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EDITORIAL

Decernotinib: A Next-Generation Jakinib

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Since the beginning of this millennium, rheumatologists have become applied cytokine biologists, taking advantage of the plethora of successful biologic agents that target cytokines for the treatment of rheumatoid arthritis (RA) and other autoimmune disorders. The mechanism of action of these agents is to block cytokines outside of the cell. However, the actions of cytokines can also be blocked by disrupting signaling pathways within the cell. This latter mechanism of action is characteristic of a recently developed class of orally administered drugs, JAK inhibitors or jakinibs. In this issue of *Arthritis & Rheumatology*, Genovese and colleagues report the results of a phase IIb study of decernotinib, a second-generation JAK-3–selective jakinib (1).

JAKs are intracellular enzymes that bind to the cytoplasmic domains of many cytokine receptors (2,3). Many of the proinflammatory cytokines that drive autoimmunity bind to receptors that rely on JAKs for intracellular signaling. Among the 4 JAKs, JAK-1, JAK-2, and Tyk-2 bind to many different cytokine receptors, whereas JAK-3 binds to only one subunit, the common γ-chain. This shared receptor subunit is utilized by a small family of cytokines that includes interleukin-2 (IL-2), IL-4, IL-7, IL-9, IL-15, and IL-21. A deficiency of the common γ-chain or JAK-3 has profound effects on immune responses (4) but does not affect other organ systems.

Tofacitinib was the first jakinib to be approved by the Food and Drug Administration (FDA) for the treatment of RA in patients with suboptimal responses to methotrexate. Tofacitinib blocks multiple JAKs, including JAK-1, JAK-2, and JAK-3; as a result, it inhibits the action of many cytokines (5). Baricitinib is another agent that blocks both JAK-1 and JAK-2, and phase III trials have shown the efficacy of baricitinib in RA (6). The most common side effects of jakinibs are infections (including serious infections), hyperlipidemia, and cytopenias (including anemia). The basis for the anemia seen in patients treated with first-generation jakinibs presumably relates to inhibition of JAK-2, which mediates erythropoietin receptor signaling, although other cytokines (e.g., IL-11) also contribute to hematopoiesis. The efficacy of tofacitinib and baricitinib illustrates the utility of targeting JAKs in the treatment of autoimmune disease but also raises the possibility that a selective, isoform-specific jakinib might be beneficial and avoid some of the side effects seen with first-generation pan-JAK inhibitors (Figure 1).

Dercenotinib is a newer jakinib (7,8) that has roughly 5-fold selectivity toward JAK-3 compared with other JAKs (JAK-1, JAK-2, and Tyk-2), based on in vitro kinase assays. Isoform specificity seems to be even better when measured using cell-based assays, with selectivity of >20-fold. Earlier this year, results from a randomized, double-blind, placebo-controlled, 12-week, dose-escalation (25–150 mg twice daily), phase IIa study in 204 patients with RA were reported (9). That study showed the efficacy of decernotinib as monotherapy in patients who had an inadequate response to ≥1 disease-modifying antirheumatic drug, as measured by the American College of Rheumatology 20% improvement criteria (ACR20) (10) and change from baseline in the Disease Activity Score in 28 joints using the CRP level (DAS28-CRP) (11), with an ACR20 response rate of ~65% among patients receiving higher doses of the drug.

The article by Genovese et al presents the results of a 24-week, dose-escalation phase IIb study using decernotinib once or twice daily in combination with methotrexate in 358 RA patients with an inadequate response to methotrexate monotherapy (1). Again, the primary end point was efficacy as defined by ACR20 and DAS28-CRP responses. As early as week 1, the response rates in the

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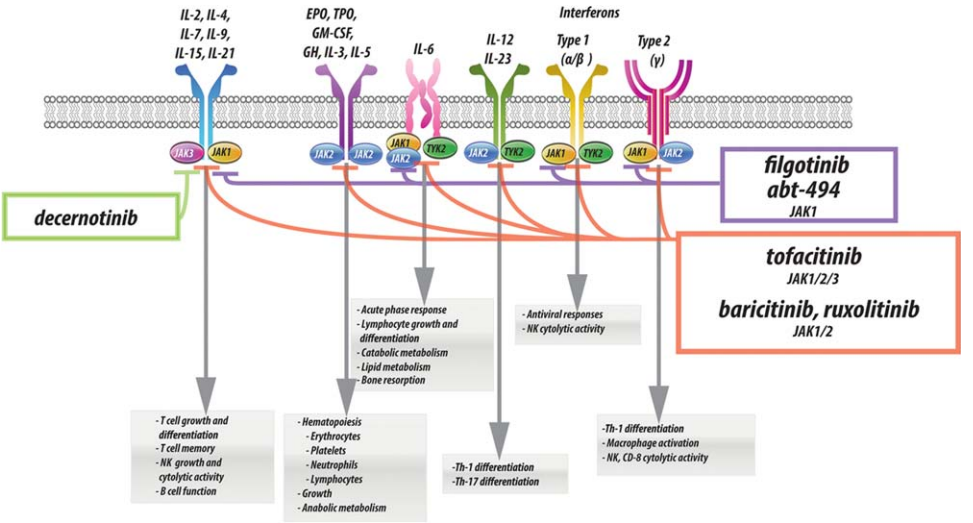

Figure 1. Mechanism of action of the JAK inhibitors (jakinibs). Type 1 and type 2 cytokines signal through JAKs, and various cytokines use different JAKs, based on association with receptor subunits. First-generation jakinibs such as tofacitinib and ruxolitinib block more than 1 JAK and thus block the effect of multiple cytokines. In principle, this could underlie their efficacy in treating rheumatic diseases but would also be responsible for some of their adverse effects, such as anemia, due to blockade of erythropoietin (EPO) signaling. Selective JAK-3 inhibitors such as decernotinib block the actions of the common γ-chain cytokines, which have crucial roles in immune cells, but should not affect other cytokines. As such, selective jakinibs should be efficacious but with fewer adverse effects. Conceivably, some efficacy could be lost if cytokines such as interleukin-6 (IL-6) are no longer blocked, but that apparently is not the case for decernotinib; however, decernotinib appears to have some side effects, such as neutropenia, that are difficult to explain for a pure JAK-3 inhibitor. TPO = thrombopoietin; GM-CSF = granulocyte–macrophage colony-stimulating factor; GH = growth hormone; NK = natural killer.

dercenotinib groups (all dosages tested) were significantly greater than the rates in the placebo group and were maintained up to 12 weeks and 24 weeks (1). Of note, these ACR20 responses were not drastically different from those in late-phase clinical trials of tofacitinib and baricitinib, in which ACR20 responses of 50–70% were observed (6,12,13). In principle, the spectrum of cytokines blocked by a selective JAK-3 inhibitor should be narrower than the range of cytokines blocked by a pan-JAK inhibitor. However, the results of both the phase IIa and phase IIb studies support the efficacy of decernotinib.

The study by Genovese and colleagues also begins to answer the question of whether improved specificity for a single JAK family member also improves safety. In addition, the study also serves as in vivo verification of this putative specificity. In the phase IIa study, adverse events included several serious infections, hyperlipidemia, increased creatinine levels, and elevated transaminase levels. Anemia developed in few patients, but neutropenia and lymphopenia were observed in all treatment groups. The adverse events observed in the phase IIb study were similar and included bronchitis, pneumonia, bronchopneumonia, cellulitis, gastroenteritis, sinusitis, and herpes zoster infection. Based on experience with other jakinibs and the role of JAK-3 in immune function, this finding is not unexpected and is entirely consistent with the mechanism of action of the drug.

Lymphopenia, which is a known adverse effect of tofacitinib, was also seen in the decernotinib trials. This adverse event also could be attributable to the effects on JAK-3–dependent cytokines such as IL-7 and IL-15 (2). Neutropenia was also observed in patients treated with decernotinib, especially at higher doses, and was moderate to severe in a few patients. This is notable insofar as patients with this complication developed infections and, in one case, death due to infection occurred. However, the development of neutropenia is puzzling, because JAK-3 does not typically impact neutrophil homeostasis (14). Cytokines involved in myelopoiesis, such as granulocyte colony-stimulating factor, signal via JAK-2, whereas other cytokines that influence hematopoiesis, such as IL-11, use a different shared receptor subunit, gp130, and signal via JAK-1, JAK-2, and Tyk-2. It is therefore possible that decernotinib is in fact blocking one of these JAKs. However, consistent with the in vivo assays showing that decernotinib spares JAK-2, little effect on hemoglobin was seen in the phase IIb trial: reductions in the hemoglobin level were observed in the group receiving 150 mg/day but not in patients receiving the other dosages. In vitro data indicate that decernotinib has very little

impact on Tyk-2. This leads to speculation that, at the dosages used, decernotinib may impact JAK-1 and thus may not be entirely selective for JAK-3.

The other adverse effect seen in the phase IIb trial was hyperlipidemia. Other jakinibs cause hyperlipidemia, and the underlying mechanisms are not particularly clear. Although tofacitinib increases the levels of both high-density lipoprotein and low-density lipoprotein cholesterol (15), it appears that the drug restores lipoprotein homeostasis and improves cholesterol efflux capacity. These effects may result from an increase in the cholesterol ester production rate through augmented activity of lecithin:cholesterol acyltransferase (15). Interestingly, the IL-6 receptor blocker tocilizumab is also associated with hyperlipidemia, and therefore tofacitinib could increase cholesterol levels through its effects on IL-6. Because IL-6 uses gp130, the hyperlipidemia seen in this trial might be construed as further evidence that decernotinib may block JAK-1. Blockade of IL-6 signaling could account for some of the efficacy of decernotinib, because IL-6 clearly drives RA pathology. However, this also muddies the water a bit: is the efficacy of decernotinib strictly due to inhibition of JAK-3 (and by inference the JAK-3–dependent common γ-chain cytokines), or does decernotinib block JAK-1 (and the attendant JAK-1–dependent cytokines) as well?

Although the clinical significance of jakinib-associated lipid level elevations has not been fully elucidated, statins can be used to reverse such hyperlipidemia (16). In this context, it is noteworthy that patients who were being treated with cytochrome P3A inhibitors or inducers (including statins) were excluded from the current study, suggesting that statins may not be used with decernotinib. In addition, patients receiving antifungal drugs would also be excluded despite the fact that patients receiving jakinibs can also have fungal infections. These interactions may be an issue for decernotinib.

Other adverse events include elevations of hepatic transaminase levels. These increases have been reported with other jakinibs, and again, the mechanism has not been determined. Whether the elevated hepatic transaminase levels are related to the therapeutic action of jakinibs (i.e., blockade of cytokine signaling) remains unknown. However, IL-22 and IL-10 are important anti-inflammatory cytokines, and a deficiency of IL-22 exacerbates experimental hepatitis (17). Despite this action, it appears that decernotinib, like tofacitinib, can be used safely with methotrexate. Elevated serum creatinine levels were also observed with decernotinib, as has been seen with other jakinibs; however, these elevations are typically so minimal that they are clinically insignificant. The mechanism driving these changes in serum parameters has not been elucidated, and it is unclear whether this relates to JAK inhibition.

In summary, 3 jakinibs have now been approved by the FDA: tofacitinib for RA, ruxolinitinib for myelofibrosis, and oclacitinib for canine allergic dermatitis. Other jakinibs, such as baricitinib, have been tested in late-phase clinical trials for the treatment of RA, psoriasis, and diabetic nephropathy. We are now in the era of second-generation jakinibs, and the studies by Genovese et al and Fleischman et al are the first to demonstrate the efficacy of a jakinib with some selectivity for a single family member, in this case JAK-3. In phase II trials, decernotinib appeared efficacious for treating RA. However, the adverse effect of neutropenia raises the possibility that this drug may impact JAKs other than JAK-3. As new second-generation jakinibs emerge, it will be important to ascertain whether neutropenia is necessarily associated with JAK-3 inhibition, and how selectivity for various JAKs influences efficacy and the adverse effect profile. Other family member–specific jakinibs in development include filgotinib, a selective JAK-1 inhibitor that appears to have efficacy in RA. In addition, jakinibs are being studied in diseases ranging from inflammatory bowel disease and psoriasis to atopic dermatitis, vitiligo, and alopecia. We are in an exciting time as we start to realize the full potential of orally administered small molecules for inhibiting the actions of cytokines, and as we learn more about the potential of the jakinibs.

AUTHOR CONTRIBUTIONS

All authors drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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