Tocilizumab as a Useful Tool for Thyroid Eye Disease in Pediatric Population: A Case Report

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Children · Immunosuppression · Thyroid eye disease · Tocilizumab

Abstract
Thyroid eye disease (TED) characterizes by inflammation and remodeling of orbital tissues. Although the majority of pediatric TED is mild, some children present progressive and severe disease. The approach to severe disease in this group of patients, especially when noncorticosteroid-responsive, is challenging. The purpose of this work was to describe the effective use of tocilizumab as second-line therapy in steroid-resistant pediatric TED. A 13-year-old female with a history of Graves’ disease presented with right eye proptosis for at least 8 months associated with mild pain on eye movements and ocular surface complaints. The ophthalmologic evaluation revealed Hertel exophthalmometry readings of 22 mm on the right eye (OD) and 19 mm on the left (OS). The remaining ophthalmic examination was unremarkable. Intravenous methylprednisolone pulses of 500 mg were initiated without any improvement after 4 treatments. Following multidisciplinary team discussion, therapy was switched to monthly tocilizumab injections at 4 mg/kg. Significant reduction of proptosis and resolution of pain and ocular surface complaints were noted immediately after the treatment switch. Exophthalmometry readings after the end of treatment that included 4 tocilizumab injections were 20 mm on OD and 19 mm on OS. No side effects were reported during the entire follow-up. Six months after treatment cessation, the patient remains stable, without any signs of orbitopathy.
relapse and no ophthalmologic complaints. This is the second case report showing the effectiveness of tocilizumab in pediatric TED and the first one showing its efficacy when steroids fail. Our results support the potential safety and efficacy of this immunosuppressor in children with TED.

Introduction

Thyroid eye disease (TED) or Grave's orbitopathy, the major extrathyroidal manifestation of Graves' disease (GD), constitutes a complex autoimmune disorder, characterized by inflammation and remodeling of orbital tissues, being associated with increased blood levels of anti-thyrotropin receptor (TSH-R) antibodies (TSHR-Ab) and other inflammatory markers [1]. TED is characterized by variable orbital inflammation that may lead to proptosis, eyelid retraction, diplopia, low visual acuity, secondary dry eye, as well as orbital and eyelid pain [2]. The disease course is typically diphasic. The first phase is characterized by an immune reaction in which predominates inflammation of ocular and orbital structures, including extra-ocular muscles, interstitial tissues, orbital fat, and lacrimal glands [1, 3]. The complex molecular changes might induce only mild symptoms as red and dry eyes or promote severe proptosis, strabismus, and, lately, facial disfigurement. Furthermore, in the acute phase of the disease, the inflammation may cause optic neuropathy, constituting a potential sight-treating condition [4]. The second or inactive phase occurs after inflammation resolution. Since the majority of patients with TED present only mild disease, this phase is frequently asymptomatic. However, in moderate and severe cases, the second phase of the disease characterizes by fibrosis and scarring sequelae that are directly related to the time of previous active inflammation [5].

The incidence of TED is not well studied [3], with different values depending on the studies. However, TED is more frequent in women, with incidence values varying between 2.67 and 3.3 cases/100,000/year in women and 0.54–0.9 cases/100,000/year in men [3, 5].

In the pediatric population, since GD has a lower incidence than in adults, TED is an uncommon finding [6]. However, children have about the same or slightly increased risk as adults to develop orbitopathy once they have developed GD [6]. Although clinically relevant TED is in general milder than in adults [3, 6], rarely, some children present progressive and severe disease, culminating in severe disfigurement and corneal exposure that may require orbital decompression [7]. Moreover, the psychological burden caused by the disease is probably higher in children than in adults, even in mild disease [8]. Therefore, it is essential to guarantee timely diagnosis and management to avoid unwanted complications [5].

Although the complete pathophysiologic process is still not understood, autoimmune mechanisms clearly play a pivot role. Consequently, treatments for TED have involved immunosuppression targeting the adaptive immune system [2, 9]. Besides hormonal control and smoke cessation, until recently, literature recommended immunosuppression with corticosteroids as TED’s first therapy in the active phase [2, 5, 10]. Although corticotherapy can frequently suppress inflammation and control the disease, its pleiotropic action induces significant morbidity. The development or aggravation of diabetes mellitus, osteoporosis, insomnia, psychosis, or hepatic lesions comprises its main side effects [2]. Regarding children, corticosteroids may induce growth retardation and puberty delay, being even more deleterious [11]. Beyond side effects, 20–25% of patients do not respond or relapse to corticosteroids [9, 10, 12]. Therefore, other immunosuppressors have emerged as alternative therapies. Since
TED is less frequent and usually milder in children, there is a dearth of literature on this population regarding alternative therapies. Therefore, the approach to severe disease in this group of patients, especially when noncortico-responsive, is challenging. Tocilizumab constitutes a humanized monoclonal antibody against interleukin 6 (IL-6). Recent studies evidence that IL-6 increases the expression of TSH-R on fibroblasts and tocilizumab use has been documented as an effective treatment for TED in adults [12–17]. Recently, tocilizumab has been also approved in children for use in systemic juvenile arthritis and polyarticular juvenile idiopathic arthritis (JIA) both by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) [18, 19].

In this case report, we describe the use of tocilizumab in a 13-year-old girl with steroid-resistant TED. To the best of our knowledge, this is the first case in the pediatric population where tocilizumab was revealed to be a good and sustainable alternative when steroids fail.

**Case Report/Case Presentation**

A 13-year-old adolescent diagnosed with GD was referred to the ophthalmology department for persistent and progressive right eye proptosis (Fig. 1a). The GD had been diagnosed 8 months before, and methimazole 5 mg per day had been prescribed, allowing good control of thyroid function. No other relevant systemic or ophthalmologic medical history was present. The patient reported gradual asymmetric and painful bulging of the right eye with at least 8 months of evolution associated with discrete redness and tearing.

On the ophthalmologic evaluation, visual acuity was 20/20 on both eyes on Snellen chart, color vision was normal, and pupils were regular and reactive with no relative afferent pupillary defect. The orthoptic evaluation revealed aligned eyes with no deviation on the cover/uncover test. Extra-ocular movements were normal, with mild pain on right eye movements, but without any limitation or hyperfunction. No pain at rest was present. Mild right upper and lower lid retraction, associated with eyelid swelling, was evident. Hertel's...
Exophthalmometry revealed findings of 22 mm on the right eye (OD) and 19 mm on the left (OS). The slit-lamp evaluation showed mild bilateral congestion of the muscle vessels, and mild conjunctival hyperemia, more pronounced on the right, with increased tear break-up time on OD. No chemosis or caruncle swelling was evident. Intra-ocular pressure was 18 mm Hg (Goldmann tonometry) on both eyes. The fundoscopic observation was normal bilaterally, without any relevant findings on the optic nerve. Spectral-domain optical coherence tomography (Heidelberg) showed normal retinal nerve fiber layer thickness and normal macula, with normal macular ganglion cell layer thickness. Serum blood tests (Table 1) revealed thyroid-stimulating hormone (TSH) level of 2.62 UI/mL (normal range 0.35–5.00), free T4 of 0.90 ng/dL (normal range 0.88–1.58), free T3 of 3.60 pg/mL (normal range 2.00–4.20), and TSHR-Ab of 29.1 U/L (normal range 0.0–1.8). Orbit computed tomography (CT) exhibited bilateral fusiform thickening of the extra-ocular muscles, more marked at the right, with sparing of tendinous insertions, and mild reduction of the right apical space, without further signs of optic nerve compression (Fig. 2).

At this moment, active moderate TED was present given persistent right eye exophthalmia and compatible CT findings, discrete right eye movement pain, and positive TSHR-Ab. Furthermore, upon further questing, the patient revealed severe anxiety related to the situation. Therefore, after a risk-benefit discussion with the parents, weekly intravenous 500 mg methylprednisolone pulses were initiated, with regular monitorization. After 4 treatments,
no clinical improvement occurred. The clinical evaluation was similar, with persistent lid retraction, ocular surface complaints, right exophthalmia, and the same Hertel exophthalmometer measurements (Fig. 1b). Analytic control at this moment revealed TSHR-Ab of 26.1 U/L, with regular thyroid function. A slight reduction of right inferior rectus muscle thickness was noted on the follow-up orbit CT, without any other change in the dimensions and density of the remaining muscles.

Therefore, due to the absence of clinical improvement and the persistence of active signs of the disease besides persisting depressed humor of the patient, it was decided to switch the therapy to tocilizumab after a multidisciplinary team discussion with pediatric rheumatology. After the obtention of the pharmacy hospital’s and ethics commission’s approvals, as well as written informed consent by the parents, monthly tocilizumab injections were started at a dose of 4 mg/kg. The patient was evaluated monthly before every subsequent injection, without any side effects reported. Proptosis reduction was noted immediately after the first injection, with a persistent improvement upon further treatments (Fig. 1c). At the end of the treatment, which included 4 monthly injections, Hertel exophthalmometry measurements were 20 mm on OD and 19 on OS. Hormonal function remained stable, and TSHR-Ab significantly dropped to 3.7 U/L.

The patient was satisfied, more confident, and without ocular surface complaints. Inflammation was controlled, and only mild nonactive TED was present due to the persistence of mild palpebral retraction.

Six months after tocilizumab suspension, the patient remains stable, without any signs of orbitopathy relapse and no ophthalmologic complaints. Rehabilitée surgery for palpebral retraction will be scheduled at an appropriate time. Analytically, thyroid function is stable (TSH 5.40 UI/mL, free T3 3.11 pg/mL, and free T4 0.91 ng/dL) and TSHR-Ab last evaluation revealed a value of 1.9 U/L. At the last follow-up visit, the girl’s psychological disposition improved, feeling more confident, without any complaints.

Discussion and Conclusion

Although the majority of cases are mild and do not need treatment, pediatric TED may cause an important disfigurement with significant and permanent disability. If it is present and not well managed at an early age, functional consequences in adult life are major, with huge limitations in social and work abilities, and consequent impact not only on personal quality of life but also on economic efficacy of the individual for himself and society. Therefore, complete and prompt control of the disease in its earlier forms is essential. When talking about children, the need for fast control of the disease is bigger. The sooner the control of the disease, the better the level of personal confidence, social integration, and school performance that patients may achieve [2, 3].

Treatment decisions are based on clinical activity, severity, and duration of the orbitopathy since anti-inflammatory treatment is significantly less effective after 18 months of disease duration [5]. The best approach to TED is still a matter of debate. Corticosteroids have been classically considered the mainstay of therapy [5]. High-dose systemic glucocorticoids have potent anti-inflammatory and immunosuppressive effects that have been applied successfully for the management of moderate-to-severe and active TED. Intravenous glucocorticoids, for their superior efficacy compared to oral steroids, have been considered the first-line treatment [5]. However, besides significant associated morbidity, a significant proportion of patients do not answer or relapse to this therapy [5, 9]. In the pediatric population, the morbidity profile of steroids is even higher. Growth restriction and puberty delay are huge problems to additionally consider [11].
Consequently, several immunosuppressors have emerged as alternatives or effective second-line therapies in nonresponsive or cortico-dependent patients. Among the most effective therapies, rituximab, tocilizumab, and teprotumumab have gained relevance [5]. However, there is still no consensus on what is the best one [5]. Especially in the pediatric population, there are no available guidelines or evidence to guide the best alternative. Teprotumumab has shown promising results; however, although approved for use in adults by FDA [20], the drug is still not available for use in Europe.

More recently, new evidence emerged suggesting mycophenolate mofetil as a first-line treatment in combination with corticosteroids. Results from recent studies show that the combination of low-dose mycophenolate sodium and intravenous methylprednisolone is safe and has superior efficacy compared to the use of steroids only [5]. This association was not considered in our case since the evidence supporting its use was only available after the time of the treatment initiation. Therefore, we could hypothesize if the addition of mycophenolate to our case would be enough for the observed clinical improvement.

Tocilizumab is a humanized monoclonal antibody against IL-6 being capable to reduce the expression of TSH-R on fibroblasts [5, 16, 21]. Then, the blockade of this via can reduce serum levels of thyroid-stimulating immunoglobulin, reducing proptosis and improving ocular motility. Numerous case reports and case series evidence the efficacy and safety of intravenous tocilizumab in patients with intolerant or resistant to steroid active TED [12, 22, 23]. Globally, it is well tolerated and rapidly effective in reducing inflammatory signs of the disease, potentially also reducing exophthalmos [14–16, 22]. A randomized clinical trial showed a significant reduction in activity scores of the disease, ocular motility improvement as well as a reduction of diplopia, and gains in visual acuity in adults with moderate-to-severe corticosteroid-resistant TED [17]. Fatigue and musculoskeletal pain were the most referred complications [17]. More recently, a multicentric observational study also concluded that tocilizumab is a useful and safe therapeutic option in adults with refractory TED, with minimal and temporary side effects [15].

In the pediatric population, tocilizumab has been approved for use in patients with JIA, with doses up to 10 mg/kg once every 4 weeks with good efficacy and tolerability [24, 25]. Considering the mechanism of IL-6 and the effects of tocilizumab, the drug can be used in several disorders in which autoinflammatory reactions are the main pathogenesis [25]. A little evidence of promising responses to tocilizumab in children is also reported in systemic lupus erythematosus [26] and juvenile dermatomyositis [27], as well as Takayasu arteritis [25]. Globally, the literature review supports the use of tocilizumab therapy as one option in the treatment of several pediatric rheumatic diseases, not limited to JIA [25].

Therefore, we considered tocilizumab as an alternative for our clinical case. The decision to switch the therapy was based on clinical assessment and emotional burden allied to positive serum TSHR-Ab levels. Serum TSHR-Ab levels are biomarkers of GD and correlate with clinical activity and severity of TED [5, 28].

We provide a case of effective use of tocilizumab in a pediatric patient, without any relevant side effects after a follow-up of 6 months. Since TED is usually mild and self-limited, we could hypothesize improvement was only due to the natural progression of the disease. However, the close temporal relationship between improvement and the first treatment favors the effectiveness of tocilizumab. Evidence regarding the tocilizumab use in pediatric TED is scarce. To the best of our knowledge, there is only one recent case report of its successful use in a girl [29]. A few differences need to be stated between both cases. Albrashdi et al. [29] used tocilizumab as an effective first-line therapy in a 9-year-old girl with progressive TED. The dosage applied by his team was 8 mg/kg, while we applied only 4 mg/kg. Although Albrashdi [29] and previous reports in JIA [24, 25] suggest a higher dose of tocilizumab, our results show that it may be possible to achieve successful
results in children with lower doses. This is a surprising and important finding since side effects may be dose-related.

Despite the differences, both cases report a rapid reduction in proptosis and inflammatory signals, as well as an improvement in the well-being of the patients, with no relevant side effects reported. The finding of new therapies, especially in this subset of patients, is extremely relevant since TED can severely affect the patient's quality of life. Numerous reports describe that TED limits daily activities and reduces self-confidence and social interactions, with higher rates of suicide in affected patients [2]. Therefore, the 2 cases show that tocilizumab seems to be a safe and effective therapy in children with TED either as a first-line treatment or as a second line in steroid nonresponders. Nevertheless, more studies, including well-designed clinical trials, are needed to establish the long-term safety and effectiveness of this therapy in larger populations of pediatric patients, as well as to determine the lowest effective dose.

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with national guidelines. Pharmacy and Therapeutics Commission of São João Hospital Center approved tocilizumab use in the patient on July 31, 2021. Written informed consent was obtained from the parents/legal guardian of the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Ana Filipa Moleiro and Jorge Meira were involved in the study design, data collection analysis and interpretation, and the drafting of the manuscript. Rodrigo Vilares-Morgado, Gonçalo Coutinho Alves, and Mariana Rodrigues were involved in data collection. Augusto Magalhães, Fernando Falcão-Reis, and Vitor Leal were involved in data interpretation and critical revision of the manuscript. Ana Filipa Moleiro, Rodrigo Vilares-Morgado, Gonçalo Coutinho Alves, Mariana Rodrigues, Fernando Falcão-Reis, Augusto Magalhães, Vitor Leal, and Jorge Meira approved the final version of the manuscript and take responsibility for the accuracy or integrity of any part of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author, Ana Filipa Moleiro.
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