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Opinion

JAK Inhibitors: New Treatments for RA and beyond

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Recent years have brought great progress in our understanding of the pathogenesis of inflammatory and immunologic diseases, thereby uncovering novel therapeutic targets. One of these newly identified targets is the Janus Kinase (JAK) / Signal Transducer and Activator of Transcription (STAT) pathway.

Janus kinases are a family of intra-cellular tyrosine kinases that are activated after stimulation of several cell surface receptors by their specific growth factors, growth hormones, chemokines and cytokines. After activation, they phosphorylate STAT transcription factors, resulting in the transportation of these STATs to the nucleus and affecting expression of specific genes. These transduced cytokine-mediated signals via the JAK-STAT pathway are pivotal for the downstream signaling of inflammatory responses and their desired, as well as pathologic affects. As such, JAK kinases are a critical conduit for translating information from a cell's extracellular environment to its nucleus, resulting in gene expression profiles corresponding to these extracellular cues.

There are four known types of JAKs: JAK1, JAK2, JAK3, and TYK2, which are predominantly, but not exclusively, expressed in hematopoietic cells. As such, JAKs can contribute substantially to the immunologic processes involved in inflammatory diseases, and with autoimmune pathologies in particular. There are currently three FDA approved oral JAK inhibitors in clinical use: Tofacitinib (Xeljanz), Ruxolitinib (Jakafi) and, most recently, Baricitinib (Olumiant). There are also a significant number of additional JAK inhibitors, with varying JAK selectivity profiles, currently undergoing clinical trials for a number of indications.

Tofacitinib (a JAK1/3 inhibitor) and Baricitinib (a JAK1/2 inhibitor) are approved to treat moderate-to-severe rheumatoid arthritis, with Tofacitinib also approved for ulcerative colitis, and active psoriatic arthritis. Ruxolitinib (a potent JAK 1/2 inhibitor) is approved for the treatment of myelofibrosis and polycythemia vera in cases where specific mutations lead to constitutive activation of JAK 2, contributing to dysregulated JAK signaling in the JAK/STAT pathway and growth factor hypersensitivity/independence.

Rheumatoid Arthritis (RA) is a well characterized autoimmune disease that affects a large patient population. Additional treatment options to methotrexate and TNF blocking injectable biologics are desirable for patients that don't respond well to these therapies, so it made sense for first-in-class JAK inhibitors that can attenuate a dysregulated immune response to initially target RA. Other prominent autoimmune indications, in addition to ulcerative colitis and inflammatory bowel diseases such as Crohn's, are currently being studies in clinical trials. A significant number of these targeted indications are dermatologic in nature, such as psoriasis (especially plaque psoriasis), atopic dermatitis, and vitiligo [1].

However, beyond these above stated indications for JAK inhibitors, there are other potential therapeutic utilities that have emerged. For example, Alopecia Areata (AA) (spot baldness), was identified as a possible indication for treatment with JAK inhibitors when a patient being treated with Tofacitinib for plaque psoriasis also saw improvements in his alopecia, which did not occur when on corticosteroids [2]. Thus, both oral and topical treatments for AA are currently being studied in clinical trials [3].

Furthermore, it has recently been demonstrated that chronic itch is dependent on neuronal JAK1 signaling in a conditional JAK 1 KO mouse model of itch, as well as efficacy in a mouse model of itch with a small molecule JAK inhibitor [4]. Approximately 15% of the general population suffers from chronic itch, which has been shown to be equivalent in terms of impact on quality of life as chronic pain. In contrast to pain, there are currently no FDA-approved treatments for chronic itch. Patients with recalcitrant itch that failed other immunosuppressive therapies showed marked improvement when treated off-label with the JAK inhibitor Tofacitinib [4]. In this case, signaling mechanisms attributed mainly to the immune system may represent novel therapeutic targets within the nervous system as well.

Graft-versus-Host Disease (GvHD) is a major and sometimes life-threatening complication of bone marrow transplantation in the treatment of blood cancers and in whole organ transplants. There are over 20,000 allogenic Hematopoietic Stem Cell Transplantations (allo-HSCT) performed annually, and approximately 30–60% get GvHD, which can result in death or significant decrease in quality of life, carrying a 50% mortality rate. Additionally, more than 30,000 solid organ transplants are performed in the US alone, of which 25–40% experience episodes of organ rejection. Current therapies to treat GvHD include intravenously administered glucocorticoids, which are often not effective and can have serious side effects such as chronic and life threatening infections. These complications limit wider application of allo-HSCT as a therapeutic approach to patients with high risk hematologic malignancies. Thus, new, safer and more

effective therapies to treat GvHD are needed. Recent advances have shown that JAK inhibitors can, in animal models and small clinical trials, reduce graft-versus-host disease while maintaining their anti-cancerous effects against leukemia [5,6,7]. Optimization of such inhibitors as a therapeutic option for GvHD and whole organ transplant would provide clinicians with a much needed alternative to current standard of care.

Other potential uses for JAK inhibitors include Multiple Myeloma (MM) (in combination with other chemotherapeutic regimens), and Peutz-Jeghers syndrome.

In the multiple myeloma case, it is the tumor bone marrow stromal cell microenvironment that stimulates a JAK-STAT proliferative program in myeloma cells [8]. In another case, it was shown that a JAK-STAT pathway stimulated in an IL-6 environment down regulated CD38 expression on multiple myeloma cells, thus making patients on the anti-CD38 antibody daratumumab become resistant to this therapy. In vitro experiments with MM cells from these relapsed patients demonstrated that significant recovery of CD38 expression on these cells could be achieved following treatment with the JAK inhibitor Ruxolitinib, co-cultured with supernatant from bone marrow stromal cells [9].

Peutz-Jeghers Syndrome (PJS) is an autosomal dominant genetic disorder characterized by the development of benign hamartomatous polyps in the gastrointestinal tract. Germline mutations in the gene encoding tumor suppressor kinase LKB1 lead to gastrointestinal tumorigenesis in PJS patients and in mouse models. Loss of Lkb1 in stromal cells was associated with induction of an inflammatory program and activation of the JAK/STAT3 pathway in tumor epithelia concomitant with proliferation. PJS patients display hallmarks of chronic inflammation, marked by inflammatory immune-cell infiltration, the stated STAT3 activation, and increased expression of inflammatory factors associated with cancer progression. Targeting either T cells, IL-6, or STAT3 signaling reduced polyp growth in Stk11+/– animals [10]. Importantly, treatment of LKB1-defcient mice with the JAK1/2 inhibitor Ruxolitinib dramatically decreased polyposis [11]. These data indicate that the cytokine mediated induction of JAK/STAT3 is critical in gastrointestinal tumorigenesis following Lkb1 mutations and suggest that targeting this pathway has therapeutic potential in Peutz-Jeghers syndrome.

Lastly, it was recently reported that a JAK 1 inhibitor delivered locally to the lungs via inhalation suppressed ovalbumin-induced lung inflammation in both murine and guinea pig asthma models and improved allergen-induced airway hyper responsiveness in mice. In a mouse model driven by human allergens, this inhibitor had a more potent suppressive effect on neutrophil-driven inflammation compared to systemic corticosteroid administration. The inhibitor reduced lung pathology, without affecting systemic Jak1 activity in these rodents [12]. Thus local inhibition of Jak1 in the lung has the potential to suppress lung inflammation without significant exposure to Jak inhibition systemically, a strategy that might be effective for the treatment of asthma if this pre-clinical data translates to humans.

These examples highlight how seemingly disparate diseases with different patho-mechanisms may be affected positively by a single agent, in this case a JAK inhibitor. This illuminates the interplay between advances in basic science and clinical therapeutics and provides a compelling narrative of the ways in which an increasingly complex understanding of medicine and ingenuity in new treatment designs can benefit patients.

Chronic inflammation has been suspected to play a contributing role to disease progression in cancer, cardiovascular disease, neurodegeneration, and organ fibrosis, to name a few. The obvious beneficial effects of the immune system in neutralizing invading pathogens, wound healing, etc. are essential to overall well-being. But when optimum homeostatic control mechanisms go awry, and dysfunctional and pathogenic inflammatory signaling mechanisms stay locked in a perpetual "on" position, such chronic, unregulated signaling leads to non-homeostatic and disease enabling gene expression profiles. A number of key cytokines that are drivers of inflammation signal through the JAK-STAT pathways. If JAK inhibitors could be dosed and utilized in such a manner as to attenuate this dysregulated signaling and reset conditions back to a more reasonable homeostatic state, then perhaps JAK inhibitors can become a more versatile therapeutic tool in the treatment of multiple diseases driven in part by chronic inflammation.

Much of the positioning of such drugs will eventually also depends on the safety profile of JAK inhibitors. Increased susceptibility to opportunistic infections, sometimes fatal, is an obvious drawback to suppressing the immune system, and this has been observed with current JAK inhibitors. Other side effects will present themselves with increased usage over time, some being related to off-target effects specific to an inhibitor's particular chemical structure. Clearly, the safety of long-term use will need to be assessed in follow-up clinical studies and safety registries. It is possible that strategic dosing regimens, where drug holidays are employed, can reduce pathologic inflammatory conditions to a satisfactory degree without significantly impairing immune surveillance abilities. Topical or other localized delivery options would further reduce systemic exposure and limit unwanted side effects. Also, JAK inhibitors with different chemical structures may have similar JAK inhibition profiles, but may interact variably in a heterogeneous patient population in regards to efficacy and, as implied above, side effect profiles. Thus, with the promise that JAK inhibitors can play a therapeutic role in the treatment of a wide range of diseases with an inflammatory and autoimmune pathology, development of multiple and chemically diverse JAK inhibitors would be desirable.

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