

WJG 20th Anniversary Special Issues (3): Inflammatory bowel disease**Biological therapy for ulcerative colitis: An update**

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Abstract

Of the diverse biological agents used for patients with ulcerative colitis, the anti-tumor necrosis factor- α agents infliximab and adalimumab have been used in large-scale clinical trials and are currently widely used in the treatment of inflammatory bowel disease patients. Recent studies have indicated that golimumab, oral tofacitinib and vedolizumab reportedly achieved good clinical response and remission rates in ulcerative colitis patients. Thus, we believe that the detailed investigation of various studies on clinical trials may provide important information for the selection of appropriate biological agents, and therefore, we have extensively reviewed such trials in the present study.

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Key words: Ulcerative colitis; Immune dysfunction; Biological therapy; Remission; Clinical trial; Inflammatory bowel disease

Core tip: In the last two years, the use of the Janus kinase 3 inhibitor (oral tofacitinib) and the $\alpha 4\beta 7$ integrin

blocker (vedolizumab) reportedly achieved good clinical response and remission rates in ulcerative colitis patients. Thus, we believe that the detailed investigation of various studies on clinical trials performed thus far may provide important information for the selection of appropriate biological agents, and therefore, we have extensively reviewed such trials in the present study.

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INTRODUCTION

Inflammatory bowel disease (IBD), which is broadly classified as ulcerative colitis (UC) and Crohn's disease (CD), is characterized by chronic intestinal inflammation. Although its causes have not been clearly understood, it is believed to be influenced by genetic susceptibility, changes in the commensal enteric flora, and immune imbalance^[1-5]. Increase in the production of T cells, cytokines, and chemokines, as well as increased trafficking of immune cells is associated with immune imbalance, and is considered as therapeutic targets for the biological treatment of IBD^[6-9]. The current treatment goals of UC include induction of clinical remission, maintenance of clinical remission, and prevention of UC-related complications^[10,11].

Although the therapeutic agents of UC, such as aminosalicylates, corticosteroids, thiopurines, and cyclosporine, are effective in most cases, biological agents are needed in cases where the disease is refractory or intolerant to therapeutic agents. Anti-tumor necrosis factor (TNF)- α agents are biological agents that are relatively safe and have been utilized for a long duration in UC patients. Anti-TNF- α agents appear to exert their effects by inhibiting the large amount of TNF- α present in the

Table 1 Summary of ACT1, ACT2, ULTRA1 and ULTRA2 trials for moderate-to-severe ulcerative colitis

Trial	Clinical scenario	Drug	Dosage	Patients (n)	Follow-up (wk)	Outcome and P value
ACT1 Rutgeerts <i>et al</i> ^[12]	Moderate- to-severe active UC	Infliximab	5 mg/kg IV	121	54	Clinical response at week 8 (placebo/5 mg/10 mg) -37.2%/69.4%/61.5% ($P < 0.001$, $P < 0.001$) Clinical remission at week 8 -14.9%/38.8%/32.0% ($P < 0.001$, $P = 0.002$) Clinical remission at week 54 -8.9%/25.7%/16.4% ($P = 0.006$, $P = 0.149$)
			10 mg/kg IV (intravenously at weeks 0, 2, and 6 and then every eight weeks)	122		
ACT2 Rutgeerts <i>et al</i> ^[12]	Moderate- to-severe active UC	Infliximab	5 mg/kg IV	121	30	Clinical response at week 8 (placebo/5 mg/10 mg) -29.3%/64.5%/69.2% ($P < 0.001$, $P < 0.001$) Clinical remission at week 8 -5.7%/33.9%/27.5% ($P < 0.001$, $P < 0.001$) Clinical remission at week 30 -3.3%/18.3%/27.3% ($P = 0.010$, $P < 0.001$)
			10 mg/kg IV	120		
ULTRA1 Reinisch <i>et al</i> ^[15]	Moderate- to-severe active UC	Adalimumab	160/80 mg SC (160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6) 80/40 mg SC (80 mg at week 0, 40 mg at weeks 2, 4 and 6)	130 130	8	Clinical remission at week 8 (placebo/ ADA160/80mg/ADA80/40 mg) -9.2%/18.5%/10.0% ($P = 0.031$, $P = 0.833$)
ULTRA2 Sandborn <i>et al</i> ^[16]	Moderate- to-severe active UC	Adalimumab	160/80 mg SC (160 mg at week 0, 80 mg at week 2, and then 40 mg every other week)	248	52	Clinical remission at week 8 (placebo/ADA) -9.3%/16.5% ($P = 0.019$) Clinical remission at week 52 -8.5%/17.3% ($P = 0.004$)

UC: Ulcerative colitis; ADA: Adalimumab.

deeper layers of colonic tissues in UC patients^[7]. In addition to anti-TNF- α agents, many studies have been performed on the use of molecules involved in varied inflammatory pathways as biological agents. However, in the present study, we aimed to focus on the mechanism of action, clinical outcomes, and future prospects of infliximab, adalimumab, and golimumab (anti-TNF- α agents); tofacitinib (a Janus kinase (JAK) 3 inhibitor); and vedolizumab (an $\alpha 4\beta 7$ integrin blocker).

ANTI-TNF- α AGENTS: CLASSIC OR NEW GENERATION

Infliximab and adalimumab, the most commonly used anti-TNF- α agents at present, are administered intravenously and subcutaneously, respectively, and have been found to be effective for the treatment of moderate-to-severe UC in clinical trials. Anti-TNF- α , which was first officially approved by the US Food and Drug Administration (FDA) for the treatment of CD in 1998, was also approved by the FDA for the treatment of UC in 2010.

Both infliximab - chimeric mouse-human recombinant monoclonal antibody (25% murine and 75% human) - and adalimumab - completely human anti-TNF- α IgG1 - exert their effects by binding to free and membrane-bound TNF- α in order to prevent TNF- α from attaching to TNF-receptor type1/receptor type2. In ACT1 and ACT2 studies that reported the effects of infliximab in UC patients^[12], no difference in

the effect was noted between the 5-mg/kg administration group and the 10-mg/kg administration group, although a marked improvement was observed in the clinical response and remission rates after 8 wk ($P < 0.001$, Table 1), along with a significant improvement in mucosal healing ($P < 0.001$). Similar effects in the clinical remission rate were observed after 30 and 54 wk of treatment (Table 1). No differences in adverse effects were noted between the infliximab and placebo groups. Moreover, infliximab is well known as a useful rescue therapy to avoid colectomy^[13,14].

In the first 8-wk multicenter randomized controlled study that utilized adalimumab, defined as ULTRA 1, the subjects were divided into 160/80 mg and 80/40 mg groups, based on the loading dose, and were then compared with the placebo group^[15]. The clinical remission rate at week 8 in the adalimumab 160/80 mg group was 2 times higher than that of the placebo group, whereas this value in the adalimumab 80/40 mg group did not differ from that of the placebo group. Thereafter, a 52-wk randomized controlled study, defined as ULTRA2, was performed, which indicated that the clinical remission rate at week 52 in the adalimumab 160/80 mg group was 2 times higher than that of the placebo group ($P = 0.004$, Table 1)^[16]. Following a subanalysis, it was observed that the anti-TNF- α naïve patient group exhibited approximately 2 times higher clinical remission rates at week 8 and week 52, respectively compared to the placebo group (21.3% *vs* 11.0%, 22.0% *vs* 12.4%). In the recently performed study on the effects of adali-

Table 2 Studies for the use of Golimumab, Tofacitinib and Vedolizumab for the treatment of ulcerative colitis

Trial	Clinical scenario	Drug	Dosage	Patients (n)	Follow-up (wk)	Outcome and P value
PURSUIT-SC Sandborn <i>et al</i> ^[23]	Moderate-to-severe active UC	Golimumab	100/50 mg SC 200/100 mg SC 400/200 mg SC (2 wk apart)	71 331 331	6	Clinical response at week 6 (placebo/GLM 200/100 mg/GLM 400/200mg) - 30.3%/51.0%/54.9% ($P < 0.0001$, $P < 0.0001$) Clinical remission at week 6 - 6.4%/17.8%/17.9% ($P < 0.0001$, $P < 0.0001$)
PURSUIT-Maintenance Sandborn <i>et al</i> ^[24]	Moderate-to-severe active UC	Golimumab	50 mg SC 100 mg SC (every 4 wk)	151 151	54	Clinical response at week 54 (placebo/GLM 50 mg/GLM100 mg) - 31.2%/47.0%/49.7% ($P = 0.010$, $P < 0.001$) Clinical remission at weeks 30 and 54 - 15.6%/23.2%/27.8% ($P = 0.122$, $P = 0.004$)
Sandborn <i>et al</i> ^[32]	Moderate-to-severe active UC	Tofacitinib	0.5 mg, 3 mg, 10 mg, 15 mg oral (twice daily for 8 wk)	31/33/33/ 49	8	Clinical response at week 8 (placebo/0.5 mg/3 mg/10 mg/15 mg) - 42%/32%/48%/61%/78% ($P = 0.39$, $P = 0.55$, $P = 0.10$, $P < 0.001$) Clinical remission at week 8 -10%/13%/33%/48%/41% ($P = 0.76$, $P = 0.001$, $P < 0.001$, $P < 0.001$) Endoscopic remission at week 8 -2%/10%/18%/30%/27% ($P = 0.14$, $P = 0.001$, $P < 0.001$, $P < 0.001$)
Gemini 1 Feagan <i>et al</i> ^[41]	Moderate-to-severe active UC	Vedolizumab	300 mg IV (at weeks 0, 2 and then every 8 or 4 wk)	Cohort 1 (225) Cohort 2 (521)	52	Clinical response at week 6 (placebo/Vedolizumab) - 25.5%/47.1% ($P < 0.001$) Clinical remission at week 6 - 5.4%/16.9% ($P = 0.001$) Clinical remission at week 52 (placebo/Vedolizumab every 8 wk/Vedolizumab every 4 wk) - 15.9%/41.8%/44.8% ($P < 0.001$, $P < 0.001$)

UC: Ulcerative colitis; GLM: Golimumab.

mumab on hospitalization for UC, the first 8 wk of adalimumab therapy indicated a significant reduction in the risk of all-cause, UC-related, and UC- or drug-related hospitalization compared to the placebo group (40%, 50%, and 47%, $P < 0.05$ for all comparisons)^[17]; however, significant differences were not observed in the rates of colectomy between the groups. The adalimumab and placebo groups did not show any differences in the adverse events^[15,16,18]. The primary failure rate of anti-TNF induction therapy is reportedly 40% in IBD clinical trials; when switching to another anti-TNF agent, the treatment becomes effective at 50%^[19]. A secondary loss of response can also occur at 1 year after anti-TNF initiation in IBD patients^[19], and solutions for the issues in anti-TNF- α treatment of UC are expected to be elucidated in the future.

Golimumab - a novel, completely human IgG1 anti-TNF- α antagonist - is subcutaneously administered and is approved for use in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis patients^[20-22]. As shown in the PURSUIT-SC study, at week 6, the clinical response and remission rates showed a noticeable change in both the golimumab 200/100 mg and 400/200 mg groups (all $P < 0.0001$, Table 2)^[23]. The PURSUIT-maintenance study, which is a phase 3, placebo-controlled, randomized withdrawal study, compared the clinical response and remission rates between the golimumab 50/100 mg group and placebo group up to week 54 at intervals of 4 wk; they observed that a notable change was observed in the golimumab 100 mg administration

group ($P < 0.001$, $P = 0.004$, Table 2)^[24]. After adjusting for the follow-up duration, no difference was noted in adverse events between the placebo and golimumab 100 mg groups.

PROMISING JAK1/JAK3 INHIBITOR AND INTEGRIN BLOCKING ANTIBODY

The JAK-STAT pathway is associated with inflammation, autoimmune diseases, hematopoietic disorders, and transplant rejection^[25-30]. Tofacitinib (formally known as CP-690550) is a selective oral inhibitor of JAK 1 and 3, which is known to inhibit the differentiation of pathogenic Th1 and Th17 cells and innate immune cell signaling^[31]. The effects of tofacitinib in active UC patients showed clinical response rates at week 8 of 32%, 48%, 61%, and 78% for the 0.5 mg, 3 mg, 10 mg, and 15 mg twice daily groups, respectively. The tofacitinib 3 mg, 10 mg, and 15 mg twice daily groups exhibited marked differences in clinical and endoscopic remission rates compared to the placebo group (all $P \leq 0.001$, Table 2)^[32]. The levels of low-density and high-density lipoprotein cholesterol increased in a dose-dependent manner, and an absolute neutrophil count of < 1500 was observed in 2% of patients in the tofacitinib group. Thus, tofacitinib is considered to be an effective and safe drug for moderate-to-severe UC patients.

$\alpha 4\beta 7$ integrin, a molecule that is expressed on circulating B and T lymphocytes, interacts with the ligand of the mucosal addressin-cell adhesion molecule

(MAdCAM-1)^[33,34]. The bound lymphocyte migrates to the lamina propria and tissues, and then induces the inflammatory cascade^[35]. Vedolizumab - a humanized monoclonal antibody that inhibits the binding of $\alpha 4\beta 7$ integrin complex and MAdCAM-1-selectively blocks gut lymphocyte trafficking^[36,37], and thus demonstrates therapeutic effects in IBD patients^[38,39]. Consequently, unlike natalizumab which is a $\alpha 4\beta 7$ and $\alpha 4\beta 1$ integrin antagonist, vedolizumab does not affect the cerebrospinal fluid T-lymphocyte immunophenotype and therefore, it does not cause progressive multifocal leukoencephalopathy^[40]. When vedolizumab (300 mg) was administered at week 0 and week 2 and then administered at intervals of 4 or 8 wk, a marked response in the clinical response and remission rates was noted after week 6 ($P < 0.001$, $P = 0.001$, respectively; Table 2)^[41]. A noticeable change in the clinical remission rate at week 52 was observed, regardless of whether the medication was administered at 4- or 8-wk intervals (all $P < 0.001$).

CONCLUSION

Biological agents have been used for UC treatment for 10 years, and various types of biological agents have been developed and used worldwide, with the most common being anti-TNF- α agents. This increase in the development of biological agents provides further immunologic information in addition to offering a wide range of drugs for use. Thus, biological agents may serve as another appropriate option for clinicians in the treatment of UC patients who may not be effectively treated with conventional drugs. Since an accurate understanding of biological agents can be achieved through clinical trials, performed as part of large-scale randomized controlled studies, we have reviewed them in detail. In the future, we believe that biological agents with superior therapeutic effects and fewer side effects, compared to those used currently, will be developed, thus bridging the therapeutic gap present in the treatment of UC patients.

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