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Tesamorelin

Updated: October 20, 2018.

OVERVIEW

Introduction

Tesamorelin is a synthetic growth hormone releasing hormone analogue used in the treatment of visceral adiposity in human immunodeficiency virus (HIV) infected patients with lipodystrophy. Tesamorelin is given subcutaneously and has major effects on glucose and lipid metabolism, but has not been linked to serum aminotransferase elevations during therapy or to instances of clinically apparent acute liver injury.

Background

Tesamorelin (tes" a moe rel' in) is a synthetic 44 amino acid polypeptide analogue of growth hormone releasing hormone (GHRH). The N terminal portion of the molecule has been modified to improve its stability and pharmacokinetics in comparison to native GHRH. Tesamorelin activates GHRH receptors in the pituitary which leads to synthesis and release of growth hormone that acts on multiple cells of the body including hepatocytes where it stimulates production of insulin like growth factor-1 (IGF-1). IGF-1 mediates many of the effects of growth hormone, which in the liver include growth, inhibition of programmed cell death, glucose update and lipolysis. Serum IGF-1 levels tend to be low in patients with obesity, diabetes and particularly in those with lipodystrophy. Tesamorelin was evaluated and found to be effective in decreasing visceral adiposity in patients with lipodystrophy associated with antiretroviral therapy of human immunodeficiency virus (HIV) infection. Tesamorelin was approved for use in the United States as therapy to reduce excess abdominal fat in HIV-infected patients with antiviral therapy-related lipodystrophy in 2010. Tesamorelin is also being evaluated as therapy of insulin resistance, obesity and nonalcoholic fatty liver. Tesamorelin is available in solution in vials of 1 mg/mL under the brand name Egrifta. The recommended dose is 2 mg daily given by subcutaneous injection. Side effects are not common but can include injection site reactions, itching, arthralgia, myalgia and peripheral edema. Tesamorelin raises IGF-1 levels and monitoring for elevations during therapy is recommended. Potential, rare adverse events include stimulation of malignant tumor growth, glucose intolerance, diabetes and hypersensitivity reactions.

Hepatotoxicity

In clinical trials in patients with HIV-associated lipodystrophy, tesamorelin therapy was not associated with de novo elevations in serum enzymes and, in some studies, was associated with decreases in preexisting ALT elevations, possibly mediated by improvements in nonalcoholic fatty liver. Instances of clinically apparent liver injury attributable to tesamorelin use have not been reported.

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

Mechanism of Injury

Tesamorelin is a synthetic polypeptide that acts upon growth hormone producing cells in the pituitary and is generally metabolized locally by the receptor bearing cells. As a polypeptide, tesamorelin is unlikely to have direct cytotoxicity. Allergic responses to its administration have not caused hepatic or systemic hypersensitivity responses.

Drug Class: Hormonal Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Tesamorelin – Egrifta Depot®

DRUG CLASS

Hormonal Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Tesamorelin	901758-09-6	C221-H366-N72-O67-S.(C2-H4-O2)x-	Polypeptide

ANNOTATED BIBLIOGRAPHY

References updated: 20 October 2018

Abbreviations: VAT, visceral adipose tissue; IGF-1, insulin-like growth factor-1.

Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 731-4.

(Expert review of hepatotoxicity published in 1999 before the availability of recombinant human growth hormone releasing hormone).

Chitturi s, Farrell GC. Adverse effects of hormones and hormone antagonists on the liver. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 605-20.

(Review of hepatotoxicity of hormonal agents; tesamorelin is not discussed).

Moy B, Lee RJ, Smith M. Gonadotrophin-releasing hormone agonists and antagonists. Natural products in cancer chemotherapy: hormones and related agents. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1764.

(Textbook of pharmacology and therapeutics).

Falutz J, Allas S, Kotler D, Thompson M, Koutkia P, Albu J, Trottier B, et al. A placebo-controlled, dose-ranging study of a growth hormone releasing factor in HIV-infected patients with abdominal fat accumulation. AIDS 2005; 19: 1279-87. PubMed PMID: 16052083.

(Among 61 patients with HIV infection and excess visceral adipose tissue [VAT] treated with tesamorelin [1 or 2 mg sc daily] or placebo for 12 weeks, change in VAT was greatest with the higher dose [-16%] vs lower dose [-4%] and placebo [-5%], while adverse event rates were similar and liver test results "did not differ between the groups").

Falutz J, Allas S, Blot K, Potvin D, Kotler D, Somero M, Berger D, et al. Metabolic effects of a growth hormone-releasing factor in patients with HIV. N Engl J Med 2007; 357: 2359-70. PubMed PMID: 18057338.

(Among 412 patients with HIV infection and excess visceral adiposity treated with tesamorelin or placebo by sc injection once daily for 26 weeks, mean VAT decreased with tesamorelin [-15%] more than placebo [+5%], and adverse event rates were similar with no liver related serious adverse events and mean serum ALT levels decreasing in both groups [-4 vs -2 U/L]).

Falutz J, Allas S, Mamputu JC, Potvin D, Kotler D, Somero M, Berger D, et al. Long-term safety and effects of tesamorelin, a growth hormone-releasing factor analogue, in HIV patients with abdominal fat accumulation. AIDS 2008; 22: 1719-28. PubMed PMID: 18690162.

(In an extension study after a 26 week randomized controlled trial, 154 patients with HIV infection and excess visceral adiposity who were treated for up to 52 weeks with tesamorelin continued to have reductions in average VAT scores, and no new adverse events were identified).

Falutz J, Mamputu JC, Potvin D, Moyle G, Soulban G, Loughrey H, Marsolais C, et al. Effects of tesamorelin (TH9507), a growth hormone-releasing factor analog, in human immunodeficiency virus-infected patients with excess abdominal fat: a pooled analysis of two multicenter, double-blind placebo-controlled phase 3 trials with safety extension data. J Clin Endocrinol Metab 2010; 95: 4291-304. PubMed PMID: 20554713.

(In a pooled analysis of 816 HIV infected patients with excess visceral adiposity treated with tesamorelin or placebo for up to 52 weeks, adverse event rates were similar in the two groups, and no liver related adverse events were mentioned).

Falutz J, Potvin D, Mamputu JC, Assaad H, Zoltowska M, Michaud SE, Berger D, et al. Effects of tesamorelin, a growth hormone-releasing factor, in HIV-infected patients with abdominal fat accumulation: a randomized placebo-controlled trial with a safety extension. J Acquir Immune Defic Syndr 2010; 53: 311-22. PubMed PMID: 20101189.

(Among 404 HIV infected patients with excess abdominal adiposity treated with tesamorelin or placebo for 6 months and then switched to placebo or given tesamorelin for another 6 months, VAT decreased with tesamorelin compared to placebo, but this effect was lost when tesamorelin was stopped while adverse event rates were similar with either treatment; no mention of ALT elevations or hepatotoxicity).

Grunfeld C, Dritselis A, Kirkpatrick P. Tesamorelin. Nat Rev Drug Discov 2011; 10: 95-6. PubMed PMID: 21283099.

(News report on the FDA approval of tesamorelin for reduction in excess abdominal adiposity in HIV infected persons with lipodystrophy).

Makimura H, Feldpausch MN, Rope AM, Hemphill LC, Torriani M, Lee H, Grinspoon SK. Metabolic effects of a growth hormone-releasing factor in obese subjects with reduced growth hormone secretion: a randomized controlled trial. J Clin Endocrinol Metab 2012; 97: 4769-79. PubMed PMID: 23015655.

(Among 60 adults with excess abdominal adiposity treated in a randomized controlled trial for 12 months, VAT decreased by 8% with tesamorelin while it increased by 11% with placebo, and there were no differences in "liver transaminases" between the two groups).

Stanley TL, Falutz J, Marsolais C, Morin J, Soulban G, Mamputu JC, Assaad H, et al. Reduction in visceral adiposity is associated with an improved metabolic profile in HIV-infected patients receiving tesamorelin. Clin Infect Dis 2012; 54: 1642-51. PubMed PMID: 22495074.

(In retrospective analyses of two large controlled trials of tesamorelin in HIV infected patients with excess VAT, those who responded to treatment with reduction in VAT also had greater reductions in triglyceride levels and measures of glucose homeostasis).

Spooner LM, Olin JL. Tesamorelin: a growth hormone-releasing factor analogue for HIV-associated lipodystrophy. Ann Pharmacother 2012; 46: 240-7. PubMed PMID: 22298602.

(Review of the safety and efficacy of tesamorelin in HIV infected patients with lipodystrophy; mentions that headache and arthralgias were the most frequent adverse events that led to discontinuation; no mention of ALT elevations or hepatotoxicity).

Stanley TL, Feldpausch MN, Oh J, Branch KL, Lee H, Torriani M, Grinspoon SK. Effect of tesamorelin on visceral fat and liver fat in HIV-infected patients with abdominal fat accumulation: a randomized clinical trial. JAMA 2014; 312: 380-9. PubMed PMID: 25038357.

(Among 48 HIV infected patients with excess visceral and hepatic fat treated with tesamorelin vs placebo for 6 months, median changes in hepatic fat were -2% vs +1%, while median ALT levels did not change in either group [20 to 20 U/L vs 19 to 17 U/L]).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to tesamorelin).

Fourman LT, Czerwonka N, Feldpausch MN, Weiss J, Mamputu JC, Falutz J, Morin J, et al. Visceral fat reduction with tesamorelin is associated with improved liver enzymes in HIV. AIDS 2017; 31: 2253-9.

(Among 176 patients with HIV infection and ALT or AST elevations who were treated with tesamorelin for reduction of visceral adipose tissue [VAT], mean aminotransferase levels decreased more in those with a decrease in VAT [ALT by -9 vs +1 U/L and AST by -4 vs 0 U/L]).

Clemmons DR, Miller S, Mamputu JC. Safety and metabolic effects of tesamorelin, a growth hormone-releasing factor analogue, in patients with type 2 diabetes: A randomized, placebo-controlled trial. PLoS One 2017; 12: e0179538. PubMed PMID: 28617838.

(Among 53 patients with type 2 diabetes treated with tesamorelin or placebo for 12 weeks, there were no changes in measures of insulin response or diabetes control (fasting glucose or HbA1c levels); no mention of ALT levels or liver related adverse events).