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REVIEW

Novel strategies for the treatment of inflammatory bowel disease: Selective inhibition of cytokines and adhesion molecules

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Abstract

The etiology of inflammatory bowel disease (IBD) has not yet been clarified and immunosuppressive agents which non-specifically reduce inflammation and immunity have been used in the conventional therapies for IBD. Evidence indicates that a dysregulation of mucosal immunity in the gut of IBD causes an overproduction of inflammatory cytokines and trafficking of effector leukocytes into the bowel, thus leading to an uncontrolled intestinal inflammation. Such recent advances in the understanding of the pathogenesis of IBD created a recent trend of novel biological therapies which specifically inhibit the molecules involved in the inflammatory cascade. Major targets for such treatment are inflammatory cytokines and their receptors, and adhesion molecules. A chimeric anti-TNF-α monoclonal antibody, infliximab, has become a standard therapy for CD and it is also likely to be beneficial for UC. Several anti-TNF reagents have been developed but most of them seem to not be as efficacious as infliximab. A humanized anti-TNF monoclonal antibody, adalimumab may be useful for the treatment of patients who lost responsiveness or developed intolerance to infliximab. Antibodies against IL-12 p40 and IL-6 receptor could be alternative new anti-cytokine therapies for IBD. Anti-interferon-γ and anti-CD25 therapies were developed, but the benefit of these agents has not yet been established. The selective blocking of migration of leukocytes into intestine seems to be a nice approach. Antibodies against α4 integrin and α4β7 integrin showed benefit for IBD. Antisense oligonucleotide of intercellular adhesion molecule 1 (ICAM-1) may be efficacious for IBD. Clinical trials of such compounds have been either recently reported or are currently underway. In this article, we review the efficacy and safety of such novel biological therapies for IBD.

INTRODUCTION

Although the etiology of inflammatory bowel disease (IBD), such as, Crohn's disease (CD) and ulcerative colitis (UC), has not yet been fully addressed, there has been remarkable progress in the understanding of this field in the past decade. In normal bowels, the immune reaction is sophisticatedly regulated while keeping a balance between the effectors and the regulators, and as a result, the homeostasis of the gut is maintained. A lot of evidences indicate that mucosal immunity is dysregulated in the bowel of IBD[1]. Two forms of IBD show distinct profiles of T cell mediated immunity. In the gut of CD, a strong Th1 reaction is induced, while the Th2 response is upregulated in the colon of UC[2]. Particularly in CD, it is evident that Th1 dominant immunity plays an important role in the pathogenesis. In UC, although the relevance of elevated Th2 cytokines to the colonic inflammation has not yet been clarified, an increased proinflammatory cytokine production is also observed which seems to be related to the inflammation. For the development of intestinal inflammation, leukocyte trafficking to the gut is an important step[3]. Adhesion molecules, such as integrins, mediate the selective binding between the leukocytes and the endothelial cells and thus the migration of leukocytes into the normal and inflamed intestine. The main classical medical treatments for IBD are steroids and immunosuppressive agents which non-specifically reduce immunity and inflammation. Recent advances in the understanding of the mechanism of bowel inflammation have led to a recent trend in the development of biological therapies which selectively inhibit the action of molecules essential to the inflammatory process. Major targets for such therapies are inflammatory cytokines and their receptors, and adhesion molecules. Re-

cently, numerous challenges have been performed to generate anti-cytokine and anti-integrin compounds to treat IBD. This article reviews the efficacy and safety of such novel biological therapies for IBD targeting cytokines, cytokine receptors and adhesion molecules.

INHIBITION OF TNF

TNF-α is a proinflammatory cytokine which is abundantly expressed in the gut of CD[4-6]. In animal models of experimental colitis, treatment with anti-TNF-α antibody has been shown to be effective in the suppression of intestinal inflammation[7,8]. As a result, this cytokine was considered to be an attractive target for the treatment of IBD and several anti-TNF reagents have thus been developed. These reagents include infliximab, CDP571, CDP870, etanercept, onercept and adalimumab. Infliximab is a chimeric IgG1 monoclonal antibody against TNF-α, which was created in late 1980s, and it has been demonstrated to be effective in reducing intestinal inflammation in CD as described below. Most of the other anti-TNF reagents are modified by a reduction of the mouse peptide sequence or are completely humanized in order to reduce the immunogenecity. Not all of the other anti-TNF reagents have been proven to be as effective in the treatment of CD as infliximab, and the efficacy of such reagents seems to be dependent, not only on the ability to neutralize soluble TNF-α, but also on the capacity to bind to the membrane-bound TNF-α on the cell surface, thereby mediating the apoptosis of the effector cells[9].

Infliximab

Infliximab was demonstrated to be effective in both the induction and maintenance therapy for refractory luminal and fistulizing CD. In a randomized double-blind placebo-controlled trial, 108 patients with moderate-to-severe CD which is resistant to conventional therapy, were treated with the single intravenous infusion of either placebo or infliximab at a dose of 5 mg/kg, 10 mg/kg or 20 mg/kg. The rates of the clinical response at 4 wk were 81% for infliximab 5 mg/kg, 50% for infliximab 10 mg/kg and 64% for infliximab 20 mg/kg, all of which were significantly higher than that for the placebo-treated group. The clinical remission rate at 4 wk was also significantly higher in the infliximab-treated group than that in the placebo-treated group (33% *vs* 4%)[10]. In a randomized, double-blind, placebo-controlled trial for the treatment of fistulizing disease, 94 CD patients with draining abdominal and perianal fistulas refractory to conventional therapy were treated with three intravenous infusions at wk 0, 2 and 6 of either a placebo or infliximab at a dose of 5 mg/kg or 10 mg/kg. The response rates were significantly greater in the infliximab 5 mg/kg group (68%) and in the infliximab 10 mg/kg group (56%) than that in the placebo-treated group (26%). The rates of a complete closure of the fistulas were also significantly higher in the infliximab 5 mg/kg group (55%) and in the infliximab 10 mg/kg group (38%) than in the placebo-treated group (13%)[11]. The effectiveness of infliximab for the maintenance therapy for inflammatory CD was assessed in a large trial called ACCENT I. Three hundred and thirty-five responders to a single infusion of infliximab were subsequently treated with 5 mg/kg infliximab at wk 2 and 6, followed by infusions of either 5 mg/kg or 10 mg/kg infliximab once every 8 wk until wk 54, or they were treated with placebo at wk 2 and 6, and subsequently every 8 wk. The rates of clinical response and remission at wk 30 and 54 was significantly greater in both groups receiving 5 mg/kg and 10 mg/kg infliximab every 8 wk than those in the placebo-treated group[12]. In addition, an analysis comparing the scheduled and episodic treatment strategies of infliximab for CD was conducted based on the ACCENT I data. The efficacy of the scheduled therapy was better than episodic strategy in terms of CDAI score, clinical remission and response rates, improvement in IBDQ score, mucosal healing and CD-related hospitalization and surgery[13]. For an evaluation of the infliximab maintenance therapy for fistulizing CD, ACCENT II trial was conducted. One hundred and ninety-six CD patients with draining perianal and enterocutaneous fistulas who responded to the induction therapy with three infusions of 5 mg/kg infliximab at wk 0, 2 and 6 received either a placebo or 5 mg/kg infliximab every 8 wk. The median time to the loss of response, response rate and complete fistula closure rate at wk 54 in the infliximab maintenance group were significantly greater than those in the placebo group[14].

Regarding the safety of infliximab treatment, it is well tolerated in the majority of the patients. In randomized controlled clinical trials, the rates of adverse events occurring in infliximab-treated patients were comparable to those in placebo-treated patients[10-12,14]. Serious side effects, however, have been reported and attention must be paid to the possible occurrence of serious infections and autoimmune disorders, as well as the theoretical threat of cancer and lymphoma. In an analysis of 500 infliximab-treated patients in Mayo Clinic, serious adverse events were observed in 8.6%, of which 6% was considered to possibly be related to infliximab[15]. Such events included serious infections, severe infusion reactions, serum sickness-like reactions, drug-induced lupus, cancer, non-Hodgkin's lymphoma and demyelinating process. The infectious complications included fatal sepsis, pneumonia, viral gastroenteritis, abdominal abscesses requiring surgery and histoplasmosis. Five deaths (1%) were observed which were likely or possibly related to infliximab. The reactivation of latent tuberculosis has been reported elsewhere[16], as a result, it is recommended that all patients be screened for latent tuberculosis before the initiation of this treatment regimen.

Infliximab is a mouse/human chimeric monoclonal antibody of which 25% is mouse peptide sequence. The murine component is ascribed to its immunogenecity, such as infusion-related reactions and serum sickness-like diseases. In such immunological reactions, the formation of antibodies against infliximab, called human anti-chimeric antibodies (HACA) is of particular concern as the presence of HACA is associated with an increased frequency of infusion reactions and the reduction in efficacy[17]. Concomitant immunosuppressive therapy and premedication with 200 mg of hydrocortisone reduce the frequency of HACA formation[17,18]. The scheduled infusions in the maintenance therapy have been shown to be associated

with the reduction of the rate of HACA formation[13]. As a result, the regular infliximab-treatment every 8 wk is likely to be beneficial for CD patients, not only for the maintenance of the remission state but also for the avoidance of infusion reactions.

The efficacy of infliximab for the treatment of UC remains controversial as two randomized controlled trials for steroid-refractory UC resulted in opposite results. A study indicated the benefit of infliximab for UC since 50% (4 of 8 patients) of the infliximab-treated patients showed treatment success, while none of the 3 patients receiving a placebo showed response[19]. However, this study was terminated prematurely because of a slow enrollment. Another study failed to show any benefit of infliximab over placebo as there was no significant difference between patients who received infliximab and placebo in the remission rates and an improvement in the activity scores[20]. Recently, two large multicenter randomized trials, ACT1 and ACT2, have been performed. In both trials, 364 patients with active UC were randomized to receive placebo or infliximab in a dose of 5 mg/kg or 10 mg/kg at wk 0, 2, 6, 14 and 22 in ACT1, and at wk 0, 2 and 6 then every 8 wk through wk 46 in ACT2. In both trials, both 5 mg/kg and 10 mg/kg infliximab showed significantly greater percentages in both the induction and maintenance of clinical remission and response, and in mucosal healing than placebo at both wk 8 and 30[21,22]. In addition, it was also recently demonstrated that infliximab is effective as a rescue therapy to avoid a colectomy or death in severe to moderately severe UC refractory to conventional therapies[23]. As a result, infliximab thus appears to also be efficacious for the treatment of UC as well as for CD.

CDP571

CDP571 is a "humanized" IgG4 antibody against TNF-α, created by genetic engineering to replace the murine component other than the binding domain with parts of a human IgG4 molecule. The resulting molecule is a chimera of 95% human and 5% mouse residues. The first study of 31 patients with active CD demonstrated that CDP571 5 mg/kg resulted in a greater decrease in the mean CDAI score at wk 2 compared with placebo[24]. After a promising pilot trial, CDP571 was tested in a placebo-controlled dose-finding trial[25]. In this study, 169 patients were randomized to receive a single intravenous infusion of either CDP571 in a dose of 10 or 20 mg/kg, or placebo. At wk 2, the clinical response rate was significantly higher in the patients treated with CDP571 (45%) than in those received a placebo (27%). Re-treatment was performed either every 8 wk with a placebo or CDP571 10 mg/kg, or every 12 wk with a placebo or CDP571 10 mg/kg (4 groups). The clinical remission rates at wk 24 in CDP571-treated groups were not significantly different from those of the placebo-treated groups. In a subsequent, randomized, double-blind, placebo-controlled, multicenter study[26], the efficacy and tolerability of CDP571 in 396 patients with active CD was evaluated. Among the patients treated with CDP571 10 mg/kg every 8 wk, the percentage of patients achieving a clinical response was significantly higher than in those receiving a placebo at wk 2 and 4. However, at wk 28 the difference was not statistically significant. As a result, CDP571 therapy showed a short term benefit in induction therapy, but it is not sufficient to maintain a long term effect. In a post-hoc exploratory analysis of a subgroup of patients with elevated baseline CRP levels, there was a significant difference in the number of patients showing a clinical response at wk 2 (CDP571, 49.5%; placebo, 15.5%), and at all time points from wk 12 to wk 28, thus leaving the possibility that CDP571 is more efficacious in a selected group of patients[26]. CDP571 failed to show a steroid sparing effect in patients with steroid-dependent CD[27]. CDP571 was well tolerated even in patients with CD who developed either infusion reactions or delayed-type hypersensitivity reactions to infliximab[28]. From these results, CDP571 was considered to be safe but not as effective as infliximab for CD and further clinical development of this antibody for the treatment of CD has thus been discontinued.

CDP870

CDP870 is a pegylated Fab fragment of humanized anti-TNF monoclonal antibody. In a placebo-controlled dose-finding study[29], 292 patients were randomized to receive a subcutaneous dose of CDP870 (100, 200, or 400 mg) or placebo at wk 0, 4, and 8. The group that received CDP870 400 mg showed greater clinical response rates than other groups at all time points. The clinical response rates of the CDP870 400 mg group were significantly higher than those of the placebo treated group at wk 2, 4, 8 and 10. The difference, however, did not reach statistical significance at wk 12. A greater dose separation was evident in the analysis of a patient subgroup with elevated CRP levels. In an exploratory analysis[30] in 119 patients with increased CRP levels ($\geqslant$ 10 mg/L), the differences in the clinical response between the 400 mg/dose (53.1%) and placebo (17.9%) were significant at 12 wk. These studies, therefore, indicated that CDP870 may be more effective in patients with elevated CRP levels. CDP870 seems to be safer and less immunogenic than infliximab. The efficacy, however, is likely to be lower than that of infliximab. The question arises whether physicians want to compromise on efficacy in the scope of better long-term safety. Further clinical trials are ongoing.

Etanercept

Etanercept is a genetically engineered fusion protein consisting of two recombinant human TNF p75 receptors linked to an Fc portion of human IgG1 fragment. The subcutaneous injection of etanercept at a dose of 25 mg twice weekly, which is an effective dose for rheumatoid arthritis, is a safe but ineffective dose for the treatment of patients with moderate to severe CD[31].

Onercept

Onercept, a recombinant, fully human, soluble p55 TNF receptor has showed efficacy to CD in an open-label pilot study (n = 12)[32]. A large, placebo-controlled, dose-finding study has been completed but the data have not yet been published. A press release by Serono (Geneve, Switzerland) revealed that the primary endpoint of this trial was not met.

Adalimumab

Adalimumab is a fully humanized anti-TNF monoclonal IgG1 antibody. This antibody is as efficacious as infliximab for the treatment of rheumatoid arthritis. *In vitro* studies revealed that this antibody is capable of inducing apoptosis in monocytes as infliximab[33]. As adalimumab does not contain a mouse peptide sequence, it is expected to be less immunogenic and more tolerable than infliximab. Two uncontrolled pilot studies of adalimumab with CD patients who had lost responsiveness or developed intolerance to infliximab[34,35] showed that subcutaneous adalimumab was well tolerated, thus suggesting a clinical benefit of adalimumab. In a phase 3, multicenter trial for active CD, clinical remission rates of patients who received adalimumab 160 mg at wk 0 and 80 mg at wk 2 was significantly higher than that of placebo at wk 4 (36% *vs* 12%)[36]. From these results, adalimumab is likely to be efficacious for the treatment of CD and it could thus be an alternative therapy for the patients who either lost responsiveness or developed intolerance to infliximab.

INHIBITION OF OTHER INFLAMMATORY CYTOKINES

Anti-IL-12 p40 antibody

IL-12, a heterodimeric molecule composed of IL-12 p40 and IL-12 p35 subunits, plays a central role in Th1 development. IL-12 is abundantly produced in the gut of CD patients[2]. In several animal models of Th1-mediated colitis, anti-IL-12 treatment effectively ameliorates intestinal inflammation[37,38]. IL-12 p40 subunit is also a component of another Th1 cytokine, IL-23, in which p40 forms a heterodimer with p19 subunit. IL-12 p40 is, therefore, a potential target for the treatment of CD in which intestinal inflammation is Th1-mediated. A double-blind, placebo-controlled randomized study of a humanized IgG1 monoclonal antibody against IL-12 p40 (ABT-874) was performed in 79 patients with active CD[39]. The patients were randomly assigned to receive seven weekly injections of 1 mg/kg anti-IL-12, 3 mg/kg anti-IL-12 or placebo subcutaneously either with or without 4 wk intervals between the first two injections. The patients who received 3 mg/kg anti-IL-12 for 7 wk showed a significantly greater clinical response rate than the patients treated with a placebo (75% *vs* 25%). The rates of remission were also higher in the 3 mg/kg anti-IL-12 group (38%) than in the placebo group (0%) but the difference did not reach statistical significance. The production of IL-12 and other Th1 and proinflammatory cytokines from patients' colonic lamina propria mononuclear cells dramatically decreased after the anti-IL-12 therapy. The most frequent adverse event was a local reaction at the injection site, which was observed with a greater rate in the anti-IL-12-treated group than in the placebo-treated group. Anti-drug antibody was formed in some patients who received anti-IL-12 antibody. No serious side effects requiring the discontinuation of the treatment, due to the anti-IL-12 therapy, were observed. Anti-IL-12 therapy is therefore considered to be a safe and effective treatment for active CD.

MRA (Anti-IL-6 receptor antibody)

IL-6 is one of the major inflammatory cytokines. IL-6 can transduce signals into cells without IL-6 receptor expression when IL-6 binds to soluble IL-6 receptor. The expression of IL-6 and soluble IL-6 receptor increases in patients with active CD[40,41]. A pilot randomized double-blind placebo-controlled trial of a humanized anti-IL-6 receptor monoclonal antibody, MRA, with active CD was performed[42]. Thirty-six patients were randomized biweekly to receive either a placebo, 8 mg/kg MRA or MRA/placebo alternately for 12 wk. The clinical remission rate with biweekly MRA was significantly higher than that with placebo (80% *vs* 31%). The acute phase responses such as ESR and CRP levels were rapidly suppressed 2 wk after the MRA injection. The incidence of adverse events was similar in all groups, and thus MRA treatment was generally well tolerated. It is, therefore, likely that anti-IL-6 receptor therapy is beneficial for active CD.

Fontolizumab (Anti-interferon-γ antibody)

Interferon-γ is a key cytokine that enhances the development of a Th1 immune response. Fontolizumab is a humanized monoclonal antibody directed against interferon-γ. A phase 2 study of fontolizumab at intravenous doses of 4 mg/kg or 10 mg/kg in 133 patients with moderate to severe active CD did not demonstrate efficacy at d 28. However, exploratory analyses based on 91 patients who received a second dose of fontolizumab at d 28 did demonstrate efficacy. This effect was most prominent in patients with elevated baseline concentrations of CRP[43]. An additional phase 2 study of fontolizumab at lower subcutaneous doses of 1.0 mg/kg or 4.0 mg/kg in 196 patients with active CD did not demonstrate efficacy at d 28[44]. These results indicate that a single dose may not be sufficient to achieve a significant improvement. Further clinical studies of fontolizumab for the induction and maintenance of remission in patients with CD are anticipated.

Anti-IL-2 receptor (CD25) antibodies

Daclizumab: IL-2 is a major T cell growth factor, which is secreted by activated T cells and acts via the high-affinity IL-2 receptor on T cells themselves to promote cell survival and proliferation. The IL-2 receptor α-chain (CD25) is a component of high-affinity IL-2 receptor and it is expressed on activated T cells. Daclizumab is a humanized monoclonal antibody to CD25, which blocks the binding of IL-2 to the IL-2 receptor. An open label pilot study of daclizumab suggested that it was beneficial for patients with active UC[45]. However, a recent placebo-controlled phase 2 trial of daclizumab at intravenous doses of 1 mg/kg twice with a 4-wk interval or 2 mg/kg every 2 wk for a total of four doses in 159 patients with active UC failed to show any efficacy[46].

Basiliximab: Basiliximab is a chimeric monoclonal antibody against CD25, which blocks the binding of IL-2 to the IL-2 receptor. Two uncontrolled pilot studies suggested that basiliximab in combination with steroids may be effective for steroid resistant UC[47,48]. A large random-

ized controlled trial is required to confirm the therapeutic benefit of this compound.

INHIBITION OF ADHESION MOLECULES

Many adhesion molecules play an important role in trafficking leukocytes into the inflamed gut wall and they are up-regulated in both CD and UC[49,50].

α4-integrins, predominantly expressed on lymphocytes, usually exist in combination with a β subunit and interact with adressins expressed on endothelium. α4β1-integrin binds to vascular cellular adhesion molecule 1 (VCAM-1) and α4β7-integrin binds to mucosal addressing cell adhesion molecule 1 (MAdCAM-1). The interaction between α4β7-integrin and MAdCAM-1 is important in mediating lymphocytes homing to the gut mucosa[51].

Leukocyte function-associated antigen 1 (LFA-1) expressed on leukocytes interacts with intercellular adhesion molecule 1 (ICAM-1), which is constitutively expressed at low levels on vascular endothelial cells and a subset of leukocytes, and they are up-regulated on many cell types in response to proinflammatory mediators[52].

Natalizumab

Natalizumab, a humanized IgG4 anti-α4-integrin monoclonal antibody, inhibits both α4β7-integrin/MAdCAM-1 interaction and α4β1/VCAM-1 binding.

In an initial small trial in 30 patients with active CD, a single 3 mg/kg intravenous infusion of natalizumab showed a short term effect in inducing remission at wk 2 and elevated circulating lymphocyte levels after the natalizumab infusion. Therefore, it is suggested that the natalizumab interrupted lymphocyte trafficking into the intestine[53]. In a large placebo-controlled randomized trial including 248 patients with moderate to severe CD, patients were treated twice at 4 wk intervals with 3 or 6 mg/kg of natalizumab or placebo. A significantly higher number of patients achieved remission at wk 6 only in the 3 + 3 mg/kg natalizumab group compared with the two infusions of placebo group (44% *vs* 27%). The clinical response rates at wk 6 in all treatment groups were significantly higher than that in the placebo-treated group (3 mg/kg natalizumab + placebo: 59%, 3 + 3 mg/kg natalizumab: 71%, 6 + 6 mg/kg natalizumab: 57% and the two infusions of placebo group, 38%)[54]. A larger phase 3 trial of ENACT-1 in 905 patients with moderate to severe CD failed to show a benefit for three intravenous infusions of 300 mg natalizumab every 4 wk. In a subgroup analysis, however, natalizumab-treated patients with concurrent immunosuppressive therapies, prior anti-TNF-α therapy or elevated CRP levels showed a significant response rate compared with placebo-treated patients[55]. Three hundred and thirty-nine patients with CD who responded to natalizumab in ENACT-1 were re-randomized to maintenance therapy with natalizumab (300 mg) or a placebo for up to 12 additional monthly infusions. In this maintenance study (ENACT-2), natalizumab demonstrated a significant superiority over the placebo in its ability to sustain both the response and remission at all consecutive time points over a 6-mo period and enabled patients to be successfully withdrawn from steroids[56]. In an uncontrolled short term pilot study in 10 patients with active UC, a single 3 mg/kg intravenous infusion of natalizumab showed a short term benefit[57].

Natalizumab is efficacious in multiple sclerosis (MS) as well[58]. In MS, α4β1 integrin/VCAM-1 binding appears to be a crucial step because antiα4β1 integrin antibody prevented the development of experimental autoimmune encephalomyelitis, a model of human MS[59]. Against these effects of natalizumab in IBD and MS, 3 patients receiving repeated treatment with natalizumab developed JC virus related progressive multifocal leukoencephalopathy (PML)[60-62]. PML, which almost invariably occurs in patients with AIDS or leukemia or in organ-transplant recipients, is a fatal opportunistic infection of the central nervous system caused by the reactivation of a clinically latent JC polyomavirus infection. Two patients with MS had been receiving the concomitant administration of interferon β-1a[60,61] and 1 patient with CD had been treated with natalizumab monotherapy[62]. These observations force us to reconsider both the efficacy and the potential risks associated with an inhibition of lymphocytes trafficking by anti-α4 integrin therapy.

MLN-02

MLN-02, a humanized anti-α4β7-integrin blocks specifically the α4β7-integrin/MAdCAM-1 interaction.

A randomized placebo-controlled trial in 185 patients with mild to moderately active CD treated with placebo, 0.5 mg/kg MLN-02 or 2.0 mg/kg MLN-02 intravenously on d 1 and 29 demonstrated that on d 57, 2.0 mg/kg MLN-02 showed significantly greater remission rates over the placebo (36.9% *vs* 20.7%). There was no significant difference between the actively treated and placebo-treated groups regarding the clinical response rates. No obvious differences in adverse events were noted among the three groups[63].

A randomized placebo-controlled trial in 181 patients with moderately active UC treated with placebo, 0.5 mg/kg MLN-02, or 2.0 mg/kg MLN-02 intravenously on d 1 and 29 demonstrated that on d 43 the remission rates were significantly higher in the actively treated groups (0.5 mg/kg: 33%, 2.0 mg/kg: 34%) than in the placebo-treated group (15%). An infusion reaction occurred in one MLN-02-treated patient who developed mild angioedema[64].

MLN-02 appears to be a generally well-tolerated and effective therapy especially for active UC, but further trials are necessary to confirm the efficacy of MLN-02 therapy for IBD.

Alicaforsen (ISIS 2302)

ISIS 2302 is a 20 base phosphorothioate oligodeoxynucleotide designed to specifically hybridize to the 3'-untranslated region of the human ICAM-1 mRNA. Treatment of ISIS 2302 *in vitro* resulted in a highly specific reduction in ICAM-1 mRNA and, consequently, a marked decrease in ICAM-1 protein expression[65]

A pilot trial in patients with moderate CD (including 15 patients treated with 13 intravenous infusions of 0.5, 1.0 or 2.0 mg/kg ISIS 2302 *vs* 5 patients with placebo over 26 d) demonstrated a higher remission rate in ISIS 2302-treated group compared with the placebo-treated group on d 33

(47% *vs* 20%)[66]. However, a placebo-controlled trial in 75 patients with steroid refractory CD failed to demonstrate efficacy was showed that the subcutaneous administration of ISIS 2302 induced only 3% of ISIS 2302-treated patients to clinical remission with complete steroid taper (0% in placebo-treated patients)[67]. Another larger randomized placebo-controlled trial also failed to show any benefit of ISIS 2302 for active CD[68]. Two hundred and ninety-nine patients with moderately active, steroid-dependent CD received placebo or ISIS 2302 (2 mg/kg intravenously three times a week) for 2 or 4 wk in mo 1 and 3. There were no differences in the steroid-free remission rates at wk 14 between the ISIS 2302-treated groups (2 wk: 20.2%, 4 wk: 21.2%) and the placebo-treated group (18.8%). However, a subgroup analysis using the area under the curve (AUC) of ISIS 2302 plasma concentration demonstrated an improvement of the clinical response for the highest AUC group (AUC > 65 μg × h/mL). This suggested that ISIS 2302 may be effective when given in adequate doses. As a result, a dose ranging pilot trial of high dose ISIS 2302 in 22 patients with active CD was conducted. The patients, who were infused with high dose ISIS 2302 (250 mg to 350 mg) intravenously three times a week for 4 wk, showed a 41% remission rate. Five patients, however, withdrew due to infusion-related symptoms[69].

A randomized placebo-controlled trial in 40 patients with mild to moderately active distal UC treated with 60 mL alicaforsen enema (0.1, 0.5, 2, or 4 mg/mL or placebo) once daily for 28 consecutive days showed a beneficial effect at the highest dose. Four mg/mL alicaforsen enema group showed a significant improvement in the disease activity index on d 29 and mo 3 in comparison to the placebo enema group[70]. An open-label, uncontrolled study in 12 patients with chronic unremitting pouchitis treated with 240 mg alicaforsen enema nightly for 6 wk demonstrated a significant improvement in the pouchitis disease activity index and an endoscopic mucosal appearance at wk 6[71].

The most consistently reported side effects of ISIS 2302 in all clinical trials were infusion reactions and a moderate increase in activated partial thromboplastin time.

CONCLUSION

Infliximab has changed the medical treatment of CD dramatically. This agent has been proven to be clearly effective for the induction and maintenance of remission for active CD meanwhile it is also generally well-tolerated. However, there are some patients who fail to respond to infliximab. In addition, some responders either lose responsiveness to infliximab during long-term therapy or develop intolerance to infliximab. The next issue will therefore be how to treat such patients who cannot be treated with infliximab. Adalimumab may be an alternative to infliximab. Anti-IL-12 and anti-IL-6 receptor therapies seem to be promising. The selective blocking of α4 integrin and α4β7 integrin also demonstrated promising results, however, the side effects still need to be fully elucidated. We await the results of further clinical trials to include such novel compounds in the algorithm for the treatment of CD. Infliximab is likely to also be beneficial for UC. In addition, some other agents seem to be effective for the treatment of UC and further clinical development is also underway. As a result, the management of UC may also dramatically improve in the near future owing to the use of such novel agents. The systematization of novel biological therapies for UC is therefore an issue that needs to be addressed in the future.

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