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Tofacitinib

Updated: June 22, 2018.

OVERVIEW

Introduction

Tofacitinib is an oral, small molecule inhibitor of Janus kinases that is used to treat moderate-to-severe rheumatoid arthritis. Tofacitinib 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

Tofacitinib (tow" fa sye' ti nib) is an orally available, specific inhibitor of Janus-associated kinases (mainly JAK1 and JAK3) 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 tofacitinib led to its evaluation in several autoimmune conditions including rheumatoid arthritis and psoriasis. In multiple, randomized controlled trials, tofacitinib was found to improve symptoms and signs of severe rheumatoid arthritis when used alone or in combination with other disease modifying antirheumatologic drugs (DMARDs). Tofacitinib was approved for use in the United States in 2012. Current indications are limited to moderate-to-severe rheumatoid arthritis after failure or intolerance to methotrexate or other non-biological DMARDs. Tofacitinib is available in tablets of 5 mg under the brand name Xeljanz. The recommended dose is 5 mg twice daily. More recently, an extended release formulation of tofacitinib (Xeljanz XR, 11 mg tablets) that allows for once daily dosing has been made available. Common side effects of tofacitinib are neutropenia, headaches, diarrhea, fatigue, hypertension and symptoms of upper respiratory tract infection. Severe adverse events may include severe infections, reactivation of latent tuberculosis, gastrointestinal perforation and de novo malignancies including Epstein-Barr virus related lymphoproliferative disorder.

Hepatotoxicity

In the large registration clinical trials, serum aminotransferase elevations occurred in 28% to 34% of tofacitinib treated subjects compared to 25% in comparator arms and 10% in placebo recipients. These elevations were typically mild and transient, but values above 3 times the upper limit of normal (ULN) occurred in 1% to 2% of patients on tofacitinib compared to <1% on placebo. 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 tofacitinib. Since approval and more wide scale availability of tofacitinib, there have been no published reports of hepatotoxicity or reactivation of hepatitis B associated with its use. Thus, clinically apparent liver injury from tofacitinib must be rare if it occurs at all.

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

Mechanism of Injury

The causes of serum enzyme elevations during tofacitinib therapy are not known. Tofacitinib is metabolized in the liver largely through the CYP 3A4 pathway and liver injury may be related to production of a toxic or immunogenic intermediate. Because it is a substrate for CYP 3A4, tofacitinib is susceptible to drug-drug interactions with agents that inhibit or induce this specific hepatic microsomal activity.

Outcome and Management

Monitoring of serum aminotransferase levels is recommended for patients starting tofacitinib. 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 are no data to suggest a cross reactivity in risk for hepatic injury between tofacitinib and other kinase inhibitors or biologic or nonbiologic DMARDs.

Drug Class: Antirheumatic Agents, Protein Kinase Inhibitors

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Tofacitinib – Xeljanz®

DRUG CLASS

Antirheumatic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

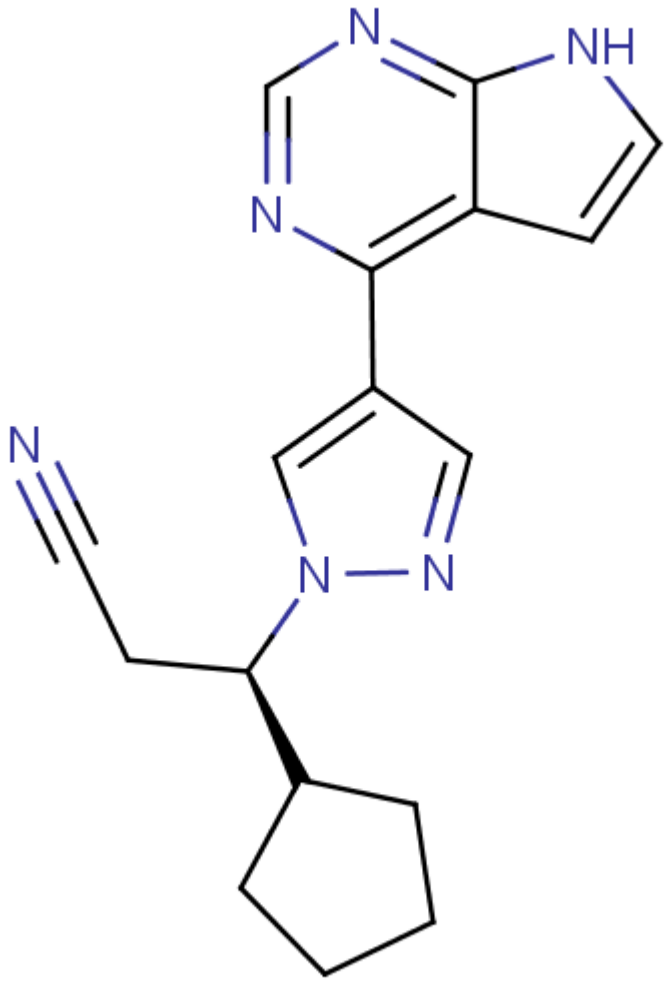
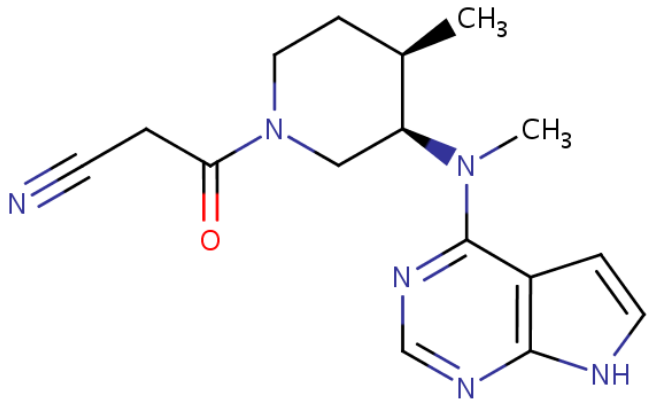
DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Ruxolitinib	941678-49-5	C17-H18-N6	

Table continued from previous page.

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Tofacitinib	477600-75-2	C16-H20-N6-O	

ANNOTATED BIBLIOGRAPHY

References updated: 22 June 2018

Zimmerman HJ. 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).

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 tofacitinib).

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; tofacitinib is not discussed specifically).

Kremer JM, Bloom BJ, Breedveld FC, Coombs JH, Fletcher MP, Gruben D, Krishnaswami S, et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. Arthritis Rheum 2009; 60: 1895-905. PubMed PMID: 19565475.

(Among 264 patients with rheumatoid arthritis treated with tofacitinib [5, 15 or 30 mg] or placebo twice daily for 6 weeks, symptomatic improvements occurred within 1 week of starting tofacitinib and the most common adverse events were headache and nausea; no mention of ALT elevations or hepatotoxicity).

Tanaka Y, Suzuki M, Nakamura H, Toyoizumi S, Zwillich SH; Tofacitinib Study Investigators. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. Arthritis Care Res (Hoboken) 2011; 63: 1150-8. PubMed PMID: 21584942.

(Among 140 patients with rheumatoid arthritis receiving methotrexate treated with tofacitinib [1, 3, 5 or 10 mg] or placebo twice daily for 12 weeks, ALT elevations occurred in 19% of patients on tofacitinib [vs 4% on placebo], but levels were above 3 times ULN in only 3% and no patient developed clinically apparent liver injury).

Papp KA, Menter A, Strober B, Langley RG, Buonanno M, Wolk R, Gupta P, et al. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a Phase 2b randomized placebo-controlled dose-ranging study. Br J Dermatol 2012; 167: 668-77. PubMed PMID: 22924949.

(Among 197 patients with plaque psoriasis treated with tofacitinib [2, 5 or 15 mg] or placebo twice daily for 12 weeks, adverse event rates were similar with tofacitinib and placebo; one patient [0.7%] discontinued therapy because of ALT elevations).

Kremer JM, Cohen S, Wilkinson BE, Connell CA, French JL, Gomez-Reino J, Gruben D, et al. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. Arthritis Rheum 2012; 64: 970-81. PubMed PMID: 22006202.

(Among 507 patients with rheumatoid arthritis with an inadequate response to methotrexate treated with tofacitinib in several doses or placebo for 12 weeks, clinical responses were better with tofacitinib and common

adverse events included diarrhea, headache and infections; ALT elevations above 3 times ULN occurring most frequently with the higher doses of tofacitinib, leading to 3 patients discontinuing therapy early).

Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S, Connell CA, et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum 2012; 64: 617-29. PubMed PMID: 21952978.

(Among 384 patients with rheumatoid arthritis treated with tofacitinib in varying doses or adalimumab or placebo for 12 weeks, ALT elevations occurred in 17% on tofacitinib vs 20% on placebo and were above 3 times ULN in 1% vs 0%).

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).

Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, Isaacs JD, et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med 2013; 159: 253-61. PubMed PMID: 24026258.

(Among 795 patients with rheumatoid arthritis [and an inadequate response to DMARDs] treated with tofacitinib [5 or 10 mg] or placebo twice daily for 3 months with extension of active treatment for 1 year, 3 tofacitinib treated patients stopped therapy early because of ALT or AST elevations, but there were no reports of clinically apparent liver injury).

Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, Gruben D, et al.; ORAL Step investigators. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet 2013; 381 (9865): 451-60. PubMed PMID: 23294500.

(Among 399 patients with rheumatoid arthritis [and an inadequate response to antitumor necrosis factor agents] treated with tofacitinib [5 or 10 mg] or placebo twice daily for 3 months, ALT elevations occurred in 17% on tofacitinib vs 13% on placebo, but were above 3 times ULN in 0.8% vs 0% and no patient developed clinically apparent liver injury).

Tofacitinib (Xeljanz) for rheumatoid arthritis. Med Lett Drugs Ther 2013; 55 (1407); 1-3. PubMed PMID: 23288133.

(Concise review of the mechanism of action, pharmacology, efficacy, safety and costs of tofacitinib shortly after its approval for in the US, mentions that elevations in ALT and AST have occurred with therapy and that "liver enzymes should be monitored regularly").

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; tofacitinib is 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; tofacitinib is not mentioned).

Wollenhaupt J, Silverfield J, Lee EB, Curtis JR, Wood SP, Soma K, Nduaka CI, et al. Safety and efficacy of tofacitinib, an oral Janus kinase inhibitor, for the treatment of rheumatoid arthritis in open-label, longterm extension studies. J Rheumatol 2014; 41: 837-52. PubMed PMID: 24692527.

(Among 4102 patients with rheumatoid arthritis treated with tofacitinib for up to 5 years in 2 open label studies following participation in placebo controlled trials, 21% of patients discontinued treatment and serious adverse events occurred in 15%, with ALT elevations above 3 times ULN in 48 patients [1.2%], 22 discontinuing treatment for this reason, and one patient having persistent ALT elevations and later diagnosis of autoimmune hepatitis requiring corticosteroid therapy).

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).

Tanaka Y, Takeuchi T, Yamanaka H, Nakamura H, Toyoizumi S, Zwillich S. Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study. Mod Rheumatol 2015; 25: 514-21 PubMed PMID: 25496464.

(Among 317 Japanese patients with rheumatoid arthritis treated with tofacitinib [1, 3, 5, 10 or 15 mg] or placebo twice daily for 12 weeks, ALT elevations above 3 times ULN occurred in 0-1.9% of tofacitinib vs 3.8% of placebo recipients and led to early discontinuation of therapy in one tofacitinib treated subject).

Cohen SB, Koenig A, Wang L, Kwok K, Mebus CA, Riese RJ, Fleischmann R. Efficacy and safety of tofacitinib in US and non-US rheumatoid arthritis patients: pooled analyses of phase II and III. Clin Exp Rheumatol 2015; 34: 32-6. PubMed PMID: 26575982.

(Pooled data on side effects from more than 3000 patients with rheumatoid arthritis focused largely on respiratory infections, diarrhea and edema; there were no cases of tuberculosis, lymphoma or serious herpes zoster infections; no mention of hepatotoxicity or reactivation of hepatitis B).

Charles-Schoeman C, Burmester G, Nash P, Zerbini CA, Soma K, Kwok K, Hendrikx T, et al. Efficacy and safety of tofacitinib following inadequate response to conventional synthetic or biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2016; 75: 1293-301. PubMed PMID: 26275429.

(Among 3517 patients with rheumatoid arthritis participating in 9 placebo controlled trials of tofacitinib, response as well as serious adverse event rates were similar among those who had never received and those who had an inadequate response to a previous course of a biological DMARD; no mention of ALT elevations or hepatotoxicity).

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. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 5 cases were attributed to drugs for rheumatoid arthritis: all 5 due to leflunomide and none to tofacitinib).

Papp KA, Krueger JG, Feldman SR, Langley RG, Thaci D, Torii H, Tyring S, et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: Long-term efficacy and safety results from 2 randomized phase-III studies and 1 open-label long-term extension study. J Am Acad Dermatol 2016; 74: 841-50. PubMed PMID: 26899199.

(Among 1861 patients with plaque psoriasis treated with tofacitinib or placebo for 16 weeks who were then all treated for up to 24 months, initial responses were maintained for the duration of treatment and risk for adverse events did not increase over time, although there were eventually 67 cases of herpes zoster and 5 deaths, none of which were considered related to tofacitinib; no mention of hepatotoxicity or reactivation of hepatitis B).

Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z, DeMasi R, et al.; ORAL Strategy investigators. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet 2017; 390 (10093): 457-68. PubMed PMID: 28629665.

(Among 1146 patients with rheumatoid arthritis treated with tofacitinib alone or with methotrexate or adalimumab for 1 year, response rates were slightly higher with addition of methotrexate [46%] and adalimumab [44%] compared to tofacitinib alone, as were ALT elevations above 3 times ULN [4% and 4% vs 2%], and 2 patients developed "drug-induced liver injury").

Zhang J, Tsai TF, Lee MG, Zheng M, Wang G, Jin H, Gu J, et al. The efficacy and safety of tofacitinib in Asian patients with moderate to severe chronic plaque psoriasis: A Phase 3, randomized, double-blind, placebo-controlled study. J Dermatol Sci 2017; 88: 36-45. PubMed PMID: 28558978.

(Among 266 Asian patients with plaque psoriasis treated with tofacitinib or placebo for 16 weeks and then "advanced" to tofacitinib, only 3 patients had ALT elevations above 3 times ULN and none developed symptoms or jaundice).

Panés J, Sandborn WJ, Schreiber S, Sands BE, Vermeire S, D'Haens G, Panaccione R, et al. Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. Gut 2017; 66: 1049-59. PubMed PMID: 28209624.

(Among 280 patients enrolled in 8 week placebo controlled trials of 2 doses of tofacitinib for Crohns disease, 180 enrolled in a maintenace trial for up to 24 weeks; total and severe adverse event rates were similar in all groups; no mention of ALT elevations or hepatotoxicity or of reactivation of hepatitis B).

Cohen SB, Tanaka Y, Mariette X, Curtis JR, Lee EB, Nash P, Winthrop KL, et al. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5+ years: integrated analysis of data from the global clinical trials. Ann Rheum Dis 2017; 76: 1253-62. PubMed PMID: 28143815.

(Analysis of long term safety of tofacitinib based upon pooled data on 6194 patients with rheumatoid arthritis found incidence rates of herpes zoster to be 3.9 per 100 patient-years, 2.7 for serious infections and 0.2 for tuberculosis, but there wer no instances of reactivation of hepatitis B mentioned).

Cohen S, Curtis JR, DeMasi R, Chen Y, Fan H, Soonasra A, Fleischmann R. Worldwide, 3-year, post-marketing surveillance experience with tofacitinib in rheumatoid arthritis. Rheumatol Ther 2018; 5: 283-91. PubMed PMID: 29470834.

(Postmarketing reports of adverse events over a 3 year period identified 4352 serious adverse events, the most frequent of which were infections [n=827, 2.6 per 100 patient-yrs] and hepatobiliary disorders were rare [n=41, 0.12 per 100 patient-yrs], but no details provided).

Valenzuela F, Korman NJ, Bissonnette R, Bakos N, Tsai TF, Harper MK, Ports WC, et al. Tofacitinib in patients with moderate to severe chronic plaque psoriasis: long-term safety and efficacy in an open-label extension study. Br J Dermatol 2018 May 21. [Epub ahead of print] PubMed PMID: 29782642.

(Among 2867 patients treated with tofacitinib for a median of 3 years, adverse events arose in 2366 [83%] patients, including 176 [6%] with herpes zoster and 1 with tuberculosis, but none with reactivation of hepatitis B or clinically apparent liver injury with jaundice).