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Teprotumumab

Updated: July 8, 2021.

OVERVIEW

Introduction

Teprotumumab is a human monoclonal antibody to the insulin-like growth factor 1 receptor which is used to treat the ophthalmopathy of Graves disease. Teprotumumab is generally well tolerated and has not been associated with serum aminotransferase elevations during therapy or with instances of clinically apparent liver injury.

Background

Teprotumumab (tep" roe toom' ue mab) is a human IgG1 monoclonal antibody directed against the insulin-like growth factor 1 receptor (IGF1R) that is used in the therapy of Graves ophthalmopathy (thyroid eye disease). Graves disease is an autoimmune disease associated with autoantibodies, hyperthyroidism and a distinctive form of eye disease marked by ocular inflammation and proptosis causing eye pain, dryness, redness, and swelling which if severe can cause diplopia (double-vision) and loss of vision. Graves ophthalmopathy is associated with autoantibodies to thyrotropin and hypertrophy of ocular fibroblasts which overexpress the IGF1 receptor. Teprotumumab causes inhibition of IGF1 binding to its receptor and preventing cell activation. IGF1 is a potent modulator of cell growth and inhibitor of programmed cell death, acting via the PI3K-AKT-mTOR pathway. The inhibition of IGF1 signaling decreases fibroblast proliferation and hypertrophy. In two randomized, placebo-controlled trials, a four month course of teprotumumab infusions led to clinical improvement in proptosis in 71% to 83% of patients compared to 10% to 20% with placebo infusions. Teprotumumab was approved as therapy of Graves ophthalmopathy in the United States in 2019, the first therapy approved specifically for this indication. Previously, only partially effective and off-label therapies for Graves ophthalmopathy were available, including weekly infusions of high doses of methylprednisolone as well as other immunomodulatory agents such as mycophenolate, azathioprine, tocilizumab, and rituximab. Teprotumumab is available as a powder for resuspension in single use vials of 500 mg under the brand name Tepezza. The recommended dose of teprotumumab is 10 mg/kg intravenously initially followed by 20 mg/kg every 3 weeks for a total of 8 doses. Common side effects include local infusion reactions, muscle spasms, nausea, diarrhea, alopecia, hyperglycemia and fatigue. Rare but potentially severe adverse reactions include exacerbation of inflammatory bowel disease, hearing loss and cognitive decline. Teprotumumab also is embryotoxic, and women of child bearing potential need to use effective means of contraceptive measures before and during therapy and for 6 months thereafter.

Hepatotoxicity

In preregistration trials of teprotumumab, abnormalities in serum aminotransferase levels were not reported. Furthermore, there were no reported hepatic serious adverse events or mention of clinically apparent liver

injury. Since approval and more general use of teprotumumab there have been no reports of clinically significant liver injury attributed to its use. However, teprotumumab has had limited clinical use and its overall safety, particularly if given in more than one course, is not fully defined.

Likelihood score: E (unlikely cause of clinically apparent acute liver injury).

Mechanism of Injury

Possible mechanisms of liver injury due to teprotumumab are not known. Monoclonal antibodies and immunoglobulins are generally taken up and metabolized intracellularly to short peptides and amino acids. On the other hand, IGF1 receptors are wide spread and have important functions in growth and development and may alter normal metabolic pathways that can affect liver function or underlying liver conditions.

Outcome and Management

Drug Class: Monoclonal Antibodies, Antithyroid Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Teprotumumab – Tepezza®

DRUG CLASS

Antithyroid Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Teprotumumab	1036734-93-6	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 08 July 2021

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 before the availability of teprotumumab).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761143Orig1s000MedR.pdf

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA multidisciplinary scientific review of the teprotumumab application which mentions that "no significant shifts in laboratory findings were noted").

Ramalingam SS, Spigel DR, Chen D, Steins MB, Engelman JA, Schneider CP, Novello S, et al. Randomized phase II study of erlotinib in combination with placebo or R1507, a monoclonal antibody to insulin-like growth factor-1 receptor, for advanced-stage non-small-cell lung cancer. J Clin Oncol. 2011;29:4574–80. PubMed PMID: 22025157.

(Among 172 patients with advanced non-small cell lung cancer treated with erlotinib with or without teprotumumab [R1507] in doses of 9 or 16 mg/kg once every 3 weeks, overall response rates were similar in all three groups [7% to 9%], while side effects more common in those receiving teprotumumab included deep vein thromboses [8%vs 0], fatigue, skin rash and discontinuations because of adverse reactions [6% vs 3.5%], no mention of ALT elevations or hepatotoxicity).

Pappo AS, Vassal G, Crowley JJ, Bolejack V, Hogendoorn PC, Chugh R, Ladanyi M, et al. A phase 2 trial of R1507, a monoclonal antibody to the insulin-like growth factor-1 receptor (IGF-1R), in patients with recurrent or refractory rhabdomyosarcoma, osteosarcoma, synovial sarcoma, and other soft tissue sarcomas: results of a Sarcoma Alliance for Research Through Collaboration study. Cancer. 2014;120:2448–56. PubMed PMID: 24797726.

(Among 163 patients with recurrent or refractory malignant sarcomas who were treated with teprotumumab [R1507] in a dose of 9 mg/kg intravenously once weekly, the overall response rate was only 2.5% and the most common adverse reactions were fatigue [20%], nausea [14%], hyperglycemia [9%], and muscle spasms [9%]), and one patient [<1%] had serum ALT elevations above 5 times ULN).

Ma H, Zhang T, Shen H, Cao H, Du J. The adverse events profile of anti-IGF-1R monoclonal antibodies in cancer therapy. Br J Clin Pharmacol. 2014;77:917–28. PubMed PMID: 24033707.

(Systematic review of the literature found 15 articles that reported adverse events of anti-IGF1R monoclonal antibodies used in cancer chemotherapy that collectively reported fatigue in [29%], skin rash [20%], nausea [18%], hyperglycemia [15%] and ALT or AST elevations [8%], but the liver enzyme elevations occurred with cixutumumab [8%] and figitumumab [13%] and not teprotumumab).

Smith TJ, Hegedüs L. Graves' Disease. N Engl J Med. 2016;375:1552–65. PubMed PMID: 27797318.

(Review of the clinical features, pathogenesis, diagnosis, natural history and management of Graves disease including discussion of Graves ophthalmopathy and the possible role of IGF1 signaling its pathogenesis).

Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, Harris GJ, et al. Teprotumumab for thyroid-associated ophthalmopathy. N Engl J Med. 2017;376:1748–61. PubMed PMID: 28467880.

(Among 88 patients with recent onset of Graves ophthalmopathy treated with 8 three-weekly infusions of teprotumumab or placebo, clinical responses occurred by 24 weeks in 43% vs 4% while adverse events included nausea [19% vs 9%], muscle spasms [19% vs 5%], diarrhea, hyperglycemia [12% vs 5%], alopecia, dry skin, paresthesias and hearing loss [7% vs 0%]; no mention of ALT elevations or hepatotoxicity).

Taylor PN, Zhang L, Lee RWJ, Muller I, Ezra DG, Dayan CM, Kahaly GJ, et al. New insights into the pathogenesis and nonsurgical management of Graves orbitopathy. Nat Rev Endocrinol. 2020;16:104–16. PubMed PMID: 31889140.

(Review of the pathogenesis of Graves ophthalmopathy and role of thyrotropin and IGF1 signaling and discussion of therapies, including teprotumumab).

Douglas RS, Kahaly GJ, Patel A, Sile S, Thompson EHZ, Perdok R, Fleming JC, et al. Teprotumumab for the treatment of active thyroid eye disease. N Engl J Med. 2020;382:341–52. PubMed PMID: 31971679.

(Among 81 patients with Graves ophthalmopathy treated with teprotumumab or placebo, clinical improvement was achieved in 83% vs 10% and most adverse events were mild-to-moderate, including muscle spasms [32% vs 10%], alopecia, nausea, weight loss and hearing loss [12% vs 0]; there was one severe infusion reaction, one patient developed IBD; no mention of ALT elevations or hepatotoxicity).

Markham A. Teprotumumab: first approval. Drugs. 2020;80:509–12. PubMed PMID: 32157641.

(Review of the mechanism of action, development, pharmacology, clinical efficacy and safety of teprotumumab shortly after its approval as therapy of Graves eye disease in the US mentions adverse reactions of muscle spasms

[25% vs 7% in controls], nausea [17% vs 9%], alopecia [13% vs 8%], diarrhea [12% vs 8%], fatigue [12% vs 7%], hyperglycemia [10% vs 1%] and hearing loss [10% vs 0], but does not mention ALT elevations or hepatotoxicity).

Ashraf DC, Jankovic I, El-Nachef N, Winn BJ, Kim GE, Kersten RC. New-onset of inflammatory bowel disease in a patient treated with teprotumumab for thyroid associated ophthalmopathy. Ophthalmic Plast Reconstr Surg 2021 Mar 8. Epub ahead of print.

(45 year old woman with Graves ophthalmopathy developed symptoms of inflammatory bowel disease [IBD] after a sixth infusion of teprotumumab, which did not resolve on stopping and ultimately required hospitalization, corticosterol, methotrexate and rituximab).

Bednarczuk T, Pearce SH. The knowns and unknowns of teprotumumab for thyroid eye disease. Lancet Diabetes Endocrinol. 2021;9:323–5. PubMed PMID: 33865499.

(Editorial on Kahaly [{2021] with overview of Graves ophthalmopathy marked by autoimmune induced inflammation and hypertrophy of periorbital connective tissue and muscle cells which overexpress IGF1 and respond to inhibition of IGF1 receptors and pointing out the need for further studies and follow up of teprotumumab therapy for maintenance of response and long-term safety).

Kahaly GJ, Douglas RS, Holt RJ, Sile S, Smith TJ. Teprotumumab for patients with active thyroid eye disease: a pooled data analysis, subgroup analyses, and off-treatment follow-up results from two randomised, double-masked, placebo-controlled, multicentre trials. Lancet Diabetes Endocrinol. 2021;9:360–72. PubMed PMID: 33865501.

(Combined analysis and follow up of 2 randomized, placebo-controlled trials of teprotumumab in 171 patients with recent onset, moderate-to-severe Graves ophthalmopathy reporting overall proptosis responses in 77% of teprotumumab vs 15% of placebo recipients and similar differences in clinical activity and double vision response, which were largely maintained in a further 6 months of follow up, while no new adverse events arose and most that occurred during therapy subsequently resolved).

Hoang TD, Nguyen NT, Chou E, Shakir MK. Rapidly progressive cognitive decline associated with teprotumumab in thyroid eye disease. BMJ Case Rep. 2021;14:e242153. PubMed PMID: 33972303.

(76 year old man with Graves ophthalmopathy developed onset of confusion and progressive cognitive decline after a 4th infusion of teprotumumab, which did not improve on stopping until he underwent plasmapheresis).

Belinsky I, Creighton FX Jr, Mahoney N, Petris CK, Callahan AB, Campbell AA, Kazim M, et al. Teprotumumab and hearing loss: case series and proposal for audiologic monitoring. Ophthalmic Plast Reconstr Surg 2021 Jun 4. Epub ahead of print.

(Case reports of 4 patients with Graves ophthalmopathy who developed hearing loss during therapy with teprotumumab including 4 women, ages 34 to 77 years, developing largely high frequency neurosensory hearing loss after 3 to 8 infusions, persisting during short term follow up).

Teprotumumab (Tepezza) for thyroid eye disease. Med Lett Drugs Ther. 2021;63(1625):87–8. PubMed PMID: 34101720.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of teprotumumab shortly after its approval for use in the US mentions common adverse events but does not mention ALT elevations or hepatotoxicity).