



## Tocilizumab use in pediatric thyroid eye disease: First documented case

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### ARTICLE INFO

#### Keywords:

Thyroid eye disease  
Pediatric  
Hyperthyroidism  
Tocilizumab

### ABSTRACT

**Purpose:** To report the first case of Tocilizumab treatment for progressive pediatric thyroid eye disease (TED) in a 9-year-old female.

**Observations:** A 9-year-old female with a history of hyperthyroidism for 4 months presented with bilateral proptosis (more in the right eye) associated with retrobulbar pain, tearing, and conjunctival and caruncular redness. The exophthalmometry reading on presentation was 21mm OD and 17 mm OS. The patient was managed with observation and control of hyperthyroidism in the beginning. However, on a subsequent visit 3 months later it was observed that the symptoms and clinical findings were rapidly worsening. The exophthalmometry reading upon subsequent follow-up was 22 OD and 22 OS. After multidisciplinary team (MDT) discussions it was decided to treat the patient with four doses of 8mg/kg Tocilizumab injection on monthly basis. Notable improvement of proptosis and resolution of pain, conjunctival and caruncular redness was observed. The exophthalmometry reading 4 months after treatment was 20 OD and 19 OS.

**Conclusion and importance:** This case report opens an important gateway for the use of Tocilizumab in progressive TED in pediatric age groups.

### 1. Introduction

Thyroid eye disease (TED) is an autoimmune condition that is associated with increased blood levels of anti-thyrotropin receptor (TSH-R) antibodies and other inflammatory markers.<sup>1</sup> The reported incidence of TED is 16 per 100,000 females and 2.9 per 100,000 males with an approximate prevalence of 0.25% with no significant ethnic predisposition in Olmsted County, USA.<sup>2</sup>

Graves' disease (GD) is the most common cause of hyperthyroidism in both adults and children, followed by toxic nodular goitre.<sup>3</sup> In contrast to the adult population, the prevalence of TED in children with Graves' disease is lower in children below the age of 5. Moreover, the severity of the TED in the pediatric age group is much less pronounced than in adult individuals. It is rare to experience optic nerve compression or exposure keratopathy in children than adults.<sup>4,5,6</sup> Nevertheless, the effect on quality of life through the psychological burden of the disease on children is probably worse than adults.<sup>7</sup>

The mainstay of treatment of moderate to severe TED has been systemic steroids.<sup>8</sup> As of late, Teprotumumab, a human monoclonal antibody that blocks insulin-like growth factor type 1 receptor (IGF-1R) and thereby impairs the activity of both IGF-1 and TSH in fibrocytes has been

approved by the U.S. Food and Drug Administration (FDA) to treat TED.<sup>9</sup> Tocilizumab is a recombinant humanized monoclonal antibody that acts as an interleukin 6 (IL-6) receptor antagonist.<sup>10</sup> Tocilizumab has been approved by the FDA for pediatric use for treatment of Systemic Juvenile Arthritis and Polyarticular Juvenile Idiopathic Arthritis.<sup>11</sup> It has been documented as an effective treatment for progressive TED in adults.<sup>12,13</sup> In this case report, we are describing the first documented pediatric use of Tocilizumab in a 9-year-old female patient with progressive thyroid eye disease.

### 2. Case report

A 9-year-old female patient, known to have hyperthyroidism for 4 months, presented to the thyroid eye clinic with proptosis and mild retrobulbar pain after being referred from a private clinic where she was being prescribed carbimazole 7.5 mg. Upon further questioning, the patient's parent reported asymmetrical painful gradual bulging of both eyes (more in the right eye) associated with redness, tearing, and burning eye sensation. Ocular examination showed visual acuity of 20/20 on the Snellen chart, near full extraocular movements, bilateral upper and lower lid retraction, normal color vision, and Hertel's

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<https://doi.org/10.1016/j.ajoc.2022.101387>

Received 13 August 2021; Received in revised form 25 January 2022; Accepted 28 January 2022

Available online 5 February 2022

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exophthalmometry findings of 21mm (right eye) and 17 mm (left eye) with base 95 mm. The intraocular pressure was 17 and 19 mmHg (millimetre of mercury) respectively. On slit-lamp examination, remarkable findings were her erythematous conjunctivae with mild chemosis, mild dry corneal surface, and mildly tilted optic discs bilaterally (Photo 1). Ocular coherence tomography retinal nerve fiber layer (OCT RNFL) and fundus photos highlighted the normal findings found in the physical examination; orthoptic assessment revealed exophoria with no extra-ocular muscle restriction nor was there any double vision. Her blood tests revealed thyroid stimulating hormone (TSH) level of 0.005 milli iU/L, free T4 of 12.7 pmol/L, and free T3 of 6.32 pmol/L. At this stage, the condition was explained to both the patient and her parents and it was decided to observe the patient closely with conservative treatment while stressing the importance of managing her hyperthyroid status.

On the subsequent visit 3 months later, her symptoms of retrobulbar pain and discomfort worsened. Her exophthalmometry readings deteriorated, mainly in the left eye, with Hertel's exophthalmometry readings of 22 mm (right eye) and 22 mm (left eye) with base 95 mm. The patient now had obvious lagophthalmos and bilateral ocular exposure (inferior superficial epitheliopathy) with increased bilateral upper lid swelling and redness with slightly worsened conjunctival and caruncular injection and chemosis. Visual acuity and color vision and OCT were stable and within normal limits (Photo 2). Due to the rapid progression, further observation versus active intervention was discussed with the patient and parents – as well as with a pediatric immunologist and pediatric endocrinologist. As per advice by the latter, an agreement was reached to bypass systemic steroid treatment – mainly due to rapid progression of the disease and the effect of systemic steroids on stunting growth in children<sup>14</sup> - and start systemic treatment with intravenous Tocilizumab injection 8mg/kg after detailed discussion with the parents, a special consent taken (explaining the treatment and possible side effects was done) and necessary approvals from the insurance company were obtained. On further multidisciplinary team discussion, it was decided to administer 4 doses of Tocilizumab on a monthly basis, taking into consideration the response to the medication and serology. The patient was seen before every subsequent monthly Tocilizumab injection in which she showed progressive improvement in both symptoms and clinical findings; including exophthalmometry readings (her last findings were 20 mm (right eye) and 18 mm (left eye) with base 95 mm) upper and lower lid retraction and swelling, conjunctival, caruncular chemosis, and lagophthalmos and ocular surface exposure (dryness). Her TSH was 0.062 milli iU/L, free T4 of 11.7pmol/L, and T3 of 5.79 pmol/L. The patient was much happier and more interactive in each succeeding visit. (Photo 3).



Photo 1. [On presentation].



Photo 2. [Progression].

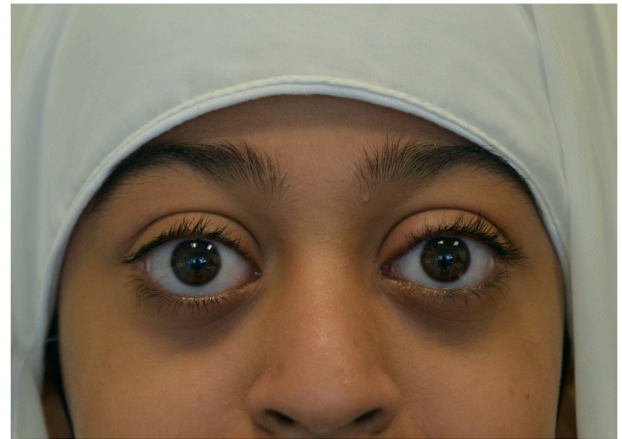


Photo 3. [After 4 Tocilizumab injections].

### 3. Discussion

Treatment options for Graves' disease are numerous and include antithyroid drugs, radioactive iodine therapy, and surgery.<sup>15</sup> Until recently, no actual effective medical therapy has been yet described for TED.<sup>16</sup> In comparison to the scarcity in the description of effective medical treatment, the pathologies of thyroid orbitopathy have been well studied in the literature, alluding to multiple causes; as emerging studies have described the orbital manifestations of TED to result from de novo adipogenesis, hyaluronan synthesis, interstitial edema, and enlargement of extra-ocular muscles. In this paradigm, orbital fibroblasts seemed to be the major effector cells. Orbital fibroblasts express both thyrotropin receptor (TSHR) and insulin-like growth factor-1 receptor (IGF-1R) at higher levels than normal fibroblasts. It was found that stimulation of both factors is involved in adipogenesis and hyaluronan production. Specifically, IGF-1R stimulation led to the production of interleukin IL-16.<sup>17</sup> This process is operated through an immune activation of a specific molecular bridge called CD40:CD154, which in turn triggers the orbital fibroblasts to produce inflammation-promoting cytokines such as IL-6, IL-8, macrophage chemoattractant protein-1, and transforming growth factor- $\beta$  to generate orbital inflammation.<sup>18</sup> Out of these cytokines, IL-6, in particular, was discovered to be present in high concentrations in people with TED, and as described earlier, IL-6 plays a significant role in the pathogenesis of the disease. Thus, it is hypothesized that inhibition of IL-6 might portray an effective role in the treatment of TED by directly reducing the inflammatory response and

fibroblast activity, and hence altering extracellular matrix remodeling.<sup>19</sup> Moreover, the medication in the premise of this case; Tocilizumab (an interleukin (IL)-6 receptor antibody) has been documented as an effective treatment for TED through case reports, randomized controlled trials, and systematic case reviews; mostly in adults (age >18 years), some of which are cited in this paper, with no studies reporting its use specifically in the pediatric population. Through our case report, we document the first use of Tocilizumab in pediatric TED, which highlights a potential wider therapeutic age range for the medication.

Classically, for the inflammatory stage of TED, the most widely used initial pharmacologic agents are intravenous or oral corticosteroids. In favor of the inflammatory stage of TED, suppression of inflammatory activity can often be achieved with corticosteroids but not without various side effects due to their pleiotropic nature. These side effects include worsening of diabetes mellitus, osteoporosis, insomnia, psychosis, and hepatic injury, and in the pediatric age group interference with growth.<sup>20</sup> This is in contrast to Tocilizumab, which is widely used in children for conditions like rheumatoid arthritis with a high safety profile and minimal to no side effects.<sup>21</sup> Similarly, in this case, there were no reported serological side effects.

TED not only affects the physiological well-being of patients but also impacts their psychological state. Sherifa et al. (2021) studied the effect of TED on children's self-perception as well as on the general psychological condition in a prospective study with 35 children and adolescents with confirmed GD. These children were found to be at higher risk of behavioral symptoms even with normalized thyroid hormone levels after anti-thyroid drug therapy. The most common associations were Anxiety/Depression and inattention.<sup>22</sup> Due to that matter, more research into a novel treatment with a lower side effect profile could potentially increase the quality of life of patients in a short time without having to anticipate the side effects, thus we conducted this case report to further encourage research into Tocilizumab being a potential agent that might carry less side effects as evidenced by a study mentioned earlier.

#### 4. Conclusions

In our case, the use of Tocilizumab hastened the improvement of TED as our patient showed improvement in proptosis, upper and lower lid swelling and retraction, and conjunctival and caruncular injection merely 2 weeks after the first treatment. The patient's psychological status improved tremendously, while there was no side effect associated with the treatment. We hope this case opens gateways for discussions about the effective-ness and possible safety of Tocilizumab in the pediatric TED. However, more studies and trials are needed to establish the effectiveness of this contemporary line of treatment and its side effect profile.

#### Patient consent

Signed consent attached.

#### Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

#### Declaration of competing interest

The authors report no conflicts of interest.

#### Acknowledgements

None.

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