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# Biologic Therapy Options for Crohn's Disease

Shunji ISHIHARA[1,2], Yoshiyuki MISHIMA[1], Kousaku KAWASHIMA[1,2]
[1]*Department of Internal Medicine II, Shimane University Faculty of Medicine, Izumo, 693-8501, Japan*
[2]*IBD Center, Shimane University Hospital, Izumo, 693-8501, Japan*
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Crohn's disease（CD）is an immune-mediated inflammatory intestinal disease of unknown etiology. In addition to conventional drugs such as 5-aminosalicylates（5-ASA）, corticosteroids, and immune-modulating drugs, biologics targeting inflammation- and immune-related molecules have been developed for treating CD. Initially, anti-tumor necrosis factor（TNF）-α antibodies were used for induction and maintenance therapies, and the clinical course of affected patients was dramatically changed because of their efficacy and safety. More recently, novel humanized biologics targeting the p40-subunit of interleukin（IL）-12/23 and α4β7-integrin have been developed, and shown to contribute to long-term therapy for CD. Although the efficacy of biologics for CD is widely recognized, how to determine which biologic is appropriate for individual patients remains largely unknown and additional studies are necessary to clarify this issue.

Key words: cystatin C, protease inhibitor, cerebrospinal fluid, inflammatory neurological diseases, neurodegenerative diseases

Corresponding author: Shunji Ishihara, MD, PhD
Department of Internal Medicine II, Shimane University Faculty of Medicine, 89-1 Enya-cho, Izumo, Shimane 693-8501, Japan
Tel: +81-853-20-2190
Fax: +81-853-20-2187
Email: si360405@med.shimane-u.ac.jp

## INTRODUCTION

Crohn's disease（CD）, one of the major forms of inflammatory bowel disease（IBD）, is characterized by a chronic immune-mediated gut disorder. In CD patients, any part of the gastrointestinal tract from the mouth to anus can be involved by transmural inflammation. The main symptoms of CD are diarrhea, melena, fever, and body weight loss, and particularly complicated anal abscesses often develop, causing distress for the patient.

The pathogenesis of CD is dependent on poorly understood complex interactions among host genetics, immunity, microbiome, and nutrients（diet composition）. Altered immune response to gut microbiota may be a primary determinant of disease risk, and can lead to chronic and excess gut immune activation［1-3］. Although numerous studies have attempted to clarify these issues, most details regarding the disease etiology of CD remain unknown.

Conventional treatment regimens for affected patients are based on suppression of excess gut inflammation, such as use of an elementary diet, 5-aminosalicylates（5-ASA）, corticosteroids, or immune-modulating drugs［4］. However, those treatments are generally insufficient to control disease activity. As a result, anti-tumor necrosis factor（TNF）-α antibodies including infliximab（IFX）and adalimumab（ADA）were developed, and the clinical course of CD was substantially changed by providing symptom relief as well as mucosal healing in affected patients［5-10］. In addition, novel biologics other than anti-TNF-α antibodies, such as monoclonal antibodies including ustekinumab（UST）［11-14］and vedolizumab（VDZ）［(15-17), have been recently developed, and shown to suppress intestinal inflammation by blocking targeted immune-related molecules［18］. The purpose of this review article is to report known pharmacological characteristics and findings showing the efficacy of each biologics ther-

apy option available for treatment of CD patients. In addition, the influence of the immunogenicity of biologics on loss of response during maintenance therapy is discussed.

## Anti-TNF-α antibodies

### *IFX*

**Structure and anti-inflammatory mechanisms**

TNF-α is a key proinflammatory cytokine involved in the pathogenesis of various immune-related diseases including CD and rheumatoid arthritis (RA). As a therapeutic for targeting this molecule, a monoclonal antibody, IFX, was generated as a chimeric monoclonal IgG antibody composed of murine variable (25%) and human constant (75%) regions (Fig. 1) [5]. IFX binds to soluble type TNF-α and exerts inflammation by neutralizing cytokine activity, while this monoclonal antibody also binds to the membrane-bound precursor of TNF-α [19, 20] and induces apoptosis in TNF-α-producing immune cells, including T cells and macrophages (Fig. 1). Such mechanisms contribute to suppression of gut inflammation in CD patients.

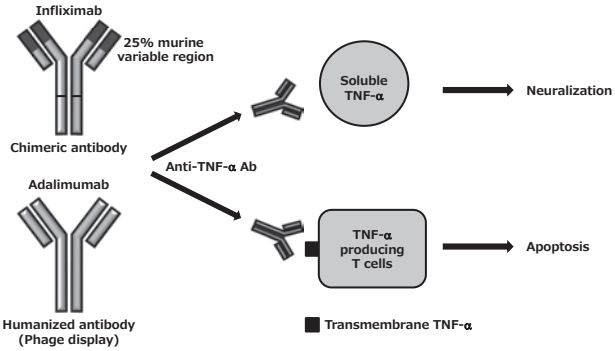


Fig. 1.
Anti-inflammatory mechanisms of infliximab and adalimumab

**Clinical efficacy of IFX for CD**

The first multicenter double-blind placebo-controlled trial of IFX in patients with moderate-to-severe CD was performed by Targan et al. [5]. Their results clearly showed that a single intravenous infusion of IFX (5 mg/kg) resulted in high rates of remission (48% vs. 4%) and efficacy (81% vs. 17%) as compared to a placebo at 4 weeks after administration.

Following that short-term study, the ACCENT-I maintenance trial was performed for assessment of long-term efficacy and safety of IFX treatment in patients with moderate-to-severe CD [6]. Following infusion of IFX at week 0, week-2 responders were randomized for repeat infusions of a placebo or IFX (5 mg/kg) at weeks 2 and 6, and then again every 8 weeks thereafter. The remission rate at week 30 (primary endpoint) was significantly higher in patients with IFX infusion (39%) as compared to the placebo group (28%). However, 22% of the patients had maintenance treatment discontinued by week 54, mainly due to lack of response.

Thereafter, ACCENT-II, a multicenter double-blind placebo-controlled trial was conducted for evaluating the efficacy of IFX maintenance therapy (5 mg/kg) in CD patients with a draining fistula, including perianal and enterocutaneous fistulas [7]. Those results revealed that fistulizing CD patients who showed a response to induction therapy with IFX continued with a sustained response over a 54-week period when IFX treatment was given every 8 weeks.

### *ADA*

**Structure and anti-inflammatory mechanisms**

ADA is a humanized IgG monoclonal antibody specific for human TNF-α and generated by a phage display method (Fig. 1). The affinity of ADA for TNF-α was found to be increased by replacing amino acids in the Fc domain of IgG. Similar to IFX, anti-inflammatory mechanisms of ADA are dependent on the neutralizing cytokine activity of soluble type TNF-α as well as induction of apoptosis in cells producing TNF-α via binding to the membrane-bound precursor [19, 20]. The frequencies of all examined adverse events including serious events were not different between the placebo and ADA groups in that study.

**Clinical efficacy of ADA**

Another study evaluated the short-term efficacy of ADA (remission induction phase) in patients with moderate to severe CD (CLASSIC-I trial)

[8]. Therapy was randomized, and selected patients received subcutaneous injections at weeks 0 and 2 with either the antibody or a placebo. ADA injections at weeks 0 (160 mg) and 2 (80 mg) induced high rates of remission (36%) and efficacy (59%) at week 4, which were significantly higher than those in the placebo group (24% and 36%, respectively).

The CHARM trial was performed for evaluating long-term efficacy and safety of ADA treatment in patients with moderate-to-severe CD, and naïve to anti-TNF-α therapy. [9]. Following open label subcutaneous injections of ADA at weeks 0 (80 mg) and 2 (40 mg), week-4 responders were randomized to treatment through week 56 with a placebo, ADA at 40 mg every other week, or ADA at 40 mg weekly. The clinical remission rates for the ADA maintenance group (every other week injection) at weeks 26 and 56 (co-primary endpoints) were 40% and 36%, respectively, and significantly higher than those for the placebo group (17% and 12%, respectively), while the frequency of adverse events in both ADA groups was similar to that in the placebo group.

### *Is withdrawal of anti-TNF-α therapy in CD patients with remission possible?*

Following reports of large-scale multicenter double-blind placebo-controlled studies, a number of real-world investigations were conducted, with those findings indicating clear efficacy and safety of anti-TNF-α therapy in patients with CD. Nevertheless, an important clinical question is whether anti-TNF-α therapy can be stopped in CD patients with sustained remission, as treatment withdrawal would reduce their burden.

In the STORI trial [21], CD patients who showed remission for at least 6 months were enrolled and prospectively investigated in regard to outcome (disease relapse) after withdrawal from IFX therapy, which showed a 1-year relapse rate of 43.9%. More recently, a study of long-term (7 years) follow-up findings of the STORI cohort demonstrated that 21.6% of those patients did not require restarting of biologics nor developed major complications, whereas 60.8% required a restart of IFX or ADA, and 17.6% had major complications [22]. Thus, stopping IFX therapy in patients with remission must be carefully considered, while additional studies to elucidate clinical predictors for outcome following withdrawal of therapy are necessary.

## Anti-IL-12/IL-23 p40 antibody

### *Ustekinumab (UST)*

**Structure and anti-inflammatory mechanisms**

UST is a humanized IgG monoclonal antibody that targets the p40 subunit of both IL-12 and IL-23, and was recently developed as a biologic (Fig 2). Following binding to the p40 subunit, this antibody inhibits binding of IL-12 and IL-23 to their receptors, which subsequently down-regulates signaling of T-helper (Th)-1- and Th-17-dependent inflammatory pathways [23, 24]. Since IL-12 and IL-23 are involved in the immune pathogenesis of CD, UST was developed for treatment of CD.

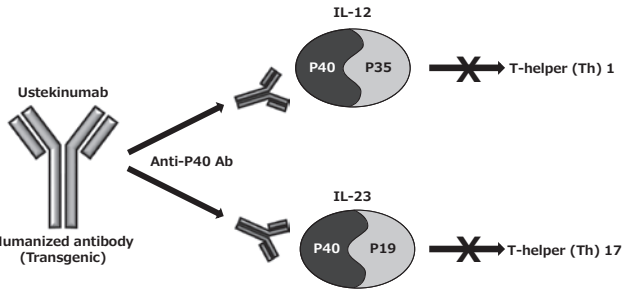


Fig. 2.
Anti-inflammatory mechanisms of ustekinumab

**Clinical efficacy of UST for CD**

The efficacy of UST has been evaluated in induction trials for moderate to severe CD patients with (UNITI-1) and without (UNITI-2) a history of anti-TNF-α therapy, as well as in a maintenance trial (IM-UNITI) [12]. In UNITI-1, the response rate at week 6 was significantly higher in the UST group (6 mg/kg) as compared to the placebo group (33.7% vs. 21.5%), while UNITI-2 found that the efficacy of UST as compared to a placebo was more noticeable in CD patients without a history of anti-TNF-α

therapy (55.5% vs. 28.7%). Patients who showed a response to UST at the induction phase were further investigated in a maintenance trial (IM-UNITI). Patients were randomly assigned and the remission rate in those receiving maintenance UST (90 mg) every 8 weeks was 53.1% at week 44, which was higher as compared to patients receiving a placebo (35.9%). Furthermore, the frequencies of adverse events during these induction and maintenance trials were similar among the treatment groups. Based on clinical efficacy and safety, UST is currently used in biologic therapy for moderate to severe CD patients in clinical practice.

## Anti-α4β 7-integrin antibody

### *Vedolizumab (VDZ)*

**Structure and anti-inflammatory mechanisms**

α4β7-integrin is expressed by lymphocytes, a specific subset of T cells, and binds to MAdCAM-1 expressed on endothelial cells, with interactions of those 2 molecules resulting in migration of circulating lymphocytes to intestinal tissues [25]. VDZ is a monoclonal IgG antibody targeting α4β7-integrin that blocks binding of lymphocytes to MAdCAM-1, thus contributing to an anti-inflammatory effect by inhibiting infiltration of lymphocytes from vessels to the intestines (Fig. 3). Since MAdCAM-1 is mainly expressed on intestinal endothelial cells [25], VDZ was developed as gut-selective antibody for CD.

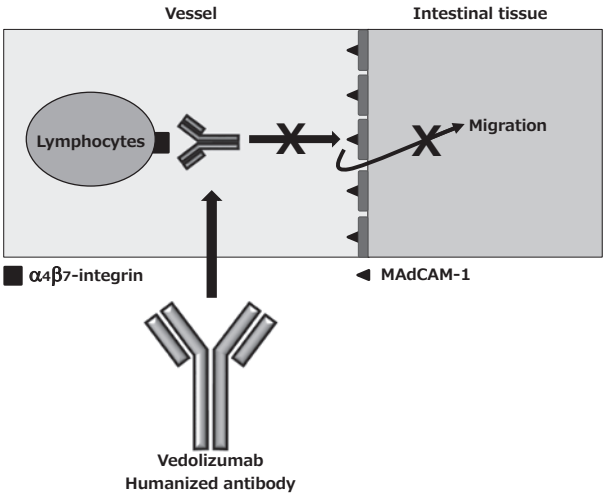


Fig. 3.
Anti-inflammatory mechanism of vedolizumab

**Clinical efficacy of VDZ for CD**

The GEMINI-2 trial was conducted as 2 integrated randomized double-blind placebo-controlled trials of VDZ in patients with active CD [15]. In the induction trial, patients in cohort-1 received VDZ (300 mg) or a placebo at weeks 0 and 2, while those in cohort-2 received open-label VDZ (300 mg) at 0 and 2 weeks, then assessments of disease activity at week 6 were performed. The remission rate after weeks 6 was 14.5% in the VDZ group and higher as compared to the placebo group (6.8%). Similar to the UST trial, patients without history of anti-TNF-α therapy were effectively treated by VDZ administration. In the maintenance trial, responders to VDZ at week 6 in either cohort were randomly assigned to receive VDZ or a placebo every 8 weeks until week 52. The remission rate after 52 weeks (39%) in the VDZ group was increased as compared to that after 6 weeks and higher as compared to the placebo group at week 52 (21.6%). Thus, the efficacy (remission rate) of VDZ in responders at week 6 was found to be gradually increased during the maintenance phase until week 52. Although the frequency of adverse events in GEMINI-2 was slightly higher in the VDZ group, a recent analysis of data from a total of 6 trials revealed a favorable safety profile, along with low incidence rates of serious infections and malignancies, over extended treatment periods [26].

## Anti-drug antibody in response to biologics

An anti-drug antibody sometimes develops in patients receiving biologic therapy. Loss of response induced by such an anti-drug antibody is caused by neutralizing drug efficacy as well as increased clearance of the drug by formation of an immune-complex, which its development is largely dependent on the immunogenicity of the administered biologic [27]. IFX is a chimeric antibody with greater immunogenicity as compared to other biologics. Anti-IFX antibodies were detected in 14.6% of the patients with IFX monotherapy during maintenance therapy (at week 30), as compared to only 0.9% of patients receiving a combination of IFX and an immunomodulatory drug (IM) [28]. Although ADA is a humanized antibody for TNF-α, the frequency

of anti-drug antibody development against ADA was relatively high. The antibody appeared during maintenance therapy (week 26) in 13.2% of patients receiving ADA monotherapy, but in only 4% undergoing combination therapy with IM [29], which might be related to increased immunogenicity due to replacement of amino acids in the Fc domain of IgG. In this regard, combination therapy is recommended for patients receiving long-term anti-TNF-α therapy. On the other hand, the frequencies of anti-drug antibodies against UST [12] and VDZ [15] during maintenance therapy (week 52) were 2.3% and 5.8%, respectively, lower as compared to cases of monotherapy with anti-TNF-α antibodies. Those results might be dependent on the low immunogenicity of UST and VDZ.

## Concluding remarks

Findings reviewed here indicate the efficacy and safety of biologics for CD. In addition to results obtained in various multicenter double-blind placebo-controlled trials, a large volume of real-world evidence regarding biological therapies for CD has been reported. Nevertheless, it remains largely unknown how to determine which biologic drug is appropriate for individual patients. The efficacy of biologics in clinical practice is likely dependent on a variety of factors, including age, gender, severity, and location of disease, as well as combination use with other drugs. Additional studies will be necessary to clarify these issues.

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