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Romosozumab

Updated: June 7, 2021.

OVERVIEW

Introduction

Romosozumab is a humanized monoclonal antibody to sclerostin which is used to treat osteoporosis. Romosozumab is generally well tolerated and has not been associated with serum aminotransferase elevations during therapy or with instances of clinically apparent liver injury.

Background

Romosozumab (roe' moe soz' ue mab) is a humanized monoclonal IgG2 antibody directed against sclerostin, an osteocyte-derived glycoprotein that inhibits bone formation via interruption of Wnt/beta-catenin signaling which results in an inhibition of osteoblast activity. Romosozumab is used to treat osteoporosis and is one of few available therapeutic agents that act to increase bone formation rather than prevent bone resorption. In large preregistration randomized, placebo-controlled trials, 12 months of romosozumab therapy resulted in a significant improvements in bone mineral density and decreased rates of both vertebral and non-vertebral fractures in comparison to placebo treatment. The efficacy of therapy wanes somewhat after 12 months. Romosozumab was approved in the United States in 2019 as therapy for osteoporosis in postmenopausal women with high risk of fractures. Romosozumab is given as monthly subcutaneous injections. Concurrent oral calcium and vitamin D supplementation is recommended. Romosozumab is available in single dose pre-filled syringes of 105 mg in 1.17 mL under the brand name Evenity. The recommended dose is 210 mg (two syringes) subcutaneously each month for no more than 12 months. If further osteoporosis therapy is needed, antiresorptive therapies should be initiated. Common side effects of romosozumab include mild local infusion reactions, headaches and arthralgia. Also reported have been rare instances of hypersensitivity reactions (angioedema, urticaria), hypocalcemia, osteonecrosis of the jaw and atypical femoral fractures. There also may be an increased risk of myocardial infarction with romosozumab therapy.

Hepatotoxicity

Mild-to-moderate serum aminotransferase elevations arise a small percentage of treated patients, but are generally asymptomatic and transient and rarely necessitate discontinuation of romosozumab injections. In registration trials of romosozumab there were no instances clinically apparent liver injury or severe hepatic adverse events. Since approval and more general use of romosozumab there have been no reports of clinically significant liver injury attributed to its use.

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

Mechanism of Injury

The possible mechanisms of liver injury due to romosozumab are unclear. Monoclonal antibodies and immunoglobulins are generally taken up and metabolized intracellularly to short peptides and amino acids.

Drug Class: Monoclonal Antibodies, Osteoporosis Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Romosozumab – Evenity®

DRUG CLASS

Osteoporosis Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Romosozumab	909395-70-6	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 08 June 2021

Nolin TD, Friedman PA. Agents affecting mineral ion homeostasis and bone turnover. In, Brunton LL, Hilal-Danan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 887-906.

(Textbook of pharmacology and therapeutics).

FDA. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761062Orig1s000MultidisciplineR.pdf

(Multidisciplinary review of romosozumab by the FDA in support of its approval for use in osteoporosis in the US with discussion of safety: pp 106-155; no mention of ALT elevations and no serious adverse hepatic events listed).

Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, Hofbauer LC, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med. 2016;375:1532–43. PubMed PMID: 27641143.

(Among 7180 postmenopausal women with osteoporosis treated with romosozumab or placebo by subcutaneous injection once monthly for 12 months [followed by denosumab for 12 months], bone mineral density increased and vertebral fractures were less frequent with romosozumab [0.5% vs 1.8%], while adverse event rates were similar in the 2 groups; no mention of ALT elevations or hepatotoxicity).

Langdahl BL, Libanati C, Crittenden DB, Bolognese MA, Brown JP, Daizadeh NS, Dokoupilova E, et al. Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with

osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial. Lancet. 2017;390(10102):1585–94. PubMed PMID: 28755782.

(Among 436 postmenopausal women with osteoporosis refractory to bisphosphonate therapy who were treated with romosozumab [120 mg sc once monthly] or teriparatide [20 µg sc daily] for 12 months, total hip bone mineral density increased on romosozumab [+2.6%] but decreased on teriparatide [-0.6%], while adverse event rates were similar; no mention of ALT elevations or hepatotoxicity).

McClung MR, Brown JP, Diez-Perez A, Resch H, Caminis J, Meisner P, Bolognese MA, et al. Effects of 24 months of treatment with romosozumab followed by 12 months of denosumab or placebo in postmenopausal women with low bone mineral density: a randomized, double-blind, phase 2, parallel group study. J Bone Miner Res. 2018;33:1397–1406. PubMed PMID: 29694685.

(Among 364 postmenopausal women with osteoporosis treated with one of 5 regimens of romosozumab for up to 24 months, lumbar spine and total hip bone marrow density continued to increase over time, with highest gains with 210 mg once monthly and adverse event rates were similar among groups; no mention of ALT elevations or hepatotoxicity).

Lewiecki EM, Blicharski T, Goemaere S, Lippuner K, Meisner PD, Miller PD, Miyauchi A, et al. A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. J Clin Endocrinol Metab. 2018;103:3183–93. PubMed PMID: 29931216.

(Among 245 men, ages 55 to 90 years, with osteopenia/osteoporosis treated with monthly sc injections of romosozumab [210 mg] or placebo for 12 months, lumbar spine bone mineral density improved more with romosozumab [12% vs 1.2%] and, although total and severe adverse event rates were similar in the two groups, there was an excess of serious cardiovascular events with romosozumab [5% vs 2.5%]; no mention of ALT levels or hepatotoxicity).

Romosozumab (Evenity) for postmenopausal osteoporosis. Med Lett Drugs Ther. 2019;61(1573):83–6. PubMed PMID: 31170119.

(Concise review of the mechanism of action, clinical efficacy, safety and costs of romosozumab shortly after its approval for use in osteoporosis in the US mentions adverse events of headache, arthralgia, hypersensitivity reactions, osteonecrosis and atypical fractures as well as increase in risk for cardiovascular events; no mention of ALT elevations or hepatotoxicity).

Drugs for postmenopausal osteoporosis. Med Lett Drugs Ther. 2020;62(1602):105–12. PubMed PMID: 32728009.

(Concise review of drugs approved for therapy of postmenopausal osteoporosis including vitamin D and calcium, bisphosphonates, denosumab, teriparatide, raloxifene, estrogens, calcitonin and romosozumab, mentions that romosozumab is associated with headache and arthralgia and, in some studies, an increased risk of severe cardiovascular adverse events; no mention of hepatotoxicity or ALT elevations with any of the agents for osteoporosis).

Tanaka S, Matsumoto T. Sclerostin: from bench to bedside. J Bone Miner Metab. 2021;39:332–40. PubMed PMID: 33206222.

(Review of the discovery and cellular actions of sclerostin, a cystine knot-containing secreted glycoprotein that blocks Wnt/beta-catenin signaling that is necessary for normal bone formation and osteoblast activity; romosozumab, a monoclonal antibody to sclerostin, lowers serum levels of this protein and increases Wnt-signaling and active bone formation by osteoblasts).