



Tocilizumab

Updated: June 18, 2015.

OVERVIEW

Introduction

Tocilizumab is a humanized monoclonal antibody to the interleukin-6 (IL-6) receptor which is used in the therapy of rheumatoid arthritis and other autoinflammatory conditions. Tocilizumab commonly causes mild serum aminotransferase elevations which are usually short lived and asymptomatic and has also been linked to rare instances of clinically apparent liver injury with jaundice.

Background

Tocilizumab (toe' si liz' ue mab) is humanized IgG1 monoclonal antibody to the IL-6 receptor that is used largely as therapy of refractory rheumatoid arthritis and other inflammatory arthritides. Tocilizumab blocks the action of IL-6, which is a key proinflammatory cytokine that mediates a wide spectrum of biologic activities including activation of T cells, differentiation of B cells, induction of acute phase reactants, proliferation of fibroblasts, and damage to cartilage and joints. IL-6 levels are elevated in patients with active rheumatoid arthritis. In controlled trials and open label studies, tocilizumab therapy led to improvements in symptoms and laboratory abnormalities associated with several forms of inflammatory arthritis. Tocilizumab was approved for use in the United States in 2010 and current indications include rheumatoid arthritis and both the polyarticular and systemic forms of juvenile idiopathic arthritis (formerly juvenile rheumatoid arthritis). Tocilizumab is considered a disease modifying antirheumatic drug (DMARD) and improves signs and symptoms of disease and decreases cartilage and tissue destruction. Tocilizumab is given by intravenous infusion every 4 weeks, in doses of 4-12 mg/kg depending upon indication and body weight. Tocilizumab is available in vials of 20 mg/mL under the brand name Actemra. The most frequent side effects are upper respiratory symptoms, headache, infusion reactions and hypertension.

Hepatotoxicity

In registration trials, serum aminotransferase elevations occurred in a high proportion (10% to 40%) of patients receiving tocilizumab. ALT elevations often rose to 1 to 3 times the ULN 2 weeks after each infusion, but decreased towards baseline by the time of the next 4-weekly administration and were usually normal within 8 weeks of stopping the infusions. In some instances (~1% to 2%), levels rose above 5 times the ULN which triggered discontinuation or temporary suspension of treatment. Interestingly, the ALT elevations were somewhat dose related and tended to recur, but did not worsen with repeated exposures. In preapproval registration trials, there were no reports of clinically apparent liver injury with jaundice, and most ALT elevations were without symptoms and with minimal or no elevations in serum bilirubin or alkaline phosphatase levels. Since its licensure and availability, however, tocilizumab therapy has been linked to several instances of

clinically apparent liver injury with jaundice. The injury arose after several months of therapy and was predominantly hepatocellular with no immunoallergic or autoimmune features. While the liver injury was severe, it was usually self-limited with complete recovery in 2 to 3 months. In at least one instance, however, the affected patient died with liver failure and hepatic atrophy that seemed to be initiated by tocilizumab therapy.

Tocilizumab is an immunosuppressive agent, but has not been implicated in causing reactivation of hepatitis B. In several cases reports, tocilizumab has been used safely and without worsening of disease in patients with concurrent chronic hepatitis C, but there has been at least one case report of mild and transient worsening of hepatitis C with its use.

Likelihood score: D (possible cause of clinically apparent liver injury).

Mechanism of Injury

Tocilizumab is a monoclonal antibody and has minimal hepatic metabolism. The mechanism by which it causes liver injury is unknown, but may be the result of its effects on the immune system or on the IL-6 pathway which is important in liver regeneration.

Outcome and Management

The mild liver injury caused by tocilizumab is generally short lived and resolves within 2 to 6 weeks. The majority of patients can continue the 4 weekly infusions, although dose reduction may be warranted. The more severe, clinically apparent liver injury caused by tocilizumab should trigger its permanent discontinuation. The effects of reexposure to tocilizumab after clinically apparent liver injury have not been reported, but rechallenge should probably be avoided. On the other hand, there is no reason to suspect that there may be cross sensitivity to hepatic injury between tocilizumab and other immune modulating biologic agents or anti-IL1 blockers such as anakinra, canakinumab and rilonacept.

Drug Class: [Antirheumatic Agents](#)

Other Drugs in the Subclass, [Interleukin Receptor Antagonists](#): [Anakinra](#), [Canakinumab](#), [Rilonacept](#), [Sarilumab](#)

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Tocilizumab – Actemra®

DRUG CLASS

Antirheumatic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Tocilizumab	375823-41-9	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 18 June 2015

Zimmerman HJ. Drugs used to treat rheumatic and musculoskeletal disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 517-53.

(Expert review of hepatotoxicity published in 1999 before the availability of tocilizumab and other monoclonal antibodies and anticytokines).

Krensky AM, Bennett WM, Vincenti F. Immunosuppressants, tolerogens, and immunostimulants. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1005-29.

(Textbook of pharmacology and therapeutics).

Bywaters EG. Still's disease in the adult. *Ann Rheum Dis* 1971; 30: 121-33. PubMed PMID: 5315135.

(Clinical description of 14 patients with adult Still disease seen at a single referral center in the UK over a 25 year period; all woman, ages 17-35 years, presenting with urticarial, macular rash, high fevers, fatigue and arthritis, high ESR but no rheumatoid factor, the majority ultimately recovering completely without residual arthritis or problems).

Andrès E, Kurtz JE, Perrin AE, Pflumio F, Ruellan A, Goichot B, Dufour P, et al. Retrospective monocentric study of 17 patients with adult Still's disease, with special focus on liver abnormalities. *Hepatology* 2003; 50: 192-5. PubMed PMID: 12630021.

(Among 17 patients with adult onset Still disease seen at a single French referral center, mean age was 27 years and 76% had moderate liver dysfunction with hepatomegaly in 47% [bilirubin 0.6-1.3 mg/dL, ALT 32-252 U/L], all having "complete recovery").

Maini RN, Taylor PC, Szechinski J, Pavelka K, Bröll J, Balint G, Emery P, et al; CHARISMA Study Group. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006; 54: 2817-29. PubMed PMID: 16947782.

(359 patients with active rheumatoid arthritis were randomized to different doses of tocilizumab or placebo with or without methotrexate; mild increases in ALT [by 45-88% from baseline] were common with the combination and with higher doses, but were transient and not associated with symptoms or jaundice).

Plushner SL. Tocilizumab: an interleukin-6 receptor inhibitor for the treatment of rheumatoid arthritis. *Ann Pharmacother* 2008; 42: 1660-8. PubMed PMID: 18957621.

(Review of pharmacology, clinical efficacy and safety of tocilizumab mentions that dose dependent liver enzyme elevations were frequent during therapy, but that "most levels returned to near normal at follow-up").

Feist E, Burmester GR. Is tocilizumab in combination with traditional DMARDs safe and effective for patients with active RA? *Nat Clin Pract Rheumatol* 2009; 5: 128-9. PubMed PMID: 19252516.

(Editorial mentions that liver enzyme elevations occur in 45% of patients treated with tocilizumab, but were transient and asymptomatic).

Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J. Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibody, in monotherapy, in patients with rheumatoid arthritis (the STREAM study): evidence of safety and efficacy in a 5-year extension study. *Ann Rheum Dis* 2009; 68: 1580-4. PubMed PMID: 19019888.

(Among 143 patients with rheumatoid arthritis who were continued in an extension trial of tocilizumab for up to 5 years, serum ALT elevations [>2.5 times ULN] occurred in 10%, but most elevations were transient and there were no serious liver related adverse events).

Furst DE. The risk of infections with biologic therapies for rheumatoid arthritis. *Semin Arthritis Rheum* 2010; 39: 327-46. PubMed PMID: 19117595.

(Review of the excess risk of infections during biologic therapy of rheumatoid arthritis mentions that the rate of infections was 2.1% in treated patients vs 0.4% in controls; infections were primarily pneumonia and skin infections, none were fatal and few were opportunistic).

Carroll MB. The impact of biologic response modifiers on hepatitis B virus infection. *Expert Opin Biol Ther* 2011; 11: 533-44. PubMed PMID: 21269234.

(Review of reactivation of hepatitis B by biologic response modifiers; tocilizumab has not been linked to reactivation of HBV, although the experience in treating patients with HBsAg has been limited).

Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. *Arthritis Res Ther* 2011; 13: R141. PubMed PMID: 21884601.

(Analysis of safety data from 5 large clinical trials and extension studies of tocilizumab in 8580 patients with rheumatoid arthritis treated for up to 5 years; ALT elevations occurred in 19-33% of patients and were above 3 times ULN in 1.1-3.7%, being more frequent with higher doses; dose reductions for ALT elevations occurred in 9.3% and stopping therapy in 2.3% of patients; however, "no evidence was seen of clinically significant hepatitis or drug-induced liver injury associated with transaminase elevations in patients treated with tocilizumab"; 11 liver biopsies showed either nonalcoholic fatty liver disease or were normal).

Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, Takei S, et al. Postmarketing surveillance of tocilizumab for rheumatoid arthritis in Japan: interim analysis of 3881 patients. *Ann Rheum Dis* 2011; 70: 2148-51. PubMed PMID: 21852254.

(Evaluation of adverse event reports during the first 1.5 years of tocilizumab availability in Japan; among 3004 reports from 1641 patients, most common were infections followed by laboratory test abnormalities and "hepatobiliary disorders" [n=269 of which 12 were serious], but no details given).

Bannwarth B, Richez C. Clinical safety of tocilizumab in rheumatoid arthritis. *Expert Opin Drug Saf* 2011; 10: 123-31. PubMed PMID: 21121872.

(Review of the adverse events reported in clinical trials of tocilizumab in rheumatoid arthritis; among 3689 patients with normal ALT levels before treatment, 10.3% had ALT elevations >3 times ULN and 2.4% above 5 times ULN, but there were no cases of clinical apparent liver injury).

Hiura M, Abe S, Tabaru A, Shimajiri S, Hanami K, Saito K, Tanaka Y, et al. Case of severe liver damage after the induction of tocilizumab therapy for rheumatoid vasculitis. *Hepatology* 2011; 41: 492-6. PubMed PMID: 21435128.

(71 year old man with refractory rheumatoid arthritis and vasculitis developed mild serum enzyme elevations during 3 months of tocilizumab therapy [bilirubin 1.3 mg/dL, ALT 67 U/L, Alk P 380 U/L, platelets 93,000/ μ L], later developing ascites, and hepatic failure, autopsy showing hepatic atrophy and little fibrosis).

Lee JS, Wang J, Martin M, Germer S, Kenwright A, Benayed R, Spleiss O, et al. Genetic variation in UGT1A1 typical of Gilbert syndrome is associated with unconjugated hyperbilirubinemia in patients receiving tocilizumab. *Pharmacogenet Genomics* 2011; 21: 365-74. PubMed PMID: 21412181.

(Two of 1187 patients with rheumatoid arthritis who developed a concurrent rise in ALT >3 times ULN and serum bilirubin >2 times ULN during tocilizumab therapy were both found to be homozygous for genetic variants of UGT1A1 associated with indirect hyperbilirubinemia and Gilbert syndrome).

Kishida D, Okuda Y, Onishi M, Takebayashi M, Matoba K, Jouyama K, Yamada A, et al. Successful tocilizumab treatment in a patient with adult-onset Still's disease complicated by chronic active hepatitis B and amyloid A amyloidosis. *Mod Rheumatol* 2011; 21: 215-8. PubMed PMID: 20931272.

(40 year old man with hepatitis B and adult onset Still disease was treated with tocilizumab while receiving entecavir and did not have a rise in HBV DNA levels or worsening of liver disease during anti-IL6 therapy).

Mahamid M, Paz K, Reuven M, Safadi R. Hepatotoxicity due to tocilizumab and anakinra in rheumatoid arthritis: two case reports. *Int J Gen Med* 2011; 4: 657-60. PubMed PMID: 21941451.

(46 year old woman with rheumatoid arthritis who was switched from methotrexate [10 years] to tocilizumab and developed fatigue after a 2nd infusion, a liver biopsy showing steatosis and "focal hemorrhagic necrosis" despite normal serum enzymes and bilirubin; later continuing tocilizumab without change in liver tests).

Mahamid M, Mader R, Safadi R. Hepatotoxicity of tocilizumab and anakinra in rheumatoid arthritis: management decisions. *Clin Pharmacol* 2011; 3: 39-43. PubMed PMID: 22287855.

(Description of same two patients as in Mahamid [Int J Gen Med 2011]).

Iebba F, Di Sora F, Tarasi A, Leti W, Montella T, Montella F. Case report: safety and efficacy of tocilizumab in a patient with rheumatoid arthritis and chronic hepatitis C. *Case Rep Med* 2012; 2012: 212381. PubMed PMID: 22431927.

(71 year old woman with chronic hepatitis C and rheumatoid arthritis refractory to therapy with methotrexate and anti-TNF agents was treated with tocilizumab with excellent response and no change in serum enzyme levels [which remained normal] during 6 months of treatment).

Drugs for rheumatoid arthritis. *Treat Guidel Med Lett* 2012; 10 (117): 37-44. PubMed PMID: 22538522.

(Concise summary on current therapies of rheumatoid arthritis mentions that side effects of tocilizumab include infusion reactions, hypertension, neutropenia, aminotransferase elevations and dyslipidemia).

De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, Cuttica R, et al; PRINTo; PRCsG. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012; 367: 2385-95. PubMed PMID: 23252525.

(Among 112 children with systemic juvenile idiopathic arthritis not responding to standard therapy in a 12 week, placebo controlled trial, ALT elevations occurred in 19% of 75 tocilizumab recipients [and were >5 times ULN in 7%], but in none of 37 placebo recipients).

Sandborg C, Mellins ED. A new era in the treatment of systemic juvenile idiopathic arthritis. *N Engl J Med* 2012; 367: 2439-40. PubMed PMID: 23252530.

(Editorial in response to De Benedetti [2012] on IL-6 antagonists as therapy of juvenile idiopathic arthritis; "the therapeutic benefits of these biologic agents will need to be weighed against the apparent risks of infection, neutropenia and liver dysfunction").

Nagashima T, Maruyama A, Kamata Y, Minota S. Unchanged serum viral load and liver function during tocilizumab treatment in a patient with rheumatoid arthritis and hepatitis C virus infection. *Rheumatol Int* 2012; 32: 2231-2. PubMed PMID: 21785953.

(53 year old Japanese man with rheumatoid arthritis and chronic hepatitis C was treated with tocilizumab for 6 months without worsening of his concurrent hepatitis C or change in ALT or HCV RNA levels).

Dragonas C, Ehrenstein B, Fleck M. Tocilizumab treatment in a patient suffering from rheumatoid arthritis and concomitant chronic hepatitis C infection. *Rheumatology (Oxford)* 2012; 51: 1520-1. PubMed PMID: 22467085.

(47 year old man with rheumatoid arthritis and chronic hepatitis C tolerated tocilizumab therapy with no change in serum enzymes of HCV RNA levels during a full year of treatment).

Mori S, Fujiyama S. Comment on: Tocilizumab treatment in a patient suffering from rheumatoid arthritis and concomitant chronic hepatitis C infection. *Rheumatology (Oxford)* 2012; 51: 2300-2; author reply 2302. PubMed PMID: 22977061.

(Letter in response to Dragonas [2012] describing a 65 year old woman with rheumatoid arthritis and chronic hepatitis C who had a flare of disease [ALT 211 U/L, HCV RNA levels rising slightly, bilirubin not given] after 8 months of tocilizumab therapy, resolving upon stopping).

Akgul O, Kilic E, Kilic G, Ozgocmen S. Efficacy and safety of biologic treatments in familial Mediterranean Fever. *Am J Med Sci* 2013; 346: 137-41. PubMed PMID: 23276893.

(Systematic review of reports on use of biologic response modifiers in familial Mediterranean fever identified no controlled trials, but 24 single reports and 7 case series describing 59 patients; agents evaluated included TNF antagonists [35], anakinra [29], and canakinumab [4], but not tocilizumab; no discussion of hepatotoxicity).

Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K, Klearman M, et al.; ADACTA Study Investigators. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet* 2013; 381 (9877):1541-50. PubMed PMID: 23515142.

(Controlled trial comparing 24 week courses of 2 monoclonal antibody therapies in 326 patients with rheumatoid arthritis; ALT elevations above 2.5 times ULN occurred in 6% on tocilizumab vs 1.9% on adalimumab, but there were no serious adverse events attributed to liver injury).

Alfreijat M, Habibi M, Bhatia P, Bhatia A. Severe hepatitis associated with tocilizumab in a patient with rheumatoid arthritis. *Rheumatology (Oxford)* 2013; 52: 1340-1. PubMed PMID: 23315786.

(62 year old man with rheumatoid arthritis developed jaundice 1 week after a 3rd monthly injection of tocilizumab [bilirubin 10.5, ALT 2296, Alk P not given], resolving within 10 weeks on prednisone; accompanied by mild pancreatitis).

Drepper M, Rubbia-Brandt L, Spahr L. Tocilizumab-induced acute liver injury in adult onset Still's disease. *Case Reports Hepato* 2013; 2013: 964828. PubMed PMID: 25374723.

(18 year old woman with Still disease developed jaundice 6 months after starting tocilizumab [bilirubin 3.6 mg/dL, ALT 2628 U/L, Alk P 110 U/L, INR 1.21], with liver biopsy showing centrolobular necrosis, and resolving within 1 month of stopping).

Giannitti C, Fineschi I, Frediani B, Fioravanti A, Galeazzi M. Efficacy and safety of tocilizumab combined with cyclosporine A in a patient with rheumatoid arthritis and concomitant chronic hepatitis C virus infection. *Clin Exp Rheumatol* 2013; 31: 816. PubMed PMID: 24021246.

(58 year old man with rheumatoid arthritis and chronic hepatitis C tolerated treatment with tocilizumab, cyclosporine and prednisone for 12 months with no worsening of ALT levels or increase in HCV RNA levels).

Genovese MC, Rubbert-Roth A, Smolen JS, Kremer J, Khraishi M, Gómez-Reino J, Sebba A, et al. Longterm safety and efficacy of tocilizumab in patients with rheumatoid arthritis: a cumulative analysis of up to 4.6 years of exposure. *J Rheumatol* 2013; 40: 768-80. PubMed PMID: 23457383.

(Analysis of long term safety data from 5 controlled trials and open label extension studies of tocilizumab given for an average of 3 years in 4009 patients with rheumatoid arthritis; 3 hepatic serious adverse events occurred, autoimmune hepatitis, steatosis and hepatic ischemia, the last being possibly related as it occurred in a patient with an anaphylactic reaction).

Burmester GR, Rubbert-Roth A, Cantagrel A, Hall S, Leszczynski P, Feldman D, Rangaraj MJ, et al. A randomised, double-blind, parallel-group study of the safety and efficacy of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional disease-modifying antirheumatic drugs in patients with moderate to severe rheumatoid arthritis (SUMMACTA study). *Ann Rheum Dis* 2014; 73: 69-7. PubMed PMID: 23904473.

(Comparison of weekly subcutaneous injections to every 4 weekly intravenous infusions of tocilizumab in 1262 patients with rheumatoid arthritis; the safety profiles were similar except for injection site reactions; some degree of ALT elevation occurred in 52% of patients and were >3 times ULN in 5% and >5 times ULN in 1%).

Bauer H, Luxembourger C, Gottenberg JE, Fournier S, Abravanel F, Cantagrel A, Chatelus E, et al.; Club Rhumatismes et Inflammation, a section of the French Society of Rheumatology. Outcome of hepatitis E virus infection in patients with inflammatory arthritides treated with immunosuppressants: a French retrospective multicenter study. *Medicine (Baltimore)* 2015; 94: e675. PubMed PMID: 25860212.

(Survey of French physicians treating patients with rheumatic diseases identified 23 patients who developed acute hepatitis E while being treated with immunosuppressive regimens [10 on anti-TNF, 4 rituximab, 2 abatacept, 2 tocilizumab and 16 receiving methotrexate, 4 leflunomide and 1 cyclosporine]; all recovered and cleared HEV RNA, some after reduction in immunosuppression and 5 with ribavirin therapy).

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 (5): 841-50. PubMed PMID: 26899199.

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. doi: 10.1016/S0140-6736(17)31618-5. Epub 2017 Jun 16. PubMed PMID: 28629665.

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 (1): 36-45. doi: 10.1016/j.jdermsci.2017.05.004. Epub 2017 May 16. PubMed PMID: 28558978.

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 (6): 1049-59. doi: 10.1136/gutjnl-2016-312735. Epub 2017 Feb 16. PubMed PMID: 28209624.

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 (7): 1253-62. doi: 10.1136/annrheumdis-2016-210457. Epub 2017 Jan 31. PubMed PMID: 28143815.

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. doi: 10.1111/bjd.16798. [Epub ahead of print] PubMed PMID: 29782642.

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 (1): 283-91. doi: 10.1007/s40744-018-0097-3. Epub 2018 Feb 22. PubMed PMID: 29470834.