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EDITORIAL

Tofacitinib: A Small Molecule for Biologic-Refractory Crohn's Disease?

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Since the treatment of chronic inflammatory diseases was revolutionized with the introduction of the therapeutic monoclonal antibody (biologic) infliximab in 1994 [1], several newer agents targeting various pathways were subsequently introduced. One of these, tofacitinib, a small molecule Janus kinase and Signal Transducer and Activator of Transcription (JAK-STAT) inhibitor, the first oral treatment for inflammatory bowel disease (IBD) to be approved in several decades, showed safety and efficacy in the treatment of ulcerative colitis (UC), receiving FDA and EMA approvals [2]. However, a phase 2b study in Crohn's disease (CD) failed to demonstrate a significant benefit [3], with the study failing to meet its primary endpoints. Notably, for the induction phase, clinical remission (CD activity index (CDAI) < 150) at week 8, was observed in 36.7% (95 CI [26.8–47.5]), 43.5% (95 CI [32.8–54.7]) and 43.0% (95 CI [32.4–54.2]) in the placebo, and the tofacitinib 5 mg and 10 mg twice daily groups, respectively. Differences were not significant between the placebo group and the tofacitinib-treated groups. Even though the primary endpoint was not met in this study, secondary endpoints did suggest a potential benefit in patients with CD. For example, mean decreases from baseline in CDAI score at week 8 were significantly larger with both tofacitinib doses ($p < 0.05$) compared with placebo. At week 8, mean decreases from baseline C-reactive protein (CRP) concentration were significantly greater with tofacitinib 5 and 10 mg twice daily ($p < 0.001$) compared with placebo. Notably, > 70% of the trial population had been previously exposed to anti-TNF biologics, a factor that negatively impacts the subsequent efficacy of subsequent biologics and other anti-inflammatory drugs [4].

Following the publication of the phase 2 randomized controlled trials, there have been reports of the real-world use of off-label tofacitinib in patients with CD. For example, the TROPIC multicenter consortium evaluated the use of tofacitinib in 73 individuals with highly refractory CD [5]. Half of the patients had failed at least two classes of biotherapies. Among the studied patients, between weeks 8 and 16 half were in clinical response, 15.1% in clinical remission, and 13.7% in corticosteroid-free clinical remission. Most strikingly, endoscopic remission (absence of ulcers) among those with baseline ulcers was reported in 44% after initiation of tofacitinib. Adverse events were minimal, with an episode of Herpes zoster and a single thromboembolic event reported. An intriguing observation derived from the TROPIC consortium study suggested that men had 4- to 5-fold increased odds of clinical response and corticosteroid-free response. Previously published data also suggest that male sex is associated with an overall increased response to biologic therapy in the setting of rheumatoid arthritis [6].

In this issue of *Digestive Diseases and Sciences*, Lee et al. [7] reported another cohort of patients with CD treated with tofacitinib in a real-world setting. Their study enrolled 44 patients, among whom 35 were assessed for efficacy. Of note, 42 had colonic involvement and only two had purely ileal disease. Penetrating or stricturing disease was present in 34.1% of the patients. Almost all of the patients were highly refractory to biologics with 93.2% failing of at least two, similar to the TROPIC consortium study,

In this cohort, the mean Harvey Bradshaw index (HBI) decreased significantly from 11.5 ± 6.5 to 7.5 ± 5.9 ($p < 0.01$) after a mean of 33.3 weeks of tofacitinib treatment with 70.8% of patients experiencing clinical response after a mean of 29.4 weeks. Moreover, a third of the patients were in clinical remission after a mean of 33.4 weeks of treatment with tofacitinib. Endoscopic outcomes were also favorable with the mean simple endoscopic severity (SES)CD score decreasing from 23.1 to 18.0 ($p = 0.02$). Overall, a quarter of the patients had endoscopic improvement. Finally, although 30.8% of the patients had normalization of CRP levels, the

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Table 1 Development of JAK inhibitors in Crohn's disease

Drug	Target	Intestinal selectivity	Development status
Tofacitinib	panJAK	No	Phase 2b failure
Filgotinib	JAK1	No	Current phase 3
Upadacitinib	JAK1	No	Current phase 3
TD-1473	Pan-JAK	Yes	Current phase 2
Pf-06651600	JAK3	No	Current phase 2a
Pf-06700841	JAK1, TYK2	No	Current phase 2a
BMS-986165	TYK2	No	Current phase 2

change in mean CRP (40.1 to 32.2 mg/l) was not statistically significant.

Therefore, data from clinical trials, as well as real-world studies, suggest a possible efficacy of tofacitinib in subgroups of patients with CD, especially those with prior exposure to multiple biologics. These data are important in clinical practice as some situations do require off-label management. So far, only biologics with three distinct mechanisms of action: anti-TNF, anti-IL12/23, and anti-integrin α4β7, are approved for CD. Since the number of patients with multiple biologic failures is constantly increasing, there is a further need for innovative therapeutic approaches. Complicated clinical situations often require additional medical intervention when surgery is not appropriate or indicated, such as when there is risk of short bowel syndrome, in the presence of extended intestinal disease, or unwillingness to undergo surgery. Innovative medical strategies include simultaneous treatment with more than one approved biologic [8], autologous hematopoietic stem cell transplantation [9] or the use of off-label biologics approved for other immune-mediated diseases. Since tofacitinib is approved for the closest immune-mediated disease to CD, UC, it appears to be the preferred choice in such situations.

Finally, targeting the JAK-STAT pathway differently, for example with an agent more selective for JAK1, may be effective. The pharmaceutical company Abbvie recently communicated in a press release on the favorable outcome of upadacitinib in a phase 3 randomized controlled trial in CD [10]. In line with this, several anti-JAK inhibitors are being or have been studied for CD and will be incorporated in the therapeutic arsenal to treat CD sooner or later (Table 1). In conclusion, this report provides further real-world data on the potential usefulness of JAK-STAT pathway inhibitors in the treatment of CD.

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