REVIEW

Korean J Intern Med 2018;33:20-27
https://doi.org/10.3904/kjim.2017.393

Novel treatments for inflammatory bowel disease

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Received: November 28, 2017
Accepted: December 4, 2017

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This paper was contributed by Korean Association for the Study of Intestinal Diseases.

Increased understanding of the immunopathology of inflammatory bowel disease (IBD) has led to the development of targeted therapies and has unlocked a new era in IBD treatment. The development of treatment options aimed at a variety of pathological mechanisms offers new hope for customized therapies. Beyond anti-tumor necrosis factor agents, selective lymphocyte trafficking inhibitors have been proposed as potent drugs for IBD. Among these, vedolizumab has recently been approved for both Crohn's disease and ulcerative colitis. Numerous other agents for IBD treatment are currently under investigation, including Janus kinase inhibitors, anti-mucosal vascular addressin cell adhesion molecule-1 agents, an anti-SMAD7 antisense oligonucleotide, an anti-interleukin-12/23 monoclonal antibody, and a sphingosine-1-phosphate receptor-1 selective agonist. These agents will likely expand the treatment options available for the management of IBD patients in the future. In this review, we discuss the efficacy and safety of novel agents currently under investigation in IBD clinical trials.

Keywords: Inflammatory bowel diseases; Janus kinase inhibitors; Anti-mucosal vascular addressin cell adhesion molecule-1 agent; Anti-SMAD7 antisense oligonucleotide; Anti-interleukin-12/23

INTRODUCTION

Inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic, disabling, and progressive disorders characterized by lifelong treatment and whose incidences are increasing in Asia [1-4]. For several decades, medical treatments for IBD were limited to non-biological therapies (i.e., aminosalicylates, thiopurines, and steroids), which provide symptomatic improvement but do not change the disease course [5]. With the advances in the understanding of the pathological mechanisms involved in IBD, new therapies have been proposed, with the most important development being the introduction of anti-tumor necrosis factor (TNF) agents [6,7]. Anti-TNF agents (infliximab, adalimumab, and certolizumab) have reduced the need for surgery and hospitalization and have improved the quality of life of patients by changing the course of the disease [8,9]. Thus, guidelines recommend the use of anti-TNF agents initially in moderate-to-severe IBD or if non-biological therapy fails [10-13]. However, these treatments have not been effective in all patients, and patients who initially responded to treatment have also lost their responsiveness over time [14-17]. Furthermore, although anti-TNF agents are generally well tolerated, their use is associated with adverse effects, including

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

risks of infection and malignancies [18-21]. For these reasons, several studies investigating new therapies have been conducted, and some novel drugs have shown potentially favorable clinical effects in IBD trials. Novel therapies include selective lymphocyte trafficking inhibitors (vedolizumab and etrolizumab), an anti-mucosal vascular addressin cell adhesion molecule-1 (anti-MAdCAM-1; PF-00547659) agent, Janus kinase inhibitors (JAK inhibitor; tofacifinib), anti-SMAD7 antisense oligonucleotide (mongersen), anti-interleukin (IL)-12/23 (ustekinumab), and the sphingosine-1-phosphate receptor-1 (S1P1) selective agonist (ozanimod). This review article discusses the characteristics, indications, efficacy and safety of these novel therapies.

RECOMMENDATIONS

Novel biologic agents

Anti-adhesion molecules

IBD consists of a chronic inflammation of the gastrointestinal tract that occurs when inflammatory mediators migrate to target organs. It is characterized by lymphocyte infiltration of the intestinal lamina propria and the process of lymphocyte migration in IBD is regulated by the interaction of several integrins with tissue specific adhesion molecules [22]. Therefore, therapies targeting lymphocyte adhesion and trafficking have been developed and have emerged as novel treatment options for IBD.

Natalizumab

Natalizumab is an anti-α_4 integrin antibody that was demonstrated to induce and maintain remission in patients with CD [23]. This agent is not selective for the gastrointestinal system; it not only interferes with integrin $\alpha\beta_7$ associated with MAdCAM-1 expressed in the gut epithelium, but it also interferes with the integrin $\alpha_4\beta_1$ associated with the vascular cell adhesion molecule 1 expressed on the epithelium of inflammatory tissues [24]. Natalizumab interferes with lymphocyte accumulation in the intestinal mucosa and induces improvement in intestinal inflammation. However, progressive multifocal leukoencephalopathy (PML) due to John Cunningham virus reactivation was reported in natalizumab-treated patients and the use of this agent has been largely reduced [25]. Natalizumab was temporarily withdrawn from the market but was re-introduced in 2006 in the United States only for patients not suitable for other immunomodulator therapy [26].

Vedolizumab

Vedolizumab is an anti-$\alpha_4\beta_7$ integrin antibody that blocks the interaction between $\alpha_4\beta_7$ integrin and MAdCAM-1. Vedolizumab also reduced the risk of systemic side effects such as the PML observed with natalizumab treatment by acting selectively in the intestine. In randomized placebo-controlled trials, vedolizumab demonstrated effectiveness for induction and maintenance of clinical response in both UC and CD. In the induction therapy trial of the GEMINI I study, 374 patients with moderate-to-severe UC patients were randomized to receive 300 mg of vedolizumab intravenously or placebo at weeks 0 and 2 and disease was evaluated at week 6 [27]. The clinical response rates at 6 weeks were 47.1% and 25.5% ($p < 0.001$), clinical remissions were 16.9% and 5.4% ($p = 0.001$), and mucosal healing was observed in 40.9% and 24.8% ($p = 0.001$), respectively for patients in the vedolizumab-treated and placebo groups. Patients who had a response to vedolizumab at 6 weeks were included in the maintenance therapy trial. A total 373 patients were randomly assigned to receive vedolizumab 300 mg or placebo every 4 or 8 weeks and disease was evaluated at week 52. The clinical remission rates were 44.8% in the every 4-week dosing group, 41.8% in the every 8-week dosing group, and 15.9% in the placebo group ($p < 0.001$). Moreover, the rate of mucosal healing and steroid-free remission was significantly higher in patients treated with vedolizumab compared to placebo.

The GEMINI II study, having the same study design as the GEMINI I study, included patients with moderate-to-severe CD and evaluated the efficacy of vedolizumab in the induction and maintenance of remission [28]. In the induction trial, clinical remission (defined as Crohn's Disease Activity Index [CDAI] ≤ 150) occurred in 14.5% of the vedolizumab-treated group and in 6.8% of the placebo-treated group ($p = 0.02$) at week 6. However, there was no statistically significant difference in clinical response (≥ 100-point decrease in the CDAI score) between the two groups at week 6. In the maintenance trial, clinical remission occurred in 36.4% and

39% of patients receiving vedolizumab every 4 weeks (p = 0.0042) and every 8 weeks (p = 0.0007) compared to 21.6% in those who received placebo at week 52. The GEMINI III study evaluated the safety and efficacy of vedolizumab for remission induction in patients with CD in which treatment with the anti-TNF agent failed [29]. At week 6, the difference in clinical remission (CDAI ≤ 150) between the vedolizumab-treated group and the placebo group was not statistically significant (15.2% and 12.1%, respectively; p = 0.433). However, at week 10, clinical remission was seen in 26.6% of the vedolizumab-treated group versus 12.1% of the placebo group (p = 0.001); furthermore, therapeutic benefits of vedolizumab in patients who had previously failed anti-TNF therapy were also observed [29]. Vedolizumab was administered to over 3,000 patients with UC or CD, with no evidence of PML occurrence and had generally a safe profile [30]. Two recent interim reports from the ongoing GEMINI long-term safety phase III extension trial of vedolizumab on UC and CD also supported the safety of vedolizumab [31,32]. Vedolizumab was approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in patients with severe UC or CD who do not respond to conventional or anti-TNF therapy.

Etrolizumab

Etrolizumab is monoclonal antibody directed against the β7 subunit of the $\alpha_4\beta_7$ and $\alpha E\beta_7$ integrins that inhibits the binding of the β_7 integrin to MAdCAM-1 and E-cadherin [33]. The EUCALYPTUS study is a placebo-controlled, randomized phase II study that evaluated the efficacy of etrolizumab in 124 patients with active UC [34]. Patients were randomly assigned to receive etrolizumab 100 mg at weeks 0, 4, and 8; etrolizumab at a 420 mg loading dose at week 0 and then 300 mg at weeks 2, 4, and 8; or matching placebo. At week 10, clinical remission (defined as Mayo Clinic Score ≤ 2, no subscore > 1) rates were 21% in the etrolizumab 100 mg group (p = 0.004), 10% in the etrolizumab 300 mg group (p = 0.048), compared to none in the placebo group. Mild and moderate adverse events occurred at a similar rate in all study groups. A phase III trial to confirm these promising results is in progress.

PF-00547659

PF-00547659 is a monoclonal antibody directed against the gut-specific endothelial adhesion molecule MAdCAM-1. In an initial randomized, double-blind placebo-controlled phase I study, 80 patients with active UC were randomized to receive single or multiple doses (3 doses 4 weeks apart) of 0.03 to 10 mg/kg of PF-00547659 or placebo given intravenously or subcutaneously [35]. Although clinical response and remission rates were not significantly higher in the PF-00547659-treated group than in the placebo group, no apparent drug-related adverse events were observed. Based on these results, phase II studies were conducted in UC and CD patients. In the TURANDOT study (NCT01620255), 357 patients with moderate-to-severe UC were randomized to receive 7.5, 22.5, and 75 mg of PF-00547659 or placebo. At week 12, clinical remission rates were 11%, 17%, and 16% for 7.5, 22.5, and 75 mg, respectively, versus 3% in the placebo group (p < 0.05) [36]. In contrast, the OPERA study (NCT01276509) evaluating moderate-to-severe CD patients did not demonstrate any benefits of treatment because of a high placebo response [37]. Adverse event rates were similar between the therapy and placebo group and no episodes of serious infection or of PML were observed. Several clinical trials have been conducted on the efficacy and safety of PF-00547659 and future phase III trials are scheduled.

Blockage of downstream signaling

Orally administered small molecule inhibitors act by interfering with intracellular signaling and have many advantages compared to therapeutic antibodies, such as reduced production costs and oral administration. One of the most advanced drugs is the JAK inhibitor tofacitinib, which has already been approved for the treatment of rheumatoid arthritis in the United States.

Tofacitinib

Tofacitinib is an oral JAK inhibitor that mainly inhibits the JAK1 and JAK3 isoforms and blocks the downstream effects of a large subset of proinflammatory cytokines including IL-2, IL-3, IL-4, IL-5, IL-6, IL-12, IL-15, IL-21, and interferon-γ. JAK-dependent intracellular signaling pathways are involved in the pathophysiology of many chronic inflammatory diseases, including rheumatoid arthritis and IBD [38,39]. Tofacitinib has been shown to be effective in a phase II trial in 194 patients with moderate to severe active UC [40]. At week 8, clinical re-

https://doi.org/10.3904/kjim.2017.393

sponses occurred in 32%, 48%, 61%, and 78% of patients receiving tofacitinib at a dose of 0.5 mg ($p = 0.39$), 3 mg ($p = 0.55$), 10 mg ($p = 0.10$), and 15 mg ($p < 0.001$), respectively, versus 42% of patients in the placebo group. Clinical remission at week 8 was observed in 33%, 48%, and 41% of patients receiving tofacitinib at a dose of 3, 10, and 15 mg, respectively, versus 10% of patients in the placebo group ($p < 0.05$). Although the overall drug safety profile was acceptable, dose-dependent elevation of low- and high-density lipoproteins was reported in patients treated with tofacitinib. In the phase III study, patients with active UC were assigned to receive tofacitinib 10 mg twice daily or placebo for 8 weeks [41]. At week 8, significantly more patients in the tofacitinib-treated group achieved remission ($p < 0.01$ and $p < 0.001$, respectively), mucosal healing ($p < 0.001$ for both), and clinical response ($p < 0.001$ for both) versus placebo. Adverse event rates were similar between the groups and rates of serious cases were not higher with tofacitinib. Tofacitinib was also evaluated in patients with moderate-to-severe active CD [42,43]. In the previous phase II trial after a 4-week induction therapy, tofacitinib failed to show any significant clinical response. However, this study might have limitations such as the short duration of study, small sample size, and high placebo response rate (47%). In a repeat phase IIb study that complemented these limitations, clinical remission at 8 weeks was observed in 44% and 43% of patients receiving tofacitinib twice daily at a dose of 5 and 10 mg, respectively, versus 37% for the placebo group. Similar findings were observed in the TNF inhibitor-experienced patients with tofacitinib 10 mg twice daily [44]. In addition, a 26-week maintenance study in patients with 128 clinical responses or clinical remissions subsequent to the induction study was conducted. The proportion of patients with clinical response or remission at week 26 was not significant because rates were 40% and 56% for 5 or 10 mg of tofacitinib twice daily versus 38% for placebo [42]. Other JAK inhibitors are currently under clinical investigation in phase II for both UC and CD.

Mongersen

Transforming growth factor β1 (TGF-β1) is a pleiotropic cytokine that has anti-inflammatory properties and is important for cell homeostasis. In CD patients, defective TGF-β1 activity is often observed, due to increased levels of SMAD7, an intracellular protein that binds to the TGF-β1 receptor preventing downstream TGF-β1-driven signaling [45]. Therefore, manipulation of TGF-β1 signaling represents a potential therapy for IBD [46]. The safety and efficacy of mongersen, an orally administered SMAD7 antisense oligonucleotide, were studied in a multicenter, double-blind, placebo-controlled phase II trial [47]. A total of 166 patients with moderate-to-severe CD were randomized to receive one of three doses of mongersen (10, 40, or 160 mg/day) or placebo for 2 weeks. The proportions of patients meeting the primary end point (CDAI < 150 on day 15 and maintenance of this score up to day 28) were 55% and 65% for the 40 and 160 mg/day groups, respectively, versus 10% in the placebo group ($p < 0.001$). The clinical response rate was significantly higher in patients receiving 10 mg (37%), 40 mg (58%), or 160 mg (72%) mongersen compared to the placebo group (17%) ($p = 0.04$, $p < 0.001$, and $p < 0.001$, respectively). Most adverse events were related to CD symptoms and complications. Currently, two phase III studies for induction and maintenance therapy of patients with active CD and a phase II study for efficacy and safety of mongersen in patients with active UC are currently in progress.

Blockade of proinflammatory cytokines

Ustekinumab

IL-12 and IL-23 are proinflammatory cytokines that share a common subunit (p40). Ustekinumab is a monoclonal IgG1 antibody targeting the p40 subunit of IL-12 and IL-23, and has been shown to be effective in the treatment of psoriatic arthritis and psoriasis [48,49]. The efficacy of ustekinumab in the induction of remission in 104 patients with moderate-to-severe CD was evaluated in a double-blind placebo-controlled study [50]. Clinical response rates for groups given ustekinumab and placebo were 53% and 30% ($p = 0.02$), respectively, at weeks 4 and 6, and 49% and 40% ($p = 0.34$), respectively at week 8. Of interest, better results were observed in patients previously given infliximab. In a phase IIb study, the efficacy of ustekinumab in the induction and maintenance of remission in patients with moderate-to-severe CD refractory to anti-TNF agents was subsequently evaluated [51]. At week 6, the clinical response was significantly increased in the ustekinumab group, while no

Table 1. Novel treatment agents for inflammatory bowel disease

Drug	Type	Target	Clinical status	
			Crohn's disease	Ulcerative colitis
Anti-adhesion molecules				
Vedolizumab	Monoclonal Ab	$\alpha_4\beta_7$ Integrin	Approved	Approved
Etrolizumab	Monoclonal Ab	β_7 Integrin	-	Phase III
Natalizumab	Monoclonal Ab	α_4 Integrin	Approved	-
PF-00547659	Monoclonal Ab	MadCAM-1	Phase II	Phase II
Blockade of the downstream signalling pathways				
Tofacitinib	Small molecule	JAK1/JAK3	Phase III	Phase III
Mongersen	Antisense oligonucleotide	SMAD7	Phase II	-
Blockade of proinflammatory cytokines				
Ustekinumab	Monoclonal Ab	IL-12/IL-23 (p40)	Approved	-
Others				
Ozanimod	Small molecule	S1P1	Phase II	Phase III

Adapted from Narula et al. [54], with permission from Nature Publishing Group.
Ab, antibody; MadCAM, mucosal vascular addressin cell adhesion molecule-1; JAK, Janus kinase; IL, interleukin; S1P1, sphingosine-1-phosphate receptor-1.

difference in clinical remission was observed. Although the primary endpoint was set at 6 weeks, both the response and remission rates were higher at 8 weeks than at 6 weeks. These results suggest that the mechanism of action ustekinumab has a slow onset, and that week 6 is perhaps too early to assess the clinical response. At week 22, patients with an initial response to ustekinumab had a significantly increased clinical response and clinical remission rate with ustekinumab as maintenance therapy. Several adverse effects have been reported, but these were similar to the adverse effects reported in the placebo group in clinical trial for CD. Ustekinumab has recently been approved by the both the U.S. FDA and the EMA for the treatment of patients with CD. Phase III trials of ustekinumab for the treatment of CD and UC are currently underway [52].

Other agents

RPC1063

Ozanimod (RPC1063) is a novel oral small molecule immunomodulatory agonist mainly for the S1P1 receptors. Ozanimod induces peripheral lymphocyte sequestration, decreasing the number of activated lymphocytes circulating to the gastrointestinal tract [53]. The first phase II study, the TOUCHSTONE study, evaluated the induction and maintenance treatment of ozanimod in 197 patients with moderate to severe UC [41]. At week 8, 16%, and 57% of patients receiving ozanimod 1 mg daily, achieved clinical remission and clinical response as compared with 6% and 37% of the placebo group, respectively. At week 32, the rates of clinical remission were 21% and 26% in patients that had received 1 and 0.5 mg of ozanimod, respectively, and 6% in in the placebo-treated group, while the clinical response rates were 51%, 35%, and 20%, respectively. The overall drug safety profile was good and the most common adverse events were anemia and headache. Ozanimod has currently entered phase III studies on induction and maintenance therapy for UC, and a phase II study on induction therapy of ozanimod in CD is currently ongoing.

CONCLUSIONS

Many novel therapies for IBD are under development. Some of these drugs have recently been approved for IBD treatment, but other drugs have begun to be marketed as indications for other diseases, while their efficacy in IBD is continuing to be explored. Table 1 summarizes the therapies discussed in this paper and the respective phases of development [54]. The emergence of

https://doi.org/10.3904/kjim.2017.393

new biological agents targeting specific pathways in IBD has led to a variety of novel treatments and opportunities for more individualized therapy for IBD patients. In the future, studies on the efficacy and safety of combination therapy of biological agents and other novel agents are needed, and studies on various biomarkers that may predict responses to biological drugs for IBD should be conducted.

Conflict of interest

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

Acknowledgments

This study was supported by a National Research Foundation (NRF) grant funded by the Korea government (NRF-2017R1A2B2009569).

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https://doi.org/10.3904/kjim.2017.393

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