REVIEW

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Current and Emerging Biologics for Ulcerative Colitis

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Conventional medical treatment for ulcerative colitis can have limited efficacy or severe adverse reactions requiring additional treatment or colectomy. Hence, different biological agents that target specific immunological pathways are being investigated for treating ulcerative colitis. Anti-tumor necrosis factor (TNF) agents were the first biologics to be used for treating inflammatory bowel disease. For example, infliximab and adalimumab, which are anti-TNF agents, are being used for treating ulcerative colitis. Recently, golimumab, another anti-TNF agent, and vedolizumab, an anti-adhesion therapy, have been approved for ulcerative colitis by the U.S. Food and Drug Administration. In addition, new medications such as tofacitinib, a Janus kinase inhibitor, and etrolizumab, another anti-adhesion therapy, are emerging as therapeutic agents. Therefore, there is a need for further studies to select appropriate patient groups for these biologics and to improve the outcomes of ulcerative colitis treatment through appropriate medical usage. **(Gut Liver 2015;9:18-27)**

Key Words: Biological therapies; Ulcerative colitis

INTRODUCTION

Ulcerative colitis is a chronic disease of unknown cause that triggers inflammation in the colon and is characterized by alternating flare-ups and remissions. The primary symptoms are blood in the stool, diarrhea, and abdominal pain. Approximately 15% of ulcerative colitis patients experience a severe clinical course, and 30% of these patients require colectomy.[1,2] Furthermore, prolonged inflammation of the intestinal tract reduces patients' quality of life and increases the possibility of colon cancer development.

The chronic inflammation in inflammatory bowel disease (IBD) is believed to be caused by the dysregulation of the immune system. Dysregulation of the immune system decreases immune tolerance of intestinal bacteria, which induces an abnormal immune response in the form of the overproduction of proinflammatory cytokines and adhesion molecules. Excessive activation of T cells and a reduction in T cell apoptosis also occur.

The treatment goal in ulcerative colitis is the induction and maintenance of remission. The primary drugs used in ulcerative colitis include 5-aminosalicylic acid (5-ASA), steroids, and immunosuppressive drugs such as azathioprine, 6-mercaptopurine (6-MP), the effectiveness of which is supported by well-known clear evidence.[3,4] However, 20% to 40% of ulcerative colitis patients do not respond to conventional medications and may receive secondary drug treatment or colectomy. As a result, various biologics that target specific immunological pathways have been studied as potential therapeutics for ulcerative colitis.[5-7]

Infliximab, an anti-tumor necrosis factor alpha (TNF-α) monoclonal antibody, is the first biologic to have received the U.S. Food and Drug Administration (FDA) approval and to be clinically used for ulcerative colitis. Recently, the TNF antagonists adalimumab and golimumab have shown significant effectiveness in large scale clinical studies, and have been in use since receiving FDA approval. Other biologics with different mechanisms have also been introduced. Recently, vedolizumab, integrin receptor antagonist, was approved by the FDA. In addition, etrolizumab, another integrin receptor antagonist and tofacitinib, Janus kinase (JAK) inhibitor are emerging as new medications. This paper presents a variety of biological agents in ulcerative colitis on the basis of the results of the studies reported so far.

TNF ANTAGONISTS

TNF-α is an inflammatory cytokine that is involved in host defense, inflammation, apoptosis, stimulation of lymphocytes,

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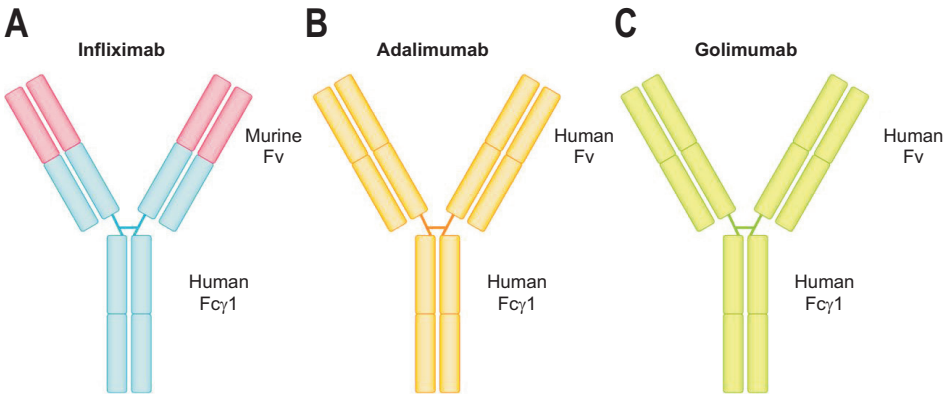

Fig. 1. Molecular structure of the three tumor necrosis factor antagonists for ulcerative colitis treatment.[7] (A) Infliximab. (B) Adalimumab. (C) Golimumab.
Fc, crystalline fragment; Fv, variable fragment; Fcγ1, human immunoglobulin G1 Fc fragment.

bone metabolism, T-B lymphocyte interaction, lymphoid organ development, and activation of immune cell functions. TNF-α is the most important cytokine that mediates intestinal tract inflammation and the expression of TNF-α increases in IBD.

Infliximab was the first TNF inhibitor to be developed and is a chimeric immunoglobulin G (IgG) monoclonal antibody against TNF-α. It is composed of a combination of human and murine proteins. The IgG molecule is composed of two identical light chains and two identical heavy chains that form a polypeptide structure (Fig. 1).[8] The IgG antibody contains two domains that are composed of the constant region Fc and the variable region Fab, which binds to the antigen. The Fab region (VK and VH domains) that binds to TNF originates from mice, whereas the Fcγ1 isotope region is of human origin; the regions comprise approximately 25% and 75% of infliximab, respectively. The Fc region binds to both soluble and cellular membrane-bound TNF.

Adalimumab is a recombined IgG1 anti-TNF-α monoclonal antibody that, unlike infliximab, is produced in a form present in the human body and thus has lower immunity. Adalimumab is the first 100% fully human monoclonal antibody against TNF and is structurally similar to the human IgG1.

Golimumab is a monoclonal antibody against TNF with a lowered immunity that was recombined into a form present in the human body. Golimumab inhibits the functions of soluble and cellular membrane-bound TNF.

1. Infliximab

Infliximab, a chimeric IgG1 monoclonal antibody for TNF-α, was the first biologic developed for IBD. Infliximab binds to the soluble or cellular membrane-bound TNF-α and fixes complement to induce cytotoxicity and T cell apoptosis. Early studies of infliximab had small sample sizes and showed mixed results. In small randomized placebo-controlled studies, infliximab showed no significant difference from placebo in steroid-resistant severe ulcerative colitis patients.[9]

However, in 2005, two large-scale multicenter randomized studies known as the Active Ulcerative Colitis Trial 1 and 2 (ACT 1 and ACT 2, respectively) showed different results (Table 1).[10] ACT 1 targeted moderate-to-severe ulcerative colitis patients who had not responded to or tolerated steroid or immunosuppressive treatments. ACT 2 targeted moderate-to-severe ulcerative colitis patients who had not responded to or tolerated steroids, immunosuppressant, and 5-ASA treatments. In both studies, subjects were divided into placebo, infliximab 5 mg/kg/iv, and infliximab 10 mg/kg/iv infusion groups, with study drugs administered at 0, 2, and 6 weeks, and then at 8-week intervals for a total of 46 weeks (ACT 1) or 22 weeks (ACT 2). Clinical response was defined as a Mayo score decline of 3 points or more and either a 30% or more relative decrease from baseline with at least 1 point decrease in rectal bleeding or a rectal bleeding score of 0 or 1. Clinical remission was defined as a Mayo score of 0–2 with each component subscore not exceeding 1. Mucosal healing was defined as an endoscopic score of 0–1. At week 8, the clinical response rates in the placebo, infliximab 5 mg/kg, and infliximab 10 mg/kg groups were 37.2%, 69.4%, and 64.5%, respectively, in ACT 1, and 29.3%, 64.5%, and 69.2%, respectively, in ACT 2. All infliximab-treated groups showed significant improvement over the placebo group. At week 30, the infliximab-treated groups showed significant improvements of 47.1% to 60.0% in clinical response rates compared to a 26.0% response in the placebo group. At weeks 8, 30, and 54 (ACT 1), the infliximab 5 mg/kg and infliximab 10 mg/kg groups showed significantly higher clinical remission rates and mucosal healing rates than the placebo group. There was a higher frequency of steroid-free remissions in the infliximab groups than the placebo group, with 22.3% and 7.2% steroid-free remissions at week 30, respectively, and 20.9% and 8.9% steroid-free remissions at week 54, respectively. Steroid dose reductions were also more frequent in the infliximab groups than the placebo group. No great difference was observed between the 5 mg/kg and 10 mg/kg doses of infliximab, indicating that 5 mg/kg is the suitable dosage for ulcerative colitis, given safety and economic factors.

A post-hoc analysis of ACT 1 and ACT 2 data was conducted to examine the relationship between serum infliximab levels and clinical outcomes. When serum infliximab concentrations were divided into quartiles, significant increases in clinical remission, clinical response, and mucosal healing were observed

Table 1. Clinical Trials Evaluating the Efficacy of Different Biologics in Patients with Ulcerative Colitis

Drug	Study	Study population	Study protocol	Primary endpoint	Efficiency
Infliximab	ACT 1[10]	N=364 Moderately to severely active UC (Mayo: 6–12)	5 mg/kg IV at week 0, 2, and 6	Clinical response at week 8	69.4% (IFX 5 mg/kg)
			5 mg/kg IV every 8 weeks after induction until week 46	Clinical response at week 54	45.5% (IFX 5 mg/kg)
	ACT 2[10]	N=364 Moderately to severely active UC (Mayo: 6–12)	5 mg/kg IV until week 22	Clinical response at week 8	64.5% (IFX 5 mg/kg)
				Clinical response at week 30	47.1% (IFX 5 mg/kg)
Adalimumab	ULTRA 1[25]	N=576 Moderately to severely active UC	160, 80, 40, 40 mg SC every 2 weeks	Clinical remission at week 8	18.5% (ADA 160 mg)
	ULTRA 2[26]	N=494 Moderately to severely active UC	40 mg SC every 2 weeks after induction	Clinical remission at week 8	16.5% (ADA 160 mg)
				Clinical remission at week 52	17.3% (ADA 160 mg)
Golimumab	PURSUIT-SC[28]	N=1,065 Moderately to severely active UC	200 mg at week 0 then 100 mg SC, at week 2	Clinical response at week 6	51.0% (GLM 100 mg)
	PURSUIT-Maintenance[29]	N=464 Moderately to severely active UC	100 mg SC every 4 weeks after induction	Clinical response at week 54	49.7% (GLM 100 mg)
Vedolizumab	GEMINI 1[5]	N=895 Moderately to severely active UC (Mayo: 6–12)	300 mg IV every 4 or 8 weeks/52 weeks	Clinical response at week 6	47.1% (VDZ 300 mg at week 0 & 2)
				Clinical response at week 52	44.8% (VDZ 300 mg every 4 weeks)
					41.8% (VDZ 300 mg every 8 weeks)
Etrolizumab	Eucalyptus[32,33]	N=124 Moderately to severely active UC	100 mg SC at week 0, 4, and 8 or 420 mg LD then 300 mg at week 2, 4, and 8	Clinical remission at week 10	21% (etrolizumab 100 mg)
					10% (etrolizumab 300 mg plus LD)
Tofacitinib	Sandborn *et al*.[6]	N=194 Moderately to severely active UC	15 mg bid for 8 weeks	Clinical response at week 8	78% (tofacitinib 15 mg bid)

ACT, Active Ulcerative Colitis Trial; UC, ulcerative colitis; IFX, Infliximab; IV, intravenous; ULTRA, Ulcerative Colitis Long-Term Remission and Maintenance with Adalimumab; SC, subcutaneous; ADA, adalimumab; PURSUIT-SC, Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment-Subcutaneous; GLM, golimumab; VDZ, vedolizumab; LD, loading dose; bid, twice a day.

at week 30 and 54 at the higher quartiles of infliximab concentration.[11]

A follow-up analysis of the tested patient outcomes from ACT 1 and ACT 2 was performed to investigate one of the primary goals of ulcerative colitis treatment: avoiding colectomy. The results showed that at week 54, the cumulative incidence rate of colectomy was 10% in the infliximab groups and 17% in the placebo group, indicating that infliximab treatment reduced the risk of colectomy by 7%.[12] In terms of hospitalizations related to ulcerative colitis through 54 weeks, there was an incidence of 20 events per 100 patient-years in the infliximab group and 40 events per 100 patient-years in the placebo group, showing a significantly lower rate in the infliximab group.[12] On the other hand, to date, no randomized controlled studies evaluated infliximab's efficacy in relapse prevention and safety in inactive ulcerative colitis cases. Although ACT 1 and ACT 2 reported relapse rates, infliximab's effect on relapse prevention in inactive ulcerative colitis cannot be determined with certainty, since

no further random reassignment to infliximab or placebo took place after week 8.

Because infliximab is a chimeric monoclonal antibody with a protein sequence that is 75% human and 25% mouse, human antichimeric antibody (HACA) formation can occur in the blood. The presence of HACA has been associated with an increased risk of infusion reactions upon drug administration and reduced clinical efficacy. During the ACT trials, 17 of the 484 patients treated with infliximab showed severe adverse events, including eight cases of pneumonia, tuberculosis, and histoplasmosis, four cases of cancer, and three cases of neurologic event (two cases of optic neuritis and one case of multifocal motor neuropathy). So far, the known common side effects of infliximab are acute infusion reaction, severe serum sickness, infection such as reactivation of tuberculosis, and lymphoma. Less common side effects include demyelinating disorders and optic neuritis. Since most infliximab-treated patients receive simultaneous steroids or immunomodulators, they should be prescreened for tuberculosis if living in areas where tuberculosis is endemic. However, as a review of its currently registered safety profile for the infliximab revealed no increase in cancer incidence rates and similar rates of serious infection and mortality compared to other treatments, infliximab may be considered a relatively safe treatment for clinical use.[13]

The UC SUCCESS study enrolled 239 moderate-to-severe ulcerative colitis patients who did not respond to 5-ASA or steroid treatment, assigned them to treatment with azathioprine, infliximab, or azathioprine plus infliximab, and observed them for 16 weeks.[14] At week 16, the primary endpoint of corticosteroid-free remission rate was higher in the infliximab plus azathioprine group than in the azathioprine and infliximab groups (39.7%, 23.7%, and 22.1%, respectively). In addition, the posttreatment clinical response rate was significantly higher in the infliximab group and the infliximab plus azathioprine group as compared to the azathioprine group (68.8%, 76.9%, and 50.0%, respectively). Mucosal healing rates also showed significantly higher increases in the infliximab group and the infliximab plus azathioprine group as compared to the azathioprine group (54.6%, 62.8%, and 36.8%, respectively). Therefore, infliximab and azathioprine combination therapy was proven to be effective in moderate-to-severe ulcerative colitis patients, similar to what was observed in the Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC).[15]

Ulcerative colitis patients who experience bloody diarrhea more than 6 times a day along with dehydration, tachycardia, severe pain, and increased C-reactive protein (CRP) require hospitalization and treatment.[16] Such acute cases of severe ulcerative colitis represent a very serious condition, and the primary treatment is intravenous steroids. However, if an appropriate response is not observed within 7 to 10 days, another treatment or an emergency colectomy is recommended. If the patient shows rapid deterioration, such as toxic megacolon or uncontrolled bleeding, surgery must be considered as the preferred course of action.

In severe ulcerative colitis patients who show no response to steroids and in whom cytomegalovirus infection has been excluded, calcineurin inhibitor such as cyclosporine 2 mg/kg or infliximab 5 mg/kg may be administered intravenously. However, it is uncertain which medication is more effective in inducing remission. In particular, the side effects and long-term efficacy of cyclosporine have been debated by clinicians. A randomized study of steroid-refractory severe ulcerative colitis patients was performed to evaluate the impact of infliximab rescue therapy on colectomy avoidance.[17] Three months after randomization for the administration of infliximab or placebo, the infliximab group showed a significantly lower colectomy rate than the placebo group (29% vs 67%) with fewer postoperative complications. In the recent Study Comparing Cyclosporine with Infliximab in Steroid-refractory Severe Attacks of Ulcerative Colitis (CYSIF), 115 severe ulcerative colitis patients who did not respond to steroids were randomly assigned to receive cyclosporine or infliximab and observed for 14 weeks.[18] There were no significant differences between the cyclosporine and infliximab groups in clinical response rates at day 7 (86% vs 84%, p=0.76) or treatment failure rates (60% vs 54%, p=0.52). There were no differences in the incidence of severe adverse events between the groups. These results indicate that infliximab is equally effective to cyclosporine in achieving short-term remission and avoiding colectomy in severe ulcerative colitis patients who do not respond to steroids.

Recently, a multicenter retrospective study of the efficacy and safety of infliximab in Korean ulcerative colitis patients was reported.[19] After infliximab treatment, 134 moderate-to-severe ulcerative colitis patients showed a clinical response rate of 87% and remission rate of 45% at week 8. Compared to results observed in Western populations, infliximab was effective as in the West. Four statistically significant predictors to increase the likelihood of clinical remission at week 8 were: no prior use of immunomodulator, CRP $\geq$3 mg/dL, Hb $\geq$11.5 g/dL, and clinical response to infliximab at week 2. Adverse events related to infliximab were observed in 15% of the cases, but most were mild and transient, indicating that infliximab was an effective and safe treatment for patients with active ulcerative colitis. In another single center retrospective study conducted in Korean moderate-to-severe ulcerative colitis patients, the clinical response rate of infliximab treatment at week 8 was 66%, similar to the ACT 1 and ACT 2 study results.[20] The predictors of nonresponse to infliximab were severe disease with a Mayo score of 11 or higher and a history of cytomegalovirus colitis within three months of infliximab treatment. In contrast, the recent study including 33 Korean moderate-to-severe ulcerative colitis patients treated with infliximab, the clinical remission rate at least once was about 70% and the remission group showed a higher Mayo score at baseline than nonremission group

(11.0±0.9 vs 9.9±1.5, p=0.04).[21]

In 40% of the patients, repeated treatment with an anti-TNF agent resulted in diminished efficacy. It is suspected that this may be due to the production of autoantibodies against the chimera, and diminished efficacy was more frequent when the treatment regimen was episodic.[22] In addition to the immunogenicity, the increases in the metabolic activities and excretions of drugs may also be causes. To minimize the decrease in treatment efficacy over time, immunomodulators are taken with anti-TNF agents to suppress the production of autoantibodies. Experts have used serum infliximab concentrations and the presence of anti-infliximab antibodies to develop a treatment algorithm for IBD.[23,24] It is recommended that HACA-positive patients should be switched to another anti-TNF agent, and if no response is observed, other medications with a mechanism different from that of anti-TNF agents should be used. If the infliximab concentration is low, it should be increased. If the infliximab concentration is high, endoscopy or other imaging tests should be performed to determine whether the disease is active, followed by a switch to another medication with a mechanism different from that of the anti-TNF agent. In regions where anti-drug antibody and serum drug concentration measurements cannot be made, nonresponsive patients can be given an increased level of 10 mg/kg or shorter administration intervals can be used to increase the response rate. If these methods fail, switching to another anti-TNF agent is possible.

2. Adalimumab

Adalimumab is a totally humanized recombinant monoclonal IgG1 antibody that, like infliximab, binds to the soluble or cellular membrane TNF-α and fixes complement to induce cytotoxicity and T cell apoptosis. Adalimumab differs from infliximab in that it is injected subcutaneously and the treatment is administered in 2-week intervals. In ulcerative colitis patients with intolerance to 5-ASA or steroids, adalimumab is another treatment option.

In two randomized, phase III clinical studies known as Ulcerative Colitis Long-Term Remission and Maintenance with Adalimumab I and II (ULTRA 1 and ULTRA 2, respectively), the safety and efficacy of adalimumab was evaluated in patients who had moderate-to-severe active ulcerative colitis despite having previously received or currently receiving concurrent treatment with corticosteroids and/or immunosuppressants such as azathioprine or 6-MP.[25,26] The ULTRA 1 study only enrolled patients with no history of anti-TNF agent therapy, while the ULTRA 2 study allowed enrollment of patients who did not respond to or tolerate anti-TNF agents. Among patients enrolled in the ULTRA 2 study, 40% had previously used other anti-TNF agents. In ULTRA 1 and ULTRA 2, the coadministration of stable dosages of 5-ASA and immunomodulators was allowed. The primary endpoint of clinical remission at week 8 was evaluated in both the ULTRA 1 and the ULTRA 2 studies. In ULTRA 2, clinical remission at week 52 and sustained clinical remission were evaluated together. In the ULTRA 1 study, 390 patients who did not receive anti-TNF agent treatment were randomly assigned to one of three treatment groups for preliminary analysis. The adalimumab 160/80 mg group was given adalimumab 160 mg at week 0 and adalimumab 80 mg at week 2. The adalimumab 80/40 mg group was given adalimumab 80 mg at week 0 and adalimumab 40 mg at week 2. Both groups were compared to the placebo group. Afterwards, patients in both adalimumab treatment groups were given adalimumab 40 mg every other week.

In ULTRA 2, 494 patients were randomly selected and given adalimumab 160 mg at week 0 and adalimumab 80 mg at week 2, followed by adalimumab 40 mg every other week from week 4 to week 50, and compared to the placebo group. From week 8 on, tapering of the steroid was allowed.

In both the ULTRA 1 and ULTRA 2 studies, patients in the adalimumab 160/80 mg group showed statistically significant increases in the induction of clinical remission as compared to the placebo group. In ULTRA 1, the clinical remission rate at week 8 was 18.5% in the adalimumab 160/80 mg group, 10.0% in the adalimumab 80/40 mg group, and 9.2% in the placebo group. The rate was significantly higher in the adalimumab 160/80 mg group, and there was no statistically significant difference between the adalimumab 80/40 mg group and the placebo group. Furthermore, in ULTRA 2, the adalimumab 160/80 mg group showed a significantly higher clinical remission rate at week 8 than that of the placebo group (16.5% vs 9.3%), and a significantly higher clinical remission rate at week 52 (17.3% vs 8.5%).

A comparison of clinical remission rates using partial Mayo scores up to week 8 revealed that the effectiveness of adalimumab did not plateau, indicating the possibility that most of adalimumab's remission-inducing efficacy would become apparent after 8 weeks. This difference from infliximab, most of the remission-inducing efficacy of which is reached by 2 weeks, is notable.

In the ULTRA 2 study, clinical response was significantly higher in the adalimumab 160/80 mg group than in the placebo group both at week 8 (50.4% vs 34.6%) and week 52 (30.2% vs 18.3%). The mucosal healing rate was also significantly higher in the adalimumab group than in the placebo group both at week 8 (41.1% vs 31.7%) and week 52 (25.0% vs 15.4%).

In the ULTRA 2 study, the clinical remission induction rate among patients who have previously used anti-TNF agents was 9.2% in the adalimumab group and 6.9% in the placebo group, showing that the clinical remission induction efficacy in this subgroup is lower than that in the general study population. With respect to sustained clinical remission and clinical remission at week 52, the results were similar for both anti-TNF agent users and the general study population. The incidence rate of serious adverse events was 12% in both the adalimumab and

placebo groups, and the incidence rate of serious infections was 1.6% in the adalimumab group and 1.9% in the placebo group, with no significant differences between the groups.

In contrast to the UC SUCCESS study of infliximab, the usefulness of combination therapy using adalimumab with an immunosuppressant still lacks established results, and requires further prospective evaluation and validation.

The results of a poststudy analysis of patient data from ULTRA 1 and ULTRA 2 showed that ulcerative colitis-related, ulcerative colitis- or drug-related, and all-cause hospitalizations in the adalimumab group were reduced by 50%, 47%, and 40%, respectively, compared to the placebo group.[27] The overall rate of colectomy in ULTRA study patients was reduced by 5% due in part to adalimumab rescue therapy, but no significant difference was observed between the adalimumab and placebo groups. Adalimumab can be self-administered at home by the patient or the patient's family member who has received instruction by health professional.

3. Golimumab

Golimumab is a fully human IgG1 monoclonal antibody that targets TNF-α, and is used as a treatment for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. The recent Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment-Subcutaneous (PURSUIT-SC) induction study included a double-blind phase II trial conducted to determine the permissible dose range of golimumab in moderate-to-severe ulcerative colitis patients.[28] A phase III trial was also conducted to confirm the dose range. In the phase III trial, the patients were divided into three groups: one group was given a 200 mg golimumab loading dose subcutaneously, then 100 mg golimumab 2 weeks later; the other treatment group was given 400 mg golimumab subcutaneously, then 200 mg golimumab 2 weeks later. Both groups were compared to a placebo group. The primary endpoint of clinical response at week 6 was 51.0% in the golimumab 200/100 mg group, 54.9% in the golimumab 400/200 mg group, and 30.3% in the placebo group.

The PURSUIT-Maintenance study was a phase III study that examined the efficacy of golimumab as maintenance therapy for moderate-to-severe ulcerative colitis patients, in which the study subjects were patients who completed golimumab induction studies including the PURSUIT-IV or PURSUIT-SC study.[29] The subjects received placebo, golimumab 50 mg, or golimumab 100 mg administered subcutaneously every 4 weeks through 52 weeks. During the 54 weeks of treatment, the golimumab 50 mg group maintained a clinical response of 47.0% and the golimumab 100 mg group maintained a response of 49.7%, both of which were significantly higher than the 31.2% response in the placebo group. Clinical remission rates at both week 30 and 54 were significantly higher in the golimumab 100 mg group compared to the placebo group (27.8% vs 15.6%, p=0.004), but not in the golimumab 50 mg group compared to the placebo group (23.2% vs 15.6%, p=0.122). The mucosal healing rates at both week 30 and 54 were 42.4% and 41.7% in the golimumab 100 mg and 50 mg groups, respectively, both of which were higher than the 26.6% healing rate in the placebo group. Serious adverse events occurred in 7.7%, 8.4%, and 14.3% of the placebo, golimumab 50 mg, and golimumab 100 mg groups, respectively. Serious infections occurred in 1.9%, 3.2%, and 3.2%, respectively. In the golimumab-treated groups, golimumab did not pose any new safety issues compared to its use in other indications. For induction therapy, the FDA recommends administering 200 mg of golimumab subcutaneously and 100 mg of golimumab 2 weeks later. For maintenance therapy, the FDA recommends administering 100 mg every 4 weeks. The European Medicines Agency (EMA) advised the administration of golimumab 50 mg every 4 weeks as maintenance therapy in patients with less than 80 kg because golimumab 100 mg is considered to have the higher risk of serious adverse drug reaction compared to 50 mg.

ADHESION MOLECULE ANTAGONISTS

Lymphocyte migration and recruitment within the intestinal mucosa is an important process in the initiation and maintenance of intestinal inflammation. The adhesion of leukocytes with the endothelial cells is mediated by integrin, chemokine receptors and endothelial adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and mucosal addressin cell adhesion molecule 1 (MAdCAM-1), which are overexpressed in IBD. Adhesion molecule inhibitors interfere with the adhesive interactions of endothelial cells and circulating immune cells, reducing the mobility of the immune cells. This medication has the potential to reduce chronic inflammation.

Natalizumab, a chimeric recombinant humanized IgG4 antibody, is one such inhibitor and acts against the α4 subunit of leukocyte adhesion molecules α4β7 integrin and α4β1 integrin. The α4β1 integrin interacts with VCAM-1.

Vedolizumab (MLN-0002) is an α4β7 integrin binding IgG1 humanized monoclonal antibody that suppresses leukocyte adhesion by blocking the interaction between MAdCAM-1 and α4β7 integrin. The biggest difference between natalizumab and vedolizumab is that natalizumab suppresses leukocyte trafficking in multiple organs including the brain, whereas vedolizumab specifically acts only on α4β7, selectively suppressing lymphocyte trafficking exclusively in the gastrointestinal tract. αEβ7 integrin interacts with E-cadherin, and its expression is increased in intraepithelial lymphocytes in the mucosal epithelium.

Etrolizumab (rhuMAb β7) is a humanized monoclonal IgG1 antibody that acts as an adhesion molecule inhibitor. It targets the β7 subunit of heterodimeric integrins α4β7 and αEβ7 and blocks the interaction between αEβ7 and E-cadherin.

1. Vedolizumab

Inhibitors of leukocyte trafficking in the intestine are touted as the next generation of IBD treatments. These suppress the interaction between the leukocyte and the gastrointestinal vessels, and block the inflammatory cells from entering the intestinal lesions. Although natalizumab, a chimeric recombinant humanized IgG4 antibody against the α4 subunit of leukocyte adhesion molecules, has shown a 48% response rate in a phase III study for Crohn's disease treatment, the risk of JC virus reactivation that can trigger progressive multifocal leukoencephalopathy (PML) was suggested in a subsequent large-scale study.[30,31]

Vedolizumab is a humanized IgG1 monoclonal antibody against α4β7 integrin that inhibits leukocyte adhesion of MAdCAM-1 specific to the bowel. Recently, the results of the GEMINI 1 study, a phase III study of the efficacy of vedolizumab in moderate-to-severe ulcerative colitis, have been reported.[5] At the time of patient randomization, the percentage of patients who have been exposed to a TNF antagonist was limited to 50% and the actual percentage of those who previously received anti-TNF therapy was approximately 48%. The screening took place 3 weeks prior to the start of the study, which included a total of 895 participants. Cohort 1 was formed via blind randomization, with 375 patients assigned to the placebo group and vedolizumab group in a 2:3 ratio. Vedolizumab group patients received two intravenous infusions of vedolizumab 300 mg over about 30 minutes, at week 0 and week 2, and were evaluated at week 6. At week 6, the clinical response was 47.1% in the vedolizumab and 25.5% in the placebo group. The clinical remission rates at week 6 were 16.9% in the vedolizumab group and 5.4% in the placebo group. The mucosal healing rates at week 6 were 40.9% in the vedolizumab group and 24.8% in the placebo group. The maintenance phase took place from week 6 to week 52. In order to meet the required sample size, an additional 521 open-label patients were recruited and identically treated with vedolizumab. The maintenance phase included 373 patients, which showed a clinical response at week 6, the primary outcome of the induction phase. They were randomized in a 1:1:1 ratio to receive 52 weeks of treatment with placebo, 300 mg of vedolizumab every 4 weeks, or 300 mg of vedolizumab every 8 weeks.

The rate of clinical remission at week 52 differed significantly between the treatment groups receiving vedolizumab 300 mg every 4 or 8 weeks and the placebo group (44.8% and 41.8% vs 15.9%). The clinical response and mucosal healing rates at week 52 differed significantly between the vedolizumab-treated group and the placebo group, but not between the group dosed at 4-week intervals and the group dosed at 8-week intervals. Glucocorticoid-free remission was 45.2% in the group receiving vedolizumab every 4 weeks, 31.4% in the group treated every 8 weeks, and 13.9% in the placebo group, with the greatest difference between the 4-week dosing interval group and the placebo group.

Vedolizumab specifically suppresses the gut-trophic α4β7 heterodimer and does not affect the α4β1 associated with leukocyte transport in the central nervous system, which reduces the risk of PML. During this study, not a single case of PML was detected. Furthermore, when examining the incidences of side effects, no differences in the rates of serious adverse events or serious infections were observed compared to the placebo group, and no anaphylaxis or serum sickness was observed. Whether or not the group with a history of TNF antagonist treatment failure showed any vedolizumab response is unknown, as the subgroup analysis has yet to be published. Additional studies are needed to determine what role vedolizumab will play in the ulcerative colitis treatment algorithm. Recently, vedolizumab was approved by the FDA for the treatment of moderate to severe ulcerative colitis adult patients which are not responding to one or more conventional treatment such as steroids, immunosuppressive agents, or TNF blocker.

2. Etrolizumab

Etrolizumab is a humanized IgG1 monoclonal antibody against the β7 subunit of α4β7 and αEβ7. It is used as an adhesion molecule inhibitor. Eucalyptus is a phase II induction study of etrolizumab in 124 patients with moderate-to-severe ulcerative colitis who did not respond to other medications, the findings of which were recently reported.[32,33] The patients were then randomly assigned to receive subcutaneous injections of 100 mg etrolizumab at week 0, 4, and 8 (etrolizumab 100 mg group) or 300 mg etrolizumab at week 2, 4, and 8 after a 420 mg loading dose (LD) of etrolizumab was subcutaneously injected (etrolizumab 300 mg plus LD group) or placebo. The primary endpoint of clinical remission at week 10 was 21% in the etrolizumab 100 mg group, 10% in the etrolizumab 300 mg plus LD group, and 0% the placebo group. Therefore, the groups that received etrolizumab treatments had higher clinical remission rates at week 10 than the placebo group. In the anti-TNF-naive patients, the clinical remission rate was 44% in the etrolizumab 100 mg group and 25% in the etrolizumab 300 mg plus LD group. However, in the patients with insufficient response with anti-TNF therapy, clinical remission rate in the etrolizumab 100 mg and 300 mg group was 5% and 4%, respectively. High αE gene expression in the colonic tissue taken at baseline was associated with clinical remission and may be the main factor to predict the effect of etrolizumab.

No serious infections were recorded in the etrolizumab-treated groups, and no significant difference between the etrolizumab-treated groups and the placebo group in the frequency of adverse events that warranted treatment discontinuation was observed, indicating that etrolizumab is safe and tolerable. Currently, a phase II open-label extension trial of etrolizumab is underway.

JAK INHIBITOR

The discovery of various cytokines and intracellular messengers as a cause of IBD has led to various research studies of biologics that target these cytokines and intracellular messengers. Tyrosine kinases, such as JAK1 and JAK3, are intracellular molecules that play an important role in the signal transmission of interleukins (ILs). Tofacitinib (CP-690,550), a JAK inhibitor that can block downstream signaling pathway and can be taken orally, was developed.

1. Tofacitinib

Tofacitinib represents a new class of JAK inhibitor that inhibits JAK1, JAK2, and JAK3 to modulate the signaling of IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 receptors that are associated with six types of cytokine functions that integrate lymphocyte activation, function, and proliferation. In addition, by inhibiting JAK1, tofacitinib blocks the activities of proinflammatory cytokines including IL-6 and interferon γ, and by inhibiting JAK2, it blocks the signaling to erythropoietin. Because of its varied anti-inflammatory actions, tofacitinib is currently used in allograft rejection prevention, rheumatoid arthritis, and psoriasis.

Recently, a phase II, double-blind, placebo-controlled study evaluated the effects of tofacitinib administration for 8 weeks in 194 moderate-to-severe ulcerative colitis patients who did not respond to steroids, immunosuppressives, or anti-TNF agents.[6] Patients were assigned to one of five treatment groups: tofacitinib 0.5 mg, 3 mg, 10 mg, 15 mg, or placebo in a 2:2:2:3:3 ratio. For 8 weeks, medications were taken twice daily, and the patients were followed for another 4 weeks.

The primary endpoint of clinical response rate at week 8 was 42% in the placebo group and 32%, 48%, 61%, and 78% in the tofacitinib 0.5 mg, 3 mg, 10 mg, and 15 mg twice daily groups, respectively ($p=0.39$, $p=0.55$, $p=0.10$, and $p<0.001$), showing a statistically significant difference only for the 15 mg twice daily group. The clinical remission rate at week 8 was 10% in the placebo group and 13%, 33%, 48%, and 41% in the tofacitinib groups, respectively, in order of increasing dosage, with the 10 mg and 15 mg twice daily groups showing statistically significant differences (all $p<0.001$). Tofacitinib dose-dependent increases in low-density lipoprotein cholesterol and high-density lipoprotein cholesterol were observed, and neutropenia which means absolute neutrophil count less than 1,500 per cubic mm was detected in three patients. In terms of serious adverse events, a single case each of postoperative abscess and anal abscess occurred in the 10 mg group. In conclusion, this study confirmed that tofacitinib was more effective than placebo in bringing about clinical response and clinical remission in moderate-to-severe ulcerative colitis patients.

In patients with active ulcerative colitis who do not respond to anti-TNF agents, tofacitinib shows clinical importance in that it can easily induce clinical response and clinical remission. However, since there have been no reports to date on remission maintenance with tofacitinib and only short-term side effects have been investigated, additional large-scale studies will be needed in the future to gather evidence regarding high remission maintenance and safety. Through this process, the role of tofacitinib in treating ulcerative colitis patients who do not respond to anti-TNF agents will be determined.

APPROVAL AND USAGE STATUS OF BIOLOGICS

The biologics which can be used in ulcerative colitis are different according to the countries. Golimumab was approved in the European Union, Canada, Switzerland, Russia, the United States, South Korea, and other countries.

In the United Kingdom, only infliximab is recommanded in the acute severe ulcerative colitis according to NICE guideline.[34] Other European countries such as Greece, France, Italy, Spain, Sweden, etc., infliximab, adalimumab, and golimumab are available for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or azathioprine, or who are intolerant to or have medical contraindications for such therapies. Recently, vedolizumab was approved for moderate to severe ulcerative colitis by the EMA.

In the United States, infliximab, adalimumab, and golimumab are available in patients with moderately to severely active disease who have had an inadequate response to conventional therapy. The FDA approved vedolizumab recently.

In Japan, infliximab and adalimumab can be used in patients with moderate to severe ulcerative colitis inadequate response to conventional therapy.

The biologics which can be used for ulcerative colitis in South Korea are infliximab and adalimumab.[35] Golimumab is expected to be available soon in South Korea.

CONCLUSIONS

The introduction of biologics for the treatment of IBD has changed the treatment paradigm for moderate-to-severe ulcerative colitis. With the use of anti-TNF agents, mucosal healing is now regarded as the treatment goal. Furthermore, interest in combination therapy using immunomodulators with anti-TNF agents, as well as in monitoring dosing for optimal results, is increasing. Recently, the anti-adhesion therapy of vedolizumab and etrolizumab with the JAK inhibitor tofacitinib have emerged in addition to the anti-TNF agent golimumab. In the treatment of ulcerative colitis, the introduction of such drugs, along with anti-TNF agents with already-proven effects, will advance new strategies of determining the order of treatment administration as well as making surgical decisions.

CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article are reported.

REFERENCES

1. Aratari A, Papi C, Clemente V, et al. Colectomy rate in acute severe ulcerative colitis in the infliximab era. Dig Liver Dis 2008;40:821-826.
2. Turner D, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. Clin Gastroenterol Hepatol 2007;5:103-110.
3. Stange EF, Travis SP. The European consensus on ulcerative colitis: new horizons? Gut 2008;57:1029-1031.
4. Choi CH, Kim YH, Kim YS, et al. Guidelines for the management of ulcerative colitis. Intest Res 2012;10:1-25.
5. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013;369:699-710.
6. Sandborn WJ, Ghosh S, Panes J, et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med 2012;367:616-624.
7. 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.
8. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. Pharmacol Ther 2008;117:244-279.
9. Probert CS, Hearing SD, Schreiber S, et al. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. Gut 2003;52:998-1002.
10. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462-2476.
11. Reinisch W, Feagan BG, Rutgeerts PJ, et al. Infliximab concentration and clinical outcome in patients with ulcerative colitis. Gastroenterology 2012;142(5 Suppl 1):S-114.
12. Sandborn WJ, Rutgeerts P, Feagan BG, et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. Gastroenterology 2009;137:1250-1260.
13. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. Clin Gastroenterol Hepatol 2006;4:621-630.
14. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology 2014;146:392-400.e3.
15. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362:1383-1395.
16. Hart AL, Ng SC. Review article: the optimal medical management of acute severe ulcerative colitis. Aliment Pharmacol Ther 2010;32:615-627.
17. Järnerot G, Hertervig E, Friis-Liby I, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 2005;128:1805-1811.
18. Laharie D, Bourreille A, Branche J, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet 2012;380(9857):1909-1915.
19. Lee KM, Jeen YT, Cho JY, et al. Efficacy, safety, and predictors of response to infliximab therapy for ulcerative colitis: a Korean multicenter retrospective study. J Gastroenterol Hepatol 2013;28:1829-1833.
20. Park SH, Yang SK, Hong SM, et al. Severe disease activity and cytomegalovirus colitis are predictive of a nonresponse to infliximab in patients with ulcerative colitis. Dig Dis Sci 2013;58:3592-3599.
21. Seo HI, Park DI, Kim TO, et al. The effect of infliximab on patients with ulcerative colitis in Korea. Intest Res 2014;12:214-220.
22. Miheller P, Kiss LS, Lorinczy K, Lakatos PL. Anti-TNF trough levels and detection of antibodies to anti-TNF in inflammatory bowel disease: are they ready for everyday clinical use? Expert Opin Biol Ther 2012;12:179-192.
23. Afif W, Loftus EV Jr, Faubion WA, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol 2010;105:1133-1139.
24. Bendtzen K, Ainsworth M, Steenholdt C, Thomsen OØ, Brynskov J. Individual medicine in inflammatory bowel disease: monitoring bioavailability, pharmacokinetics and immunogenicity of anti-tumour necrosis factor-alpha antibodies. Scand J Gastroenterol 2009;44:774-781.
25. 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.
26. 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.e1.
27. Feagan BG, Sandborn WJ, Lazar A, et al. Adalimumab therapy is associated with reduced risk of hospitalization in patients with ulcerative colitis. Gastroenterology 2014;146:110-118.e3.
28. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014;146:85-95.
29. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014;146:96-109.e1.

30. Chen Y, Bord E, Tompkins T, et al. Asymptomatic reactivation of JC virus in patients treated with natalizumab. N Engl J Med 2009; 361:1067-1074.
31. Targan SR, Feagan BG, Fedorak RN, et al. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. Gastroenterology 2007;132:1672-1683.
32. Vermeire S, O'Byrne S, Keir M, et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. Lancet 2014;384:309-318.
33. Vermeire S, O'Byrne S, Williams M, et al. Differentiation between etrolizumab (rhumab beta7) and placebo in the eucalyptus phase II randomized double-blind placebo-controlled induction study to evaluate efficacy and safety in patients with refractory moderate-to-severely active ulcerative colitis. Gastroenterology 2013;144(5 Suppl 1):S36.
34. Stenke E, Hussey S. Ulcerative colitis: management in adults, children and young people (NICE Clinical Guideline CG166). Arch Dis Child Educ Pract Ed 2014;99:194-197.
35. Health Insurance Review & Assessment Service [Internet]. Seoul: Health Insurance Review & Assessment Service; c2013 [cited 2014 Jun 21]. Available from: http://www.hira.or.kr.