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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Omadacycline. [Updated 2020 Jan 9].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Omadacycline

Updated: January 9, 2020.

OVERVIEW

Introduction

Omadacycline is an oral, tetracycline-like antibiotic used to treat moderate-to-severe infections including community-acquired pneumonia and acute bacterial skin and skin structure infections caused by susceptible organisms. Oral omadacycline use has been associated with serum enzyme elevations during therapy but has not been implicated in cases of clinically apparent acute liver injury.

Background

Omadacycline (oh mad" a sye' kleen) is an oral, broad spectrum tetracycline like antibiotic with potent activity against both aerobic and anaerobic gram-positive and gram-negative organisms. Omadacyline is a semisynthetic derivative of minocycline that is classified as an aminomethylcycline. It has a broader spectrum of activity than standard tetracyclines including activity against tetracycline-resistant organisms and methicillin resistant Staphylococcus aureus (MRSA). Omadacyline also has excellent oral absorption and both intravenous and oral preparations have been developed. In multiple clinical trials, omadacycline was found to be effective in community acquired pneumonia and serious acute skin and skin structure associated infections (cellulitis, abscess, deep tissue infections). The tetracyclines act by inhibition of protein synthesis by binding to the 30S subunit of microbial ribosomes. Human cells are less susceptible to this inhibition. Omadacycline was approved for use in community acquired pneumonia and skin and skin structure infections in 2018. It is available as 100 mg of lyophilized power in single dose vials for reconstitution and intravenous use as well as 150 mg tablets for oral use under the brand name Nuzyra. Omadacycline is generally given as a loading dose initially, followed by a daily intravenous or oral maintenance dose for a total of 7 to 14 days. Side effects of omadacycline include gastrointestinal upset, nausea and diarrhea, and more rarely, rash and hypersensitivity reactions. Tetracyclines can cause vertigo and tinnitus, skin photosensitivity reactions, and staining of developing teeth (in children or when taken by a pregnant mother) for which reason the tetracyclines should not be used in pregnant women or in children below the age of nine.

Hepatotoxicity

In clinical trials of omadacycline usually conducted in critically ill patients with major infections, serum aminotransferase elevations arose in 4% of patients and to above 5 times ULN in 1.5%. Nevertheless, the abnormalities were generally transient and asymptomatic and were no more frequent than with comparator antibiotic treated subjects. Nevertheless, other tetracycline antibiotics are well known causes of drug induced liver injury. In particular, high doses of intravenous tetracycline are known to cause severe hepatic microvesicular steatosis with lactic acidosis and severe hepatic dysfunction (LASH syndrome) for which reason

intravenous tetracycline has been withdrawn from use. This complication has not been reported with intravenous omadacycline, eravacycline or tigecycline. The tetracyclines have also been linked to idiosyncratic liver injury with autoimmune features that generally arise with long term use and has most commonly been associated with minocycline. This complication also has not been reported with omadacycline, eravacycline or tigecycline.

Likelihood score: E* (unproven but suspected cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which omadacycline might cause liver injury is unknown. Omadacycline is not metabolized in the liver to an appreciable extent which may explain its relative lack of hepatotoxicity. It does not appear to interact with cytochrome P450 enzymes and has not been reported to cause significant drug-drug interactions.

Outcome and Management

Patients on intravenous omadacycline who develop serum aminotransferase elevations that rise above 5 times the upper limit of normal or are accompanied by jaundice or symptoms should have omadacycline discontinued. Whether there is cross sensitivity to hepatic injury among the various tetracyclines is not known but switching to another class of antibiotics would be more appropriate than changing to another tetracycline-like agent in patients who develop significant hepatic injury while receiving omadacycline.

Drug Class: Antiinfective Agents, Tetracyclines

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Omadacycline – Nuzyra®

DRUG CLASS

Antiinfective Agents

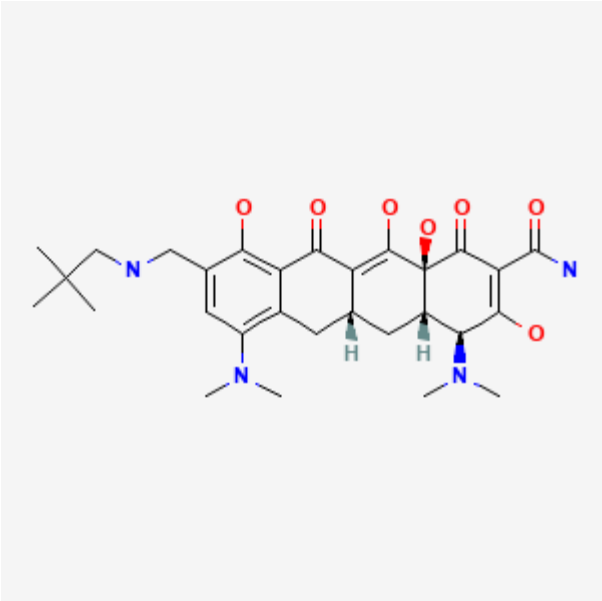
COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE

Table continued from previous page.

Omadacycline	389139-89-3	C29-H40-N4-O7	

ANNOTATED BIBLIOGRAPHY

References updated: 10 April 2019

Zimmerman HJ. Tetracyclines. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999. p. 599-602.

(Expert review of tetracycline and liver injury published in 1999 long before the availability of omadacycline; the tetracyclines cause two forms of drug induced liver injury, microvesicular fat and liver failure occurring after 4-10 days with high doses of parenteral tetracyclines and an idiosyncratic liver injury that occurs with the oral agents, doxycycline causing a cholestatic and minocycline a hepatocellular injury which may be associated with autoimmune features).

Moseley RH. Tetracyclines. Hepatotoxicity of antimicrobials and antifungal agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 468.

(Expert review of tetracycline induced liver injury; mentions that the hepatotoxicity of intravenous tetracycline is of historic interest only as it is no longer given parenterally; both doxycycline and minocycline have been associated with idiosyncratic liver injury; omadacycline and eravacycline are not mentioned).

MacDougall C. Protein synthesis inhibitors and miscellaneous antibacterial agents. In, Brunton LL, Hilal-Dandan R, Knollman KC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 1049-65.

(Textbook of pharmacology and therapeutics).

Available at: https://www.accessdata.fda.gov/scripts/cder/daf/

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy; mentions serious adverse events associated with omadacycline are consistent with those seen with other tetracyclines and the most frequent were nausea, vomiting, infusion site reactions ALT elevations, headache, insomnia and diarrhea; ALT elevations occurred in 3.7-4.1% of omadacycline vs 3.6% in linezolid and 4.6% in moxifloxacin treated subjects, and no subject developed clinically apparent liver injury with jaundice that could be attributed to omadacycline).

Noel GJ, Draper MP, Hait H, Tanaka SK, Arbeit RD. A randomized, evaluator-blind, phase 2 study comparing the safety and efficacy of omadacycline to those of linezolid for treatment of complicated skin and skin structure infections. Antimicrob Agents Chemother. 2012;56:5650–4. PubMed PMID: 22908151.

(Among 219 adults with complicated skin and skin structure infections treated with omadacycline vs linezolid, clinical response rates were similar [97% vs 93%] as were adverse event rates, ALT elevations occurring in 3% of both groups).

Markham A, Keam SJ. Omadacycline: first global approval. Drugs. 2018;78:1931–7. PubMed PMID: 30471003.

(Review of the mechanism of action, history of development, pharmacology, clinical efficacy and safety of omadacycline shortly after its first approval for use in the US; mentions that ALT or AST elevations arose in 3-4% of patients treated with omadacycline but that similar rates were reported in patients on comparator antibiotic regimens).