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Teprotumumab Intolerance: A Case Report

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ABSTRACT

Background: Teprotumumab is a fully human monoclonal antibody targeting the insulin-like growth factor-1 receptor (IGF-1R), is approved for the treatment of thyroid eye disease (TED). While generally well tolerated, systemic IGF-1R blockade can precipitate significant extra-orbital adverse events, including metabolic dysregulation and ototoxicity.

Case Presentation: A 39-year-old female with a history of Graves' disease complicated by severe active orbitopathy, multinodular goiter, type 1 diabetes mellitus, and childhood Hodgkin's lymphoma treated with radiotherapy was initiated on intravenous teprotumumab (10 mg/kg initial dose, followed by 20 mg/kg every three weeks). Following her second dose (1,700 mg), the patient started to develop acute systemic, metabolic, and otologic toxicities, including myalgia, nausea, vomiting, diarrhea, fatigue, hyperglycemia, auditory abnormalities, headache, and xerosis.

Conclusion: Clinically significant metabolic and otologic adverse events can emerge early during teprotumumab therapy. Proactive multidisciplinary surveillance incorporating baseline and serial audiometry alongside rigorous glycemic monitoring is essential to detect treatment-limiting toxicities early and prevent irreversible compilaction.

Key words: Teprotumumab; Case report; Thyroid eye disease

INTRODUCTION

Teprotumumab is a fully human monoclonal antibody approved for the management of TED that functions by binding to and inhibiting the IGF-1R. By blocking IGF-1R signaling which is upregulated in orbital fibroblasts and lymphocytes in TED. Teprotumumab attenuates orbital inflammation, hyaluronan synthesis, and soft-tissue expansion, thereby improving proptosis, diplopia, and clinical activity scores. Administered as an intravenous infusion every three weeks for a total of eight doses. It has systemic inhibition of IGF-1R that impacts extra-

orbital tissues, accounting for its systemic adverse events.[1,2] In pivotal clinical trials and real-world cohorts, teprotumumab is generally well tolerated, the patients completing the full eight-infusion regimen and 5% to 12% discontinuing therapy early due to adverse events. Most patients experience mild-to-moderate side effects secondary to systemic IGF-1R blockade, including muscle spasms (25%), nausea (17%), alopecia (13%), diarrhea (13%), fatigue (12%), and dysgeusia (8%).[3] However, a smaller subset of patients develops serious, treatment-limiting toxicities most notably hearing impairment (10% to 15% in clinical trials, and higher in real-world studies) [3] and hyperglycemia (8.1%, predominantly in patients with preexisting diabetes or prediabetes) that necessitate close clinical monitoring or treatment cessation.[4]

CASE PRESENTATION

A 39-year-old female with a known medical history of Graves' disease complicated by severe thyroid orbitopathy, multinodular goiter, and type 1 diabetes mellitus presented for management of active TED. Her past medical history was also notable for childhood Hodgkin's lymphoma, which had been treated with radiotherapy.

Upon multidisciplinary evaluation by endocrinology and ophthalmology, the patient exhibited clinical features of active TED, including eyelid retraction, restriction of extraocular movements, proptosis, and blurred vision. Following consensus between endocrinology and ophthalmology, a management plan was established to initiate intravenous teprotumumab at a starting dose of 10 mg/kg as a single infusion, followed by 20 mg/kg every three weeks for seven additional doses, each administered over 90 minutes. Prior to treatment initiation, the patient was referred to the ear, nose, and throat clinic for a baseline audiometric evaluation. The endocrinologist counseled the patient thoroughly regarding the proposed regimen and potential adverse effects, and the patient provided informed consent to proceed. On the day of the initial infusion, the patient was clinically and hemodynamically stable and afebrile. She received her first dose of intravenous teprotumumab (850 mg) without acute complications. Three weeks later, she returned for her second infusion (1,700 mg intravenously), which was initially tolerated without immediate infusion-related reactions. However, following the second administration, the patient developed a constellation of adverse symptoms, including myalgia, nausea, vomiting, diarrhea, pronounced fatigue, exacerbated hyperglycemia, auditory abnormalities, headache, and dry skin. She refused to complete the treatment course as this adverse effects are severly affected her quality of life.

DISCUSSION

This case illustrates the rapid onset of multi-systemic, metabolic, and otologic toxicities following early exposure to teprotumumab, specifically manifesting as hyperglycemia, auditory impairment, and fatigue alongside gastrointestinal and musculoskeletal symptoms. In pooled analyses of pivotal randomized controlled trials and multicenter real-world cohorts, while mild-to-moderate fatigue is reported in approximately 12% of treated patients, hyperglycemia (8.1% in clinical trials, and substantially higher in real-world cohorts)[4] and hearing impairment (10% to 15% in clinical trials, and higher in real-world practice)[3] represent serious clinical risks that frequently require medical intervention or therapy discontinuation.[3,5]

Mechanistically, IGF-1R shares substantial structural homology and downstream intracellular signaling pathways with the insulin receptor, while systemic IGF-1R blockade also increases growth hormone secretion and impairs peripheral insulin sensitivity.[6,7] Consequently, systemic IGF-1R inhibition can induce peripheral insulin resistance and impair glucose homeostasis, posing a heightened risk of severe glycemic decompensation in patients with underlying type 1 or type 2 diabetes mellitus or prediabetes.[6,7] Simultaneously, endogenous IGF-1 plays a critical neurotrophic and cytoprotective role within the inner ear, protecting cochlear hair cells from metabolic and ischemic stress (Highland et al., 2021; Najjar & Yu, 2022). Inhibition of cochlear IGF-1R signaling can disrupt cochlear hair cell and spiral ganglion homeostasis, manifesting clinically as muffled hearing, aural fullness, tinnitus, or sensorineural hearing loss.[8,9] Unlike most systemic side effects of teprotumumab, ototoxicity carries a documented risk of permanence.[8] As a result, adverse symptoms such as fatigue, gastrointestinal disturbances, and metabolic dysregulation may persist throughout this washout window, although up to 74% of patients with systemic adverse events achieve symptom resolution following treatment cessation.[5]

In our patient, management consisted of holding further teprotumumab infusions, implementing intensive blood glucose surveillance, and promptly adjusting her antidiabetic regimen. Following shared decision making, the patient elected to decline subsequent doses, which led to clinical resolution of her acute symptoms at her one-month outpatient follow-up.

CONCLUSION

Clinically significant otologic, metabolic, and systemic toxicities can emerge early during the course of teprotumumab therapy. This case underscores the necessity of proactive, multidisciplinary risk mitigation specifically baseline and serial audiometry alongside rigorous fasting blood glucose and HbA1c surveillance, as well as screening for underlying gastrointestinal disease to optimize patient safety, guide timely dose holds or discontinuation, and prevent irreversible sequelae.

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