LETTER TO THE EDITOR

INTESTINAL RESEARCH

pISSN 1598-9100 • eISSN 2288-1956
https://doi.org/10.5217/ir.2022.00098
Intest Res 2023;21(1):168-169

The role and prospect of tofacitinib in patients with ulcerative colitis

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Treatment strategies for inflammatory bowel disease (IBD) such as ulcerative colitis (UC) and Crohn's disease are changing from simple symptom control to complete remission of the disease itself. With the advent of anti-tumor necrosis factor (anti-TNF) therapy, a dramatic change occurred in the treatment and prognosis of IBD. For more than a decade, anti-TNFs were the only biologics approved for patients with UC; however, newer medication with different mechanisms of action are now available.[1,2] Vedolizumab, a monoclonal antibody targeting α4β7 integrin, was shown to exhibit significant clinical response and remission in moderate to severe UC compared to placebo in the GEMINI trial.[3,4] Ustekinumab, a monoclonal antibody that targets the p40 subunit shared by interleukin-12 and -23, was also confirmed to be effective in the UNIFI trial.[5]

For patients who have previously used anti-TNFs, a therapeutic drug monitoring-guided approach is recommended. However, there is no consensus as to the first-line treatment in patients with moderate to severe UC. In general, efficacy, including rapidity of drug action, is an important factor in selection for severe UC. On the other hand, in the cases of moderate UC, safety aspects, including side effects can be considered first. In pivotal randomized controlled trials in patients with acute severe UC, infliximab significantly lowered the colectomy rate (odds ratio, 4.9; 95% confidence interval, 1.4–17; P=0.017).[6] Since it has been confirmed in many studies including a meta-analysis, intravenous infliximab is preferentially recommended in acute severe UC.[7,8] In contrast, vedolizumab and ustekinumab may be better than anti-TNFs for first-line treatment of moderate UC. They did not differ from placebo in terms of the incidence of side effects and did not require combination treatment with immunomodulators.[3,5]

Tofacitinib, all Janus kinase inhibitor, is the first small-molecule drug approved as a first-line treatment for UC. In the OCTAVE 1 and OCTAVE 2 trials in patients with severe UC, tofacitinib 10 mg demonstrated more effective clinical remission than placebo (18.5% vs. 8.2%, P=0.007 and 16.6% vs. 3.6%, P<0.001, respectively).[9] Tofacitinib cannot be directly compared with other biologics in the absence of head-to-head trials in patients with UC. As a result of a meta-analysis, efficacy in first-line treatment was confirmed as similar to that of other biologics.[10] However, in a recent study, tofacitinib was recommended as second-line or higher treatment when there was no response to other biologics. The main reason was safety concerns, such as serious cardiovascular events, cancer, and infections. In addition, tofacitinib is an ideal second-line treatment because, unlike biologics, the clinical response rate is similar in patients with and without biological experience.

The role and position of tofacitinib as a first-line treatment for induction in patients with moderate to severe UC needs to be explored. Although it has obvious limitations in terms of safety, it can be a possible therapeutic option in the following aspects: First, it is a promising therapeutic option with rapid onset of action. Second, since it is a small molecule, there is no immunogenicity, and theoretically, loss of response does not occur. In addition, it shows a relatively high response rate even

Received July 26, 2022. **Revised** August 19, 2022. **Accepted** August 27, 2022.
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when re-administered to patients who have discontinued treatment. Third, because it is an oral drug, there is a high rate of patient satisfaction, and it is more cost-effective than a biological drug.

The key to the recent treatment of IBD is to recognize diversity and establish an individualized treatment strategy. When selecting a first-line treatment, not only efficacy and safety, which are the most important factors, but also effective time to onset, extraintestinal manifestations, patient preference, and cost must be considered. Recently, clinical decision support tools have been actively studied and their application in clinical practice is thought to be of great help in making treatment choices.

In conclusion, a drug treatment algorithm for moderate to severe UC has not been established because there is no head-to-head trial for each drug. Tofacitinib was approved for use in Korea in March 2018 as a promising therapy for patients with moderate to severe UC. Tofacitinib may be used on a case-by-case basis in patients who do not respond to conventional therapy or other biologics.

ADDITIONAL INFORMATION

Funding Source

The author received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

Lee J is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Data Availability Statement

Not applicable.

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