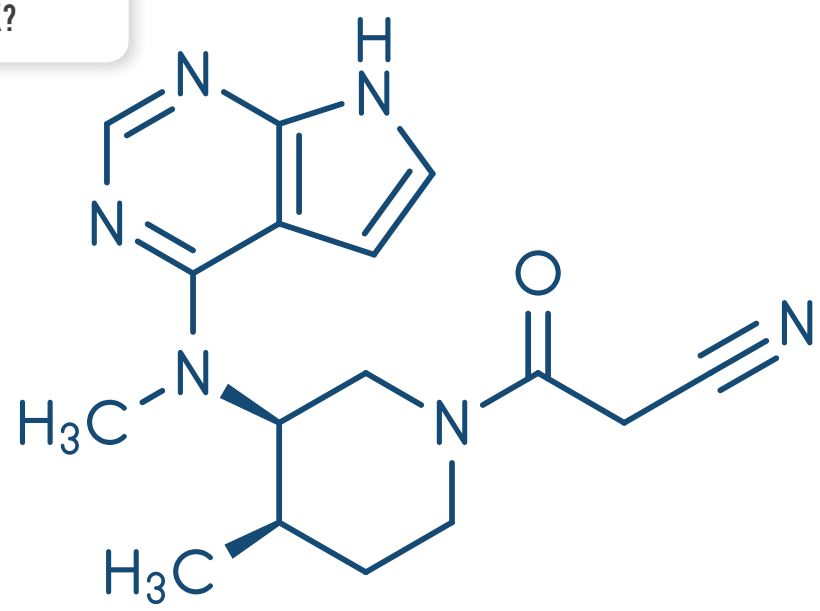

TOFACITINIB (XELJANZ) – HOW DOES IT WORK?

The treatment of inflammatory bowel disease (IBD) was revolutionized 20 years ago when the first antibody against tumor necrosis factor α (TNFα) was introduced, infliximab [1]. This biological drug has been followed by additional antibodies against TNF and other targets such as the gut-homing integrin α4β7 (vedolizumab) and the p40 subunit on interleukin 12 and 23 (ustekinumab) [2].

Biologicals have many benefits, but one hurdle is administration by IV infusion or subcutaneous injections. An additional disadvantage is the risk of immunogenicity, neutralizing endogenous antibodies directed against the drugs, that may result in very individual clearance rates and loss of response. The half-life of antibodies is quite long with wash-out periods over weeks in case of adverse events or switch of therapy [3].

After one year of treatment, only about 50% of patients still respond to the biological therapy [4]. Thus, the need for additional therapeutic options for IBD is evident. Small molecules targeting alternative immunological mechanisms are being introduced for the treatment of IBD with the benefits of negligible immunogenicity, pharmacokinetic stability, short half-life and oral route of administration [3]. In this class of drugs, the first treatment available for IBD is tofacitinib (Xeljanz), a small molecule inhibiting the intracellular Janus-Kinase (JAK) enzymes with a half-life of 3 hours. Tofacitinib has shown efficacy in ulcerative colitis (UC) and was approved by EMA for this indication in 2017 [5]. In addition, other JAK-inhibitors with varying affinity to the different JAKs are awaited for UC as well as Crohn's disease (CD) [4].

The pathogenesis behind UC and CD is not fully elucidated. Therefore, all available therapies target the inflammatory activity and not the primary trigger of the inflammation. The hallmark of IBD is perpetual inflammatory activity in the intestinal mucosa fueled by innate and adaptive immune cells, which are produced in the bone marrow and reach the intestinal inflammation through circulation. The innate immune system is comprised of circulating monocytes (that transform into macrophages in the tissue) and granulocytes. These cells exert their anti-microbial effect after migrating over the endothelium and reaching the gut mucosa.

In addition, antigen-presenting dendritic cells resident in the intestinal wall with no identified circulating precursor are also regarded as innate immune cells. This "first line of defense", is immediately activated when the integrity of the epithelium is broken. The innate cells recognize non-self surface structures that are common to pathogens. Granulocytes have direct anti-microbial effect against microorganisms, while dendritic cells as well as macrophages have the capacity to present antigens from the invading pathogens to the T- and B-cells (adaptive immunity) and thereby activate specific responses. The innate response is initiated within hours of an infectious assault while the adaptive T- and B-cells may need several days to become fully functioning. However, the latter immune cells can mediate a very efficient elimination of the pathogen and leave the commensal bacteria intact thanks to the specificity of the T-cell receptors and antibodies towards the invading microbes in question. In IBD patients, the innate as well as the adaptive immune responses are fully activated for reasons not known [6-9].

Depending on the activated adaptive T-helper cells (Th), the immune response is labeled as Th1, Th2 or Th3. CD is driven by cytokines such as IFN-γ and IL-12, classically labeled Th1 immunity. UC is fueled by IL-4, IL-5, and IL-13, a ➤

HOW DOES TOFACITINIB WORK?

combination of cytokines driving a Th2 immune response. TNF-α and IL-23 are important for all IBD, and particularly IL-23 has been associated with Th17 immunity [3, 6-9]. So far, antibodies in the clinic have been directed against one or two specific cytokines; TNF (infliximab, adalimumab and golimumab), and IL-12/IL-23 (ustekinumab against both). Tofacitinib does not inhibit cytokines directly, but instead targets a family of tyrosine kinases, JAK 1, JAK2 and JAK3, and thereby simultaneously inhibits several parallel cytokine signaling pathways activated in IBD [3].

JAK1, JAK2, and JAK3 relay signals from transmembrane cytokine receptors into the immune cells by associating with the intracellular part of the receptor and phosphorylate tyrosine residues on the cytokine receptor which leads to recruitment of signaling transducers and activators of transcription (STAT). The STATs subsequently relocate to the nucleus of the cell and activate transcription of immune-associated genes. Each cytokine induces specific transcriptional changes through this general signaling pathway. The inflammation observed in IBD is dependent on IL-12 and IL-23, which are associated with Th1 and Th17 inflammatory responses via JAK2, and IFN-γ, IL-2, IL-4, IL-6, and IL-21 which drive a broad range of adaptive immune responses through JAK1 and JAK3 [3, 4].

Tofacitinib competes with adenosine triphosphate (ATP) for the JAKs, with preferences for JAK1 and JAK3 and less affinity to JAK2, and thereby inhibits ATP-dependent phosphorylation and subsequent activation of the pro-inflammatory signal cascade. The inhibition reduces production of pro-inflammatory cytokines such as IL-2, IL-4, IL-6, IFN-γ, and IL-12; which are all important for the proliferation of T- and B-cells. In addition, the innate immune system involving monocytes and granulocytes is also down-regulated by tofacitinib through interference of lipopolysaccharide signaling.

Tofacitinib has proven efficacious in several autoimmune diseases such as rheumatoid arthritis, psoriatic arthritis, and UC. Tofacitinib does not seem to inhibit the inflammation seen in CD proficiently enough for clinical efficacy [3, 10]. However, JAK-inhibitors with other specificities against the different JAKs have shown efficacy in early clinical trials in CD, supporting the idea that IBD is dependent on JAKs but with different activation pattern depending on the disease UC or CD [4, 11].

The broad function of JAKs also explains the side effects observed in the clinical trials with tofacitinib. Besides the anticipated risk of infections due to immunosuppression, the clinician must be aware of the potential risk of bone marrow suppression and neutropenia through the inhibition of JAK2, which mediates signals from granulocytemonocyte colony stimulating factor (GM-CSF). A dose-dependent increase in low-density lipoprotein (LDL) as well as high-density lipoprotein (HDL) has also been observed in the clinical trials, but the mechanism behind this effect is still not completely understood [12, 13]. Due to the selected inhibition of a several different pathways, tofacitinib should not be used in combination with other immunosuppressants or biologicals.

In conclusion, tofacitinib is the first of a series of awaited small molecules targeting the JAK-signaling in immune cells with a broad effect on several cytokines and pathways. The novel target for immunomodulation together with the benefits of oral route and short half-life make this new class of drugs an important addition to the available therapies for IBD.

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