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Baricitinib

Updated: October 20, 2018.

OVERVIEW

Introduction

Baricitinib is an orally available small molecule inhibitor of Janus kinases that is used to treat moderate-to-severe rheumatoid arthritis. Baricitinib is associated with transient and usually mild elevations in serum aminotransferase levels during therapy but has yet to be linked to cases of clinically apparent acute liver injury.

Background

Baricitinib (bar" i sye' ti nib) is an orally available, specific inhibitor Janus-associated kinases (mainly JAK1 and JAK2) that is used to treat moderate-to-severe rheumatoid arthritis. The Janus kinases are critical steps in immune activation as well as in hematopoiesis. The immunomodulatory effects of baricitinib have led to its evaluation in several autoimmune conditions including rheumatoid arthritis and psoriasis. In multiple randomized controlled trials, baricitinib was found to improve symptoms and signs of severe rheumatoid arthritis when used alone or in combination with other disease modifying anti-rheumatologic drugs (DMARDs). Baricitinib was approved for use in the United States in 2018, the third small molecule JAK inhibitor to receive approval (after tofacitinib in 2012 and ruxolitinib in 2011). Current indications are limited to moderate-to-severe rheumatoid arthritis after failure or intolerance to anti-tumor necrosis factor agents with or without non-biological DMARDs. Baricitinib is also under evaluation as therapy of for other autoimmune conditions including psoriasis and atopic dermatitis. Baricitinib is available in tablets of 2 mg under the brand name Olumiant. The recommended dose is 2 mg once daily. Common side effects are nausea, diarrhea, fatigue, neutropenia, cholesterol and creatinine elevations, herpes simplex and zoster infections, and symptoms of upper respiratory tract infection. Severe adverse events may include severe infections, reactivation of latent tuberculosis, increased risk of malignancy, gastrointestinal perforation and vascular thromboses.

Hepatotoxicity

In the large prelicensure clinical trials, serum aminotransferase elevations occurred in up to 17% of baricitinib treated subjects compared to 11% in placebo recipients. These elevations were typically mild and transient and values above 5 times the upper limit of normal (ULN) occurred in <1% of patients on baricitinib. The elevations occasionally led to early discontinuations, but more often resolved even without dose adjustment. In prelicensure studies, there were no instances of clinically apparent liver injury attributed to baricitinib. Since approval and more wide scale availability of baricitinib, there have been no published reports of hepatotoxicity associated with its use.

Likelihood score: E* (unlikely to be a cause of idiosyncratic clinically apparent liver injury but has had limited general availability and was associated with ALT elevations in prelicensure clinical trials).

Mechanism of Injury

The cause of mild serum enzyme elevations during baricitinib therapy is not known. Baricitinib is largely excreted unchanged in urine and stool and less than 10% undergoes hepatic metabolism, largely via CYP 3A4. The metabolism of baricitinib is not affected by CYP inhibitors or inducers, but its renal excretion can be affected by probenecid.

Outcome and Management

Monitoring of serum aminotransferase levels is recommended for patients starting baricitinib. Serum aminotransferase elevations above 5 times the upper limit of normal should lead to temporary cessation. If serum enzyme elevations do not resolve or improve within a few weeks of stopping, or if symptoms of liver injury or jaundice arise, baricitinib should be permanently discontinued. There does not appear to be cross reactivity in risk for hepatic injury between baricitinib and tofacitinib or other biologic or non-biologic DMARDs.

Drug Class: Antirheumatic Agents, Protein Kinase Inhibitors

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Baricitinib – Olumiant®

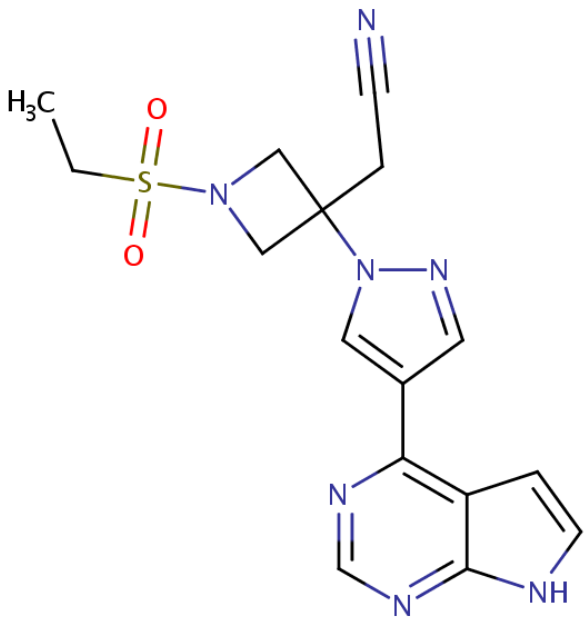
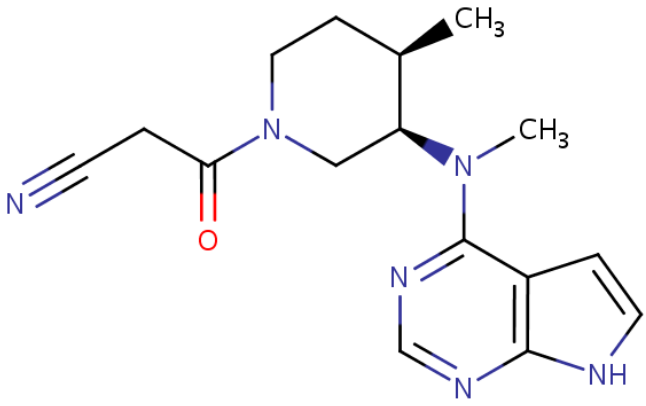
DRUG CLASS

Antirheumatic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Baricitinib	1187594-09-7	C16-H17-N7-O2-S	
Tofacitinib	477600-75-2	C16-H20-N6-O	

ANNOTATED BIBLIOGRAPHY

References updated: 20 October 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 protein kinase inhibitors such as tofacitinib and baricitinib).

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 kinase inhibitors including imatinib, gefitinib, erlotinib and crizotinib, but not baricitinib).

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; baricitinib is not discussed specifically).

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).

(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).

van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Meijide JA, Wagner S, Forejtova S, et al.; ORAL Standard Investigators. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012; 367: 508-19. PubMed PMID: 22873531.

(Among 717 patients with rheumatoid arthritis on methotrexate treated with tofacitinib [5 or 10 mg] or adalimumab or placebo for 52 weeks, clinical response rates were higher for tofacitinib [52-53%] than placebo [28%] and adverse events were more common [with two cases of pulmonary tuberculosis]; ALT elevations during the first 3 months occurred in 26% on tofacitinib vs 17% on placebo).

Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, Gruben D, et al.; ORAL Solo Investigators. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med 2012; 367: 495-507. PubMed PMID: 22873530.

(Among 611 patients with rheumatoid arthritis treated with tofacitinib [5 or 10 mg] or placebo twice daily for 3 months, clinical response rates were higher with tofacitinib, and adverse events included headache, infections, neutropenia and increases in serum cholesterol; ALT elevations above 3 times ULN occurred during the first 3 months in <1% of both groups).

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; batricitinib and tofacitinib are not discussed).

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; baricitinib and tofacitinib is not mentioned).

Keystone EC, Taylor PC, Drescher E, Schlichting DE, Beattie SD, Berclaz PY, Lee CH, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Ann Rheum Dis 2015; 74: 333-40. PubMed PMID: 25431052.

(Among 301 patients with rheumatoid arthritis and an inadequate response to methotrexate treated with baricitinib [1, 2, 4 or 8 mg] or placebo daily for 12 weeks, clinical response rates were higher with the higher doses of baricitinib, while rates of ALT elevations were similar in all groups and no patient suffered a liver related serious adverse event).

Papp KA, Menter MA, Abe M, Elewski B, Feldman SR, Gottlieb AB, Langley R, et al.; OPT Pivotal 1 and OPT Pivotal 2 investigators. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two randomized, placebo-controlled, phase III trials. Br J Dermatol 2015; 173: 949-61. PubMed PMID: 26149717.

(Among 1861 patients with plaque psoriasis treated with tofacitinib [5 or 10 mg] or placebo twice daily for 16 weeks, higher rates of improvement occurred with tofacitinib [42% to 59%] than placebo [9% to 11%], while adverse event rates were similar overall; ALT elevations above 3 times ULN occurred in 0.6% vs 0.2% of patients).

Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, Beattie SD, et al. Baricitinib in patients with refractory rheumatoid arthritis. N Engl J Med 2016; 374: 1243-52. PubMed PMID: 27028914.

(Among 527 patients with rheumatoid arthritis refractory to tumor necrosis factor inhibitors who were treated with baricitinib [2 or 4 mg] or placebo daily for 24 weeks, clinical response rates were higher with baricitinib as were adverse events [61% and 67% vs 55%], including mild and transient ALT elevations [14% and 17% vs 10%], but no patient developed ALT elevations over 5 times ULN or suffered a liver related serious adverse event).

Papp KA, Menter MA, Raman M, Disch D, Schlichting DE, Gaich C, Macias W, et al. A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis. Br J Dermatol 2016; 174: 1266-76. PubMed PMID: 26800231.

(Among 271 patients with plaque psoriasis treated with baricitinib [2, 4, 8 or 10 mg] or placebo daily for 12 weeks, clinical responses were more frequent with baricitinib, particularly with higher doses while adverse event rates [including ALT elevations] were similar in all groups).

Markham A. Baricitinib: first global approval. Drugs 2017; 77: 697-704. PubMed PMID: 28290136.

(Review of the development of baricitinib, its clinical efficacy and safety mentions that of 3464 patients treated in prelicensure clinical trials 6% developed adverse events leading to drug discontinuation, 3.4% developed herpes zoster, 3.2% serious infections, 0.7% malignancies and 0.3% died; aminotransferase elevations arose in 1.4% of patients but "most cases were transient").

Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, Del Carmen Morales L, Reyes Gonzaga J, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med 2017; 376: 652-62. PubMed PMID: 28199814.

(Among 1307 patients with rheumatoid arthritis receiving methotrexate, addition of baricitinib led to higher clinical response rates than did adalimumab or placebo, while adverse event rates were higher with active therapies and ALT elevations arose in 27% on baricitinib, 24% on adalimumab vs 17% on placebo, but were above 5 times ULN in 1% or less in all three groups).

Dougados M, van der Heijde D, Chen YC, Greenwald M, Drescher E, Liu J, Beattie S, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. Ann Rheum Dis 2017; 76: 88-95. PubMed PMID: 27689735.

(Among 684 patients with rheumatoid arthritis refractory to DMARDs treated with baricitinib [2 or 4 mg] or placebo daily for 24 weeks, clinical response rates were higher with baricitinib while serious adverse event rates were similar, although mean changes in ALT levels were greater with baricitinib [+6 U/L] and adalimumab [+5 U/L] than with placebo [+1 U/L]).

Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M, Zerbini CA, et al. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. Arthritis Rheumatol 2017; 69: 506-17. PubMed PMID: 27723271.

(Among 588 patients with rheumatoid arthritis treated with baricitinib or methotrexate or the combination, clinical response rates were highest in patients receiving baricitinib while ALT elevations arose in 33% on methotrexate alone, 16% on baricitinib alone and 34% on both, but ALT values aborve 5 times ULN were rare occurring in 1% or less and there were no hepatic severe adverse events).

Sanchez GAM, Reinhardt A, Ramsey S, Wittkowski H, Hashkes PJ, Berkun Y, Schalm S, et al. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. J Clin Invest 2018 Jun 11. [Epub ahead of print] PubMed PMID: 29649002.

(Among 18 patients with various interferon mediated autoinflammatory conditions treated with baricitinib for an average of 3 years, all except 5 had marked improvements in clinical symptoms and signs; no mention of ALT elevations or hepatotoxicity).

Keystone EC, Genovese MC, Schlichting DE, de la Torre I, Beattie SD, Rooney TP, Taylor PC. Safety and efficacy of baricitinib through 128 weeks in an open-label, longterm extension study in patients with rheumatoid arthritis. J Rheumatol 2018; 45: 14-21. PubMed PMID: 28811354.

(Among 301 patients enrolled in a controlled trial of baricitinib [2, 4, or 8 mg daily] fpr 24 weels [Keystone 2015], 171 entered an open label extension study [4 or 8 mg daily], and 133 completed 128 weeks of treatment, among whom ALT elevations occurred in approximately 25% but were above 5 times ULN in 1% or less; one patient developed a self-limited acute hepatitis B that was apparently nosocomially acquired and unrelated to therapy).

Guttman-Yassky E, Silverberg JI, Nemoto O, Forman SB, Wilke A, Prescilla R, et al. Baricitinib in adult patients with moderate-to-severe atopic dermatitis: a phase 2 parallel, double-blinded, randomized placebo-controlled multiple-dose study. J Am Acad Dermatol 2018 Feb 1. [Epub ahead of print] PubMed PMID: 29410014.

(Among 124 adults with atopic dermatitis treated with baricitinib [2 or 4 mg] or placebo daily for 16 weeks, clinical response rates were higher with baricitinib [57% and 61% vs 37%] as were adverse event rates [46% and 71% vs 49%]; no mention of ALT elevations or hepatotoxicity).

Drugs for rheumatoid arthritis. Med Lett Drugs Ther 2018; 60 (1552): 123-8. PubMed PMID: 30044766.

(Review of drugs for rheumatoid arthritis mentions that baricitinib is an orally available, small molecule inhibitor of JAK kinases and that its potential adverse side effects include serum ALT elevations).

Baricitinib (olumiant) for rheumatoid arthritis. Med Lett Drugs Ther 2018; 60 (1551): 120-1. PubMed PMID: 30036348.

(Concise review of the mechanism of action, clinical efficacy and safety of baricitinib shortly after its approval for use in rheumatoid arthritis in the US, mentions that elevations in liver enzymes have been reported to occur).