of interest to declare.

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