Commentary: Janus kinase inhibitors and their use in autoimmune ocular inflammatory disorders

Each autoimmune inflammatory disease has a cytokine profile of its own which is important in pathogenesis of that disease. Management of autoimmune inflammatory diseases requires regulation of associated elevated cytokine signaling and further its uncontrolled cytokine effects. Previously, inhibition of cytokine functions by monoclonal antibodies against cytokines or their receptors has been successfully used to control inflammatory diseases.[1]

The Janus kinase (JAK) family of nonreceptor tyrosine kinases that transduce signals from cytokines are key intracellular components of cytokine signaling. Recently, there has been interest in the management of systemic autoimmune inflammatory diseases by moderating them.[1] In mammals, the JAK–signal transducers and activators of transcription (STAT) pathways are constituted of four JAK kinases (JAK1–3 and tyrosine kinase 2 [TYK2]) and seven STATs (STAT1–6, including homologs STAT5a and STAT5b).

The all-important "signaling cascade" is initiated by cytokine binding to its receptor (cytokine receptor).

- This leads to association/rearrangement of the receptor subunits
- This leads to JAK activation by transphosphorylation
- Activated JAKs phosphorylate the receptors, allowing STATs to bind to the receptor
- This leads to the STATs become phosphorylated
- The phosphorylated STATs then form either homo- or heterodimers, which translocate into the nucleus where

they bind their cognate promoter elements to regulate transcription of target genes.[1]

Each cytokine receptor is known to recruit a specific combination of JAK kinases. This becomes important and allows for potentially targeting of JAKs in the management of autoimmune inflammatory diseases.[1]

The interest in Janus kinase inhibitors (JAKinibs) started after the identification of JAK3 as a key regulator of lymphocytes and the development of tofacitinib. Herein, we specifically first take the example of a systemic autoimmune inflammatory disease like rheumatoid arthritis (RA) to understand tofacitinib. Cytokines including tumor necrosis factor (TNF) alpha, interleukin (IL)-1, IL-6, IL-7, IL-15, IL-17, IL-18, IL-21, IL-23, IL-32, IL-33, and granulocyte-macrophage colony-stimulating factor (GM-CSF) have vital roles in pathogenesis of RA.[2] Of these, TNF, IL-1, and IL-6 signaling pathways have previously been successfully targeted with biological drugs. IL-6 inhibitor tocilizumab, a monoclonal antibody, thus finds a role in the management of RA.[3] However, these biological agents are large proteins. They require either intravenous or subcutaneous injection and may cause immunogenicity. IL-6 signals through the above mentioned JAK kinases (JAK1, JAK2, and/or TYK2) which phosphorylate and activate STAT3. This has led to obvious interest in smaller molecule inhibitors of the cytokine signaling pathways. Herein, may lie the role of a Janus kinase inhibitor like tofacitinib. Tofacitinib, a Janus kinase (JAK3/JAK1) inhibitor, is the first JAK inhibitor approved by the US Food and Drug Administration in November 2012 and European Medicines Agency in March 2017 for the treatment of moderate-to-severe active RA in patients with an inadequate response to methotrexate. Tofacitinib (5 mg twice daily) alone and in combination with methotrexate is found to be efficacious and the clinical response is felt to be similar to TNF antagonists.[4,5] Tofacitinib has a rapid onset of action of 2–4 weeks (in combination with methotrexate) compared with placebo[4] and is generally well-tolerated with adverse reactions like infections (that are also otherwise typical for biologics), reduction in CD4 + T cell count, elevation of cholesterol levels, headache, and slight reversible increases in serum creatinine levels.[1] The increased risk of herpes zoster distinguishes its safety profile from that of biological agents. But the relative short half-life of these JAKinibs makes it possible to expect a quick reversal of their immunosuppressive effect in case of an infection.[1]

As far as ocular inflammatory disorders are concerned, IL-2, IL-6, and IL-23 all activate JAK-STAT signaling and use of monoclonal antibodies like daclizumab, tocilizumab, and ustekinumab that block them have previously been reported to be efficacious in uveitis. Thus understandably, JAKinibs targeting JAK-STAT signaling may be felt to be effective in uveitis. Indeed, there are initial reports of a favorable clinical response of ocular inflammation to tofacitinib. In two patients from a single previous publication (refractory uveitis and scleritis), where tofacitinib was used in combination with methotrexate,[6] as well as, in one patient in a recent publication[7] (Vogt–Koyanagi–Harada Disease), where tofacitinib was used in combination with oral prednisolone, clinical effect of tofacitinib was noted approximately 4 weeks after the initiation of therapy and this is similar to the previous experience in RA.[4] An 8-week administration of topical tofacitinib has been reported to be well tolerated with reduction of markers of ocular surface inflammation in dry eye disease.[8] Thus, the role of JAKinibs like tofacitinib, for ocular inflammatory disorders, both in the presence and absence of systemic disease is indeed exciting and definitely warrants further interest.

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