EDITORIAL

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Understanding the Role of Adalimumab in the Treatment of Moderately to Severely Active Ulcerative Colitis

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See "Efficacy and Safety of Adalimumab in Moderately to Severely Active Cases of Ulcerative Colitis: A Meta-Analysis of Published Placebo-Controlled Trials" by Zong Mei Zhang, et al. on page 262-274, Vol. 10. No. 2, 2016

Ulcerative colitis (UC) is a chronic inflammatory colonic disease with repetitive episodes of remission and relapse. Although the precise etiology of UC remains unclear, interactions between the immune system and the environment and, in particular, interactions between the genetic make-up and gut microbiota are considered to be the main factors responsible for UC development.[1] Recently, the therapeutic options for UC have increased, and several biologic agents, including anti-tumor necrosis factor (anti-TNF) agents (infliximab, certolizumab pegol, adalimumab, and golimumab) and anti-integrin molecules (natalizumab and vedolizumab), are now available in clinical practice.[2] These biologic agents could be an optimal choice for the treatment of patients with moderately to severely active UC who have not been successfully treated with conventional therapies consisting of steroids and/or immunomodulators.[3,4] In the absence of head-to-head trials, recently, two network meta-analyses have been conducted to compare the efficacy of various biologic agents in the treatment of moderately to severely active UC. Danese *et al*.[5] showed that biologic agents (adalimumab, golimumab, infliximab, and vedolizumab) were superior to a placebo in terms of induction or maintenance of clinical remission and suggested that infliximab is more likely to induce a favorable clinical outcome than adalimumab. Stidham *et al*.[6] demonstrated that biologic agents (infliximab, adalimumab, and golimumab) are effective in the induction and maintenance of remission of UC and showed that no single agent is clinically superior to any other.

Adalimumab is a fully human IgG1 monoclonal antibody against TNF-α. Phase III trials in patients with moderately to severely active UC have demonstrated the safety and efficacy of adalimumab in inducing and maintaining clinical remission at an induction dose of 160/80 mg (week 0/week 2) and a maintenance dose of 40 mg every other week.[7,8] Colombel *et al*.[9] showed that long-term treatment with adalimumab for up to 4 years is well tolerated and is beneficial for patients with moderately to severely active UC. Based on these results, adalimumab has been approved worldwide for the treatment of adult patients with moderately to severely active UC.

When deciding upon a biologic agent, several parameters including patient preference, potential for immunogenicity, and cost-effectiveness as well as comparative efficacy and safety should be considered. Because adalimumab is administered subcutaneously and requires a short time for therapy, which consists of a single injection, this agent can be used conveniently and easily at home. A prospective survey to assess the preferences of patients for selecting anti-TNF agents revealed that the majority of patients preferred agents that were administered by subcutaneous injection rather than by intravenous infusion.[10] Associations between immunogenic events (such as infusion reactions and loss of response) and antibodies to infliximab or adalimumab have been demonstrated. According to data from Ben-Horin *et al*.,[11] antiadalimumab antibodies do not cross-react with infliximab, and switching between infliximab and adalimumab is often advocated when the response to one drug is lost. Cost issues might also guide treatment choice. However, data on the cost-effectiveness of biologic agents are still lacking.

Recently, Zhang *et al*.[12] reported a meta-analysis of the efficacy and safety of adalimumab for patients with moderately to severely active UC who are unresponsive to conventional therapies. In that study, three randomized controlled trials were included to compare the efficacy and safety of adalimumab to a placebo. The authors revealed that adalimumab was more effec-

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tive than the placebo in producing clinical remission, a clinical response, and mucosal healing, and inflammatory bowel disease questionnaire responses at week 8 and week 52 without significant severe side effects. These results suggest that adalimumab is an effective option for inducing and maintaining clinical remission in patients with moderately to severely active UC who are unresponsive to conventional therapies. The combined use of infliximab and thiopurine therapy was superior to infliximab monotherapy in patients with UC who were naïve to both agents.[2] Zhang *et al*.[12] showed that adalimumab was superior to a placebo at week 8 in patients with UC receiving immunomodulator therapy, whereas similar remission rates at week 8 were observed in the adalimumab and placebo groups who were not receiving immunomodulator therapy. These results indicate that the combination of adalimumab and an immunomodulator might be superior to adalimumab monotherapy in patients with UC.

In the absence of head-to-head trials, these results could be helpful in choosing adalimumab as a treatment option for patients with moderately to severely active UC. However, this study has some limitations; the number of included studies was relatively small, and the analyzed follow-up period was not longer than 1 year. Furthermore, randomized clinical comparative studies differ from real-life clinical practice with regard to various conditions, such as inclusion and exclusion criteria, disease severity, and indications. Therefore, further systematic reviews and meta-analyses including long-term follow up and real-life clinical data are needed to clarify the role of adalimumab in patients with moderately to severely active UC. Moreover, head-to-head comparison studies would ultimately produce a concrete conclusion for choosing appropriate anti-TNFs and immunomodulators.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. de Souza HS, Fiocchi C. Immunopathogenesis of IBD: current state of the art. Nat Rev Gastroenterol Hepatol 2016;13:13-27.
2. Danese S, Vuitton L, Peyrin-Biroulet L. Biologic agents for IBD: practical insights. Nat Rev Gastroenterol Hepatol 2015;12:537-545.
3. Park SC, Jeen YT. Current and emerging biologics for ulcerative colitis. Gut Liver 2015;9:18-27.
4. Kim EH, Kim DH, Park SJ, et al. Infliximab versus cyclosporine treatment for severe corticosteroid-refractory ulcerative colitis: a Korean, retrospective, single center study. Gut Liver 2015;9:601-606.
5. Danese S, Fiorino G, Peyrin-Biroulet L, et al. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. Ann Intern Med 2014;160:704-711.
6. Stidham RW, Lee TC, Higgins PD, et al. Systematic review with network meta-analysis: the efficacy of anti-tumour necrosis factor-alpha agents for the treatment of ulcerative colitis. Aliment Pharmacol Ther 2014;39:660-671.
7. Sandborn WJ, van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2012;142:257-265.e3.
8. Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. Gut 2011;60:780-787.
9. Colombel JF, Sandborn WJ, Ghosh S, et al. Four-year maintenance treatment with adalimumab in patients with moderately to severely active ulcerative colitis: Data from ULTRA 1, 2, and 3. Am J Gastroenterol 2014;109:1771-1780.
10. Vavricka SR, Bentele N, Scharl M, et al. Systematic assessment of factors influencing preferences of Crohn's disease patients in selecting an anti-tumor necrosis factor agent (CHOOSE TNF TRIAL). Inflamm Bowel Dis 2012;18:1523-1530.
11. Ben-Horin S, Yavzori M, Benhar I, et al. Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. Gut. Epub 2015 Apr 20. http://dx.doi.org/10.1136/gutjnl-2015-309290.
12. Zhang ZM, Li W, Jiang XL. Efficacy and safety of adalimumab in moderately to severely active cases of ulcerative colitis: a meta-analysis of published placebo-controlled trials. Gut Liver 2016;10:262-274.