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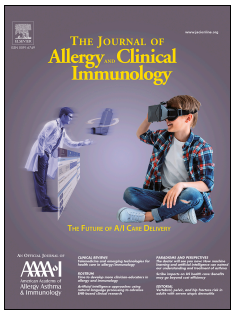

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PII: S0091-6749(22)00386-4

DOI: https://doi.org/10.1016/j.jaci.2022.03.014

Reference: YMAI 15511

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 16 February 2022

Revised Date: 16 March 2022

Accepted Date: 18 March 2022

Please cite this article as: Schlapbach C, Conrad C, TYK-ing all the boxes in psoriasis, *Journal of Allergy and Clinical Immunology* (2022), doi: https://doi.org/10.1016/j.jaci.2022.03.014.

TYK-ing all the boxes in psoriasis

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Conflict of interest

C.S.: CS has received honoraria as adviser from Abbvie, LEO Pharma, Lilly, and Novartis and has received research funding from PPM Services.

C.C.: CC has received honoraria as adviser from AbbVie, Actelion, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Galderma, Incyte, Janssen, LEO Pharma, MSD, Novartis, Pfizer, Samsung, and UCB.

Word count: 1357

Key Words:
TYK2, TYK2 inhibitor, deucravacitinib, psoriasis, IL-23, T_H17, IL-17, type I interferon, IFN, JAK, JAK inhibitor

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Over the last two decades, we have witnessed a paradigm shift in the management of psoriasis. Based on the increasing knowledge about the pathogenesis of psoriasis, monoclonal antibodies targeting the TNF/IL-23/IL-17 pathway have been developed. Particularly IL-17 and IL-23 blockers have shown an excellent safety and efficacy profile in the treatment chronic plaque psoriasis(1). Yet, there is an unmet need for effective and safe oral and topical treatments as well as for strategies to personalize treatment, halt disease progression, and prevent comorbidities. The appreciation of cytokines as key drivers of immunopathology has thus spurred efforts to target their associated signaling pathways, most prominently the Janus Kinase–Signal Transducer and Activator of Transcription (JAK–STAT) pathway(2). JAKs are essential signaling mediators downstream of cytokines of the type I and II family (Fig 1). The JAK family consist of four members (JAK1, JAK2, JAK3 and TYK2) which combine in various fashion with different type I and type II cytokine receptors (Figure 1a). Once the receptor is activated by its cognate cytokine, JAKs activate STAT proteins which then translocate to the nucleus, bind to DNA, and activate gene transcription(2). Thus, JAK-STAT signaling is at the heart of immunological communication, as evidenced by the striking immunological phenotypes of humans and mice carrying mutations in JAK or STAT genes(2).

JAK inhibitors of various selectivity for the different JAK family members have thus been developed. JAK inhibitors of the first-generation (ruxolitinib, tofacitinib) target two (JAK1/2) or three different JAKs (JAK1/2/3) and have shown clinical efficacy in inflammatory diseases such arthritis and inflammatory bowel disease(2). Yet, they are associated with a number of concerning adverse events that are, at least in part, the consequence of their broad activity against multiple JAK isoforms. Furthermore, they have shown incomplete efficacy in inflammatory skin diseases such as psoriasis. This might be a direct consequence of their low activity against TYK2, which mediates pathogenic interleukin (IL)-23 signaling, a key cytokine driving expansion and maintenance of T_H17 and T_C17 cells(1). Second generation JAK inhibitors more selectively target a single JAK isoform, thereby holding the promise of higher and more specific efficacy and less adverse events(2). Indeed, selective JAK1 inhibitors (e.g. upadacitnib, abrocitinib) have shown high efficacy and tolerability in atopic dermatitis. The development of TYK2-selective inhibitors has made it possible to target the pathogenic IL-23/IL-17 axis in psoriasis and, accordingly, clinical trials with various TYK2 inhibitors (e.g. prepocitinib, ropsacitinib, deucravacitinib) have shown encouraging results. Taken together, selective TYK2 inhibitors hold the promise to broaden our therapeutic armamentarium against psoriasis.

Within the group of the selective JAK inhibitors in clinical development, the TYK2 inhibitor deucravacitinib holds a special place. Typically, JAK1/2/3 inhibitors bind to the adenosine tri phosphate (ATP)-binding site of the catalytic domain of the JAK, resulting in competitive inhibition of the kinase (Figure 1b). However, the ATP-binding domain shows high sequence homology among the different JAKs, reducing selectivity of such a therapeutic approach. Deucravacitinib on the other hand binds to the regulatory domain and thus inhibits TYK2 via an allosteric mechanism(3) (Figure 1b). Allosteric inhibition presents several key advantages: It is highly specific, allows for modulation rather than elimination of kinase activity, and works even when the endogenous ligand – in the case of JAKs ATP - is bound. As result, deucravacitinib shows ≥100-fold greater selectivity for TYK2 versus JAK1/3 and ≥2000-fold greater selectivity for TYK2 versus JAK2(3, 4) *in vitro*. *In vivo* in humans, deucravacitinib was effective in a phase 2 clinical trial of psoriasis and lacked certain specific adverse effects observed in clinical trials of JAK1-3 inhibitors (neutropenia, elevation in liver enzyme and serum creatinine levels, dyslipidemia)(5). Thus, one key explanation for the expected favorable efficacy and safety profile of deucravacitinib in psoriasis is its unique mode of action and high specificity for TYK2.

Another unique property of TYK2 inhibitors might lie in their activity against type I interferon signaling. In recent years, molecular and genetic studies have identified additional inflammatory pathways in psoriasis, providing evidence that psoriasis is a heterogeneous disease, which requires personalized disease characterization for treatment optimization. One of these pathogenic inflammatory pathways is driven by type I interferons (IFN-α and IFN-β), which are produced by so-called plasmacytoid dendritic cells early during disease development(6). Type I IFNs trigger chronic activation of conventional dendritic cells to produce TNF and IL-23, which eventually drives the subsequent Th17 cascade and plaque formation in psoriasis. While the type I IFN pathway is dominant in early phases of psoriasis development, it usually is relayed by the TNF/IL-23/IL17 pathway in chronic plaque psoriasis (Figure 2). However, in leading edges of unstable plaques or in acute forms of psoriasis, such as erythrodermic or guttate psoriasis, type I IFNs remain the predominant inflammatory cytokines(6). In fact, several risk gene variants associated with psoriasis have been identified within the type I IFN pathway (one of them being *TYK2*!), which further supports the clinical relevance of this pathway in psoriasis. Moreover, type I IFNs are associated with systemic inflammation and acute flares in patients with generalized pustular psoriasis(7). As type I IFN signaling is – besides IL-12, IL-23, and the IL-10 family of cytokines – mediated by TYK2, inhibition of TYK2 provides an intriguing therapeutic option that simultaneously targets both acute and chronic forms of psoriasis (Figure 2).

In this issue, Catlett et al. analyzed blood samples from a randomized, placebo-controlled phase II trial of deucravacitinib in patients with moderate to severe psoriasis(8). The data provided in the article, which suggest a lack of dose- and time-dependent changes in blood biomarkers of JAK1-3 inhibition, further support *in vivo* selectivity of deucravacitinib for TYK2 over JAK1-3. In addition, the authors investigated skin biopsies from lesional skin at days 1, 15, and 85 for changes in biomarkers of both the IL-23/IL17 and the type I IFN pathway through analyses of differentially expressed genes. TYK2 inhibition lead to suppression of the IL-23/IL-17 pathway and to normalization of type I IFN response genes. These findings further support the idea that deucravacitinib, besides showing robust efficacy in chronic plaque psoriasis through inhibition of IL-23 signaling, could indeed target acute forms of psoriasis and prevent new flares by inhibiting type I IFN signaling. Furthermore, deucravacitinib might also provide an intriguing treatment option for other type I IFN mediated diseases and drug side effects such as lupus or anti-TNF induced paradoxical psoriasis, which represents an ongoing type I IFN driven innate inflammation(9).

However, inhibition of type I IFNs might also have its risks given their essential role in anti-viral immunity. Patients with a complete genetic loss of TYK2 function all show an immunodeficient phenotype. Interestingly, however, a genetic partial loss-of-function variant of TYK2 is protective against autoimmunity without increasing susceptibility for infections(10).

IFN response genes show considerable overlap between type I (IFN-α and IFN-β) and type II IFNs (IFN-γ). Hence, their normalization during deucravacitinib treatment might – compared to what Catlett and colleagues proposed here(8) – not be entirely attributed to the blockade of type I IFN signaling. TYK2 inhibition also blocks signaling of IL-12, which in turn promotes the differentiation of IFN-γ producing T_H1 cells (Figure 2). Thus, it remains to be dissected to what extend inhibition of the IL-12/T_H1 pathway contributes to the effect of deucravacitinib.

Beyond IL-12, IL-23, and type I IFN, TYK2 also mediates signaling of the IL-10 family of cytokines, which includes IL-10, IL-19, IL-20, IL-22, IL-24, and IL-26. It will be interesting to decipher potential redundancies and distinct functional relevance for these cytokines in patients under TYK2-inhibition. Particularly IL-26 represents an interesting candidate as it has been implicated in various human

diseases including psoriasis and Crohn's disease. However, its functions are only partly mediated via its receptor (IL-20R1/IL-10R2), and thus via TYK2 signaling, since IL-26 can also bind nucleic acid enabling it to activate endosomal toll like receptors.

The recent identification of additional cytokine pathways illustrates the complexity of psoriasis and suggests that distinct inflammatory pathways coexist in individual patients and may vary over time. Personalized molecular characterization of these pathways might help us in our therapeutic decision-making. Precision medicine should be facilitated by the discovery of biomarkers, which would help to define these distinct pathways and the responsiveness to various therapies.

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Figure Legends

Figure 1a. Association of various cytokine receptors with Janus kinases. Different cytokine receptors associate with different Janus kinases (JAKs), which transduce intracellular signals upon binding of the extracellular ligand. Depending on their selectivity and target, JAK-inhibitors allow the inhibition of a certain combination of specific biological functions. *EPO, erythropoietin; granulocyte colony-stimulating factor (G-CSF); GH, growth hormone; GM-CSF, granulocyte–macrophage colony-stimulating factor; IL, interleukin; IFN, interferon; LIF, leukaemia inhibitory factor; NK, natural killer; TPO, thrombopoietin; Th, T helper; Treg, T regulatory; TYK, tyrosine kinase*.

Figure 1b. Kinase- versus pseudokinase-targeted JAK inhibition. While first generation JAK inhibitors directly inhibit kinase activity by binding to the kinase or ATP-binding domain (ATP-competitive inhibition), deucravacitinib allosterically inhibits TYK2 activation by interacting with the pseudokinase or regulatory domain. Given the high sequence homology within the respective kinase domains of the different JAKs, the pseudokinase domain provides an intriguing target site to increase selectivity of JAK inhibition.

Figure 2: Pathogenesis of psoriasis, highlighting key cytokines signaling through TYK2. Koebnerization leads to sustained activation of plasmacytoid dendritic cells (pDCs) and production of large amounts of type I interferons (IFNs). Type I IFNs in turn activate dermal dendritic cells (dDCs) to produce IL-23. IL-23 stimulates TH17 and TC17 cells to produce TH17 cytokines, which trigger the epidermal phenotype of plaque psoriasis. Receptors of Type I IFNs and IL-23 signal through TYK2. *TYK2i = TYK2 inhibition (e.g. deucravacitinib)*.