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A Practical Approach to JAK Inhibitors for Inflammatory Bowel Disease in 2020

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In May 2018, the US Food & Drug Administration approved the use of tofacitinib for moderately to severely active ulcerative colitis (UC). This represents the first Janus kinase (JAK) inhibitor approved in inflammatory bowel disease (IBD). I hope that this review article provides a practical approach to using tofacitinib in clinical practice, as well as provide updates on other JAK inhibitors currently in development.

Update on Tofacitinib Efficacy and Safety

JAKs are important in intracellular signaling. Think of them as one of the important bridges between a cytokine activating a cell surface receptor and transcription of genes in the nucleus. Each cytokine receptor is associated with two JAK molecules.[1] When a cytokine finds its receptor, the associated JAKs are activated. These activated molecules in turn phosphorylate receptors that dock signal transducer and activator of transcription protein (STAT) molecules, which then move to the nucleus of the cell to activate new gene transcription. There are four JAK molecules: JAK1, JAK2, JAK3, and TYK2. JAK1 is associated with the cytokines interleukin-2, interferon-gamma, interferon-alpha, and interleukin-6. JAK2 is associated with interferon-gamma, interferon-alpha, interleukin-12, interleukin-23, interleukin-6, and erythropoietin. The JAK3 kinase is associated with interleukin-2. Finally, the TYK2 kinase is associated with interferon-alpha, interleukin-12, and interleukin-23. Tofacitinib, at low doses, inhibits JAK1 and JAK3, while at higher doses, it appears to inhibit JAK1, JAK2, and JAK3.

In the pivotal induction trials of tofacitinib in moderate to severe ulcerative colitis, OCTAVE1 and OCTAVE2, over 1100 patients were enrolled.[2] They were randomized in a 4:1 ratio to receive either tofacitinib 10 mg or placebo twice daily. The primary endpoint of the study was clinical remission at week 8. This was defined by a total Mayo score of less than or equal to 2, with no sub score greater than 1, and rectal bleeding score of 0. In OCTAVE1, 18.5% of tofacitinib-treated patients achieved the endpoint, compared to only 8.2% of placebo-treated patients (p=0.007). In OCTAVE2, the clinical remission rates at week 8 were 16.6%

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in tofacitinib-treated patients and 3.6% in placebo-treated patients ($p<0.001$). It should be noted that this endpoint was significantly higher in both the anti-tumor necrosis alpha (TNF) naive and anti-TNF-experienced populations within the study. Clinical response, defined by a three point and 30% reduction in the Mayo score, occurred in 55% to 60% of tofacitinib-treated patients versus 29% to 33% of placebo-treated patients in OCTAVE1 and 2 ($p<0.001$ for both comparisons). Mucosal healing was defined as a Mayo endoscopic sub score of 0 or 1, and this endpoint was reached at 8 weeks in 28-31% of tofacitinib-treated patients, versus 12% to 16% of placebo-treated patients ($p<0.001$ for both).

One notable attribute of tofacitinib is its rapid onset of action. A *post hoc* analysis of the induction trials examined patient-reported outcomes at the individual patient level based on patient symptom diaries, and statistically significant differences in the rectal bleeding and stool frequency subscores versus placebo were seen as early as three days after initiating the drug.[3]

Patients who completed the induction trials and had a clinical response were then randomized to treatment in the OCTAVE Sustain maintenance trial to 5 mg twice daily, 10 mg twice daily, or placebo for 52 weeks.[2] The primary endpoint was clinical remission at 52 weeks. This endpoint was achieved in 41% of patients receiving 10 mg twice daily, 34% of those receiving 5 mg twice daily, and only 11% of those receiving placebo ($p<0.001$ for both comparisons). Clinically and statistically significant differences were seen between both doses of tofacitinib and placebo for secondary and points including clinical response, sustained mucosal healing, and sustained steroid-free remission among baseline remitters.

Health-related quality of life parameters also improved on tofacitinib.[2,4] Using the endpoint of remission according to the Inflammatory Bowel Disease Questionnaire (IBDQ) (>170 points), between 40% and 43% of patients receiving tofacitinib in the induction trials achieved this endpoint, and this was between 17% and 22% better than the rate achieved in placebo-treated patients. In the maintenance trial, 38% of tofacitinib-treated patients achieved this endpoint, which was 24% better than the rate in placebo-treated patients. Improvements in 36-Item Short Form Survey (SF 36) scores were significantly higher with tofacitinib compared to placebo.

A small case series from the University of Michigan explored the potential role of high-dose tofacitinib for treatment of patients with acute severe ulcerative colitis.[5] A dose of 10 mg three times daily for three days was employed in addition to the patients' usual treatments. Three of four patients saw significant improvement; however, two of these three patients underwent elective colectomy for multifocal dysplasia. The role of tofacitinib in acute severe ulcerative colitis remains unclear.

The prescribing information for tofacitinib carries a boxed warning about risk of serious infections and malignancies.[6] In the UC induction trials, the rate of any infection was higher in the tofacitinib-treated patients. In the maintenance trial in UC, the rates of adverse events, serious adverse events and serious infections were similar between tofacitinib and placebo. The overall infection rate was higher with tofacitinib, but the rate of withdrawal from the study due to adverse events was lower with tofacitinib. Approximately 5% of the patients treated with tofacitinib 10 mg twice daily in the maintenance trial developed herpes zoster, compared to 1.5% of those treated with 5 mg twice daily and 0.5% of those treated with placebo. A total of 65 herpes zoster cases were identified in OCTAVE Sustain and OCTAVE Open (the open-label extension trial).[7] Over two-thirds of these cases involved one or two adjacent dermatomes. Less than 10% of cases were disseminated zoster, and only five zoster cases resulted in study discontinuation. The incidence of zoster among patients on the 10 mg BID dose was 6.6 per 100 person-years, and the overall incidence was 4 per 100 PY. The incidence rate of herpes zoster did not appear to rise with increasing duration of tofacitinib exposure. Risk factors for zoster included age, prior anti-TNF failure, and Asian race. Higher increases in total cholesterol, HDL, LDL, and triglycerides were seen with tofacitinib compared to placebo.[8] Decreases in C-reactive protein correlated significantly with increases in lipids. The incidence of major adverse cardiovascular events was less than 1 per 100 person-years.

In mid-2019, the FDA released a drug safety communication regarding a potential risk of

thromboembolism with tofacitinib.[9] At the time of the drug's approval for rheumatoid arthritis, the FDA had required the manufacturer to perform a safety study of tofacitinib in RA patients who were at least 50 years old and carried at least one risk factor for cardiovascular disease. Patients were treated with 5 mg BID, 10 mg BID (which isn't a dose approved in RA), or an anti-TNF agent. In the interim analysis, 19 cases of thromboembolism had been reported among 3,884 person-years of follow-up in the 10 mg BID group, compared to three cases among 3,982 person-years of follow-up in the anti-TNF-treated group, yielding an incidence rate ratio of 7. Mortality was 1.8 times higher in the 10 mg BID group compared to the anti-TNF group. Based on this analysis, the 10 mg BID arm of the ongoing RA safety trial was changed to 5 mg BID. A boxed warning about thromboembolism was added to the tofacitinib prescribing information. The indication for tofacitinib was also restricted to those patients with moderate to severe UC who had failed anti-TNF therapy. In the UC clinical development program, a total of four cases of pulmonary embolism and one case of deep venous thrombosis was reported in the open-label study.[10]

In two phase IIb studies of tofacitinib for moderate to severe Crohn's disease, the primary induction endpoint of a Crohn's Disease Activity Index (CDAI) score of less than 150 points at week 8 was not achieved, nor was the primary endpoint of CDAI of less than 150 points at week 26 for maintenance.[11] Reductions in CRP were significantly better than with placebo in induction, but not reductions in fecal calprotectin.

How I Use Tofacitinib in Clinical Practice

Given the FDA restrictions on its indication, I am no longer using tofacitinib in biologic-naïve UC patients. However, it remains an excellent second-line agent. Indeed, in a 2018 meta-analysis of randomized trials of UC patients who were biologic-exposed, tofacitinib emerged with the strongest treatment effect with respect to induction of clinical remission (OR, 12.6; 95% CI, 2-5-64), and induction of mucosal healing (OR, 4.7; 95% CI, 2.2-9.9).[12] It is potent and fast-acting. It would seem to be an ideal agent for patients with IBD-related spondyloarthropathy as well.

When counseling patients about the safety, I remind the patients that the safety profile in many ways is similar to that of an anti-TNF medication. I notify them about the approximately 5% to 6% risk of herpes zoster if they remain on the 10 mg BID dose for one year. Of course, with the recombinant zoster vaccine, this risk can be mitigated significantly. I don't require that they be fully vaccinated before starting—recall that the zoster risk in the induction phase was minimal. I also tell them that there may or may not be an elevated risk of thromboembolism with the drug, that we will attempt to reduce the dose to 5 mg BID after the 8-16 week induction period, but if that is not successful, we will increase the dose back up to 10 mg BID. I also recommend that they have CBC, hepatic biochemistries, and lipid profile checked every three months.

Update on Other Janus Kinase Inhibitors in IBD

There are a couple of selective JAK1 agents currently in development for IBD. Theoretically, selective JAK1 antagonists may "widen the therapeutic window", allowing for higher doses to achieve efficacy without compromising safety. In the phase IIb FITZROY study, 174 patients with moderate to severe Crohn's were randomized to treatment with filgotinib 200 mg daily or placebo for 10 weeks.[13] The primary endpoint was CDAI score <150 points at week 10. This endpoint was achieved in 47% of the overall filgotinib-treated patients and 23% of those treated with placebo (p=0.0077). The differences were even greater in the anti-TNF-naïve population (60% versus 13%). Reductions of at least 100 points in CDAI were seen in 59% of the filgotinib-treated patients versus 41% of those receiving placebo (p=0.0453). A reduction in the Simple Endoscopic Score for Crohn's Disease (SES-CD) by at least 50% at week 10 was seen in 25% of filgotinib treated patients versus 14% in the placebo group (p=0.16). Improvements in health-related quality of life as measured by mean change in IBDQ scores occurred 34% of filgotinib-treated patients vs. 18% of placebo-treated patients. Serious adverse events (9% vs 4%) and serious infections (3% vs 0%) were seen more often with filgotinib. Study withdrawals due to adverse events occurred in 18% of the filgotinib group and 9% of the placebo group.

The effects of upadacitinib (ABT-494), another selective JAK1 inihibitor, were recently studied in moderate to severe Crohn's disease in a phase II study.[14,15] This was a highly refractory population—96% had failed anti-TNF agents, and between 37% and 51% had been exposed to a non-anti-TNF biologic. Multiple doses were studied, and new endpoints were examined. Dual primary endpoints were clinical remission, defined as stool frequency ≤1.5 and abdominal pain score ≤1, at week 16, and endoscopic remission, defined as SES-CD≤4, at week 12 or 16. Both endpoints were achieved with at least one dose of upadacitinib. Steroid-free remission based on CDAI occurred at week 16 with multiple doses of upadacitinib. Rates of overall adverse events were broadly similar, although rates of serious adverse events ranged from 5% to 28% with upadacitinib compared to 5% with placebo. Serious infections occurred in 0% to 8% of upadacitinib-treated patients, versus 0% with placebo. In an extension study out to week 52, patients who were clinical and endoscopic responders at week 16 saw dose-dependent improvements in modified clinical remission (stool frequency ≤2.8 and abdominal pain score ≤1) and endoscopic remission.[15,16] Dose-dependent reductions in fecal calprotectin were also observed. It's interesting to note that we now have two phase II trials with selective JAK1 inhibitors in Crohn's disease that were positive, while the two phase II trials with tofacitinib in Crohn's disease were negative, lending credence to the hypothesis that the selectivity may allow greater efficacy without compromising safety.

Preliminary results of the phase II U-ACHIEVE study of upadacitinib in ulcerative colitis were recently presented.[17] A total of 250 patients, over three-quarters of whom had prior biologic use, were randomized to four different doses of a once daily extended release (ER) formulation of upadacitinib or placebo daily. (Based on pharmacokinetic studies, the 15 mg ER was thought to be equivalent to 6 mg BID of immediate release [IR], and 30 mg ER was thought to be equivalent to 12 mg BID of IR.) The primary endpoint was clinical remission as per adapted Mayo score (no physician global assessment) at week 8. This endpoint was met for the 15 mg, 30 mg, and 45 mg doses (14.3%, 13.5%, and 19.6%, respectively, vs 0% for placebo; $p<0.05$ for all three). The major secondary endpoint of endoscopic improvement (Mayo endoscopic subscore, 0-1) was significant for all four doses of upadacitinib, ranging from 14.9% with 7.5 mg daily to 35.7% with 45 mg daily, versus 2.2% with placebo ($p<0.05$ for all). The rate of serious adverse events was highest in the placebo treated patients. Serious infections ranged from 0% to 3.6% in the upadacitinib-treated patients, versus 4.3% in placebo group. Only one case of herpes zoster was identified. A histologic remission endpoint (Geboes score <2) was significant for the three higher doses of upadacitinib. A "mucosal healing" endpoint combining endoscopic and histologic improvement was also significant for multiple doses of upadacitinib.[18]

A colon-release, gut-restricted non-selective JAK inhibitor was recently examined in a phase 1b study.[19] A total of 40 patients with moderate to severe ulcerative colitis were randomized in a double-blind fashion to 20 mg, 80 mg, or 270 mg of TD-1473 or placebo daily for 28 days. Significant reductions in CRP were seen with two of the doses, and favorable trends in clinical response and endoscopic improvement were seen. This may be another means to "widen the therapeutic window" of JAK inhibitors.

CONCLUSION

In summary, JAK inhibition represents a potent, fast-acting mechanism of action for reducing inflammation in IBD. Tofacitinib is approved for moderately to severely active ulcerative colitis in patients who have failed anti-TNF therapy. The selective JAK1 inhibitors appear to have efficacy in moderate to severe Crohn's disease, and upadacitinib appears to be efficacious in ulcerative colitis. In the coming years we will learn much more about the operating characteristics of this promising group of drugs. ■

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