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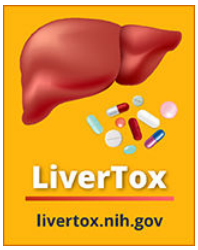


Ruxolitinib

Updated: June 4, 2018.

OVERVIEW

Introduction

Ruxolitinib is a Janus kinase inhibitor that is used in the treatment of intermediate or high risk myelofibrosis. Ruxolitinib is associated with transient and usually mild elevations in serum aminotransferase during therapy, but has not been linked to cases of clinically apparent idiosyncratic acute liver injury but has been shown to be a cause of reactivation of hepatitis B.

Background

Ruxolitinib (rux" oh li' ti nib) is an orally available, specific inhibitor of Janus kinase subtypes 1 and 2 (JAK1 and JAK2). JAK1 and JAK2 are non-receptor tyrosine kinases that are critical components of pathways that lead to production and secretion of hematologic growth factors and inflammatory cytokines. These pathways are important in hematologic cell differentiation and proliferation and in inflammatory reactions. Mutations in JAK1 and JAK2 are frequent in patients with myelofibrosis, and inhibition of these kinases can result in antiproliferative and antiapoptotic effects in malignant cells. Ruxolitinib has been shown to improve symptoms, cause shrinkage of spleen size and decrease circulating cytokine levels in patients with myelofibrosis and polycythemia vera independent of the known presence of Janus kinase mutations. Ruxolitinib was approved for use in the United States in 2011 for therapy of intermediate and high risk myelofibrosis. It is available in tablets of 5, 10, 15, 20 and 25 mg under the brand name Jakafi. The recommended starting dose is 15 mg twice daily, with subsequent dose modifications based upon tolerance and effectiveness. Dose adjustments for liver or kidney dysfunction are also recommended. Common side effects include fatigue, diarrhea, bruising, dizziness, dyspnea and headache. Sudden withdrawal of ruxolitinib is associated with rapid relapse of symptoms which can be severe with fever, respiratory distress, anemia and features of the systemic inflammatory response syndrome.

Hepatotoxicity

In the large clinical trials, serum ALT elevations occurred in 25% of ruxolitinib treated subjects versus 7% of placebo recipients. The ALT elevations were generally self-limited, asymptomatic and mild and were ≥5 times ULN in only 1.3% of patients. In the prelicensure clinical trials, no cases of clinically apparent liver injury were reported. Among listed causes of death in one trial of ruxolitinib for myelofibrosis was one attributed to hepatic failure; this instance, however, was considered unrelated to ruxolitinib. Since its approval and more wide scale use, there have been several published reports of reactivation of hepatitis B in patients with HBsAg and even anti-HBc without HBsAg in serum. A rise in HBV DNA levels was identified within 1 to 6 months of starting ruxolitinib and was associated with ALT levels and jaundice in some patients. HBV DNA levels decreased

rapidly upon starting anti-HBV therapy with entecavir and all patients recovered. In one instance, HBV DNA levels declined with lowering of the dose of ruxolitinib, but then rose again when the dose was increased.

Likelihood score: C (probable cause of reactivation of hepatitis B in susceptible patients).

Mechanism of Injury

The causes of serum enzyme elevations during ruxolitinib therapy are not known. Ruxolitinib is metabolized in the liver largely through the CYP 3A4 pathway and liver injury may be related to production of a toxic intermediate. Ruxolitinib is susceptible to drug-drug interactions with agents that inhibit or induce hepatic CYP 3A4 activity. Because of its effects on intracellular signaling involved in immune responses, ruxolitinib (and possibly other JAK1 and JAK2 inhibitors) is capable to increasing HBV replication which can result in clinically apparent reactivation of hepatitis B.

Outcome and Management

Serum aminotransferase elevations above 5 times the upper limit of normal (if confirmed) or any elevations accompanied by jaundice or symptoms should lead to dose reduction or temporary cessation. There does not appear to be cross reactivity in risk for hepatic injury between ruxolitinib and other kinase inhibitors. Ruxolitinib is capable of causing reactivation of hepatitis B and other opportunistic infections and patients should be screened for evidence of HBV infection before starting chemotherapy, including testing for HBsAg and anti-HBc. Those who are reactive for these virologic markers should be tested for serum HBV DNA and be considered for prophylaxis against HBV reactivation with a nucleoside analog such as tenofovir or entecavir. Alternatively, patients can be monitored for HBV DNA levels and therapy initiated with a significant rise (one or two log10 IU/mL compared to baseline).

Drug Class: Antineoplastic Agents, Protein Kinase Inhibitors

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ruxolitinib – Jakafi®

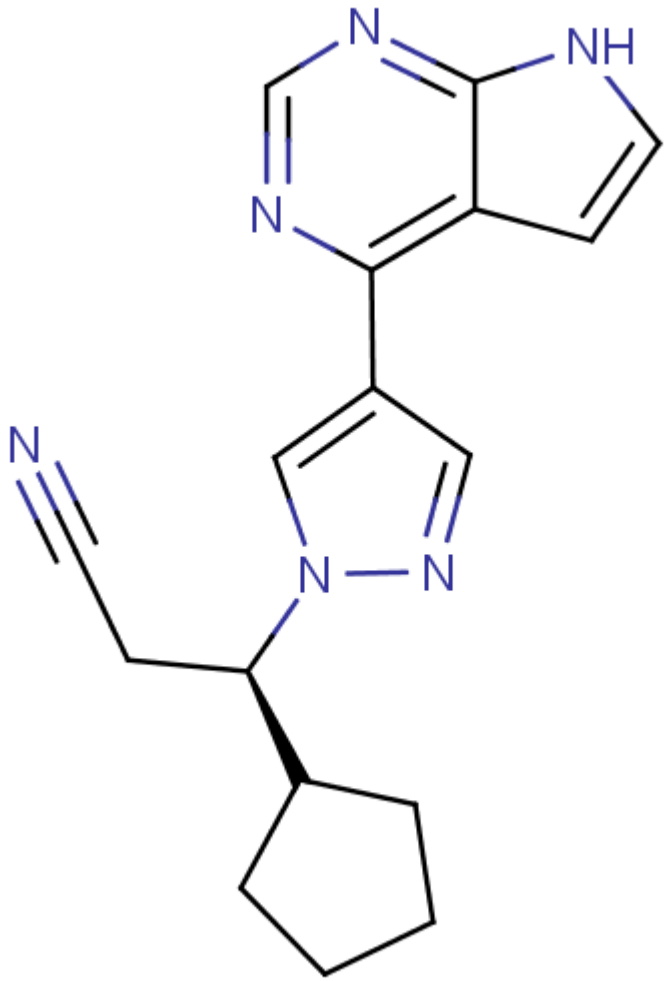
DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Ruxolitinib	941678-49-5	C17-H18-N6	

ANNOTATED BIBLIOGRAPHY

References updated: 04 June 2018

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 tyrosine kinase inhibitors such as ruxolitinib).

DeLeve LD. Erlotinib. Cancer chemotherapy. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 556.

(Review of hepatotoxicity of cancer chemotherapeutic agents discusses several tyrosine kinase inhibitors including imatinib, gefitinib, erlotinib and crizotinib, but not ruxolitinib).

Chabner BA, Barnes J, Neal J, Olson E, Mujagic 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. 1731-54.

(Textbook of pharmacology and therapeutics).

Verstovsek S, Kantarjian H, Mesa RA, Pardanani AD, Cortes-Franco J, Thomas DA, Estrov Z, et al. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. N Engl J Med 2010; 363: 1117-27. PubMed PMID: 20843246.

(Among 153 patients with myelofibrosis treated with varying doses of ruxolitinib, the optimal regimen was 15 mg twice daily, with subsequent dose modifications, a regimen that yielded a 50% rapid, objective response regardless of JAK mutation status; side effects included dose related thrombocytopenia and anemia while nonhematologic side effects were uncommon [<6%] and included diarrhea, fatigue, headache, and peripheral edema; no mention of ALT elevations of hepatotoxicity).

Tefferi A, Pardanani A. Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis. Mayo Clin Proc 2011; 86: 1188-91. PubMed PMID: 22034658.

(Among 47 patients with myelofibrosis who discontinued ruxolitinib treatment, most patients had an acute relapse of symptoms within a few days or weeks of stopping and 5 required hospitalization because of suspected systemic inflammatory response syndrome with high fevers, respiratory distress, thromboses and anemia, often responding to corticosteroid therapy).

Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, Catalano JV, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med 2012; 366: 799-807. PubMed PMID: 22375971.

(In a study of 309 patients with intermediate or high risk myelofibrosis treated for up to 1 year, objective responses [reduction in spleen volume] occurred in 42% of ruxolitinib, but <1% of placebo treated subjects; adverse events more common with ruxolitinib included thrombocytopenia [70% vs 30%], anemia [96% vs 87%], bruising [19% vs 9%] and dizziness [15% vs <1%]; no mention of ALT elevations or hepatotoxicity).

Ruxolitinib (Jakafi) for myelofibrosis. Med Lett Drugs Ther 2012; 54 (1387): 27-8. PubMed PMID: 22469651.

(Concise review of efficacy and safety of ruxolitinib as therapy for myelofibrosis, mentions severe withdrawal symptoms when the drug is stopped that may require corticosteroids).

Harrison C, Kiladjian JJ, Al-Ali HK, Gisslinger H, Waltzman R, Stalbovskaya V, McQuitty M, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med. 2012; 366; 787-98. PubMed PMID: 22375970.

(Among 219 patients with intermediate or high risk myelofibrosis treated with ruxolitinib or best available therapy for at least one year, improvement in clinical symptoms and shrinkage of spleen size occurred with ruxolitinib, but rarely without; listing of severe adverse events included one death from hepatic failure, but it was considered unrelated to ruxolitinib therapy).

Verstovsek S, Mesa RA, Gotlib J, Levy RS, Gupta V, DiPersio JF, Catalano JV, et al. Efficacy, safety and survival with ruxolitinib in patients with myelofibrosis: results of a median 2-year follow-up of COMFORT-I. Haematologica 2013; 98: 1865-71. PubMed PMID: 24038026.

(Among 155 patients with myelofibrosis treated with ruxolitinib, 100 continued on therapy with a median follow up of 2 years; most common side effects were dose related thrombocytopenia and anemia and nonhematologic side effects of bruising, headache and diarrhea; no mention of hepatotoxicity or ALT elevations).

Kantarjian HM, Silver RT, Komrokji RS, Mesa RA, Tacke R, Harrison CN. Ruxolitinib for myelofibrosis--an update of its clinical effects. Clin Lymphoma Myeloma Leuk 2013; 13: 638-45. PubMed PMID: 24238036.

(Review of the efficacy and safety of ruxolitinib as therapy of myelofibrosis, the major severe side effects being hematologic; no discussion of hepatotoxicity or ALT elevations).

Spraggs CF, Xu CF, Hunt CM. Genetic characterization to improve interpretation and clinical management of hepatotoxicity caused by tyrosine kinase inhibitors. Pharmacogenomics 2013; 14: 541-54. PubMed PMID: 23556451.

(Review of genetic associations of serum ALT and bilirubin elevations during therapy with tyrosine kinase inhibitors focusing on lapatinib and pazopanib).

Shah RR, Morganroth J, Shah DR. Hepatotoxicity of tyrosine kinase inhibitors: clinical and regulatory perspectives. Drug Saf 2013; 36: 491-503. PubMed PMID: 23620168.

(Review of the hepatotoxicity of 18 tyrosine kinase inhibitors approved for use in cancer in the US as of 2013; aminotransferase elevations occurred in 18% of patients in registration trials of ruxolitinib, but were rarely above 5 times ULN and cases of clinically apparent liver injury have not been reported).

Cervantes F, Vannucchi AM, Kiladjian JJ, Al-Ali HK, Sirulnik A, Stalbovskaya V, McQuitty M, et al.; COMFORT-II investigators. Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. Blood 2013; 122: 4047-53. PubMed PMID: 24174625.

(In a 3 year open label extension of a trial of ruxolitinib versus placebo in patients with myelofibrosis [Harrison 2012], 106 patients remained on ruxolitinib for an average of 3 years, responses were maintained with continuation of therapy and adverse events were mostly mild, the most common being diarrhea; no mention of ALT elevations or hepatotoxicity).

Verstovsek S, Passamonti F, Rambaldi A, Barosi G, Rosen PJ, Rumi E, Gattoni E, et al. A phase 2 study of ruxolitinib, an oral JAK1 and JAK2 Inhibitor, in patients with advanced polycythemia vera who are refractory or intolerant to hydroxyurea. Cancer 2014; 120: 513-20. PubMed PMID: 24258498.

(Among 34 patients with polycythemia vera treated with ruxolitinib, 97% had an objective response and side effects were not common and generally mild; no mention of ALT elevations or hepatotoxicity).

Galli S, McLornan D, Harrison C. Safety evaluation of ruxolitinib for treating myelofibrosis. Expert Opin Drug Saf 2014; 13: 967-76. PubMed PMID: 24896661.

(Review of the mode of action, pharmacology, clinical efficacy and safety of ruxolitinib does not discuss frequency of ALT elevations during therapy or clinically apparent hepatotoxicity).

Caocci G, Murgia F, Podda L, Solinas A, Atzeni S, La Nasa G. Reactivation of hepatitis B virus infection following ruxolitinib treatment in a patient with myelofibrosis. Leukemia 2014; 28: 225-7. PubMed PMID: 23929216.

(49 year old woman with thrombocytopenic myelofibrosis and HBsAg in serum [HBeAg and HBV DNA <10 IU/mL] developed rising levels of HBV DNA within 5 months of starting ruxolitinib [20 mg twice daily], decreasing with lowering dose [15 mg twice daily] and increasing again with full dose, but without liver test abnormalities [ALT normal, HBV DNA 38,300 IU/mL] and HBV DNA levels declining with lowering dose again).

Shen CH, Hwang CE, Chen YY, Chen CC. Hepatitis B virus reactivation associated with ruxolitinib. Ann Hematol 2014; 93: 1075-6. PubMed PMID: 24173089.

(72 year old man with essential thrombocythemia and HBsAg in serum [ALT 22 U/L] developed abnormal liver tests 8 months after starting ruxolitinib [peak bilirubin 1.8 mg/dL, ALT 291 U/L, HBV DNA 7 log10 copies/mL], resolving within 8 weeks of stopping ruxolitinib and 6 weeks of starting entecavir).

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.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 49 were attributed to antineoplastic agents [5.5%], 3 of which were attributed to kinase inhibitors [imatinib, lapatinib], but none to ruxolitinib).

Kirito K, Sakamoto M, Enomoto N. Elevation of the hepatitis B virus DNA during the treatment of polycythemia vera with the JAK kinase inhibitor ruxolitinib. Intern Med 2016; 55: 1341-4. PubMed PMID: 27181544.

(64 year old woman with polycythemia vera [ALT normal, HBeAg negative, HBV DNA 5.4 log10 copies/mL] developed liver test abnormalities 1 month after starting ruxolitinib [bilirubin normal, ALT 352 U/L, HBV DNA 7.2 log10 copies/mL], responding within 2 weeks of starting entecavir with normal ALT and HBV DNA 3.6 log10 copies/mL).

Perricone G, Vinci M, Pungolino E. Occult hepatitis B infection reactivation after ruxolitinib therapy. Dig Liver Dis 2017; 49: 719. PubMed PMID: 28410914.

(Two men, ages 57 and 73 years, with polycythemia vera and anti-HBc without HBsAg in serum developed increasing levels of HBV DNA [from 39 to 840 IU/mL and <10 to 42.2 million IU/mL] 2 and 5 months after starting ruxolitinib, both responding to entecavir therapy, but one developing self-limited, but severe acute hepatitis).