Treatment of corticosteroid-resistant thyroid eye disease with subcutaneous tocilizumab

Within the last decade, novel biologics have emerged as a promising treatment for thyroid eye disease (TED), both as primary therapy and as an alternative to methotrexate or radiation in patients with steroid-refractory disease. Upregulation of several cytokines, including interleukin-6 (IL-6), have been implicated in the pathogenesis of TED.[1] Tocilizumab (RoActemra, Hoffman-La Roche, Basel, Switzerland) is a recombinant humanized monoclonal antibody inhibitor of the IL-6 receptor. Its off-label intravenous use has been previously described in 2 case reports and a randomized trial to demonstrate clinical improvement in corticosteroid-resistant TED.[2–4]

Although intravenous tocilizumab is well-tolerated in this patient population,[5] intravenous administration is time-consuming and resource intensive, and an expensive off-label use of an U.S. Food and Drug Administration (FDA)-approved medication is generally not covered by insurance. Prior studies have demonstrated that the safety and efficacy of tocilizumab are unchanged when administered subcutaneously (SC) versus intravenously in patients with rheumatoid arthritis.[6] In addition, a recent case series of 2 patients with TED demonstrated symptomatic improvement with 4 doses of 162 mg of tocilizumab delivered SC.[7] To date, however, there have been no published reports that explore the immunological response of TED patients treated with SC tocilizumab, or whether the achieved suppression of disease activity lasts more than 6 months after the initiation of therapy.

In this case series, the authors present the clinical course of 9 patients aged 40–84 years with chronic, active, symptomatically moderate to severe TED that improved with SC tocilizumab after other interventions failed or were not considered acceptable alternatives. Four patients treated in private practice (R.Z.S.) were clinically euthyroid at presentation and either had corticosteroid-refractory disease or refused initial treatment with corticosteroids secondary to comorbidities. The remaining 5 patients were treated at an academic medical centre (E.W.); they had corticosteroid-resistant and external beam radiation-resistant disease. Four failed immunosuppressive therapy with methotrexate. Three patients failed surgical decompression.

All patients showed clinical improvement after treatment with SC tocilizumab with an average drop in clinical activity score (CAS) of 2.8 points. In those for whom thyroid stimulating immunoglobulin (TSI) was followed, levels decreased or remained steady after administration of subcutaneous tocilizumab. The cases are summarized in Table 1. Informed consent was obtained for each patient before treatment. All patients with TED treated with subcutaneous tocilizumab by the authors between 2018 and 2020 were included in the study. This review is compliant with the provisions of the Health Insurance Portability and Accountability Act of 1996 and adhered to the World Medical Association's ethics principles for medical research involving human subjects outlined in the Declaration of Helsinki.

Tocilizumab was originally approved for the treatment of rheumatoid arthritis. It has since received FDA approval for use in giant cell arteritis and juvenile idiopathic arthritis.[8] This biologic hinders IL-6, a cytokine implicated in several autoimmune diseases, including TED,[9] from exerting its pro-inflammatory effects. Blockage of IL-6 results in decreased lymphocyte activation and B- and T-cell homeostasis.

The 9 cases described in this series demonstrate the range of both clinical and immunological responses to subcutaneous tocilizumab in treating moderate-to-severe, longstanding, corticosteroid-, methotrexate-, radiation-, and surgery-resistant TED. Improvements in proptosis, eyelid edema, diplopia, extraocular movement, visual acuity, color vision, and TSI level were noted. After initiation of subcutaneous tocilizumab, the patients were followed for an average of 24.6 weeks, with a range of 7 to 84 weeks. A positive clinical response was observed for each member of the cohort; CAS decreased by an average of 2.8 points, with an average pretocilizumab score of 4 (range 2–7) and an average post-tocilizumab score of 1.2 (range 0–3).

In the subcohort in which TSI was followed after initiation of therapy, 3 of 4 patients demonstrated meaningful declines in TSI, with a 70% reduction occurring as quickly as 4 weeks after treatment onset (patient 1). This response was notably sustained in patient 4, who experienced a continued decline in TSI 36 weeks after the first injection and 13 weeks after the last injection. In the 3 TSI-responsive patients, a decline in TSI was, on average, noted within 9 weeks of the first tocilizumab injection, a time course that compares favourably to a previous report of 4–5 months for intravenous tocilizumab.[10] This TSI response may represent a disease-modifying effect of tocilizumab in TED, which appears intact via subcutaneous administration.

That refractory, chronic, corticosteroid-resistant TED patients, well into the course of their disease, responded to an 8-week or longer course of subcutaneous tocilizumab is highly significant. Copperman et al[7] achieved significant CAS reduction with 4 doses of 162 mg subcutaneous tocilizumab administered over the course of 4 or 8 weeks. Similarly, we observed reduction in CAS and TSI after a series of 8 or longer weekly SC injections. Intravenous tocilizumab, in contrast, was studied over a 12-week period in patients treated within 5 months to 5 years of disease presentation.[2]

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Table 1—Summary of studied patients' demographics, disease histories, treatment regimens, and outcomes

Patient No.	Age, y	Sex	Race	Tobacco Use	Time Since TED Diagnosis at Initial Presentation	VISA/CAS on Presentation	Length of Pretocilizumab Treatment	Pretocilizumab Treatment Regimen	Pretocilizumab TSI (IU/L)	Pretocilizumab VISA/CAS	Tocilizumab Regimen	Post-Tocilizumab TSI	Post-Tocilizumab VISA/CAS
1	74	F	Caucasian	Nonsmoker	18 mo	2/2	1 mo	• Chronic oral prednisone 1 mg daily (for comorbid polymyalgia rheumatica)	3.13	4/4	162 mg/mL, subcutaneous, weekly (8 injections)	2.2	1/1
2	67	F	Caucasian	Smoker	1 y	2/2	3 mo	• None	2.33	4/4	162 mg/mL, subcutaneous, weekly (8 injections)	1.76	2/2
3	84	F	Caucasian	Ex-smoker	60 y	3/3	4 mo	• IV methylprednisolone 500 mg weekly (7 infusions)	2.55	6/6	162 mg/mL, subcutaneous, weekly (8 injections)	2.53	2/2
4	75	F	Caucasian	Nonsmoker	2 mo	2/2	5 mo	• IV methylprednisolone 500 mg weekly (12 infusions)	39.5	5/5	162 mg/mL, subcutaneous, weekly (8 injections)	5.65	3/3
5	56	F	Asian	Nonsmoker	2 y	5/5	5 mo	• IV solumedrol 1 g q 3 days (3 infusions) • Methotrexate 10 mg weekly • Surgical decompression • EBRT (20 Gy in 10 sessions) • Plasmapheresis	35	3/3	162 mg/mL, subcutaneous, weekly (continuously)	n/a	0/0
6	40	F	Caucasian	Smoker	1 y	5/5	5 mo	• IV solumedrol 1 g q 2 days (3 infusions) • IV solumedrol 1 g q 2 days (3 infusions) + 250 mg weekly (6 infusions) • Surgical decompression with fat removal • High-dose maintenance oral prednisone • EBRT (20 Gy in 10 sessions) • IV. Solumedrol 125 mg weekly (6 infusions)	9.4	7/7	162 mg/mL, subcutaneous, weekly (continuously)	n/a	2/2
7	59	F	Asian	Nonsmoker	3 mo	7/7	9 mo	• IV solumedrol 1 g q 2 days (3 infusions) • IV solumedrol 1 g q 2 days (3 infusions) • Surgical decompression • Methotrexate 10 mg weekly • EBRT (20 Gy in 10 sessions) • IV solumedrol 125 mg weekly (6 infusions) • High-dose maintenance oral prednisone causing Cushing-like side effects	n/a	2/2	162 mg/mL, subcutaneous, weekly (continuously)	n/a	0/0
8	62	F	Caucasian	Smoker	30 mo	6/6	30 mo	• IV solumedrol 1 g q 2 days (3 infusions) • IV solumedrol 1 g q days (3 infusions) • EBRT (20 Gy in 10 sessions) • IV solumedrol 125 mg weekly (6 infusions)	14.54	3/3	162 mg/mL, subcutaneous, weekly (continuously)	n/a	0/0

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Table 1—*Continued*

Patient No.	Age, y	Sex	Race	Tobacco Use	Time Since TED Diagnosis at Initial Presentation	VISA/CAS on Presentation	Length of Pretocilizumab Treatment	Pretocilizumab Treatment Regimen	Pretocilizumab TSI (IU/L)	Pretocilizumab VISA/CAS	Tocilizumab Regimen	Post-Tocilizumab TSI	Post-Tocilizumab VISA/CAS
9	62	M	Asian	Nonsmoker	18 mo	4/4	23 mo	• Methotrexate 10 mg weekly (increased to 22.5 mg) • IV solumedrol 1 g q 2 days (3 infusions) • EBRT (20 Gy in 10 sessions) • IV solumedrol 125 mg weekly (6 weeks) • Methotrexate 10 mg weekly (increased to 20 mg and unable to wean)	15	2/2	162 mg/mL, subcutaneous, weekly (continuously)	n/a	1/1

IV, intravenous; EBRT, external beam radiation therapy; n/a, not applicable (not measured).

Other biologics have been used to treat TED. Notably, teprotumumab, an inhibitor of insulin-like growth factor I receptor, achieved FDA approval in January 2020 for the reduction of proptosis in corticosteroid-naïve patients within 9 months of diagnosis.[11]

Teprotumumab approval was achieved as an orphan drug with a combination of phase I and phase II data and a total treated population of 76 patients. An additional 5 enrolled patients discontinued treatment secondary to severe adverse events. Compared with tocilizumab, the 24-week intravenous infusion treatment of teprotumumab is significantly more expensive, associated with significant adverse effects, and unavailable in a subcutaneous formulation (Table 2). Additionally it has not been tested for patients with moderate to severe steroid-, methotrexate-, radiation-, or surgery-resistant disease. Rituximab, an anti-CD20 monoclonal antibody, has also been studied as a treatment for TED and has demonstrated significant TSI and CAS reduction in multiple studies.[12–14] However, it does not currently have FDA approval for this indication. Like teprotumumab, rituximab is unavailable in a subcutaneous formulation and more expensive than tocilizumab as an IV infusion (Table 2). Unlike teprotumumab, it has been studied in corticosteroid-resistant TED patients late in the course of their disease.[12,13]

Studies have demonstrated that subcutaneous administration of monoclonal antibodies is associated with fewer severe systemic reactions and decreased risk of thrombosis.[15] None of the patients in this series experienced significant side effects. Patients 1 and 3 experienced incidental improvement in comorbid polymyalgia rheumatica and rheumatoid arthritis, respectively. Though our series includes 9 patients only, our cohort compares favourably with teprotumumab, for which significant side effects have been noted.[16] Although tocilizumab may have an immunosuppressive effect, so do medications (corticosteroids, methotrexate, etc.) that are routinely used to treat TED for which our patients were either nonreactive or intolerant. The cost of a course of subcutaneous tocilizumab has been estimated to be more than 3 times less expensive than an intravenous course, even excluding the accessory costs of intravenous therapy.[7] Together with efficacy, diminished discomfort, ease of treatment, and financial viability afforded by subcutaneous administration,[17,18] the outcomes of this series are significant enough to support further exploration of this alternative to intravenous therapy and other biologics.

This study is the largest cohort of subcutaneous tocilizumab to date. Despite the heterogeneity in treatment regimens pursued before the initiation of subcutaneous tocilizumab, we observed rapid, clear clinical improvement in all patients after the onset of treatment with tocilizumab, suggesting that this drug may be an effective alternative to steroids or oral antimetabolites in cases of refractory disease or inability to wean. As a retrospective case series, this study is limited by lack of a control arm and a heterogeneous dataset. To confirm the generalizability of these findings, a randomized control trial is needed. Future studies should also include treating

Table 2—Summary and comparison of the characteristics of biologic treatments for thyroid eye disease

Points of Comparison	Teprotumumab	Tocilizumab	Rituximab
FDA approval (for TED?) Patients treated	2020 (yes) 76 (phases I and II) 5 d/c SAE	2010 (no)	1997 (no)
Cost/dose: 68 kg pt (USD)	USD14 900/500 mg (dose 20 mg/kg after first dose of 10 mg/kg) USD40 528/dose	USD1100/ 162 mg SubQ USD491/80 mg IV: dose 8 mg/kg USD3 339 per dose IV	1000 mg/dose = USD9 818
Cost per treatment: 68 kg pt (USD)	q 3 weeks × 6 mo IV = USD303, 960	4 monthly doses = IV USD13 356 SubQ 4 weekly doses = USD4 400	Treatment q 2 weeks IV = USD19 636
Route of administration	IV	IV or SubQ	IV
Adverse effects[20–23]	• Hearing loss (10%) • Hyperglycemia (10%) • Muscle spasms (25%) • Alopecia (13%)	• Hypercholesterolemia (10%) • Neutropenia (10%) • Elevated liver enzymes (5%) • Infusion reactions (7%–8%)	• Infusion reactions (23%–32%) • Rash (15%) • Angioedema (11%) • Infections (serious 5%, overall 31%) • Hepatitis B reactivation (rare) • Progressive multifocal leukoencephalopathy (rare) • Cytopenias (lymphopenia 40%, neutropenia 6%, anemia 3%, thrombocytopenia 2%) • Cardiac events (1%–2%) • Hyperglycemia (9%)
Studied in steroid-naïve patients?	Yes	No	No
Recurrence rate	50% proptosis Steroid 12%	50% proptosis 7% hyperemia 7% CAS	Uncertain
Effect on TSI?	Not published, unlikely	Possibly yes	Yes

pt, patient; d/c SAE, discontinued due to serious adverse event; IV, intravenous; SubQ, subcutaneous; CAS, clinical activity score; TED, thyroid eye disease; TSI, thyroid stimulating immunoglobulin.

steroid-naïve patients early in the course of their disease, with comparison to the tocilizumab and teprotumumab intravenous trial. Additionally, dosage optimization, and efficacy with the use of adjuvant hyaluronidase to increase absorption should also be studied.[19]

As novel biologics to treat TED[19–22] become more prevalent, each monoclonal antibody should to be studied with the same trial design. Provided with this information we may be able to determine which drug affects which symptoms optimally (i.e., tocilizumab—inflammation, teprotumumab—proptosis), which drug is disease modifying[23] versus symptom minimizing, and whether combination treatment regimens, perhaps in lower doses, that optimize outcomes can be developed.

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Footnotes and Disclosure

The authors have no proprietary or commercial interest in any materials discussed in this article.