Janus Kinase Inhibitors for Inflammatory Bowel Disease

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Contributor: Su Young Kim

Janus kinase inhibitors are small-molecule drugs that can be administered orally and are relatively inexpensive, thus offering an additional option for treating Inflammatory bowel disease (IBD). They have been shown to be effective in patients with ulcerative colitis (UC), but they are less effective in those with Crohn's disease (CD).

Keywords: janus kinase inhibitor ; inflammatory bowel disease ; small molecule drugs

1. Introduction

Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is caused by chronic inflammation of the gastrointestinal tract [1]. Targeted biological therapies have significantly changed the management of IBD and other immune-mediated inflammatory conditions by significantly improving outcomes. Infliximab, a tumor necrosis factor (TNF)-alphareceptor blocker, was the first monoclonal antibody approved for use for the treatment of IBD in 1998. It was followed by three other anti-TNF molecules, adalimumab, golimumab, and certolizumab. Since then, other pathways have been targeted using ustekinumab and vedolizumab, which target the interleukin (IL) 12/23 axis and the lymphocyte tracking pathway, respectively. However, as these drugs cannot be administered orally, the costs associated with their delivery and monitoring are a burden for both the healthcare system and patients [2]. Therefore, a small molecule drug called the Janus kinase (JAK) pathway inhibitor, which reinforces these shortcomings, was approved for IBD treatment.

The JAK family comprises four intracellular tyrosine kinases, JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), and seven transcriptional activators, which include signal transducers and intracellular transcription factors (STATs). The binding of these factors activates the JAK-STAT pathway via different cytokine receptors and leads to changes in the levels of immune mediators, such as interferons and interleukins [3]. Among the latter, IL-6 and IL-12 and IL- 23 are important drivers of disease activity in IBD [4][5]. Specifically, IL-6 is activated by JAK1, JAK2, and TYK2 via the STAT3 pathway, IL-23 via JAK2 and the STAT3 pathway, and TYK2, via the STAT4 pathway [6]. In psoriasis, rheumatoid arthritis, and other immune-mediated inflammatory conditions, blocking the JAK-STAT signaling pathway has proven to be effective in the treatment of these diseases. In the past few years, considerable interest has been devoted to the clinical development of JAK inhibitors for IBD, as the pathways involved in its pathogenesis are similar [7]. This new drug is currently being actively studied, and tofacitinib is a representative study; however, drugs other than tofacitinib are currently under active development. There is a need to review these newly developed drugs.

2. Tofacitinib in UC

In 2020, Sands et al. concluded OCTAVE Open, a long-term extension, open-label study of the OCTAVE trials that included patients already in remission on 10 mg tofacitinib twice daily; efficacy endpoints (clinical response, mucosal healing (Mayo subscore of 0 or 1) and remission) were assessed at baseline and 2, 12, and 24 months after the conclusion of OCTAVE Open. In most patients, remission was maintained following the de-escalation of tofacitinib therapy (10 mg twice daily) after 52 weeks [8]. Specifically, a clinical response was maintained in 84% of patients and remission in 75% after 52 weeks of treatment. The authors also analyzed the effects of dose escalation to tofacitinib 10 mg twice daily in patients who had lost response to tofacitinib 5 mg twice daily as maintenance therapy. A clinical response was recovered in 65% after 12 months, and 49% of patients had disease remission.

In 2021, Sandborn et al. assessed the safety and efficacy of tofacitinib 5 and 10 mg twice daily in patients who had previously failed to respond to TNF inhibitors [9]. Efficacy was assessed from the phase 3 OCTAVE Induction 1 and 2 studies of 1139 patients, the phase 3 OCTAVE Sustain maintenance study of 593 patients, and the open-label, long-term extension OCTAVE Open study with a dose-escalation subgroup of 59 patients who had received tofacitinib 5 mg twice

daily in OCTAVE Sustain, and those who had received tofacitinib 10 mg twice daily in OCTAVE Open. Among all of these patients, 541 patients responded to TNF inhibitors, and 583 did not. This study demonstrated that tofacitinib was effective and safe even in patients with disease that was previously unresponsive to TNF inhibitor treatment.

Data from the clinical use of tofacitinib in patients with UC have been reported in several retrospective studies. In 2019, Weisshof et al. conducted a retrospective observational study of the use of tofacitinib in IBD patients [10]. Those who medically tolerated previous drugs were treated orally with 5 or 10 mg tofacitinib twice daily. Clinical and adverse events were evaluated at 8, 26, and 52 weeks. Remission was defined as the complete disappearance of clinical symptoms, and endoscopic improvement as outcomes defined by a decrease in the Mayo subscore. At least 8 weeks of treatment with tofacitinib were completed by 58 patients (93% patients with failed anti-TNF). At that time, 21 patients (36%) had a clinical response, and 19 (33%) had clinical remission. Steroid-free remission at 8 weeks was achieved in 15 patients (26%), in 21% of 48 patients followed for 26 weeks, and in 27% of the 26 patients followed for 12 months. The study showed that tofacitinib induced a clinical response in 69% of patients with moderate to severe anti-TNF-resistant IBD, including 27% who were in steroid-free clinical remission by 1 year of treatment. Tofacitinib is thus an effective therapeutic option for patients with severe anti-TNF-resistant IBD.

In 2020, Honap et al. published the results of a retrospective observational cohort study performed at four centers in the UK and consisting of 134 UC patients treated with tofacitinib. The patients were enrolled from October 2018 to October 2019 and, initially, orally administered the standard tofacitinib induction dose of 10 mg twice daily; after at least 8 weeks, the dose was reduced to 5 mg twice daily [11]. In this group, 83% of the patients had previously received at least one biologic. Clinical response was defined as a reduction in the simple clinical colitis activity index (SCCAI) or the partial Mayo score (PMS) ≥ 3, and clinical remission as a SCCAI ≤ 2 or a PMS ≤ 1. The results showed that 74% of patients responded to tofacitinib at week 8, with steroid-free remission occurring in 44% of patients at week 26. Only 23% of patients who continued tofacitinib in the primary non-response setting were in steroid-free remission at week 26. Previous exposure to biologics did not affect either the response or the remission rate. However, dose escalation restored the clinical response in about half of the patients in whom it had been lost.

3. Tofacitinib in CD

In 2017, Panés et al. conducted two randomized, placebo-controlled, multicenter, phase 2b studies that evaluated the efficacy of tofacitinib as induction and maintenance therapy for CD [12]. In both, 280 adult patients with moderate to severe CD and an inadequate response to or intolerance of previously administered immunomodulators (TNF inhibitors, corticosteroids) were randomized to receive induction therapy for 8 weeks with placebo or tofacitinib 5 or 10 mg twice daily. Those who achieved clinical remission (Crohn's disease activity index (CDAI) < 150) were rerandomized to maintenance therapy with placebo or tofacitinib 5 or 10 mg twice daily for 26 weeks. The primary endpoint was the clinical response-100 (decrease in the CDAI ≥ 100 from the induction study baseline) or clinical remission at week 26. At week 8, clinical remission was achieved in 43.5% of the patients treated with 5 mg tofacitinib twice daily and in 43.0% of those treated with 10 mg twice daily, in contrast to 36.7% in the placebo group. The differences were not significant. Although in patients treated with either dose of tofacitinib, the mean decrease in C-reactive protein (CRP) was higher than in the placebo group, there was no correlation with the mean changes in fecal calprotectin at week 8. In the maintenance study, 180 patients were rerandomized. The numbers of patients with a clinical response (decrease in the CDAI ≥ 100 from baseline) or clinical remission (CDAI < 150) were not significantly different in the tofacitinib 5 mg group (40%), the tofacitinib 10 mg group (56%), and the control group (38%). However, levels of CRP and fecal calprotectin were significantly lower in the tofacitinib 10 mg group than in the placebo group. The authors concluded that primary efficacy endpoints were not significantly different in the treated vs. the placebo group, although there was evidence of a mild therapeutic effect.

In 2020, Fenster et al. conducted a retrospective cohort study to examine the real-world efficacy and safety of the off-label use of tofacitinib in patients with CD or unclassified IBD (IBD-U) [13]. Seventy-six patients with CD and IBD-U, 98.7% of whom had previously been treated with biologic therapy and 48.7% of whom had failed at least two biologic therapies, were followed for a median of 7.6 months. During induction therapy (75.0%) and maintenance therapy (65.3%), the dose of tofacitinib in most patients was 10 mg twice daily. The primary outcome was a clinical response (> 50% reduction in symptoms) at 8 and/or 16 weeks. Secondary outcomes were corticosteroid-free response/remission, clinical remission (no IBD symptoms), and endoscopic remission (ulcer resolution). Of the 73 patients for whom data were recorded for weeks 8 and 16, 46.6% had a clinical response, 39.7% had a corticosteroid-free clinical response, 15.1% had a clinical remission, and 13.7% had a corticosteroid-free clinical remission. At the last documented assessment (n = 75), a clinical response was determined in 42.7% (20% in clinical remission), and no or a lost response in 57.3%. Univariate comparisons of the baseline characteristics of the patients based on the clinical response at 8/16 weeks did not show significant differences in

disease location, whereas male sex, body mass index, and baseline hemoglobin level were significant factors. Male sex was associated with an increased odds of a clinical response (adjusted odds ratio, 5.4) and a corticosteroid-free clinical response (adjusted odds ratio, 4.2). In patients with baseline ulceration, endoscopic remission occurred in 44% of patients starting tofacitinib treatment. Treatment outcomes were not statistically different according to the number of failed biologics prior to the initiation of tofacitinib therapy. Tofacitinib was discontinued in 4.5% of patients, most frequently due to no response (30.3%) or a loss of response (15.8%). The study showed that tofacitinib was effective in achieving a clinical response in a subset of patients with CD and IBD-U refractory to previous biologic therapies. No new significant safety issues were reported with the use of tofacitinib in these patients.

4. Other Jak Inhibitors

The authors also conducted a double-blind, phase II trial that included adult patients with moderate to severe CD and an inadequate response to or intolerance of immunosuppressive agents or anti-TNF inhibitor [14]. The patients were randomly assigned to the placebo group or to one of the following treatment groups: 3, 6, 12, or 24 mg upadacitinib twice daily or 24 mg upadacitinib once daily. They were assessed by ileocoloscopy at week 12 or 16 of the induction period. Patients completing week 16 were rerandomized to 36 weeks of maintenance therapy with upadacitinib. The primary outcome was clinical remission (average daily stool frequency score of 1.5 and abdominal pain score of 1.0) at week 16 and endoscopic remission (simple endoscopic score for CD of 4 and a 2-point reduction from baseline, with no subscore > 1) at week 12 or 16, determined using the multiple comparison procedure, modeling, and the Cochran-Mantel-Haenszel test, with a 2-sided level of 10%. Among the 220 patients enrolled in the study, clinical remission was achieved in 13% of those treated with 3 mg, 27% of those treated with 6 mg, 11% of those treated with 12 mg, 22% of those treated with 24 mg twice daily, 14% of those treated with 24 mg once daily, and 11% of those who had received the placebo. Endoscopic remission was achieved in 10%, 8%, 8%, 22%, and 14% of patients treated with upadacitinib but in none of the patients in the placebo group. Endoscopic remission increased with an increasing dose during the induction period. The authors concluded that efficacy was maintained for most endpoints through week 52 during the induction period. In a phase II trial in CD patients, upadacitinib induced endoscopic remission in a significant proportion of patients compared to placebo. The benefit/risk profile of upadacitinib supports its further development for the treatment of CD.

Filgotinib is an oral JAK1 selective inhibitor. Its half-life of 6 h for the parent compound and 23 h for the active metabolite allows once-daily dosing [7]. In 2021, Feagan et al. assessed a phase 2b/3, double-blind, randomized, placebo-controlled trial including two induction studies and one maintenance study, conducted in 341 study centers in 40 countries for filgotinib treatment of ulcerative colitis [15]. Patients were randomly assigned to receive filgotinib 100 mg, filgotinib 200 mg, or placebo, and the patients entered the maintenance study. The primary outcome was clinical remission (Mayo endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a 1-point decrease in stool frequency from induction baseline for a subscore of 0 or 1) at week 10 and week 58. Some patients discontinued treatment but the proportion of patients who achieved clinical remission at week 10 was larger in the group treated with 200 mg of filgotinib than in the placebo group (induction study A: 26.1% vs. 15.3%, induction study B: 11.5% vs. 4.2%). Clinical remission at week 58 was achieved in 37.2% of patients receiving 200 mg of filgotinib compared to 11.2% in the placebo group. There was no significant difference in clinical response between filgotinib 100 mg and placebo at week 10, but the difference at week 58 was significant (23.8% vs. 13.5%). The incidence of severe adverse events and adverse events of interest was similar between treatment groups. The authors found that filgotinib 200 mg was well tolerated and effective in inducing and maintaining clinical remission in patients with moderately to severely active UC.

In 2017, Vermeire et al. conducted a randomized, double-blind, placebo-controlled phase II study that recruited patients from 52 centers in nine European countries [16]. Eligible patients ranged in age from 18 to 75 years and had a history of ileal, colonic, or ileocolonic CD (evaluated by colonoscopy and supported by histology) for 3 months or more prior to screening and a CDAI between 220 and 450 during the screening period. Enrolled patients were randomized (3:1) to receive filgotinib 200 mg once daily or placebo for 10 weeks. An interactive web-based response system was used to stratify patients according to prior anti-TNF exposure, CRP concentration at screening (≤10 mg/L or >10 mg/L), and oral corticosteroid use at baseline. The primary endpoint was clinical remission (CDAI < 150) at week 10. After 10 weeks, the patients were assigned to filgotinib 100 mg once daily, filgotinib 200 mg once daily, or placebo, depending on their responses, for an observation period lasting an additional 10 weeks. Between February 3, 2014, and July 10, 2015, 174 patients with active CD as evaluated by central read endoscopy were enrolled (130 in the filgotinib 200 mg group and 44 in the placebo group). In the intention-to-treat population, 60 of 128 patients (47%) treated with filgotinib 200 mg achieved clinical remission at week 10, compared to 10 of 44 patients (23%) treated with placebo ($p = 0.0077$). In the pooled analysis of all filgotinib and placebo exposures for 20 weeks, serious treatment-emergent adverse events developed in 14 of 152 (9%) patients treated with filgotinib and 3 of 67 patients treated with placebo. The authors concluded that filgotinib therapy could induce clinical remission in CD patients and that the safety profile was acceptable.

The safety and efficacy of pepicitinib were studied in a phase 2b dose range trial that included 219 adult patients with moderate to severe UC who were randomized to receive placebo or peficitinib 25, 75, or 150 mg or peficitinib 75 mg twice daily [17]. Although the dose response at 8 weeks was not statistically significant, a clinical response, mucosal healing, and remission were achieved in patients receiving pepicitinib > 75 mg once daily. Clinical improvement was accompanied by improvement according to the IBD questionnaire and the normalization of inflammatory biomarkers.

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