Tofacitinib Citrate

Introduction

Tofacitinib citrate, chemically named as (3R,4R)-3-[4-methyl-3-[N-methyl-N-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropionitrile citrate, is a white or almost white powder, which is lightly soluble in water, very slightly soluble in methanol, and practically insoluble in acetone. Tofacitinib citrate is a novel, oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. The structure of tofacitinib citrate is showed in figure 1.

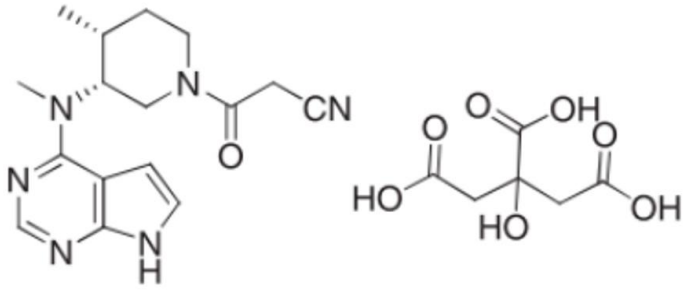

Fig. 1 Structure of tofacitinib citrate

Used as a Janus kinase (JAK) inhibitor

- **Introduction of Janus kinase**

  Janus kinase (JAK) is a family of intracellular, non-receptor tyrosine kinases that transduce cytokine-mediated signals via the JAK-STAT pathway (Figure 2). The JAK family is comprised of several different subtypes, notably JAK1, JAK2, JAK3 and TYK2 in addition to a multitude of STAT proteins, STAT 1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6. The pathway is initiated by a ligand/cytokine acting as an extracellular signal and binding to a receptor on the cell membrane which in turn causes a structural or conformational change and thus consequent activation of the implicated JAK isoforms that are either homodimers or heterodimers [3].

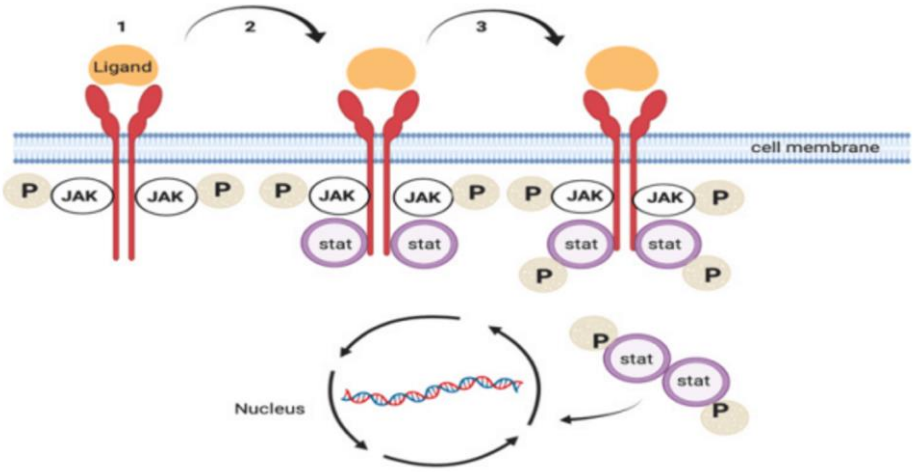

Fig. 2 Simplified representation of the JAK/STAT

Signaling pathway 1 in figure 2: Ligand binding to the extra-cellular domain of the homodimer or heterodimer cytokines receptor, the latter is activated and auto-phosphorylation occurs, signaling pathway 2: STAT proteins bind to the activated receptor, signaling pathway 3: STAT proteins are phosphorylated followed by nucleus translocation and protein synthesis.

It's reported that STAT4 SNPs are associated with rheumatoid arthritis, polymorphisms of STAT3 are associated with psoriatic arthritis, JAK1&JAK2&JAK3 are associated with ulcerative colitis.

- **Mechanism of action**

  Tofacitinib citrate inhibits the phosphorylation and activation of JAKs. JAKs cannot phosphorylate the cytokine receptors. Consequently, the receptors cannot contact with STATS. These latter are not phosphorylated and activated. Therefore, they cannot translocate to the nucleus. Gene transcription and cytokine production are inhibited. Figure 3 shows the simplified action mechanism diagram.

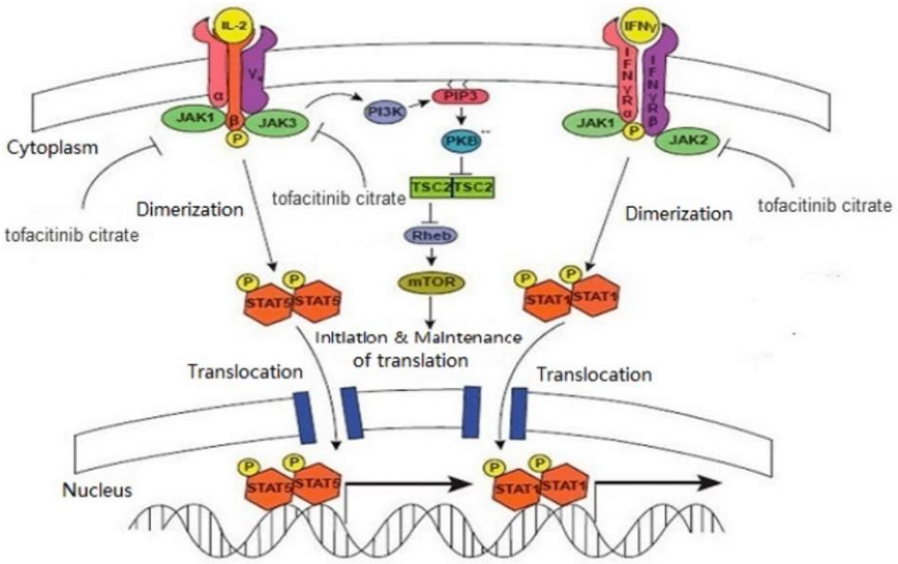

Fig. 3 Action Mechanism of tofacitinib citrate

- Side effects

  Along with its needed effects, a medicine may cause some unwanted effects.

  Although not all of these side effects may occur.

  Common side effects:

  - headache
  - upper respiratory tract infection
  - cold-like symptoms
  - diarrhea
  - skin rash
  - vomiting

  Serious side effects:

  - blood clots
  - pneumonia
  - cancer
  - gastrointestinal perforations
  - infection
  - cellulitis
  - shingles
  - high blood pressure

References

1. Rakieh, C.; Conaghan, P.G. Tofacitinib for treatment of rheumatoid arthritis. *Advances in Therapy*, 2013, 30(8):713-726.
2. Tegtmeyer, K.; et al. Off-label studies on tofacitinib in dermatology: a review. *Journal of Dermatological Treatment*, 2019, 6485:1-11.
3. Robert Harrington, Shamma Ahmad Al Nokhatha and Richard Conway. JAK Inhibitors in Rheumatoid Arthritis: An Evidence-Based Review on the Emerging Clinical Data. *J Inflamm Res*. 2020; 13: 519–531.

Source: https://www.alfa-api.com/products/tofacitinib-citrate.html