ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Janus Kinase Signaling in Inflammatory Bowel Disease

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G&H What is the current understanding of the role of Janus kinase signaling in the pathogenesis of inflammatory bowel disease?

BC Cytokines have direct involvement in the pathogenesis of inflammatory bowel disease (IBD) by controlling intestinal inflammation. Janus kinase (JAK) plays a key role in mediating the signal transduction pathway for many different proinflammatory cytokines. Thus, the inhibition of the JAK family, which includes JAK1, JAK2, JAK3, and TYK2, can lead to the restriction of multiple different cytokine pathways that are involved in immune function, such as interleukin (IL)-6, IL-12, and IL-23. These inflammatory pathways are important in susceptibility to ulcerative colitis and Crohn's disease.

G&H Does JAK signaling differ between ulcerative colitis and Crohn's disease?

BC We do not necessarily know how JAK signaling may differ between the 2 diseases. There are likely more similarities than differences, as evidenced by the fact that many of the advanced IBD therapies are used for both of these diseases.

G&H What is the rationale for treating IBD by targeting JAK signaling rather than using another therapeutic approach?

BC Because JAK signaling is involved in the downstream effects of multiple cytokines, blocking it can allow for broader therapeutic opportunity than the use of a monoclonal antibody, which may target a limited number of cytokines. For example, ustekinumab (Stelara, Janssen) blocks only IL-12 and IL-23 and, thus, is more targeted. The inflammatory pathways involved in IBD are complex and varied; therefore, a treatment that can affect multiple inflammatory cytokines, as a JAK inhibitor can, may be an effective approach. Additionally, JAK inhibitors are small molecules and, therefore, have no immunogenicity, as opposed to monoclonal antibodies. JAK inhibitors also generally have short half-lives, leading to rapid onset of action as well as quick washout in the case of side effects.

G&H How effective is the JAK inhibitor tofacitinib for the treatment of IBD?

BC Tofacitinib (Xeljanz, Pfizer) is the only JAK inhibitor currently approved in IBD. Tofacitinib is a pan-JAK inhibitor, which means that it blocks all of the JAK receptors (JAK1, JAK2, JAK3, and TYK2). The OCTAVE trials demonstrated the efficacy of this drug for the treatment of ulcerative colitis. During induction, patients treated with tofacitinib 10 mg twice daily achieved remission at 8 weeks significantly more often than patients who received placebo in both OCTAVE 1 (18.5% vs 8.2%; *P*=.007) and OCTAVE 2 (16.6% vs

3.6%; *P*<.001). In the maintenance study, patients treated with either tofacitinib 5 mg or 10 mg twice daily were significantly more likely to be in remission at 52 weeks than patients treated with placebo. Subsequent analyses of the OCTAVE induction studies also showed that treatment effect can be seen as quickly as 3 days following the start of therapy.

Studies have also looked at the use of tofacitinib for Crohn's disease but did not meet the primary or secondary outcomes, so the investigational program was not continued. However, even though the primary outcome was not met, there was some evidence for biologic effects of tofacitinib in Crohn's disease with nonstatistically significant dose-related improvements in C-reactive protein and fecal calprotectin. In addition, the TROPIC consortium has published a real-world case series of over 60 patients with Crohn's disease in which tofacitinib has been efficacious as an off-label therapy.

G&H Which JAK inhibitors are currently in development for IBD treatment?

BC There are currently a number of JAK inhibitors under investigation for both ulcerative colitis and Crohn's disease. These next-generation JAK inhibitors are more selective. For example, upadacitinib (Rinvoq, AbbVie) and filgotinib (Gilead) both target JAK1. These agents are in phase 3 studies for both ulcerative colitis and Crohn's disease. There are other molecules that target TYK2 that are in phase 2 studies. Also under investigation is the gut-selective, pan-JAK inhibitor TD-1473 (Theravance Biopharma), which targets JAK receptors in the gastrointestinal tract and has low plasma exposure.

G&H Has selective JAK inhibition been shown to affect clinical efficacy or safety?

BC It has been speculated that selective inhibition may have some beneficial effects in terms of efficacy and safety profile as well as lack of off-target effects. However, at this point, these potential benefits are still theoretical because selective JAK inhibitors are only in phase 2 or 3 studies. Research is needed in much larger patient populations and in postmarketing studies. Thus far, there have not been any new signals of concerning effects or in the safety profiles of these selective inhibitors, but only limited numbers of patients have been studied.

G&H Are there other potential advantages to blocking only specific JAKs?

BC Nonselective JAK inhibitors may have more off-target effects than selective JAK inhibitors. For example, hematopoietic or blood cell–related side effects such as anemia or neutropenia may be seen with JAK2 inhibition. Therefore, selectively inhibiting JAK1 minimizes some of these potential side effects.

In addition, the biggest safety concern seen with tofacitinib thus far is venous thromboembolism. A large study of patients with rheumatoid arthritis found that 10-mg doses of tofacitinib were associated with increased rates of pulmonary embolism and death in patients over the age of 50 years who had 1 or more cardiac risk factors. These findings led to restrictions on the use of tofacitinib. In the United States, patients must have first failed a tumor necrosis factor (TNF) inhibitor or other biologic therapy prior to using tofacitinib. However, increased rates of venous thromboembolisms have not been observed in patients with ulcerative colitis or Crohn's disease who were treated with tofacitinib. It is known that the baseline risk of venous thromboembolism is higher in patients with IBD, likely related to the degree of bowel inflammation, so it may be that controlling luminal disease may lead to an overall reduction in the risk of thromboembolism. It is possible but unknown whether selective JAK inhibition may lead to a lower rate of venous thromboembolism than a pan-JAK inhibitor. This will need to be closely monitored in clinical trials and postmarketing cohorts.

> With monoclonal antibody biologics, there is concern that antibodies will develop that can decrease effectiveness and lead to side effects. The same concern is not present with small molecule therapies such as JAK inhibitors.

One of the biggest infectious concerns with JAK inhibition is reactivation of herpes zoster. Dose-dependent increases in the risk of shingles infection have been observed with tofacitinib at rates greater than those seen with anti-TNF therapy. If patients are undergoing treatment with tofacitinib, it is recommended that they be vaccinated with the recombinant shingles vaccine. It is currently unknown if selective JAK inhibition may

decrease the risk of herpes zoster infection compared with tofacitinib. More will be learned with the completion of the ongoing phase 3 studies of selective JAK1 inhibitors.

G&H Might particular IBD patient subgroups respond better to selective JAK inhibition?

BC Even among selective JAK inhibitors, there are differences in the potency of the inhibition of specific receptor isoforms. For example, two JAK1-selective agents may have a different degree of blockade, leading to differential effects on cytokine profiles. It is not known exactly how these differences may manifest in terms of the efficacy or safety of the drugs, or even in their applicability toward specific disease phenotypes, such as fistulizing disease. Filgotinib is being studied in a dedicated clinical trial for treatment of perianal Crohn's disease for this reason. It is too early to determine whether a particular population of patients may benefit from selective JAK inhibition.

G&H Are there any other advantages or benefits to JAK inhibition?

BC One of the big advantages of JAK inhibition in general is not having a risk of immunogenicity. With monoclonal antibody biologics, there is concern that antibodies will develop that can decrease effectiveness and lead to side effects. The same concern is not present with small molecule therapies such as JAK inhibitors. That means that patients can start and stop therapy without the same concern as some of the biologics. JAK inhibitors also have a shorter half-life, which can lead to a quicker onset of action. Studies of tofacitinib have shown that some of the effects of the drug can be seen as soon as 3 days. Similarly, the drug can wash out relatively quickly in the case of adverse events.

As mentioned previously, JAK inhibition has the potential to affect multiple cytokine-dependent pathways as opposed to biologic drugs, which may target a single cytokine. Because it is not known whether the inflammatory pathway is the same for every patient with IBD, such inhibition may provide a broader effect to reduce inflammation than a cytokine-specific drug. However, there is still much to learn about the pathogenesis of IBD in general, and the future of therapy is likely improved personalized therapy—in other words, understanding which specific pathway may be most significant in an individual patient and then selecting the therapy that targets that pathway. Until this can be achieved, the potential to impact a number of different cytokine pathways with a single drug could be advantageous. It will be interesting to learn more about the specific impact of the selective inhibition of the JAK inhibitors currently in phase 2 and 3 studies and whether it is beneficial.

G&H What are the main limitations or challenges associated with JAK inhibition?

BC Right now, the main limitation in clinical practice is that there is only 1 approved JAK inhibitor for ulcerative colitis, and none for Crohn's disease, and that its use is restricted to being a second-line agent after failing another biologic therapy for IBD owing to the risks of venous thromboembolism seen in the rheumatoid arthritis population. Another limitation is that JAK inhibitor use is contraindicated in pregnancy. There are limited human data, and animal studies have suggested possible teratogenicity with tofacitinib. Adequate contraception is advised for patients taking tofacitinib.

G&H Where does JAK inhibition currently fit in terms of treatment approaches for IBD?

BC Tofacitinib is currently approved only for ulcerative colitis. Likely the best position for it in the treatment algorithm is in patients who have previously failed a TNF inhibitor. Patients who fail a TNF inhibitor or other monoclonal antibody are a highly refractory population and their response to the next biologic drug has been shown to be lower. Interestingly, the treatment effect seen thus far with tofacitinib in patients who have previously failed a TNF inhibitor is similar to that in patients who are naive to TNF inhibitors. A network meta-analysis by Dr Siddharth Singh and colleagues has suggested that tofacitinib is the preferred second-line treatment after a patient has failed a TNF inhibitor. I think a good place to use tofacitinib is as second-line treatment after a TNF inhibitor in patients who do not have significant risk factors for a venous thromboembolism.

G&H Might there be potential approaches to optimize treatment with JAK inhibitors, such as combination therapy?

BC There has not been much advancement in terms of combination approaches for advanced IBD therapies. Traditionally, combination therapy meant using an immunomodulator, such as 6-mercaptopurine, azathioprine, or methotrexate, with a TNF inhibitor or an anti-integrin molecule. Clinical trials of JAK inhibitors for IBD typically prohibit concomitant use of immunomodulators. Limited data from rheumatoid arthritis have not shown a benefit for combining tofacitinib with methotrexate as compared with monotherapy using tofacitinib. However, in the future, researchers may look at using advanced

therapies together. For example, a natural potential combination may be using a JAK inhibitor with a drug such as vedolizumab (Entyvio, Takeda). Vedolizumab has a very good safety profile and is a gut-specific therapy, so there is minimal concern about potential combined immunosuppressive risk when using it with a JAK inhibitor. In highly refractory patients, there may be consideration to combine a JAK inhibitor with a TNF inhibitor or ustekinumab, but there are no controlled studies and limited real-world data to guide doctors in these approaches. The clinical scenarios where such combinations may be seen include patients who have multiple inflammatory conditions for which 2 different drugs may be prescribed, such as rheumatoid arthritis or psoriatic arthritis in addition to IBD. Before routine use of these types of combination therapies can be considered, they would need to be studied carefully to understand both the potential beneficial effects as well as the possible adverse events.

G&H What are the priorities of research in this area?

BC Currently, the main priority is understanding the potential benefits of selective JAK inhibition vs pan-JAK inhibition. It is important to learn whether selective inhibition will yield better efficacy and/or improved safety. In addition, a deeper understanding is needed of the cells that rely on JAK signaling and their role in intestinal inflammation. This will be critical in developing personalized therapeutic approaches. As more JAK inhibitors come to the market, real-world studies are also needed to refine management of these drugs, better optimize the therapies, and determine their placement in the treatment algorithm.

Disclosures

Dr Cohen has served on the advisory board of, and as a consultant for, AbbVie, Celgene/Bristol Myers Squibb, Pfizer, Sublimity Therapeutics, Takeda, and TARGET RWE; has worked with CME companies for Cornerstones and Vindico; and has done speaking engagements for AbbVie.

Suggested Reading

Danese S, Argollo M, Le Berre C, Peyrin-Biroulet L. JAK selectivity for inflammatory bowel disease treatment: does it clinically matter? *Gut*. 2019;68(10):1893-1899.

Deepak P, Alayo QA, Khatiwada A, et al. Safety of tofacitinib in a real-world cohort of patients with ulcerative colitis [published online July 3, 2020]. *Clin Gastroenterol Hepatol*. doi:10.1016/j.cgh.2020.06.050.

Pérez-Jeldres T, Tyler CJ, Boyer JD, et al. Targeting cytokine signaling and lymphocyte traffic via small molecules in inflammatory bowel disease: JAK inhibitors and S1PR agonists. *Front Pharmacol*. 2019;10:212.

Salas A, Hernandez-Rocha C, Duijvestein M, et al. JAK-STAT pathway targeting for the treatment of inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol*. 2020;17(6):323-337.

Sandborn WJ, Ghosh S, Panes J, et al. Efficacy of upadacitinib in a randomized trial of patients with active ulcerative colitis. *Gastroenterology*. 2020;158(8):2139-2149.e14.

Sandborn WJ, Su C, Sands BE, et al; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2017;376(18):1723-1736.

Singh S, Murad MH, Fumery M, Dulai PS, Sandborn WJ. First- and second-line pharmacotherapies for patients with moderate to severely active ulcerative colitis: an updated network meta-analysis. *Clin Gastroenterol Hepatol*. 2020;18(10):2179-2191.e6.