Tofacitinib

Tofacitinib (INN) is a drug of the janus kinase (JAK) inhibitor class, discovered and developed by the National Institutes of Health and Pfizer. Tofacitinib is marketed as **Xeljanz** and **Jakvinus**.

It is currently approved for the treatment of rheumatoid arthritis (RA) in the United States and other countries.

It has demonstrated effectiveness in the treatment of psoriasis in Phase 3 studies. It is being studied for treatment of inflammatory bowel disease,[1][2] and other immunological diseases, as well as for the prevention of organ transplant rejection.[3][4][5][6]

1 Approvals and indications

1.1 Rheumatoid arthritis

In November 2012, the U.S. FDA approved tofacitinib "to treat adults with moderately to severely active rheumatoid arthritis who have had an inadequate response to, or who are intolerant of, methotrexate."[7] It was later approved in Japan, Switzerland and others (but not the EU). It is marketed as Xeljanz in all regions except for Russia where it will be marketed as Jakvinus or Jaquinus.[8]

2 Mechanism

It is an inhibitor of the enzyme janus kinase 1 (JAK1) and janus kinase 3 (JAK 3), which means that it interferes with the JAK-STAT signaling pathway, which transmits extracellular information into the cell nucleus, influencing DNA transcription.[9]

In a mouse model of established arthritis, tofacitinib rapidly improved disease by inhibiting the production of inflammatory mediators and suppressing STAT1-dependent genes in joint tissue. This efficacy in this disease model correlated with the inhibition of both JAK1 and 3 signaling pathways, suggesting that tofacitinib may exert therapeutic benefit via pathways that are not exclusive to inhibition of JAK3.[10]

3 Research history

The potential significance of JAK3 inhibition was first discovered in the laboratory of John O'Shea, an immunologist at the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health (NIH).[11] In 1994, Pfizer was approached by the NIH to form a public-private partnership in order to evaluate and bring to market experimental compounds based on this research.[11] Pfizer initially declined the partnership but agreed in 1996, after the elimination of an NIH policy dictating that the market price of a product resulting from such a partnership would need to be commensurate with the investment of public taxpayer revenue and the "health and safety needs of the public."[11] Pfizer worked with O'Shea's laboratory to define the structure and function of JAK3 and its receptors, and then handled the drug discovery, preclinical development, and clinical development of tofacitinib in-house.[12]

The drug was coded as CP−690,550[13] during development. Its original recommended INN (rINN) was **tasocitinib**,[14] but that was overruled during the INN approval process as being inoptimally differentiable from other existing INNs, so the name *tofacitinib* was proposed and became the INN.

In November 2012, the U.S. Food and Drug Administration (FDA) approved tofacitinib for treatment of rheumatoid arthritis. Two rheumatologists interviewed by the magazine Nature Biotechnology complained that they were "shocked" and "disappointed" at the $2,055 a month wholesale price.[12]

A 2014 study showed that tofacitinib treatment was able to convert white fat tissues into more metabolically active brown fat, suggesting it may have potential applications in the treatment of obesity.[15]

4 Clinical trials

4.1 Rheumatoid arthritis

Phase II clinical trials tested the drug in rheumatoid arthritis patients that had not responded to DMARD therapy. In a tofacitinib monotherapy study, the ACR score improved by at least 20% (ACR-20) in 67% of patients versus 25% who received placebo; and a study that combined the drug with methotrexate achieved ACR-20 in 59% of patients versus 35% who received methotrexate alone.

The most important side effects in Phase II studies were increased blood cholesterol levels (12 to 25 mg/dl LDL and 8 to 10 mg/dl HDL at medium dosage levels)

and neutropenia.[16] Phase III trials testing the drug in rheumatoid arthritis started in 2007 and are scheduled to run until January 2015.[17]

In April 2011, four patients died after beginning clinical trials with tofacitinib. According to Pfizer, only one of the four deaths was related to tofacitinib.[18]

By April 2011, three phase III trials for RA had reported positive results.[19]

In November 2012, the U.S. FDA approved tofacitinib "to treat adults with moderately to severely active rheumatoid arthritis who have had an inadequate response to, or who are intolerant of, methotrexate."[7] FDA approved only the 5 mg twice-daily dose on the grounds that a higher dose was not considered to have an adequate risk-to-benefit ratio.[20]

4.2 Psoriasis

Tofacitinib is a current investigational drug in psoriasis. Tofacitinib has demonstrated its effectiveness for plaque psoriasis in Phase 3 randomized, controlled trials in comparison to placebo and to etanercept.[20][21][22] In particular, a 10 mg twice-daily dose of tofacitinib was shown to be noninferior to etanercept 50 mg subcutaneously twice weekly.[22]

4.3 Ulcerative colitis

The phase 3 OCTAVE study of Tofacitinib in ulcerative colitis started in 2012 and completed in 2015.[23]

4.4 Alopecia areata

Based on preclinical studies in a mouse model of the disease,[24] tofacitinib has been investigated for the treatment of alopecia areata. Early case reports[25][26] suggested potential efficacy, as did a phase II open-label clinical trial,[27] published in tandem with a phase II clinical trial showing the same for ruxolitinib.[28]

4.5 Vitiligo

In a June 2015 case report, a 53-year-old woman with vitiligo showed noticeable improvement after taking tofacitinib for five months.[29]

4.6 Atopic dermatitis

The results of using Tofacitinib in 6 patients with recalcitrant atopic dermatitis was published in the September 2015. All saw improvement in their atopic dermatitis without any adverse events.[30]

5 Safety and side effects

Tofacitinib was not approved by European regulatory agencies because of concerns over efficacy and safety.[31] Animal studies with tofacitinib conducted prior to human trials showed some carcinogenesis, mutagenesis, and impairment of fertility.[32]

5.1 Warnings and precautions

Tofacitinib is required by US FDA to have a boxed warning on its label about possible injury and death due to problems such as infections, Lymphoma and other malignancies which can arise from use of this drug.[7] Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving tofacitinib. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with tofacitinib while on immunosuppressive medications. Patients are warned to avoid use of tofacitinib citrate during an "active serious infection, including localized infections." Doctors are advised to use it with caution in patients that may be at increased risk of gastrointestinal perforations. Laboratory Monitoring is recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. Tofacitinib claims to have no contraindications, however doctors are advised to reduce the patient's dosage when combined with "potent inhibitors of Cytochrome P450 3A4 (CYP3A4)," such as ketoconazole), or one or more combined medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 such as fluconazole. Furthermore, immunizations with live vaccines should be avoided by tofacitinib users.[32]

5.2 Adverse reactions

The most commonly reported adverse reactions during the first three months in controlled clinical trials (occurring in greater than or equal to 2% of patients treated with tofacitinib citrate monotherapy or in combination with DMARDs) were upper respiratory tract infections, headache, diarrhea, and nasopharyngitis (the "common cold").[32]

6 References

[1] Vuitton, Lucine; Koch, Stéphane; Peyrin-Biroulet, Laurent (31 October 2013). "Janus Kinase Inhibition with Tofacitinib: Changing the Face of Inflammatory Bowel Disease Treatment". *Current Drug Targets*. **14** (12): 1385–1391. doi:10.2174/13894501113149990160. PMC 3713609. PMID 23627915.

[2] Zand, Martin S. (July 2013). "Tofacitinab in Renal Transplantation". *Transplantation Reviews*. **27** (3): 85–89. doi:10.1016/j.trre.2013.04.001. PMC 3713609. PMID 23849222.

[3] Allan D. Kirk; Stuart J. Knechtle; Christian P. Larsen; Joren C. Madsen; Thomas C. Pearson; Steven A. Webber (21 July 2014). *Textbook of Organ Transplantation Set*. John Wiley & Sons. pp. 245–. ISBN 978-1-118-88962-6.

[4] Wojciechowski, D; Vincenti, F (September 2013). "Tofacitinib in kidney transplantation.". *Expert opinion on investigational drugs*. **22** (9): 1193–9. doi:10.1517/13543784.2013.811231. PMID 23841583.

[5] Myrvang, H (26 June 2012). "Transplantation: Tofacitinib safe and effective in renal transplant recipients.". *Nature reviews. Nephrology*. **8** (8): 432. doi:10.1038/nrneph.2012.120. PMID 22735765.

[6] Kalluri, Hari Varun (2012). "Current state of renal transplant immunosuppression: Present and future". *World Journal of Transplantation*. **2** (4): 51. doi:10.5500/WJT.v2.i4.51. PMC 3782235.

[7] "FDA approves Xeljanz for rheumatoid arthritis". 6 Nov 2012.

[8] Pfizer Provides Update on Global Regulatory Approvals and Launches of XELJANZ® (tofacitinib citrate) for the Treatment of Rheumatoid Arthritis. July 2013

[9] "Tasocitinib". *Drugs in R&D*. **10** (4): 271–284. 2010. doi:10.2165/11588080-000000000-00000. PMC 3585773. PMID 21171673.

[10] Ghoreschi, K.; Jesson, M. I.; Li, X.; Lee, J. L.; Ghosh, S.; Alsup, J. W.; Warner, J. D.; Tanaka, M.; Steward-Tharp, S. M.; Gadina, M.; Thomas, C. J.; Minnerly, J. C.; Storer, C. E.; Labranche, T. P.; Radi, Z. A.; Dowty, M. E.; Head, R. D.; Meyer, D. M.; Kishore, N.; O'Shea, J. J. (2011). "Modulation of Innate and Adaptive Immune Responses by Tofacitinib (CP-690,550)". *J Immunol*. **186** (7): 4234–4243. doi:10.4049/jimmunol.1003668. PMC 3108067. PMID 21383241.

[11] "Seeking Profit for Taxpayers in Potential of New Drug", Jonathan Weisman, *New York Times*, 18 March 2013 (subscription firewall)

[12] Ken Garber (9 January 2013). "Pfizer's first-in-class JAK inhibitor pricey for rheumatoid arthritis market". *Nature Biotechnology*. **31** (1): 3–4. doi:10.1038/nbt0113-3. PMID 23302910.

[13] Kremer, J. M.; Bloom, B. J.; Breedveld, F. C.; Coombs, J. H.; Fletcher, M. P.; Gruben, D.; Krishnaswami, S.; Burgos-Vargas, R. N.; Wilkinson, B.; Zerbini, C. A. F.; Zwillich, S. H. (2009). "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 & Rheumatism*. **60** (7): 1895–1905. doi:10.1002/art.24567. PMID 19565475.

[14] Herper, Matthew (2 March 2011). "Why Pfizer's Biggest Experimental Drug Got A Name Change". Forbes. Retrieved 3 March 2011.

[15] Moisan A, et al. White-to-brown metabolic conversion of human adipocytes by JAK inhibition. *Nature Cell Biology*, 8 December 2014. doi:10.1038/ncb3075

[16] "EULAR: JAK Inhibitor Effective in RA But Safety Worries Remain". MedPage Today. June 2009. Retrieved 9 February 2011.

[17] Clinical trial number *NCT00413699* for "Long-Term Effectiveness And Safety Of CP-690,550 For The Treatment Of Rheumatoid Arthritis" at ClinicalTrials.gov

[18] Matthew Herper. "Pfizer's Key Drug Walks A Tightrope". *Forbes*.

[19] "Two Phase III Studies Confirm Benefits of Pfizer's Tofacitinib Against Active RA". 28 Apr 2011.

[20] Di Lernia, V.; Bardazzi, F. (2016-01-01). "Profile of tofacitinib citrate and its potential in the treatment of moderate-to-severe chronic plaque psoriasis". *Drug Design, Development and Therapy*. **10**: 533–539. doi:10.2147/DDDT.S82599. ISSN 1177-8881. PMC 4743637. PMID 26889081.

[21] Papp KA, Menter MA, Abe M, et al. for the OPT Pivotal 1 and OPT Pivotal 2 Investigators. (7 July 2015). "Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: results from two, randomised, placebo-controlled, Phase 3 trials.". *Br J Dermatol*. **173**: 949–61. doi:10.1111/bjd.14018. PMID 26149717.

[22] Bachelez H, van de Kerkhof PC, Strohal R, et al. for the OPT Compare Investigators. (Aug 8, 2015). "Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial.". *Lancet*. **386** (9993): 552–61. doi:10.1016/S0140-6736(14)62113-9. PMID 26051365.

[23] A Multicentre, Randomized, Double-blind, Placebo-controlled, Parallel-group Study Of Oral Cp-690,550 As An Induction Therapy In Subjects With Moderate To Severe Ulcerative Colitis

[24] Xing, Luzhou; Dai, Zhenpeng; Jabbari, Ali; Cerise, Jane E.; Higgins, Claire A.; Gong, Weijuan; de Jong, Annemieke; Harel, Sivan; DeStefano, Gina M. (2014-09-01). "Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition". *Nature Medicine*. **20** (9): 1043–1049. doi:10.1038/nm.3645. ISSN 1546-170X. PMC 4362521. PMID 25129481.

[25] Craiglow, Brittany G.; King, Brett A. (2014-12-01). "Killing two birds with one stone: oral tofacitinib reverses alopecia universalis in a patient with plaque psoriasis". *The Journal of Investigative Dermatology*. **134** (12): 2988–2990. doi:10.1038/jid.2014.260. ISSN 1523-1747. PMID 24940651.

[26] Jabbari, Ali; Nguyen, Nhan; Cerise, Jane E.; Ulerio, Grace; de Jong, Annemieke; Clynes, Raphael; Christiano, Angela M.; Mackay-Wiggan, Julian (2016-08-01). "Treatment of an alopecia areata patient with tofacitinib

results in regrowth of hair and changes in serum and skin biomarkers". *Experimental Dermatology*. **25** (8): 642–643. doi:10.1111/exd.13060. ISSN 1600-0625. PMC 4963264. PMID 27119625.

[27] Kennedy Crispin, Milène; Ko, Justin M.; Craiglow, Brittany G.; Li, Shufeng; Shankar, Gautam; Urban, Jennifer R.; Chen, James C.; Cerise, Jane E.; Jabbari, Ali (2016-09-22). "Safety and efficacy of the JAK inhibitor tofacitinib citrate in patients with alopecia areata". *JCI insight*. **1** (15): e89776. doi:10.1172/jci.insight.89776. PMC 5033755. PMID 27699252.

[28] Mackay-Wiggan, Julian; Jabbari, Ali; Nguyen, Nhan; Cerise, Jane E.; Clark, Charlotte; Ulerio, Grace; Furniss, Megan; Vaughan, Roger; Christiano, Angela M. (2016-09-22). "Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata". *JCI insight*. **1** (15): e89790. doi:10.1172/jci.insight.89790. PMC 5033756. PMID 27699253.

[29] "Tofacitinib Citrate for the Treatment of Vitiligo: A Pathogenesis-Directed Therapy.".

[30] Levy LL, Urban J, King BA (2015). "Treatment of recalcitrant atopic dermatitis with the oral Janus kinase inhibitor tofacitinib citrate". *Journal of the American Academy of Dermatology*. **73** (3): 395–399. doi:10.1016/j.jaad.2015.06.045. PMID 26194706.

[31] Nordqvist, Christian (27 April 2013). "Pfizer's Arthritis Drug Xeljanz (tofacitinib) Receives A Negative Opinion In Europe". Medical News Today. Retrieved 2 August 2013.

[32] "XALEJANZ PRESCRIBING INFORMATION @ Labeling.Pfizer.com".

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