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Ramucirumab

Updated: May 29, 2017.

OVERVIEW

Introduction

Ramucirumab is a human monoclonal antibody to the vascular endothelial growth factor (VEGF) receptor 2 and is an antiangiogenesis agent used in the therapy of advanced colorectal, gastric and lung cancers. Ramucirumab has not been linked to serum enzyme elevations during therapy or to instances of idiosyncratic acute liver injury, but has been reported to worsen liver failure in patients with decompensated cirrhosis (Child Class B or C).

Background

Ramucirumab (ra" mue sir' ue mab) is a recombinant human monoclonal IgG1 antibody to the vascular endothelial growth factor receptor 2. Receptors for VEGF are present on endothelial cells, and the engagement of VEGF with these receptors promotes cell proliferation and angiogenesis. Inhibition of VEGF receptor 2 signaling decreases formation of new blood vessels, which plays an important role in growth and spread of cancer cells. When used in combination with other antineoplastic agents, ramucirumab has been shown to extend progression-free and overall survival in several forms of advanced cancer. Ramucirumab was approved in the United States in 2014 for use in refractory, advanced gastric and metastatic non-small cell lung cancer. Indications were broadened in 2015 to include metastatic colorectal cancer. Ramucirumab is available in solution in single use vials of 100 mg in 10 mL or 500 mg in 50 mL (10 mg/mL) under the brand name Cyramza. The typical dose is 8 or 10 mg/kg intravenously at intervals of every 2 or 3 weeks based upon indication the other antineoplastic agents used in combination. Ramucirumab has significant adverse side effects. Common adverse events include diarrhea, fatigue, anorexia, epistasis, hypertension, neutropenia, and stomatitis. Uncommon, but potentially severe adverse events include arterial thromboembolic events, severe hypertension, infusion reactions, impaired wound healing, worsening of cirrhosis, thyroid dysfunction, renal dysfunction including proteinuria and nephrotic syndrome, and embryofetal toxicity.

Hepatotoxicity

In large clinical trials, serum aminotransferase elevations were no more frequent in patients receiving ramucirumab than in those on placebo and receiving other antineoplastic agents (such as capecitabine, docetaxel or paclitaxel). Subsequent to its approval and more general use, there have been no publications describing clinically apparent liver injury attributable to ramucirumab. Ramucirumab is generally given with other potent antineoplastic agents, and it is often difficult to attribute serum enzyme elevations or clinically apparent liver injury to a specific agent being used. In trials of ramucirumab in patients with hepatocellular carcinoma and advanced liver disease, worsening of liver failure was more frequent with the monoclonal antibody therapy than

with placebo; that may have been due to its other, non-hepatic adverse effects, such as edema, hypertension and proteinuria.

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

Mechanism of Injury

The mechanism by which ramucirumab might cause liver injury is not known. Like other monoclonal antibodies, ramucirumab is unlikely to have intrinsic hepatotoxicity, is metabolized to smaller peptides or amino acids by many cells and does not affect the hepatic drug metabolizing enzymes or transporting molecules.

Outcome and Management

The liver injury attributed to ramucirumab has invariably been self-limited and not associated with symptoms or jaundice. Its effects on fluid balance may adversely affect patients with advanced cirrhosis, in whom it should be avoided.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ramucirumab – Cyramza®

DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Ramucirumab	947687-13-0	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 29 May 2017

Abbreviations used: NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; HER, human epidermal growth factor.

Zimmerman HJ. Hepatotoxic effects of oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 673-708.

(Expert review of hepatotoxicity published in 1999, well before the availability of most monoclonal antibody therapies).

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 569-91.

(Review of hepatotoxicity of immunosuppressive drugs; mentions that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists").

Chabner BA, Barnes J, Neal J, Olson E, Mujagiv H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-53.

(Textbook of pharmacology and therapeutics).

Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, Safran H, et al.; REGARD Trial Investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014; 383 (9911): 31-9. PubMed PMID: 24094768.

(Among 355 patients with previously treated, refractory, advanced gastric cancer treated with ramucirumab [8 mg/kg] or placebo intravenously every 2 weeks, median overall survival was improved by therapy [5.2 vs 3.8 months] while rates of adverse events were similar except for a higher rate of hypertension [16% vs 8%]; no mention of ALT elevations or hepatotoxicity).

Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, Hironaka S, et al.; RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014; 15: 1224-35. PubMed PMID: 25240821.

(Among 665 patients with previously treated advanced gastric cancer treated with paclitaxel, overall survival was improved by addition of ramucirumab [median 9.6 vs 7.4 months] and side effects that were more frequent with ramucirumab included hypertension, neutropenia, fatigue and anemia; "liver injury or failure" occurred in 16.5% vs 12.5%, but no details given).

Garon EB, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN, Goksel T, Park K, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 2014; 384 (9944): 665-73. PubMed PMID: 24933332.

(Among 1253 patients with NSCLC treated with docetaxel with or without ramucirumab, overall survival improved with addition of ramucirumab [median 10.5 vs 9.1 months], while rates of adverse and serious adverse events were similar, although hypertension, neutropenia and hemorrhage were more frequent with ramucirumab; no mention of ALT elevations or hepatotoxicity).

Mackey JR, Ramos-Vazquez M, Lipatov O, McCarthy N, Krasnozhon D, Semiglazov V, Manikhas A, et al. Primary results of ROSE/TRIO-12, a randomized placebo-controlled phase III trial evaluating the addition of ramucirumab to first-line docetaxel chemotherapy in metastatic breast cancer. J Clin Oncol 2015; 33: 141-8. PubMed PMID: 25185099.

(Among 1144 patients with metastatic HER-2 negative breast cancer treated with docetaxel, addition of ramucirumab did not increase median overall survival [27.3 vs 27.2 months] and adverse and serious adverse event rates were similar, but more patients on ramucirumab had fatigue, hypertension, febrile neutropenia, hand-foot syndrome and stomatitis; no mention of ALT elevations or hepatotoxicity).

Zhu AX, Park JO, Ryoo BY, Yen CJ, Poon R, Pastorelli D, Blanc JF, et al; REACH Trial Investigators. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma

following first-line therapy with sorafenib(REACH): a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol 2015; 16: 859-70. PubMed PMID: 26095784.

(Among 565 patients with advanced hepatocellular carcinoma [HCC] who were treated with ramucirumab [8 mg/kg every 2 weeks] vs placebo, overall survival was not significantly better with ramucirumab [9.2 vs 7.6 months], while adverse events were more frequent with more edema, ascites, hypertension, proteinuria and liver injury [51% vs 37%], but no details provided).

Tabernero J, Yoshino T, Cohn AL, Obermannova R, Bodoky G, Garcia-Carbonero R, Ciuleanu TE, et al.; RAISE Study Investigators. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. Lancet Oncol 2015; 16: 499-508. PubMed PMID: 25877855.

(Among 1072 patients with refractory, metastatic colorectal cancer treated with ramucirumab [8 mg/kg] or placebo, median overall survival was greater with ramucirumab therapy [13.3 vs 11.7 months] as were serious adverse events including neutropenia [38% vs 23%], hypertension [11% vs 3%], and fatigue [12% vs 8%], but not liver injury [12% vs 10%]).

Larkins E, Scepura B, Blumenthal GM, Bloomquist E, Tang S, Biable M, Kluetz P, et al. U.S. Food and Drug Administration approval summary: ramucirumab for the treatment of metastatic non-small cell lung cancer following disease progression on or after platinum-based chemotherapy. Oncologist 2015; 20: 1320-5. PubMed PMID: 26446239.

(Summary of the clinical results of registration trials of ramucirumab for NSCLC that led to its FDA approval; no mention of ALT elevations or hepatotoxicity).

Ramucirumab (Cyramza) for gastric and GEJ cancer. Med Let Drugs Ther 2015; 57: e74-5 (on line only: not in PubMed)

(Concise review of the mechanism of action, efficacy, safety and costs of ramucirumab shortly after its approval in the United States; mentions that new onset or worsening of encephalopathy, ascites, or hepatorenal syndrome has occurred in patients with Child-Pugh B or C cirrhosis during ramucirumab therapy).

Vahdat LT, Layman R, Yardley DA, Gradishar W, Salkeni MA, Abraham Joy A, Garcia AA, et al. Randomized phase II study of ramucirumab or icrucumab in combination with capecitabine in patients with previously treated locally advanced or metastatic breast cancer. Oncologist 2017; 22: 245-54. PubMed PMID: 28220020.

(Among 153 patients with previously treated, advanced or metastatic breast cancer treated with capecitabine with icrucumab, ramucirumab or placebo, overall survival was similar in all 3 groups, while side effects were more frequent with the monoclonal antibody treated groups; ALT elevations occurred in 9.6% on ramucirumab vs 10.2% on capecitabine alone, and none had elevations above 5 times ULN).