Submitted: 13.01.2024
Accepted: 01.08.2024
Early publication date: 05.12.2024

Endokrynologia Polska
DOI: 10.5603/ep.98913
ISSN 0423–104X, e-ISSN 2299–8306

The position of monoclonal antibodies and small molecules in the treatment of thyroid orbitopathy

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Abstract

Since the European Thyroid Association guidelines for the management of thyroid orbitopathy (TO) were published in 2016, a number of randomised clinical trials (RCTs) investigating the use of biologic drugs for the treatment of moderate to severe and active TO have been published. Therefore, new recommendations for its treatment were developed and published in 2021. Treatment of active TO includes 2 types of immunosuppressive agents: non-specific and specific. Specific immunosuppressive agents used to treat TO include adalimumab (ADA), infliximab (IFX), etanercept (ETA), rituximab (RTX), tocilizumab (TCZ), teprotumumab (TEP), and batoclimab (BAT). In the manuscript, we present a review of the literature on RCTs, retrospective studies, and case reports on their use in the treatment of TO. The authors emphasise the beneficial effects of TEP, indicating, however, the lack of data on its long-term efficacy and safety and the lack of head-to-head comparison with *i.v.* glucocorticosteroids and its huge limitation is also the high price of the drug. TCZ is a therapeutic option for glucocorticosteroid-resistant TO and should be considered for second-line treatment (due to the cost of treatment, among other reasons) or first-line treatment in patients with contraindications to *i.v.* glucocorticosteroids. Given its side-effect profile, especially some risk of optic nerve neuropathy (DON), RTX is considered by the authors as a second- or even third-line treatment option. The current 2021 European Group on Graves' Orbitopathy (EUGOGO) recommendations include RTX, TCZ, and TEP among the second-line drugs for the treatment of moderate to severe and active TO. BAT is under clinical trials. Given the numerous advantages of biologic drugs over glucocorticosteroids, further RCTs are indicated to confirm their possible place also as first-line treatment in TO.

Key words: *Graves'/Basedow's disease; treatment, monoclonal antibodies, small molecules*

Introduction

Since the European Thyroid Association (ETA) guidelines for the management of thyroid orbitopathy (TO) were published in 2016 [1], many randomised clinical trials (RCTs) investigating the use of biological drugs for the treatment of moderate to severe and active TO have been published [2–5]. Therefore, new recommendations for the treatment of TO were prepared and published in 2021 [6, 7].

The pathogenetic basis of TO is an autoimmune response. A key role in this process is played by T lymphocytes and autoantibodies that recognise common autoantigens for both thyroid and orbital tissues such as thyrotropic hormone receptor (TSH-R) and insulin-like growth factor 1 receptor (IGF-1R), which are also expressed on fibroblasts and orbital preadipocytes [8, 9]. IGF-1R is a ubiquitous surface receptor involved in various cellular responses, including apoptosis modulation, cell survival enhancement, cell growth and proliferation, and cell motility and migration [10, 11]. IGF-1R regulates the movement of lymphocytes in the orbit, hyaluronic acid (HA) synthesis, adipogenesis, and determines the phenotypes and functions of T and B lymphocytes [12]. IGF-1R is overexpressed on orbital fibroblasts and fibrocytes in both active and inactive TO [13]. Overexpression of IGF-1R and its interaction with TSH-R is a key pathogenetic lesion in this disease [10, 14]. TSH-R and IGF-1R create a physical and functional complex on the cell membrane of fibroblasts, B lymphocytes and T lymphocytes [15]. Autoantibodies to IGF-1R bind to this complex, leading to increased production of HA and several proinflammatory cytokines by T lymphocytes and monocytes and adipose tissue proliferation [16–19].

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TSH-R induces 2 signalling pathways mediated by G protein: the adenylyl cyclase/cyclic adenosine monophosphate (cAMP) pathway and the phosphoinositide 3-kinase (PI3K)/ protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway [20]. With the improvement of the tests for antibodies to TSH-R, it has been shown that both the inhibitory fraction (TBI) and the stimulatory fraction (TSI) of antibodies to TSH-R are highly and significantly correlated with the activity and severity of TO [21]. TSH-R as well as IGF-1R are involved in adipogenesis and share the same intracellular signalling through the PI3K/AKT/mTOR pathway. The relationship between TSH-R and IGF-1R in enhancing adipogenesis in TO suggests co-localisation of these 2 receptors on orbital fibroblasts [10].

Two types of immunosuppressive therapy are used to treat active TO: nonspecific and specific.

In nonspecific immunosuppression, the blocking agent prevents the immune system from attacking any antigen, but also impairs the body's ability to defend itself against infection. In specific suppression, the blocking agent restricts the immune system from attacking one or a specific number of antigens.

Nonspecific immunosuppressive therapies used to treat TO include glucocorticosteroids, azathioprine, cyclosporine, methotrexate, and mycophenolate. The results of an experimental study on the administration of anti-thymocyte globulin in the treatment of moderate to severe active and steroid-resistant TO were also published [22].

Glucocorticosteroids inhibit inflammation and immune response through direct and indirect genomic effects, and non-genomic mechanisms involving stimulation of lipocortin synthesis by inhibiting the production of leukotrienes, among others. They also inhibit the formation and release of cytokines and cell adhesion factors, fibroblast activity, and the production of collagen and glycosaminoglycans [23, 24].

Cyclosporine inhibits calcineurin, preventing the secretion of interleukin-2 by CD4+ T lymphocytes [25].

Azathioprine, a prodrug converted first to 6-mercaptopurine (6-MP) and then to the corresponding nucleotide, thioinosinic acid, which inhibits the purine synthesis necessary for cell proliferation through false nucleotide attachment [26, 27].

Methotrexate inhibits the enzyme dihydrofolate reductase, which in turn inhibits DNA, RNA, and protein synthesis [28–30].

Mycophenolate inhibits inosine monophosphate dehydrogenase, leading to inhibition of the guanosine monophosphate synthesis pathway de novo, resulting in depletion of the guanosine triphosphate pool inhibiting lymphocyte proliferation [3, 31].

Specific immunosuppressive drugs used to treat TO include etanercept (ETA), adalimumab (ADA), infliximab (IFX), rituximab (RTX), tocilizumab (TCZ), teprotumumab (TEP), and batoclimab (BAT).

Discussion

The current 2021 European Group on Graves' Orbitopathy (EUGOGO) recommendations [6] include RTX, TCZ, and TEP among second-line drugs for the treatment of moderate to severe and active TO. BAT is undergoing clinical trials [32].

Tumour necrosis factor alpha (TNF-α) inhibitors

The pathogenesis of TO is associated with an increase in pro-inflammatory cytokines, including tumour necrosis alpha (TNF-α); therefore, TNF-α antagonists such as ADA, ETA, and IFX have found application in its treatment [33–36].

TNF-α inhibitors are monoclonal antibodies, antibody fragments, or fusion proteins. IFX is a monoclonal, chimeric, human-mouse (75%: 25% protein structure) immunoglobulin G1 (IgG1)-class antibody with a molecular weight of 149 kDa; ADA is a purely human IgG1-class antibody with a molecular weight of 148 kDa; ETA, is a fusion protein consisting of the extracellular portion of the TNFR2/p75 receptor (this portion binds TNF-α) fused to the Fc fragment of IgG1 [37].

Infliximab (IFX)

Only single case reports of successful use of IFX in the treatment of TO have been presented.

Komorowski et al. demonstrated the beneficial effect of treating a 58-year-old patient with active TO refractory to steroid therapy with a single dose of IFX [intravenous (*i.v.*) 300 mg — 3.7 mg/kg body weight, administered during 2 hrs.], documented by a significant reduction in inflammatory (clinical) activity index (CAS reduction from 7/10 to 3/10 points), severity as defined by the NO SPECS score, as well as a reduction in inflammatory activity on magnetic resonance imaging (MRI) 5 weeks after IFX infusion [34].

Durrani et al. presented a case report of treatment with IFX (*i.v.* 5 mg/kg body weight) of a 46-year-old patient with active OT and optic nerve neuropathy (DON), with therapeutic success in the form of reduction of clinical activity score (CAS) (from 10/10 to 3/10 points) and disappearance of optic disc oedema 72 hours after the drug application [38].

Etanercept (ETA)

Paridaens et al., in a pilot study, presented 10 patients with mild to moderate TO treated with ETA [25 mg twice weekly subcutaneous (*s.c.*) for 12 weeks]. The av-

Table 1. *Monoclonal antobodies used in the treatment of thyroid orbitopathy (TO)*

	In vitro study	Case report	Retrospective/prospective study	RCT	Cost of the treatment
IFX		Komorowski et al. [34] (n = 1) Durrani et al. [38] (n = 1), DON			
ETA		Boskovic et al. [39] (n = 1)	Paridaens et al. [33] (n = 10)		
ADA	Van Steensel et al. [35] (n = 10)		Ayabe et al. [36] (n = 10)		
RTX			Karasek et al. [43] (n = 10)	Stan et al. [40] (n = 25) Salvi et al. [41] (n = 9) Salvi et al. [42] (n = 32)	0.5 g single dose 1698 EUR 4914 USD [75]
TCZ		Russell et al. [47] (n = 2) Rymuza et al. [53] (n = 1) Albrashdi et al. [5] (n = 1)	Pérez-Moreiras et al. [48] (n = 54) Sánchez-Bilbaoet al. [49] (n = 48) Ceballos-Macíaset al. [50] (n = 8) Dorado Cortezet al. [51] (n = 10) Moi [52] (n = 10)	Perez-Moreiraset al. [2] (n = 32)	Four doses 4266 € 14,519 $ [75]
TEP		Clinical cases in DON treatment [64–68]	Jain et al. [4] (n = 6) Diniz et al. [63] (n = 21)	Smith et al. [60] (n = 42) Douglas et al. [5] (n = 41) Douglas et al. [61] (n = 51)	Per course of treatment is about 360,000 USD Not approved in the EU [75]
BAT			Jones et al. [82] (n = 7)	Kahaly et al. [83] (n = 65)	

Monoclonal antibodies used in the treatment of TO. IFX — infliximab; ETA — etanercept; ADA — adalimumab; RTX — rituximab; TCZ — tocilizumab; TEP — teprotumumab; BAT — batoclimab; N — number of patients in the study; RCT — randomised clinical trial; EU — European Union

erage duration of TO was 4 months (2–6 months). All patients were euthyroid for at least 2 months. The average CAS score before treatment was 4, which decreased to 2.6 after 6 weeks of treatment, and 1.6 after 12 weeks of treatment (a 60% reduction). However, 3 patients had a recurrence of TO after discontinuing ETA. The authors showed that ETA significantly reduces inflammatory activity in mild-to-moderate TO, positively affecting TO inflammatory activity (CAS) rather than disease severity [33].

Similarly, a good therapeutic effect of ETA was achieved by Boskovic et al. who presented a patient with TO and rheumatoid arthritis (RA). Eighteen months after the diagnosis of TO, due to the insufficient efficacy of previous RA treatment, ETA was used in combination with methotrexate. ETA was administered at a dose of 25 mg twice a week *s.c.* After 4 months, there was an improvement in ocular symptoms, a reduction in exophthalmos from 23 mm to 21 mm, as well as a reduction in disease activity from CAS 4 to 1 point and a reduction in oculomotor muscle oedema on computed tomography (CT) scan. There was also a reduction in thyrotropin receptor antibody (TRAb) levels from a baseline of 4.54 to 1.54 IU/mL [39].

Adalimumab (ADA)

Van Steensel et al. in an in vitro experimental study examined the effects of imatinib mesylate and ADA in a whole orbital tissue culture system [35]. Orbital adipose tissue collected from TO patients (n = 10) was cultured with or without imatinib mesylate or ADA. Platelet-derived growth factor subunit B (PDGF-B) and TNF-α mRNA expression levels were determined in orbital tissue, and interleukin 6 (IL-6) and hyaluronan levels were determined in tissue culture supernatants. ADA significantly ($p = 0.005$) reduced IL-6 concentrations and the degree of its reduction non-significantly correlated positively with TNF-α mRNA levels in orbital tissue. The researchers showed that ADA reduces IL-6 concentrations but did not affect hyaluronate production in the orbit. Therefore, it can be expected that ADA mainly reduces inflammation [35].

Ayabe et al. presented the results of a retrospective study conducted in a group of 10 patients in the active phase of TO to evaluate the efficacy of ADA administered *s.c.* (10 weeks of treatment, one injection of 80 mg followed by an injection of 40 mg twice a week) [36]. Six of the 10 patients showed a reduced inflammation as assessed by the CAS index, while 3 showed an increase, and one remained unchanged. One patient experienced a significant complication (hospitalisation for sepsis). Analysing the data from all 10 patients, there was no significant change in the CAS index after 3 months of ADA treatment. Analysing separately the 5 patients with high baseline CAS index (> 4) showed a significant regression (by a mean of 5.2 ± 2.7; $p < 0.01$) after ADA treatment. Four of the 5 patients also reported subjective improvement in TO symptoms. There was no improvement in proptosis or ocular motility disturbances [36].

The study results and case reports suggest that anti-TNF-α therapy may benefit patients with TO. Nevertheless, all the mentioned authors point to the need for larger studies to confirm its efficacy and safety.

Rituximab (RTX)

RTX is a chimeric monoclonal antibody directed against the CD20 antigen, a membrane protein expressed on the surface of mature B lymphocytes and pre-B lymphocytes, blocking B lymphocyte activation and differentiation. Reports on its efficacy in TO treatment are ambiguous.

Stan et al. [40] conducted a prospective, randomised, double-blind, placebo-controlled clinical trial that included 25 (13 received RTX) patients with moderate to severe and active TO, in which they compared the efficacy of RTX (2×1000 mg) versus placebo. The authors showed no advantage of RTX over placebo in reducing both inflammatory activity (CAS) and TO severity (NOSPECS) at 24 and 52 weeks of follow-up. Measured by CT scan, muscle volume and orbital fat volume were not significantly altered from baseline in either group. Proptosis decreased by an average of < 1 mm in both groups at 52 weeks, and a reduction of ≥ 2 mm was observed in 3 of 10 placebo-treated patients and 2 of 10 RTX-treated patients. Improvement in the severity of orbitopathy according to NOSPECS was observed in 20% of subjects, a reduction in CAS score was observed in 31%, and adverse effects were observed in 62% of patients. Two patients, in the RTX group, developed DON during the study. The effect of RTX was estimated to be comparable to placebo [40].

Salvi et al. [41] in a study defined as an open pilot study examined a group of 9 patients with TO (7 with active TO, 2 with mild inflammatory symptoms) comparing the efficacy of RTX with that of intravenous methylprednisolone (*i.v.* MP) treatment in 20 consecutive patients. Patients treated with RTX received 1,000 mg *i.v.* twice with a 2-week interval and treatment with *i.v.* MP was administered at a dose of 500 mg for 16 weeks. TO activity was evaluated using the CAS score, and its severity was classified using the NOSPECS classification. CAS values before RTX administration were 4.7 ± 0.5 and decreased to 1.8 ± 0.8 at the end of follow-up (significantly more compared to *i.v.* MP). Proptosis decreased significantly after RTX in both patients with active and inactive TO. Recurrence of active TO was not observed in RTX-treated patients, but it occurred in 10% of *i.v.* MP-treated patients, who also had a higher incidence of side effects (45 *vs.* 33% of patients). All patients achieved a significant reduction in peripheral B lymphocytes after the first RTX infusion [41].

In another randomised, double-blind study [European Clinical Trials Database (EudraCT) 2007-003910-33], Salvi et al. compared RTX with *i.v.* MP in patients with moderate to severe and active TO [42]. Thirty-two patients were randomly assigned to receive *i.v.* MP (7.5 g) or RTX (2000 or 500 mg). The researchers showed a significantly better response to RTX compared to *i.v.* MP. At week 24, all patients treated with RTX showed a reduction in OT activity, compared to 69% in the group receiving *i.v.* MP. At week 52, no patient in the RTX group showed a recurrence of OT activity, as opposed to 31% in the *i.v.* MP group. Patients treated with RTX had better ocular mobility scores after 52 weeks. The total number of rehabilitative surgical procedures performed during follow-up (after 76 weeks) was 12 in 16 patients in the *i.v.* MP group and 5 in 15 patients in the RTX group [42].

Similar results have also been shown with very low-dose RTX [43]. The study was conducted in 10 patients with moderate to severe and active TO treated

with a single dose of 100 mg of RTX. Indications for RTX administration were persistently high TO activity (n = 4) or its recurrence (n = 3) after previous treatment with *i.v.* MP (mean cumulative MP dose was 7.3 ± 1.9 g) or contraindications to *i.v.* MP therapy (n = 3). The researchers assessed changes in CAS score, proptosis, thyrotropin hormone receptor antibody levels, and reductions in CD19+ and CD20+ B lymphocytes. There was a significant decrease in CAS after one month (2.0 ± 0.8), after 6 (0.8 ± 0.4) and 12 months (0.4 ± 0.9) compared to baseline values (3.6 ± 0.9). Proptosis compared to the mean baseline value of 22.3 ± 1.6 mm decreased non-significantly at one month and 6 months (21.8 ± 1.6 and 21.5 ± 1.7 mm, respectively) and significantly from baseline at 12 months (21.1 ± 1.8 mm) after RTX treatment. Two patients (20%) developed DON requiring orbital decompression after treatment [43].

Given the side effect profile and especially the risks of DON, RTX is considered a second- or even third-line treatment option.

Tocilizumab (TCZ)

TCZ is a monoclonal antibody against the receptor for IL-6. IL-6 is a pro-inflammatory cytokine produced by various cells, including fibroblasts, monocytes, and T and B lymphocytes, which are involved in the pathogenesis of TO [8].

The US Food and Drug Administration (FDA) approves TCZ for the treatment of active moderate to severe rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, giant cell arteritis syndrome, interstitial lung disease associated with systemic sclerosis, cytokine release syndrome (CRS), and coronavirus disease 2019 (COVID-19), and studies are being conducted on its use in the treatment of TO [2, 44–46]. According to current guidelines on TO treatment strategies, TCZ has been indicated as one of the recommended second-line therapies for moderate to severe and active TO [6, 7].

Russell et al. reported the results of a small study (2 patients) in which they showed that TCZ significantly affects both inflammatory activity and severity of TO in patients with contraindication to *i.v.* MP treatment [47]. The first patient underwent oral steroid therapy, and visual acuity (VA) decreased to a count of fingers (CF) in right eye and 20/200 in left eye. Combination treatment with *i.v.* MP and methotrexate were started, and although there was clinical improvement, treatment had to be discontinued due to lack of glycaemic control, insomnia, more than 30 kg weight gain, as well as gastrointestinal pain and diarrhoea. Bilateral endoscopic orbital decompression was performed, and treatment with TCZ (8 mg/kg body weight once a month *i.v.*) was started at that time. CAS at the time of TCZ inclusion was 6 points. Within 2 months of starting TCZ treatment, her VA improved to 20/30 in each eye, and CAS decreased to 2 points. The second patient was a patient with comorbidities of TO and RA. His CAS score was 6, and his TSI ratio was 432% of the reference value. After 3 weekly doses of 500 mg *i.v.* MP, there was clinical improvement in TO, but there was weight gain, insomnia, and gastrointestinal complications. TCZ was administered (8 mg/kg once a month *i.v.*), which resulted in immediate clinical improvement, and within 4 months, CAS had dropped to 1 point, and TSI decreased to 165% of the reference value [47].

Perez-Moreiras et al. reported the results of an RCT that included patients with moderate to severe and active OT who had not responded to prior *i.v.* MP treatment (n = 32) [2]. Patients were treated with monotherapy *i.v.* TCZ at a dose of 8 mg/kg body weight once a month administered for up to 12 weeks while evaluating treatment results up to week 28. The researchers demonstrated a reduction in CAS (86% achieved CAS < 3 *vs*. 35% in the placebo group, $p < 0.005$) at week 16 of treatment. There was an insignificant effect on proptosis reductions at week 28 (mean reduction of 1.5 mm), while there was no effect on diplopia or quality of life. TCZ was well tolerated; the most common side effects were infections and headaches [2].

Pérez-Moreiras et al. also presented the results of a retrospective long-term study examining 114 patients with steroid-resistant TO treated with TCZ, of whom 54 met the study inclusion criteria [48]. The authors obtained an absolute response in the form of CAS reduction to 1 or 0 points in 74% (37/50) of patients after the fourth dose of TCZ (at week 16) with normalisation of TRAb level in 55% (23/42) of patients. A relative response with a CAS reduction of ≥ 2 points was achieved in 90.9% of patients (40/44) after the first dose of TCZ (at week 4). After the last dose of TCZ, reduction of proptosis (reduction of ≥ 2 mm) was found in 78% of patients (42/54), eyelid retraction (reduction of ≥ 2 mm) in 75% of subjects (33/44), and regression of diplopia 68% (19/28). Four patients experienced recurrence, defined as an increase in CAS of ≥ 2 points within 6 months of stopping treatment. Most side effects were mild in severity [48].

Another study of 48 patients (95 affected eyes) who did not respond to the standard *i.v.* MP treatment regimen showed a similar high efficacy of TCZ [49]. TCZ was administered at 8 mg/kg body weight — *i.v.* every 4 weeks or 162 mg *s.c.* weekly, either as monotherapy or in combination with conventional immunosuppressive drugs (methotrexate: 7.5–25 mg/*s.c.* or *per os* (*p.o.*)/week and azathioprine: 100–150 mg/*p.o.*/day). According to the EUGOGO group severity classification, all patients had a moderate to severe form of TO, and DON was diagnosed in 7 patients included in the study. The mean baseline

CAS score was 4.64 ± 1.5, and the mean CAS score after one year of treatment was 1.05 ± 1.27 points. After a mean follow-up of 16.1 ± 2.1 months, 79 of 95 (83.2%) and 88 of 95 eyes (92.6%), respectively, achieved CAS ≤ 3 and the expected clinical response (CAS reduction of at least 2 points). The mean baseline intraocular pressure was 19.05 ± 4.1 mm Hg, which decreased to 16.73 ± 3.4 mm Hg after one year of treatment. In patients with DON, the mean baseline best corrected visual acuity (BVCA) was 0.84 ± 0.18, and after one year of TCZ treatment it was 0.86 ± 0.18. Clinical improvement in this small group did not result in statistically significant differences (p = 0.451). The drug was well tolerated, and most patients showed clinical improvement (92%) [49].

Similarly, in a small study, 8 glucocorticosteroid-resistant patients with moderate to severe and active OT showed a beneficial effect of TCZ (*i.v.* 8 mg/kg body weight/month) assessed by CAS scale and proptosis measurement [50]. The mean TRAb level at the beginning of treatment was 291.9 ± 96.4% of the reference value, the mean inflammatory activity assessed through the CAS scale was 4.1 ± 0.3, and the mean proptosis was 21.2 ± 3.2 mm. After TCZ treatment, the mean TRAb level decreased to 172.7±54% of the reference value (p = 0.001), the mean CAS value to 1.1 ± 0.6 (p = 0.001), and the mean proptosis to 19.3 ± 2 mm (p = 0.02) [50].

Dorado Cortez et al. presented the results of a single-centre prospective study involving *i.v.* TCZ treatment for active corticosteroid-resistant TO. Ten patients were included in the study, including 3 with DNO. There was a significant improvement in CAS in 100% of patients included in the study, with a 4.5 ± 1.2-point reduction (p = 0.003). There was also a significant reduction in TSI after treatment, from 21.7 ± 22.9 at baseline to 4.0 ± 3.3 U/L. On average, 3 infusions were needed to reduce TSI levels significantly. The authors concluded that TCZ treatment may be beneficial in TO with DON and is effective regardless of the initial TSI level [51].

Moi et al. presented the results of a retrospective study of 10 patients with moderate to severe TO refractory to standard *i.v.* MP treatment with TCZ (*i.v.* 8 mg/kg body weight per month in monotherapy for 6 months, followed by *s.c.* 162 mg once a week for another 6 months and once every 2 weeks for an additional 6 months). The mean CAS value at the start of TCZ treatment was 4.80 ± 1.13 points. All patients showed a reduction in CAS; the mean value after 6 months was 0.70 ± 0.82 points. Half of the patients had a CAS value of 0 after 6 months. Proptosis decreased from 23.20 ± 2.10 mm to 20.60 ± 2.01 mm after 6 months (mean reduction 2.90 ± 1.37 mm). Mean TRAb levels decreased from 12.79 ± 11.92 U/L at the start of the study to 3.20 ± 4.57 U/L after 6 months. Treatment was generally well tolerated. Mild to moderate side effects were observed in 4 patients [52].

Rymuza et al. presented a case report on the use of TCZ in a 40-year-old patient after previous unsuccessful multistage TO treatment. The earlier treatment included 2 cycles of *i.v.* MP, at cumulative doses of 4.25 g (with subsequent orbital decompression) and 7.5 g, respectively, and subsequent radiotherapy (20 Gy in 10 fractions) along with oral glucocorticosteroid replacement therapy. At the beginning of treatment with TCZ (*i.v.* 8 mg/kg body weight, once a month for 4 months), the CAS score was 6 points, and proptosis was 28 mm in the right eye and 27 mm in the left eye. After 4 months of treatment, there was the resolution of pain, reduction of the CAS score to 2 points, and reduction of proptosis to 24 mm in the right and left eyes. The treatment was well tolerated, and no serious side effects were reported. The positive effects of TCZ treatment were maintained over a 2-year follow-up period [53].

Similarly, effective treatment with TCZ (*i.v.* 8 mg /kg body weight, once a month for 4 months) was presented as first-line treatment in a 9-year-old girl with a history of hyperthyroidism for 4 months and progressive TO [54].

The presented results of clinical trials and a case report evaluating the effect of TCZ in patients with TO refractory to first-line treatment showed promising results. The main limitation of these studies is the lack of a control group due to their retrospective nature and small study groups. TCZ is a therapeutic option for glucocorticosteroid-resistant TO. It should be considered as a second-line treatment due to the cost of treatment, or as a first-line treatment in patients with contraindications to *i.v.* MP. However, given its numerous advantages over steroids (high response rate and lower rate of adverse events), further RCTs should be conducted to evaluate the possible place of TCZ as first-line treatment for moderate to severe and active TO.

Teprotumumab (TEP)

There are high expectations with the inclusion of a monoclonal antibody against the receptor for IGF-1 (IGF-1R), TEP, for the treatment of active TO. IGF-1R is overexpressed in fibroblasts and orbital lymphocytes in TO patients. It forms a functional complex and mediates signal transduction through TSH-R [10–12]. TEP is a fully humanised monoclonal IgG1 inhibitory antibody. It binds to the cysteine-rich domain of human IGF-1R with high affinity, preventing binding to endogenous ligands (IGF-1 and IGF-2) and leading to internalisation and degradation of IGF-1R, thus stopping the IGF-1R signalling cascade [55–57].

TEP is approved in the US for the treatment of TO and is administered as an intravenous infusion every 3 weeks for up to 8 infusions [60]. The first dose is 10 mg/kg body weight, and the next 7 infusions are given at 20 mg/kg body weight. The infusion time is initially 90 minutes, which can be reduced to 60 minutes after the first 2 infusions if TEP is well tolerated [58]. TEP is not currently approved in the EU [6].

The pharmacokinetics of TEP administered *i.v.* are consistent with those of other IgG1 antibodies [59]. The pharmacokinetics of *i.v.* administration of TEP follow a 2-compartment model with an average clearance of 0.27 L/day and an average elimination half-life of 20 days. At the therapeutic dose of TEP, a minimum concentration of > 20 mg/mL is achieved, which is predicted to maintain > 90% IGF-1R saturation [59].

The efficacy of TEP in patients with moderate to severe and active TO has been studied in randomised, double-masked clinical trials (NCT01868997 and NCT03298867): the phase III OPTIC trial [5] and an earlier phase II trial [60], as well as the open-label expanded OPTIC trial (OPTIC-X), which included patients from the OPTIC trial who did not respond to treatment or had a relapse during post-treatment follow-up [61].

Patients were randomized to receive 8 *i.v.* infusions of TEP (10 mg/kg body weight in the first dose, followed by 20 mg/kg body weight) or placebo, administered at 3-week intervals for 21 weeks. Treatment efficacy was measured at week 24 (3 weeks after the last infusion) [5, 60].

In the study by Smith et al., 42 patients were included in the study group, and the primary endpoint was a CAS reduction of 2 points or more and a reduction in proptosis of 2 mm or more at week 24. 69% of TEP-treated patients compared to 20% of the placebo group achieved the primary endpoint at week 24 ($p < 0.001$), and differences between groups increased at further time points, reaching 73% of patients in the TEP-treated group (*vs.* 14% in the placebo group). No serious adverse events were reported, and the only adverse event was hyperglycaemia in patients with comorbid diabetes [60].

Similar results were presented by Douglas et al., who at week 24, showed a significantly higher percentage of patients who achieved a reduction in proptosis of more than 2 mm in the TEP group compared to the placebo group (83% *vs.* 10%, $p < 0.001$). Diplopia disappeared in 53% of patients (compared to 25% of patients in the placebo group), and the mean CAS score reduction was 3.4 points (59% *vs.* 21%, $p < 0.001$) [5].

Jain et al., in a retrospective study of 6 patients previously enrolled in a phase III clinical trial of TEP (OPTIC, NCT03298867) with active TO who received 24 weeks of TEP treatment and had pre- and post-treatment orbital imaging (CT or MRI), demonstrated a reduction in extraocular muscles (EOM) and orbital fat volume in the TEP group [62]. The total volume of EOM within each orbit was significantly reduced after TEP treatment in all patients showing no statistical difference at the time compared to the control group of subjects without TO. The authors also showed a reduction in total orbital fat volume in all subjects of the study group. Overall EOM inflammation based on the MRI signal intensity ratio was reduced in 8/8 orbits ($n = 4$ patients, $p < 0.01$) [4].

The OPTIC-X trial was conducted in 7 US states and 5 European centres. It was an open extension of the OPTIC trial, in which patients matching the inclusion criteria could participate immediately after the OPTIC trial or at any time during the follow-up period [61]. The OPTIC-X study included 51 patients who had previously received a placebo ($n = 37$) or TEP ($n = 14$) and who did not have a response in terms of proptosis reduction or had a relapse (proptosis increase of ≥ 2 mm and/or CAS increase of ≥ 2 points) during the 48-week follow-up period in the OPTIC study. Patients who received a placebo in the OPTIC trial received a first course of TEP or a second course (if they had previously received TEP), consisting of 8 infusions over 24 weeks [63]. In the OPTIC-X trial, 33 of the 37 placebo-treated patients in the OPTIC trial (89.2%) responded to TEP treatment with an average proptosis reduction of 3.5 ± 1.7 mm. The response to treatment was comparable to the results obtained in the OPTIC trial, although patients had a longer duration of TO. The beneficial effect of TEP was sustained in > 85% of patients with reductions in proptosis (29 of 32 patients, 90.6%), diplopia (12 of 14 patients, 85.7%), and CAS reduction to 0 or 1 (20 of 21 patients, 95.2%) up to 27 weeks after the last infusion. Of the 5 patients who did not respond to TEP treatment in the OPTIC trial, 2 had a response in the OPTIC-X trial in the form of a reduction in proptosis of > 1.5 mm from baseline. Of the patients responding to TEP treatment in the OPTIC trial who developed relapse, 5 of 8 patients (62.5%) had a response after re-treatment (mean reduction in proptosis of 1.9 ± 1.2 mm from baseline in the OPTIC-X trial and 3.3 ± 0.7 mm from baseline in the OPTIC trial). The results presented here show that re-treatment with a second course of TEP can be effective in TO [61].

Ugradar et al. [62] conducted a post hoc analysis of the results of TEP treatment in 2 placebo-controlled phase II [60] and phase III RCTs [5]. Twenty-four patients (10 men, 14 women) with proptosis reduction from baseline < 2 mm at week 12 who received TEP were included in the study. Eight patients were from the Phase III study, and 16 were from the Phase II

study. In the TEP group, of the 24 patients who did not show improvement in terms of a proptosis reduction of ≥ 2 mm from baseline after 12 weeks, 15 (63%) showed clinically significant improvement of ≥ 2 mm at week 24. At 12 weeks, 22 patients (92%) in the TEP group experienced a significant reduction in CAS (≥2 points), and by week 24, all patients had achieved this reduction. Twenty-two of 24 patients (92%) in the TEP group had grade > 0 diplopia at the start of the study. At 12 weeks, 12 of 22 patients (55%) had improved diplopia by ≥ 1 degree (Gorman diplopia scale). At 24 weeks, 16 patients (73%) had improved diplopia by ≥ 1 degree. The authors showed variability in the time needed for a clinically significant response to TEP; therefore, some patients may require a longer time to achieve a therapeutic response [62].

Diniz et al. presented the results of a population study that included 21 patients with active TO treated with TEP according to the recommended standard dose and regimen. At 24 weeks of treatment, there was a significantly significant mean reduction in exophthalmos of 2.5 ± 1.8 mm ($p < 0.001$), a reduction in CAS score of 2.2 ± 1.4 points ($p < 0.001$), and an improvement in ocular motility of 16.9 ± 19.3 degrees ($p < 0.001$). The use of standard TEP treatment in 3 patients with DON refractory to *i.v.* MP treatment showed significant improvement after initiation of treatment persisting until week 24 [63].

Several clinical cases have also been published on the successful use of TEP in the treatment of DON in patients with no response to conventional *i.v.* MP and radiotherapy [64–68]. This may be an effective treatment option, but due to limited data, studies comparing the efficacy of TEP with the current gold standard treatment, orbital decompression surgery [69], are needed.

TEP is generally well tolerated, and most patients in clinical trials completed the treatment course. The most common adverse events (AE) were muscle cramps (25%), nausea (17%), alopecia (13%), diarrhoea (13%), fatigue (10%), hearing deterioration (10%), and hyperglycaemia (8%) [4, 5, 60, 61]. During RCTs of TEP treatment, hyperglycaemia was generally mild, and most patients with hyperglycaemia had pre-existing diabetes [70, 71]. Most hearing impairment during clinical trials was transient and resolved without treatment [5, 60], but long-term and potentially irreversible hearing loss cases have been reported [72–74].

The general inclusion of TEP in routine clinical practice is currently limited by the lack of comprehensive data on its long-term efficacy and safety, the lack of a head-to-head comparison with *i.v.* glucocorticoids, and the drug cost. The cost of TEP per course of treatment is about 360,000 USD for a 75-kg patient, more than 5000 times higher than the cost of *i.v.* MP [75].

Batoclimab (BAT)

Transmission of maternal antibodies to the foetus is made possible by proteins called neonatal Fc receptors (FcRn). FcRn is a beta-2 macroglobulin-associated protein with structural similarity to the major class I tissue compatibility receptor (MHC-I) family. FcRn is monomorphic, undergoes quasi-ubiquitous expression, and is expressed in various body tissues, including epithelium, endothelium, hematopoietic cells, intestinal cells, kidney, liver, and placenta [76, 77]. FcRn prevents IgG catabolism by inhibiting their lysosomal degradation and facilitating their extracellular release at physiological pH, consequently prolonging the half-life of IgG. By competitively binding to the IgG binding site on FcRn, BAT blocks FcRn-mediated IgG recycling, resulting in increased degradation and elimination with subsequent reduction in IgG levels [76]. This mechanism can be used in a variety of autoimmune diseases where degradation of IgG molecules can be achieved by blocking FcRn receptors, which is a logical therapeutic approach [78–83].

There are currently numerous clinical trials of FcRn antagonists in various autoimmune diseases, including chronic inflammatory demyelinating polyneuropathy, rheumatoid arthritis, primary Sjogren's syndrome, bullous pemphigoid, and optic neuritis spectrum but also in thyroid orbitopathy (NCT05015127) [78].

BAT (IMVT-1401) is a selective, fully human monoclonal antibody with high affinity for the IgG binding site on the FcRn. It may provide clinical benefit to TO patients by reducing pathogenic IgG levels including TRAb [84].

Jones et al. reported the results of a multicentre, open-label, proof-of-concept (POC) phase 2a trial conducted at 4 centres in Canada in 7 patients with positive TRAb, moderate to severe and active TO (CAS score ≥ 4 points) (NCT03922321) [82]. At the qualification for the study, the mean CAS score was 5.4 ± 1.1 and the proptosis was 23.1 ± 3.3 mm. The main aim of the study was to evaluate the safety, tolerability, and pharmacodynamic effects of BAT. BAT was administered as a weekly *s.c.* injection of 680 mg for 2 weeks, followed by a weekly *s.c.* injection of 340 mg for 4 weeks; the observation period was 11 weeks. Clinical efficacy was assessed weekly by evaluating proptosis reduction (reduction of ≥ 2 mm in the study eye without worsening in the other eye). A positive response as a CAS score reduction was defined as a CAS score of 0 or 1 point. All 7 patients completed the 6-week treatment period, and 5 (71.4%) completed the 12-week follow-up phase. Serum IgG levels decreased by an average of 64.8% and TRAb by 56.7% at week 6 compared to baseline. Similar reductions were also observed for each IgG subclass. Three of the 7 patients

achieved proptosis reductions of ≥ 2 mm (42%) with an average group reduction of 1.3 mm, and 4 patients achieved CAS reductions to 0 or 1 point. Three of the 7 patients had a combined response regarding proptosis and CAS reduction. All AEs were mild to moderate in severity, and no participant reported serious AE or treatment discontinuation due to AE. The most common AEs were increased tearing, fatigue, and dizziness (n = 2 for each) [82].

Kahaly et al. were the first to report the results of a multicentre, randomised, double-blind, placebo-controlled phase 2b study that was conducted at 19 centres in Canada, Europe, and the United States (NCT03938545) to evaluate 3 BAT dosing regimens (680 mg, 340 mg, and 255 mg) versus placebo administered weekly for 12 weeks [83]. The authors evaluated the effect of BAT treatment on serum TRAb, IgG, and 4 IgG subclasses and the response in terms of a ≥ 2 mm reduction in proptosis, a reduction in CAS score (gaining 0 or 1 point), and a reduction in diplopia (improvement of ≥ 1 grade on the Gorman diplopia scale) at 12 weeks after baseline. The authors showed an early (after 2 weeks) and significant (30–60%) reduction in total IgG levels in all 3 groups receiving different doses of BAT compared to the placebo group. They also showed a significant and dose-dependent reduction in TRAb levels with a peak at week 12 ($p < 0.001$ for BAT 680 and 340 mg and $p < 0.05$ for 255 mg *vs.* placebo). There was a significant response in terms of reduction in proptosis in the BAT group compared to the placebo ($p < 0.05$) at multiple time points (at weeks 4, 5, and 11 in the BAT 680 mg group, and at weeks 5, 9, 11, and 13 in the BAT 340 mg group). However, there was no significant difference in proptosis between the BAT and placebo groups at week 12 after baseline. A significant difference in CAS response (score of 0 or 1 only) was also observed in the BAT groups ($p < 0.05$) at weeks 7 (255 mg) and 11 (680 mg) after starting treatment compared with placebo.

Comparative CT scans from before treatment and 12 weeks after BAT were available for 11 patients. A dose-dependent, significant ($p < 0.03$) reduction in EOM volume was observed 12 weeks after baseline for BAT 680 and 340 mg compared with placebo. No improvement from baseline was observed on the Gorman scale for assessing the severity of diplopia.

The randomised trial was discontinued due to an unexpected increase in serum cholesterol levels; therefore, data from 65 of the planned 77 patients were analysed. After the study was discontinued, post hoc analysis showed a dose-dependent increase in low-density lipoprotein cholesterol (LDL-C) at week 11 after baseline (58.9%, 29.2, 16.7%, and –3.1% in the BAT 680 mg, 340 mg, 255 mg, and placebo groups, respectively), with the increase reversible within 8 weeks of drug discontinuation [83].

Both studies [82, 83] showed significant reductions in TRAb and total serum IgG levels after BAT treatment. The randomised trial showed no significant difference between the BAT and placebo groups in response to a reduction in proptosis after 12 weeks. However significant differences were observed at several earlier time points. In addition, EOM volume decreased significantly at 12 weeks, while quality of life improved after 19 weeks in the BAT group with a dose of 680 mg. BAT was generally well tolerated, with decreases in albumin and increases in lipids that resolved after drug discontinuation.

Low-molecular-weight (small molecules) inhibitors for TSH and IGF-1 receptor

The goal of new research on alternative treatments for TO is to target the main autoantigens of the disease and/or molecules that play a key role in the immune response, like receptors for TSH and IGF, including the use of low-molecular-weight so-called small molecules [85]. Small molecule TSH-R antagonists bind to the transmembrane region of the receptor, acting in an allosteric pattern to block signalling but not binding of TSH or TRAb [86]. These compounds are becoming a new class of therapeutic agents with great potential for treating patients with Graves' disease (GD) or TO [87, 88].

Turcu et al. demonstrated in an in vitro study that a small reversible TSH-R antagonist (NCGC00229600) reduces HA synthesis in orbital fibroblasts/adipocytes in TO [89]. It inhibited basal production of cAMP, phospho-Akt protein (pAkt), and HA, and their production stimulated by TSH-R-stimulating autoantibodies in undifferentiated orbital fibroblasts. Inhibition of HA production was dose-dependent, with a half-maximal inhibitory dose of 830 nM.

K1-70 is a TSH-R antagonist that may offer new therapeutic tools for the treatment of patients with GD and TO. It binds specifically to TSHR with high affinity (4×1010 mol/L) and prevents TSH and TRAb from binding to the receptor, thereby blocking the stimulatory effects of these ligands [90].

Furmaniak et al. published the results of an open-label phase I study (NCT02904330) using ascending dose and different routes of administration (single intramuscular (*i.m.* or *i.v.*) of K1-70, evaluating the safety, tolerability, pharmacokinetics, and reduction of clinical TO symptoms in a group of 18 GD patients treated with antithyroid drugs [91]. K1-70 was administered *i.m.* in 12 patients in doses of 0.2 mg, 1 mg, 5 mg, and 25 mg, and 6 patients received K1-70 *i.v.* in doses of 50 or 150 mg. The expected pharmacodynamic effects occurred af-

ter a single dose of 25 mg *i.m.* or 50 mg or 150 mg *i.v.* and fT3, fT4, and TSH values reached the reference range for hypothyroidism. There was also a clinically significant improvement in symptoms of both GD (reduced tremors, better sleep, improved mental concentration, reduced toilet urgency) and TO (reduced proptosis from 1 mm (25 mg *i.m.*) to 8 mm (50 mg *i.v.*), inflammatory activity as determined by the CAS scale (by 1 point without significance), and reduction in hypersensitivity to light and lacrimation [91]. All subjects at all doses tolerated K1-70 well. No serious AEs were reported, and a better response to K1-70 was achieved with the *i.v.* route of administration.

Linsitinib (OSI-906) is a highly selective small molecule dual inhibitor of the IGF-1R and insulin receptor (IR) [92]. Linsitinib inhibits the intrinsic tyrosine kinase activity of IGF-1R by binding to the cytoplasmic tyrosine kinase domain, and it inhibits autophosphorylation upon ligand binding to IGF-1R and IR, blocking IGF-1-induced activation of further signalling pathways such as AKT and ERK [93].

Gulbins et al. reported the results of a study evaluating the efficacy of linsitinib in treating active and chronic phase TO in a mouse experimental model [94]. Linsitinib was administered orally daily, 7 days a week, for 4 weeks. Three different doses were tested in the group with active TO. The 60 and 30 mg/kg body weight doses were not well tolerated. They resulted in decreased in activity and weight loss, while the 10 mg/kg body weight dose provided good tolerability throughout the study. The 10 mg/kg dose was also used in the group with chronic TO. Linsitinib prevented autoimmune hyperthyroidism in the early stage of the disease by reducing morphological changes suggesting hyperthyroidism and blocking T-cell infiltration, as assessed by CD3 staining. In late-stage disease, linsitinib had a primary effect in the orbital region. Linsitinib reduced the immune infiltration of T cells (CD3 staining) and macrophages (F4/80 and TNFa staining) in the orbit, suggesting an additional direct effect on the autoimmune response. Treatment with linsitinib normalised the amount of brown adipose tissue in both the early and late TO groups. In an in vivo MRI study in the chronic phase group, inflammation was reduced, as assessed by decreased muscle swelling and brown adipose tissue formation. The authors showed that linsitinib effectively prevented the development and progression of TO in an experimental mouse model of GD.

Recently, the FDA authorised the initiation of a randomised, double-masked, placebo-controlled phase 2b study to evaluate the safety, pharmacokinetics, and efficacy of linsitinib administered orally twice daily, versus placebo, for 24 weeks in the treatment of patients with active moderate to severe TO. The results are unpublished at present.

Conclusions

The current EUGOGO guidelines [6] and the consensus statement of the American and European Thyroid Associations [75], recommend multidisciplinary treatment of TO and emphasise the well-established role of high doses of intravenous glucocorticoids by clinical studies and clinical use. The authors emphasise the beneficial effects of TEP, indicating, however, the lack of data on its long-term efficacy and safety and the lack of head-to-head comparison with *i.v.* glucocorticosteroids and its huge limitation is also the high price of the drug. TZC is a therapeutic option for glucocorticosteroid-resistant TO. It should be considered for second-line treatment (due to the cost of treatment, among other reasons) or first-line treatment in patients with contraindications to *i.v.* glucocorticosteroids. Given its side-effect profile, especially some risk of optic nerve neuropathy (DON), RTX is considered by the authors as a second- or even third-line treatment option. Given the numerous advantages of biologic drugs over glucocorticosteroids, further RCTs are indicated to confirm their possible place also as first-line treatment in TO [95].

Conflict of interest

Authors declare no conflict of interests.

Funding

This work was supported by the Medical University of Silesia, grant PCN-1/112/N/2/0.

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