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Current status of monoclonal antibody therapy for the treatment of inflammatory bowel disease

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Abstract

Crohn's disease and ulcerative colitis are complex diseases that have required the use of multiple modalities to aid in treatment. With an increasing understanding of the underlying pathogenetic mechanisms and identification of specific therapeutic targets, monoclonal antibody treatment has been an ideal strategy for inducing and maintaining remission in these patients. This article addresses approved agents and the supporting data justifying their use in Crohn's disease and ulcerative colitis, the safety of and immunologic reactions to these agents, as well as newer agents for treatment.

Keywords

Crohn's disease; infusion reaction; monoclonal antibody; tumor necrosis factor; ulcerative colitis

Inflammatory bowel disease (IBD) includes both Crohn's disease (CD) and ulcerative colitis (UC) and affects approximately 1.4 million people in the USA [1]. Each of these entities has a distinct clinical phenotype but there are commonalities underpinning their pathogenesis. The pathogenesis of IBD includes a complex interaction between innate and adaptive immune cells, intestinal vasculature, and local immune modulators and cytokines. Ultimately, it is the balance between tolerance to the intestinal microbiota and a proinflammatory response that can lead to IBD [2].

Tumor necrosis factor (TNF) plays a key role in the pathogenesis of some forms of IBD [3]. In healthy individuals, there is an intact mucosal epithelium and mucous production, promoting exclusion of luminal bacteria, as well as a continual sampling of the intestinal micoflora. As intestinal dendritic cells, epithelial cells and macrophages sample luminal bacteria, there is a consequent activation of regulatory T cells in the local tissues, as well as in secondary lymphoid organs, accounting for the overall suppressed tone of the normal mucosal immune response [4-7]. In IBD, increased permeability of the epithelium leads to entry of luminal bacteria; these bacteria are sampled by cells in the lamina propria, leading to the production of proinflammatory cytokines, which promote the activation of inflammatory T-cell subgroups (Th1 and Th17 cells), causing inflammatory cytokine production and greater local infiltration of inflammatory cells [2].

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TNF-α is a prototypical proinflammatory cytokine with pleiotropic effects on cells of the innate and adaptive immune system as well as on local blood vessels. It promotes the production of additional proinflammatory cytokines and chemokines (IL-1 and IL-6) and mediates additional inflammatory effects, such as the secretion of tissue-altering enzymes (matrix metalloproteinases [MMPs], collagenase and elasatase), as well as activation of local cell populations that can alter tissue architecture. TNF-α also upregulates the expression of adhesion molecules on vascular endothelial cells within the tissue such as vascular cell adhesion molecule and intercellular adhesion molecule-1, leading to greater accumulation of leukocytes in the tissues [8]. This effect is partly mediated via adhesion molecules such as α4β7-integrin, which are cell-surface glycoproteins that help give stability to the interaction between inflammatory cells and the high endothelial venules [9,10]. Given these pleiotropic effects of TNF-α, it was initially recognized as an ideal target for therapy in IBD. However, as our understanding of these diseases has advanced, so has the number of potential targets for monoclonal antibody (mAb) therapy. These include antibodies against inflammatory cytokines, chemokines and adhesion molecules. What has evolved is a broader understanding of disease pathogenesis as well as a unique appreciation of what clinical end points are relevant for long-term clinical care in these diseases.

This article will discuss the approved mAb treatments for CD and UC. For the approved agents, seminal clinical trials will be discussed as well as longer-term data, if available. The article will also discuss issues related to this class of agents including immunogenicity, safety and emerging treatments.

Monoclonal antibody therapy: disease oriented

Crohn's disease

Infliximab—Infliximab (Remicade®, Centocor [CA, USA]) is a IgG1 (murine [25%] and human [75%]) chimeric mAb targeted against TNF-α (Tables 1 & 2) [11]. Studies over the past 12 years have documented the efficacy of this agent in induction and maintenance of response and remission in treatment-refractory inflammatory CD, fistulizing disease as well as prevention of disease recurrence in postoperative patients. Infliximab is given as an intravenous infusion over 2 h. In 1997, the first short-term placebo-controlled trial of infliximab was conducted in 108 patients with treatment-refractory moderate-to-severe CD (CD activity index – CDAI 220–400). These patients were given a single infusion of placebo, 5 mg/kg of infliximab, 10 mg/kg of infliximab or 20 mg/kg of infliximab. At week 2, a clinical response (CDAI decrease of 70 points) was seen in 61% of infliximab patients versus 17% of placebo patients; 27% of infliximab patients were in clinical remission (CDAI <150) compared with 4% of placebo patients. By 12 weeks after the single infusion, 24% of infliximab patients were in remission compared with 8% of placebo patients. A clear dose–response relationship for clinical remission was not seen, leading to the subsequent use of the 5 mg/kg dose (in some cases 10 mg/kg) [12]. Other studies have shown similar success with infliximab for therapy of refractory and fistulizing disease (Hungary: 46.0% and Milan: 31.3%) [13,14].

The ACCENT I trial proved that infliximab was efficacious as a maintenance therapy. Patients who received either 5 or 10 mg/kg of infliximab every 8 weeks were 2.7 (95% CI: 1.6–4.6) times more likely to sustain clinical remission compared with placebo and 4.2 (95% CI: 1.5–11.5) times as likely to discontinue steroids. The median time to loss of response was 38 weeks for infliximab-treated patients. Combined with the prior data, these findings showed that infliximab may induce and maintain a steroid-spar-ring remission for many patients with moderate-to-severe CD [15]. In a separate analysis, the authors examined an episodic treatment strategy compared with scheduled dosing and found that scheduled treatment had a greater improvement in CDAI and mucosal healing at 54 weeks, fewer surgeries and hospitalizations, and a lower proportion of antibody formation [16].

Long-term data for the efficacy of infliximab beyond 1 year are growing. A single-center study with 614 patients followed for 55 months showed that 63.4% of infliximab patients sustained clinical benefits (defined by symptom improvement). A total of 50% of this group did need at least one intervention in dose escalation or changing the schedule of the infusion during the follow-up period. Of the patients on steroids, 70% remained steroid free for the duration of the study. Although promising, there was a 42.3% hospitalization rate and 23.5% abdominal surgery rate, which was greatest in those receiving episodic compared with scheduled therapy [17].

The presence of fistulae in CD is a well-recognized complication, affecting between 10 and 33% of patients [18]. Present *et al.* examined the effect of infliximab on 94 patients with abdominal or perianal fistulae [19]. In a randomized, placebo-controlled trial, infliximab at 5 mg/kg, 10 mg/kg or placebo was given at 0, 2 and 6 weeks. A total of 62% of all infliximab patients compared with 26% of placebo patients reached the primary end point of a 50% reduction in draining fistulas from baseline. Fistula closure was seen in 46% of all infliximab patients compared with 13% of placebo-treated patients. Time to response was a mean of 2 weeks with mean response duration of 86 days [19]. This was the first clear evidence that infliximab was efficacious in the treatment of fistulizing CD.

With advances in imaging, the true definition of fistulae healing has come into question. Recent studies using endoscopic ultrasound and magnetic resonance have documented active inflammation prior to treatment with anti-TNFs; 46% of these patients had cessation of drainage, a common end point in trials, but only 28% showed complete healing on magnetic resonance imaging [20]. In the future, studies will need to address the small sample size and investigators will need to determine how to best assess for fistulae healing – clinically or radiographically [21].

A smaller cohort study of 26 patients with perianal fistulizing disease showed 50% complete remission after infliximab treatment. Factors associated with remission included the absence of active intestinal disease and active proctitis [22]. A subsequent study of 99 patients with perianal CD also showed promise: 42.5% with ulcers, 18.2% with strictures and 32.3% with fistula had a complete response (closure of all fistulae) with infliximab [23]. For longer term outcomes, the ACCENT II study followed fistulizing patients who had an initial response to infliximab at 14 weeks. In this randomized placebo-controlled trial, 36% of patients in the infliximab group (5 mg/kg every 8 weeks) compared with 19% in the placebo group had the absence of draining fistula at the end of the study [24].

More recently, a small study assessed the role of infliximab in postoperative recurrence in CD patients undergoing an ileocolic resection (n = 24) who received either inflixmab or placebo induction followed by an every 8-week infusion. There was endoscopic recurrence in 9.1% of infliximab patients compared with 84.6% in the placebo group. Clinically, 0% in the infliximab group versus 38.5% in the placebo group had a recurrence as measured by CDAI [25]. While the numbers of patients in this study were small, these findings provided evidence that anti-TNF-α mAb therapy has a place in post-operative management for CD alongside immunomodulator treatments.

Adalimumab—Adalimumab (Humira®, Abbott Labs [IL, USA]) is a fully human anti-TNF mAb (Tables 1 & 2). This drug is given subcutaneously, thus avoiding the need for infusions that are required with infliximab administration. In addition, it is a fully human antibody, which has been proposed to decrease its immunogenicity, avoiding the production of anti-mAbs that have been reported with infliximab. However, it has become clear that any of these agents, including adalimumab, can induce antibody formation that can be associated with local or systemic reactions.

The CLASSIC-I trial, a 4-week, double-blind, placebo-controlled, randomized trial, demonstrated that adalimumab can be used for the induction of remission in patients with moderate-to-severe CD. In patients receiving doses of 80 mg of adalimumab or greater at week 0 and 40 mg of adalimumab or greater at week 2, there was a statistically significant difference in patients achieving remission compared with placebo (24% with 80 mg/40 mg, 36% with 160 mg/80 mg and 12% with placebo, respectively). CDAI, IBD quality of life assessment (IBDQ) and C-reactive protein (CRP) values were also improved in the adalimumab-treated groups. From this trial, the authors concluded that a 160-mg induction dose followed by 80 mg at week 2 was effective in inducing remission [26].

The CLASSIC II study followed patients who achieved remission in the first trial and randomized them to either placebo, or adalimumab 40 mg weekly or every other week. Adalimumab treatment was superior to placebo at 56 weeks (79% remission every other week, 83% weekly) in maintaining a response measured as a 100-point decrease in the CDAI. In addition, most patients were able to discontinue steroids by the end of the trial. In the open-label study of those who did not respond by week 4 in the CLASSIC I trial, only 46% of patients were in remission, suggesting that an early response may predict the likelihood of a sustained response at 56 weeks [27].

Short-term response and remission to adalimumab were documented in the CARE study, which was a large (n = 945) Phase III trial that evaluated the use of 160/80-mg induction at week 0 and 2 and then 40 mg every other week. In all patients, there was a 43% remission rate, as defined by a Harvey–Bradshaw Index of less than 5, and 52% at week 20. Results at week 4 (49%) and week 20 (61%) were better in the TNF antagonist-naive group compared with those with prior infliximab exposure. Rates were similar to other larger trials [28].

CHARM, a large Phase III trial, showed that adalimumab administered weekly or every other week was superior to placebo for maintaining remission at 56 weeks (36% every other week, 41% weekly and 12% placebo). In this study, weekly administration of adalimumab at 40 mg per week resulted in a response that was as efficacious as adalimumab dosing every other week. Steroid-free remission was greater in the treatment versus placebo group, with 20–29% of patients (depending on the group) being steroid-free at 56 weeks [29].

An intention-to-treat analysis of the CHARM study demonstrated that more patients in the continuous treatment group were in clinical remission compared with placebo (49–51% for adalimumab vs 38% for placebo). Concomitant improvements in CDAI and IBDQ, as well as a reduction in hospitalizations and fewer surgeries, were seen in the continuous versus induction/reinitiation group [30].

A 60% decrease in all-cause hospitalization and a 64% decrease in CD-related hospitalization was also reported over the 12-month follow-up in patients treated with adalimumab, with an effect noticeable as early as 2 weeks after randomization in the trial [31]. Overall, adalimumab was shown to be beneficial in inducing and maintaining remission. The route and timing of administration, touted as being more acceptable to patients, coupled with the documented (but similar to infliximab) long-term benefits, improved quality of life, endoscopic remission and reduced hospitalization rates made this a valuable agent for the treatment of CD patients.

With adalimumab approved in 2007, clinicians hoped to use this medication in those patients who were infliximab primary nonresponders, secondary nonresponders or who experienced intolerable infusion reactions. The GAIN study evaluated the use of adalimumab in patients who had persistent symptoms on infliximab therapy or were intolerant to this latter agent. The 4-week, randomized, double-blind placebo-controlled trial of 325 patients showed that 21% of patients achieved remission compared with 7% of the placebo group. Other notable findings included a decrease in CDAI of 70 points in 52% of patients, a decrease in median CRP and

an improvement in the IBDQ [32]. Thus, adalimumab provided a viable alternative to infliximab therapy, especially in those patients who experienced infusion reactions, despite the fact that these antibodies are fully human and are not necessarily less immunogenic.

Similarly for fistulizing disease, the CHARM study showed that at week 26, 30% of patients exhibited fistula closure, and by week 56, 33% of patients demonstrated fistula closure. Of those with an early response to adalimumab, 100% maintained fistula closure at week 56, showing a possibly early and sustained response for patients with fistulous disease [26].

However, of recent interest is the finding that many patients who lose response to one anti-TNF agent have a less robust response to a second anti-TNF agent, suggesting that the actual inflammatory pathway within the tissue may change with time, possibly driven by antibody blockade of that path (i.e., the dominant inflammatory pathway is no longer TNF-mediated). This may be due to one of multiple causes of loss of response, including antibody formation with either enhanced clearance of blockade of antigen binding versus a change in the inflammatory pathway. Within all anti-TNF studies, the best response remains in the anti-TNF-naive group. This finding has opened the door for other mAb therapies targeting distinct inflammatory pathways (e.g., anti-IL-12/23 and anti-IL-17) [33].

Certolizumab—Certolizumab (Cimzia®, UCB Pharma, Belgium) is a humanized anti-TNF mAb (Tables 1 & 2). Unlike the agents mentioned earlier, it does not have a Fc portion and therefore has less *in vitro* complement activation, antibody-dependent cellular cytotoxicity or induction of apoptosis [34,35]. This drug is provided as a subcutaneous injection: 400 mg given at 0, 2 and 4 weeks for induction, and every 4 weeks thereafter for maintenance.

For patients with moderate-to-severe CD, the certolizumab induction protocol demonstrated a greater reduction in CDAI at 6 and 26 weeks compared with placebo; however, a statistically significant remission rate was not observed compared with placebo at 26 weeks (PRECISE 1). Infliximab-treated patients showed a statistically insignificant clinical response at week 26, as measured by CDAI [36]. A small cohort in Switzerland (FACTS survey) showed that 54% of patients developed a response at week 6 and 40% of patients were in remission [37]. Due to the significant placebo effect in the Phase II trial [38], PRECISE 2 studied maintenance with certolizumab after open-label induction. Patients who responded to the induction phase were randomized to placebo or 400 mg of certolizumab every 4 weeks. At week 26, 48% of certolizumab patients compared with 29% of placebo patients showed remission based on CDAI, including those previously treated with infliximab [39]. For patients who do not show an initial response with certolizumab at 6 weeks, there is a moderate chance of remission with certolizumab compared with placebo.

Recently, PRECISE 3 reported results of the long-term use of certolizumab. For those patients without any drug interruption, 66.1% of patients had a response at week 80 and 62.1% of patients were in remission based on the Harvey–Bradshaw Scale [40]. Overall, the PRECISE studies show that there is a role for the use of certolizumab in moderate-to-severe CD for both induction and remission in selected patients, possibly in mildly active disease and anti-TNF-naive patients [36,38-40].

Although PRECISE 1 showed little benefit for infliximab-experienced patients, an Italian group reported some efficacy through a compassionate use program for those who had lost response or had intolerance to infliximab. A total of 52% of patients who received an induction dose achieved a clinical response and 42% of patients had a clinical remission based on change in the Harvey–Bradshaw Index [41].

For patients with fistulizing disease, the FACTS survey documented a 50% response rate of fistula closure with certolizumab [37].

General considerations regarding the class of TNF antagonists

The clinical experience with the use of anti-TNF agents has provided the field with new insights relating to the concepts of the role of induced cell death (apoptosis), primary versus secondary nonresponse and mucosal healing. The absence of response to the initial course of an anti-TNF agent does not necessarily mean that TNF is not a critical cytokine in the inflammation seen in a given patient but may reflect the fact that some patients may require greater neutralization of TNF or, more broadly, that the effects of some anti-TNF therapies may have greater effects on the mucosal inflammatory response. Dose escalation was shown to be effective in patients who lost response in ACCENT I. In order to be entered into this study, a patient had to demonstrate a 70-point drop in CDAI. Raising the dose from 5–10 or 10–15 mg/kg restored a response in the majority of patients. Thus, an initial nonresponse would call for dose escalation before deeming that patient anti-TNF nonresponsive. Furthermore, both infliximab and adalimumab bind membrane-bound TNF, either inducing apoptosis of cytokine-producing cells or providing negative signals to these cells. In the former case, the induction of apoptosis of TNF-producing cells also inhibits the production of other inflammatory cytokines and chemokines (e.g., IL-1, IL-6 and IL-8), resulting in a more global suppression of inflammation. In the latter case, ‘reverse signaling’ can suppress the production of such cytokines and chemokines [42]. If neutralization of TNF alone is all that is required, then any of the agents should express similar efficacy. Secondary nonresponders are those individuals who achieved a response/remission initially with an anti-TNF agent but have lost this response/remission with time. This ‘loss of response’ reflects either the presence of antibodies to the agent (and this can occur with any anti-TNF or biologic agent) that promote clearance (metabolism) or neutralize activity of the antibody or is a marker for a change in the inflammatory process occurring at the level of the tissue. While good methods to detect the latter are currently unavailable, we are able to measure antibodies to the biologic agent either directly or by measuring the level of the agent in the blood, which is probably more clinically relevant. If an antibody promotes clearance there will be no measurable drug in a venous blood sample by week 2 post-infusion. Various strategies can be employed to bypass the production of antibody in this setting.

A second, more recently appreciated, issue relates to the assessment of mucosal healing and understanding what the achievement of this end point actually connotes. An endoscopic substudy of ACCENT 1 demonstrated that scheduled maintenance therapy with infliximab resulted in more improvements in mucosal ulceration and higher rates of mucosal healing compared with the episodic group (50% in week 2 responders compared with 7% in the episodic group) [43]. A recent study by Regueiro *et al.* showed that only 9.1% of patients (n = 11) treated with infliximab after ileocolic resection developed endoscopic recurrence compared with 84.6% (n = 13) of placebo patients [25]. Inherently, one would assume that mucosal healing could have implications for long-term response and maintenance of bowel function. Mucosal healing as an end point has been incorporated into all newer trials of not only the anti-TNFs but also other biologic agents.

An additional new concern is the question of combination versus monotherapy in CD. The results of the SONIC trial published this year provided great insight into this question. In this randomized, double-blind trial, patients with moderate-to-severe CD were randomized to infliximab plus placebo pills, azathioprine plus placebo infusion or combination therapy. At week 26, 56.8% of combination therapy patients were in steroid-free remission compared with 44.4% in the infliximab-alone group and 30% in the azathioprine-alone group. Similar trends were noticed at week 50 and with the mucosal healing end points [44].

Adhesion molecule antagonists

An alternative to anti-cytokine therapies is to block the entry and attraction of cells into the inflamed tissue. At present, there is only one such agent available for use in CD, but problems with this monoclonal antibody have resulted in alternative approaches to the prevention of cell trafficking, including more selective inhibitors and chemokine inhibitors.

Natalizumab—Natalizumab (Tysabri®, Elan Pharma [Dublin, Ireland]), is a monoclonal antibody against the integrin α4, which is 95% humanized and 5% murine-derived (Tables 1 & 2). By binding to the α4 chain, it disrupts leukocyte adhesion to the endothelium and subsequent migration into the gut mucosa. Tissue studies show that endothelial cells from IBD patients demonstrate increased α4-mediated leukocyte adhesion [45]. By blocking this pathway, the concept is that there would be a decrease in inflammation and CD severity due to reduced cell traffic into inflamed tissues. Natalizumab is administered via an intravenous infusion.

Four large studies have examined the use of natalizumab for the treatment of CD. The first study by Gordon *et al.* was a randomized, placebo-controlled trial of 30 patients with mild-to-moderate disease. Patients received one 3 mg/kg infusion of natalizumab or placebo. The primary outcomes were change in CDAI score from week 0 to week 2 and clinical remission. For those in the treatment group, a statistically significant change in CDAI was seen at 2 and 4 weeks post-infusion; however, this difference was not significant when compared with the placebo group. There was no difference in remission rates at week 12 [46].

A multicenter induction trial involving 248 patients with moderate-to-severe CD was published by Ghosh *et al.* in 2003 [47]. Patients received two infusions, 4 weeks apart. There were four treatment groups including placebo, 3 mg/kg of natalizumab (with or without placebo) and 6 mg/kg of natalizumab (no placebo). The primary outcome was remission at week 6 defined by a CDAI less than 150. At week 6, there was no difference in remission for most of the groups. However, at week 8, the groups given two doses of natalizumab had significantly more patients in remission compared with placebo (6 mg/kg 43%, 3 mg/kg 41% and placebo 16%). Clinical response, a secondary outcome, was significant in all natalizumab-treated groups compared with placebo. There was no benefit seen with higher doses of the medication [47]. Although the primary outcomes of this trial were not met, the secondary outcomes suggested some longer term benefit for this drug.

ENACT-1, a trial of natalizumab 300 mg intravenously at week 0, 4 and 8 for patients with moderate-to-severe CD investigated remission rates at week 10 of treatment. Unfortunately, a comparable percentage of patients in the natalizumab arm (37%) and the placebo arm (30%); ($p = 0.12$) achieved remission. Differences in response rates in the two groups neared significance (natalizumab 56%, placebo 49%; $p = 0.05$). In ENACT-2, patients who responded at week 10 were randomized to natalizumab every 4 weeks or placebo infusions, for a total of 56 weeks. Sustained clinical response was statistically significant at the end of this trial (61 vs 28%); however, the results may have been confounded by a larger number of smokers in the placebo group compared with the treatment group [48].

In a *post-hoc* analysis, those patients with an elevated CRP in ENACT-1 did have both statistically significant response and remission rates by week 10. ENCORE aimed to examine this group in 509 patients with moderate-to-severe CD. In a multicenter, randomized, double-blind, placebo-controlled trial, patients with elevated CRPs and CDAI between 220 and 450 were randomized to natalizumab 300 mg intravenously or placebo at weeks 0, 4 and 8. Primary outcome, clinical response by week 8, occurred in 48% of patients compared with 32% in the placebo group. By week 12, remission was documented in 38% of treated patients compared with 25% of the placebo group ($p = 0.001$) [49]. These results suggest that in those patients

with severely refractory disease with signs of inflammation, natalizumab is a reasonable option to try to induce remission. However, concerns over increased risk of progressive multifocal leukoencephalopathy have hampered its use as a first-line agent, despite the fact that most cases of progressive multifocal leukoencephalopathy in natalizumab occurred in multiple sclerosis and there was only one case in IBD [50].

Etanercept—Etanercept is a soluble TNF receptor that binds TNF and has demonstrated efficacy in the therapy of rheumatoid arthritis. A small (n = 43) randomized, double-blind placebo-controlled trial conducted in 2001 showed little efficacy of etancerpet 25 mg administered subcutaneously twice weekly for the treatment of moderate-to-severe CD. At 4 weeks, there was no statistically significant difference between the placebo and treatment groups for clinical response [51]. However, the dose used in this trial was the same as that used in the treatment of rheumatoid arthritis and it is possible that higher doses may be required to achieve efficacy.

Ulcerative colitis

Whether TNF-α plays a central role in UC is more controversial. In some studies, elevated levels of TNF-α have been found in the stool and serum of patients with UC [52-54]. In a cottontop tamarin model of colitis, administration of antibody to TNF resulted in clinical and histologic improvement [55]. For patients with moderate-to-severe disease, refractory to aminosalicylates, steroids and immunomodulators, monoclonal antibodies could induce remission, spare surgery and improve quality of life. Thus far, however, the results using anti-TNFs for the control of UC have been less than impressive.

Infliximab—Initially, studies using infliximab were small and showed varying results. Sands *et al.* showed that in 11 patients with severe, intravenous steroid-refractory UC, only 50% of patients who received either 5, 10 or 20 mg/kg of infliximab had a clinical response at 2 weeks in this double-blind, placebo-controlled trial. Summary of end points included: five out of eight showed decreases in the Truelove and Witts severity scale, five out of six had endoscopic improvement, and all had a decrease in erythrocyte sedimentation rate and CRP [56]. A larger randomized placebo-controlled trial of infliximab at weeks 0 and 2 showed no statistically significant difference between the groups at 6 weeks for rate of remission defined by the Ulcerative Colitis Severity Score (30 vs 39%, respectively). Endoscopic improvement, measured by the Baron score, was not statistically different between the groups at 6 weeks [57]. Similar results were reported by others in small open-label series with response rates between 50 and 70% and remission rates between 25 and 70% [58-60].

To evaluate both induction and maintenance efficacy of infliximab, the ACT 1 and 2 trials were conducted. Patients with moderate-to-severe UC were randomized to receive placebo or infliximab (5 or 10 mg/kg) at weeks 0, 2, 6 and every 8 weeks thereafter. ACT 2 had a follow-up of 30 weeks. In this latter trial, by week 8, there was a 64% response rate for 5 mg/kg and a 69% response rate for 10 mg/kg compared with 29% in the placebo group, a difference that persisted to 30 weeks (25.6, 35.8 and 10.6%, respectively). This trial demonstrated the potential role of infliximab in the induction and short-term maintenance of response. ACT 1, with a 54-week follow-up, showed similar rates of clinical remission for 5 and 10 mg/kg of infliximab (34.7 and 34.4%, respectively) at the end of the study. Both trials showed improvement in mucosal healing compared with placebo and an overall decrease in daily steroid use. Approximately 20% of patients in the infliximab group at week 30 were in clinical remission and steroid free [61]. This larger trial helped to clarify some of the mixed data seen in prior infliximab trials for UC.

Another approach to understanding a role for infliximab was to see whether infliximab prevented colectomy in patients with severe UC. In a double-blind trial of infliximab versus placebo, 45 patients were followed for up to 3 months with the primary outcome being death or colectomy. Patients in the placebo group were 4.9-times more likely to undergo colectomy compared with infliximab-treated patients (95% CI: 1.4–17). For those who avoided colectomy (14 out of 24), none had a change in clinical course (as measured by the Seo index) or endoscopic improvement. At interim follow-up of approximately 6 months, the authors reported two additional patients who underwent colectomy [62]. The underlying issue in this study is that a large number of placebo-treated patients also avoided colectomy. Given the fact that these patients were supposedly intravenous steroid refractory, one would have assumed that the colectomy rate would have been 100% in this population. In the short-term, infliximab infusion may play a role in decreasing rates of colectomy for moderate-to-severe UC, but longer-term data are needed.

Bressler *et al.* reported on a Canadian cohort of steroid-refractory hospitalized patients who received infliximab. The primary end point was avoidance of colectomy during hospitalization and discharge home. A total of 76% of patients achieved this end point and 69% had a durable response with steroid-free remission at 4 months [63].

The ACT investigators recently published colectomy data after a 54-week follow-up. Overall, 10% of the infliximab group compared with 17% of the placebo group underwent colectomy. This corresponded to a absolute risk reduction of 7% (95% CI: 0.01–0.12). One caveat of the study was that 13% of the patients were lost to follow-up and had incomplete colectomy data. The secondary end points of UC-related hospitalizations per 100 patient-years and UC-related surgeries/procedures were fewer for the combined infliximab groups compared with placebo [64]. The authors comment on the low colectomy rate in their population as these were a group of outpatients, making colectomy a relatively infrequent event.

Longer-term data are limited with regard to the use of infliximab in UC. Experience in the UK shows a 73.7% sustained clinical response rate over a median 17-month follow-up with 55.3% of these patients in remission. This cohort, however, included both steroid-dependent and steroid-refractory patients. Seven out of 38 patients (18.4%) had undergone colectomy at a median of 5 months after starting treatment [65].

The combined use of both commonly used rescue therapies (cyclosporine A [CsA] and infliximab) has been the topic of a few small observational trials. Maser *et al.* showed a 42% colectomy rate after 1 year and only 37% of patients achieved steroid-free remission [66]. Similarly, Leblanc *et al.* showed that in 46% of patients who received CsA and infliximab sequentially, there was a 46% rate of colectomy [67]. Both of these studies had a infectious complication rate of 16%. A recent study of 16 patients confirmed these findings, reporting that 37.5% underwent colectomy at a median of 47 days, suggesting that if an early response is not seen, colectomy is inevitable [68]. Currently, there are no head-to-head trials comparing CsA and infliximab; however, the CONSTRUCT study should help to answer this question in the future.

Although TNF may not play a central role in UC pathogenesis, it may have a role in postoperative wound healing. TNF-α is important for neutrophil chemotaxis and adhesion in inflammation, and mediating fibroblast recruitment and stimulation [69-71]. Therefore, an increase in postoperative complications in patients who received preoperative infliximab may be a concern. In a study of 151 patients, 17 patients received a median of two infliximab doses approximately 2 months before surgery; half of the patients were on antimetabolite treatment and 40% were on CsA. A role for steroid use was not completely explored and it is recognized that these latter agents are responsible for many postoperative complications. For infliximab-

treated versus nontreated patients, there was a trend towards a greater number of surgical (30 vs 18%) and infectious (18 vs 8%) complications. This did not differ by the type of surgery (subtotal colectomy vs ileal pouch anal anastomosis). The combination of CsA and infliximab led to a higher overall complication rate (80 vs 29%; $p < 0.05$), with a statistically significant greater number of infectious complications [72].

A meta-analysis by Yang *et al.* showed a nonsignificant short-term infectious postoperative complication risk (odds ratio [OR]: 2.24; 95% CI: 0.63–7.95) and a short-term noninfectious post-operative complication risk (OR: 0.85; 95% CI: 0.50–1.45) [73]. The contribution of infliximab versus other medications was difficult to obtain in this meta-analysis owing to study heterogeneity and small sample sizes. These studies suggest that in patients who are considering further medical treatment for UC versus surgery, physicians should counsel patients about an increase in short-term postoperative complications, especially with regard to combined therapies and steroid use.

Infliximab also has been investigated for treatment of pouchitis (50% risk of occurrence by 5 years) [74], with or without fistulizing complications. In one study looking at chronic pouchitis, patients were treated with infliximab 5 mg/kg at 0, 2 and 6 weeks. At 10 weeks, six patients out of seven had complete clinical response and five out of seven had complete fistula closure. The median pouchitis severity index decreased by 7 points in the study [75].

Adalimumab—Adalimumab therapy, with its lesser potential for immunogenicity, is another possible treatment option for patients with UC intolerant to aminosalicylate or steroid therapy. A small, 24-week, open-label study was conducted with 20 patients with moderate-to-severe UC based on the Mayo score, 13 of who were infliximab nonresponders or intolerant to infliximab. Doses were 160 mg at week 0, 80 mg at week 2, 40 mg at week 4 and then 40 mg every other week. Clinical response at week 8, the primary end point measured by the Mayo score, was achieved in 25% of patients (23% infliximab treated and 29% infliximab naive). Only one patient (infliximab naive) had clinical remission at week 8. At week 24, 25% had clinical remission. More patients achieved mucosal healing by week 8 in this trial compared with clinical response or remission [76]. Long-term efficacy of adalimumab for mucosal healing has been seen in patients treated for up to 2 years [77].

For patients with mild-to-moderate UC who failed infliximab or were intolerant, adalimumab provides a 49.5% chance of remaining colectomy-free at 23 months based on a small single-center series [78].

Currently, larger randomized controlled trials are in progress to assess the benefit and role for adalimumab in the treatment of UC. It offers several advantages to infliximab treatment; however, current data for long-term remission are still needed.

Safety

With biologic therapies targeting specific factors involved in immunosurveillance, concerns over side effects and safety have been monitored with both short- and long-term trials. This section will briefly discuss the clinical precautions that should be taken for patients receiving biologics and safety monitoring concerns. Substantial reviews of this topic exist in other publications [79].

A history of TB exposure should be taken and a purified protein derivative (PPD) or Quantiferon assay or chest x-ray be performed in patients who are going to receive any anti-TNF agent [80]. TNF is a central cytokine in the control of mycobacterial infection. Inhibition of this pathway can lead to reactivation and dissemination of infection. Hepatitis B reactivation is a smaller concern; however, reactivation has been reported, and therefore hepatitis B surface

and core antibodies should be checked [81]. The data are less clear cut with regard to patients with a history of malignancy or dysplasia, and appropriate evaluation should be pursued.

A meta-analysis of 24 trials in CD using TNF antagonists evaluated three major safety concerns: death, malignancy and serious infection. There was no difference in death between anti-TNF and control groups for all trials (0.21 vs 0.05%). Malignancy was found in five patients receiving open-label treatment in studies prior to those that included placebo randomization; however, the overall frequency was not different (0.24 vs 0.39%). Serious infections were also similar between groups (2.09 vs 2.13%) [82].

Infectious complications are varied. In a series of 500 anti-TNF-treated patients, 48 had an infection requiring antimicrobial treatment, 20 had serious infection needing hospitalization and two died of sepsis [83]. For those on other immunosuppressive treatment, there appears to be an increased risk of fungal infections and opportunistic infection [84,85].

Malignancy, a potentially longer-term side effect, is a rare but reported event with monoclonal antibody treatment. Lymphoma risk has been discussed as a possible side effect, but it is unclear if increased risk is due to treatment or the underlying disease [86]. A series of 18 patients with hepatosplenic T-cell lymphoma, an aggressive cancer, was reported in infliximab-treated patients [87]. To date, this number is close to 28 [88]. The combination of an anti-metabolite and anti-TNF appears to be important in the development of this lymphoma. In fact, hepatosplenic T-cell lymphoma has been described in association with azathioprine/6-mercaptopurine alone in the absence of an anti-TNF agent but the reverse has not been seen. Longer-term data across all agents is still needed to better understand the malignancy risk of these medications.

Antibodies to monoclonal drugs & autoimmunity

Monoclonal antibody therapy is complicated by the potential for the human immune system to form antibodies to these drugs. Antibodies can be formed to the Fv and Fc regions or to murine epitopes [89]. In fact, the ability of patients to develop antibodies to the biologic agent is not necessarily reliant on whether the antibody is murine or human but whether there is a greater degree of foreignness. In ACCENT I, the development of antibodies was: 30% in the episodic treatment group, 10% in the 5 mg/kg maintenance group and 7% in the 10 mg/kg maintenance group. Concomitant immunomodulator therapy was associated with a slightly lower rate of antibody formation [90]. Clinical response and clinical remission, however, were not related to the presence of antibodies at week 54. A smaller cohort published by Baert *et al.* showed that in patients receiving 5 mg/kg infliximab for induction, 61% developed antibodies. A concentration of 8.0 μg/ml or greater was associated with a shorter duration of clinical response and a 2.40 increased risk of infusion reactions [91]. However, it is clear from these studies that maintenance therapy is a potent inhibitor of antibody development and should be used in all patients.

Other trials have also reported data with regard to antibody formation. In the GAIN study, no patients developed anti-adalimumab antibodies, but the presence of drug in the blood may have affected the assay. Two patients out of 299 in CLASSIC I developed antibodies to adalimumab. In CLASSIC II, 2.6% of patients had anti-adalimumab antibodies. These patients were not on other immunosuppression and the antibodies did not appear to affect their remission at week 56. Antibodies to certolizumab were also measured in PRECISE (9% of patients positive after induction) but these did not seem to impact clinical response. Also, as alluded to previously, the presence of antibodies to the anti-TNF agents is not a reason to change therapy. Most antibodies to monoclonal antibodies do not alter metabolism or activity.

Thus, to reduce immunogenicity of infliximab, doses should be given in a scheduled nonepisodic fashion. Immunomodulator therapy and pretreatment with hydrocortisone 200 mg may further reduce antibody formation [92]. If one suspects that a patient is losing response to therapy, measuring the drug level (since the antibody maybe clearing the drug more rapidly) may be useful to determine change in dose, schedule or agent [89].

Autoimmunity, or the development of antinuclear antibodies and anti-dsDNA antibodies, is another important issue related to monoclonal antibody treatment. After 24 months of anti-TNF treatment, 56.8% of patients were noted to have positive antinuclear antibodies, most occurring in the first few months of treatment. Most of these were anti-dsDNA antibodies. Female sex and the development of a facial rash were associated [93]. These antibodies might portend an increase risk for adverse events [94]. A true lupus-like reaction has been poorly characterized in this patient population as serum sickness reactions related to anti-TNF therapy may mimic the signs and symptoms of systemic lupus erythematosus.

Infusion reactions

Antibodies to infliximab are thought to be related to some of the infusion reactions seen. Infusion reactions to infliximab occur in approximately 5–20% of patients [95]. Infusion reactions can either be acute (within 10 min up to 24 h) or delayed (up to 5–7 days after infusion). In ACCENT I, patients with antibodies to infliximab had a 12% absolute increase in infusion reactions [90]. Data from our own infusion center have documented an overall incidence of infusion reactions of 6.1%, most of which were mild [96].

Acute infusion reactions can have symptoms including flushing, headache, dizziness, chest discomfort, fevers and stridor [92]. The overwhelming majority include nonallergic-type reactions with direct release of mediators from mast cells and basophils. These can be managed by slowing the infusion rate, administering intravenous fluids, and prescribing acetaminophen, antihistamines and/or steroids.

Delayed infusion reactions, which are type III immune complex-mediated reactions, are associated with joint pain, rash and fatigue. As mentioned previously, in the setting of a positive antinuclear antibody test, these reactions can be confused with systemic lupus erythematosus. Cheifetz *et al.* reported a 0.3% incidence (n = 479) of delayed reactions, suggesting that this event is rare [96]. Prevention of delayed infusion reactions includes pretreatment with diphenhydramine, second-generation non-sedating anti-histamines, acetaminophen and, in difficult-tocontrol patients, steroids after the infusion. Increasing the dose and shortening the interval between infusions can help these patients tolerate repeat infusions.

Newer agents

Several new targets for monoclonal antibody therapy have been proposed and evaluated [97]. IL-12, IL-12/23 combination and IL-6 receptor (IL-6R) are new options for possible treatment of CD. Early anti-IL-12 data demonstrated a significant response at week 7 but remission rates across treatment and placebo groups did not differ [98]. Agents in trial include more selective adhesion molecule inhibitors (anti-α4β7 [vedolizumab]), anti-cell adhesion molecule inhibitors (abatacept) and newer anti-cytokine therapies (anti-IL-17). The development of these reagents was based upon a growing knowledge base regarding IBD pathogenesis. Earlier, less successful therapies included an anti-IL-2 receptor (anti-CD25) targeting T-cell activation, as well as basiliximab (Simulect®) and daclizumab (Zenapax®) where the preliminary findings were not strong. Clearly, as new targets are defined and specific responsive populations are identified, the landscape will change. This has been seen with anti-IL-12, which has not been met with success in follow-up clinical trials, but MLN02 still holds promise for maintenance of remission.

Expert commentary & five-year view

The last 15 years have given rise to tremendous advances in the treatment for IBD. As more information about the pathogenesis of IBD is developed, clinicians will have new drug targets to help with treatment. Currently, the field has a few efficacious monoclonal antibody treatments to help achieve a clinical response and induce and maintain remission. However, the optimal timing for the use of these medications in the treatment of IBD needs to be determined. Several investigators have become proponents of the earlier use of biologic therapies, so-called 'top-down' therapy [99]. The argument is that a more aggressive assault on the inflammatory cascade would result in better long-term control, alteration of the natural history of disease and the prevention of irreversible tissue damage that permanently alters the function of an organ. The preliminary studies support this concept and provide an option to the problematic use of steroid therapy in CD. It is also clear that combination therapy will be more advantageous than any single agent. However, such an approach leads to greater concerns about safety. If more than one immune/inflammatory pathway is inhibited, the effect on normal host defense and immunosurveillance mechanisms will more likely become evident. One glaring example of this latter concept is the development of hepatosplenic T-cell lymphoma, an unusual malignancy in the general population but one that has been seen with the combination of an anti-TNF and 6-mercaptopurine/azathioprine. While thankfully the occurrence of this adverse event is rare, it does remain a concern. One way to avoid this potential issue is to use one agent to induce remission with another used for maintenance. Such an approach would mitigate some of the concerns regarding increased safety risk. Combination therapy offers the advantage of targeting several pathways that contribute to the overall inflammatory process.

Understanding which inflammatory pathway is dominant in a given patient at the time of his or her diagnosis would be optimal in terms of designing specifically tailored therapy that would have the greatest impact in the long term. With the expansion of genomic and genetic epidemiology studies in the field, the next 5 years should also begin to offer insights into specific aspects of disease, including one's ability or inability to respond to a specific therapy [100].

There is a growing appreciation for the need to use biologic therapy earlier in the course of therapy for both CD and UC. The data to date suggest that earlier intervention results in an alteration of the natural history of the disease. However, this early intervention should be focused on patients whose clinical course would be more likely to be aggressive, such as those patients with early-onset disease, patients with fistulizing disease and patients with fibrostenotic disease. It is expected, as alluded to earlier, that if we identify markers of a more aggressive clinical course (e.g., the presence of multiple high-titer antibodies to microbial agents [anti-*Saccharomyces cerevisiae* antibodies/antineutrophil cytoplasmic antibodies/ antibodies against CBir flagellin]), early intervention will also be the normal course in such patients.

Thus, the future of monoclonal antibody treatment for IBD will see not only the development of new agents focused on novel targets but also the refinement of standard use of the current agents, addressing not only efficacy and safety, but also answering the questions regarding optimal monitoring of response, avoidance of immunogenicity, and improvements in endoscopic healing and quality of life.

Key issues

- Monoclonal antibody treatment has been shown to be effective for the induction of clinical remission, response, endoscopic healing and longer-term outcomes for quality of life, hospitalizations and surgeries.

- TNF-α levels are increased in Crohn's disease and, to a lesser extent, in ulcerative colitis, making it an ideal target for anti-TNF monoclonal antibody therapy.
- Other cytokines/chemokines/adhesion molecules involved in the inflammatory pathway in inflammatory bowel disease could serve as suitable drug targets in the future. Proof-of-concept relating to the importance of each of these specific factors will require testing in well-defined patient populations. Different patients probably utilize distinct pathways.
- Immunogenicity of a monoclonal antibody can be a limiting factor in the use of these agents. Adjunct immunosuppression can help to overcome this but the best approach is the use of regularly scheduled maintenance infusions.
- Antibody and drug level measurement can help to guide treatment in patients who lose response.
- Infusion reactions should not preclude further therapy. Treatment with medications or adjusting the infusion rate can help to overcome such reactions.
- Future use of combination biologic therapy targeting distinct processes is likely but will be governed by safety concerns.

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Table 1

Clinical response induction data for monoclonal antibodies for Crohn's disease.

Author/trial	Treatment groups/induction dose	Response rate	Response definition	Patient population	Comment	Ref.
Infliximab						
Targan *et al.*	Placebo	17%	CDAI decrease of 70 points at week 4	Moderate-to-severe CD	This was the first study so patients were consequently naive to biologic therapy by definition and were sicker overall (hence very low placebo rate)	[12]
	5 mg/kg	81%				
	10 mg/kg	50%				
	20 mg/kg	64%				
		65% overall				
ACCENT I	Week 0: 5 mg/kg Week 2 and 6 and 8 weeks after: placebo (group 1) 5 mg/kg (group 2) 5 mg/kg for weeks 2 and 6, and 10 mg/kg for every 8 weeks (group 3)	58% at 2 weeks	Decrease of CDAI 70 points from baseline and 25% reduction in total score at week 2	Active CD with CDAI: >220	By definition, only those who responded to 5 mg/kg could advance in this trial, which skews the overall data. However, this sets the stage for dose escalation in those who lose response	[15]
Adalimumab						
CLASSIC I	Week 0/2:		Remission as defined by CDAI <150 at week 4	Moderate-to-severe CD naive to anti-TNFs	Remission rates were comparable to those achieved with infliximab	[26]
	Placebo	12%				
	40/20 mg	18%				
	80/40 mg	24%				
	160/80 mg	36%				
CHARM	Week 0: 80 mg Week 4: 40 mg	91% of patients who received this dose met the week 4 end point	Decrease in CDAI >70 points from baseline at week 4	Moderate-to-severe CD	Primary end point of trial was remission at week 26/54	[29]
GAIN	Week 0/2:		Response was CDAI 70-point decrease from baseline or CDAI >100	Patients with persistent symptoms or intolerant to infliximab	Showed that patients could be safely and effectively switched to Humira® after losing response to infliximab	[32]
	Placebo	CDAI 70: 34%				
		CDAI 100: 25%				
	160/80 mg	CDAI 70: 52%				
		CDAI 100: 38%				
Certolizumab						

Author/trial	Treatment groups/induction dose	Response rate	Response definition	Patient population	Comment	Ref.
PRECISE 1	Week 0, 2 and 4 and then every 4 weeks		Decrease of CDAI of 100 points at week 6	Moderate-to-severe CD, CRP >10	High placebo rate obscured clinical effect	[36]
	Placebo	27%				
	400 mg	35%				
PRECISE 2	Week 0, 2 and 4	64%	Decrease of CDAI of 100 points at week 6	Moderate-to-severe CD	Study was designed for maintenance, not to evaluate induction	[39]
	400 mg					
Natalizumab						
Gordon *et al.*	One infusion		Remission as defined by change in mean CDAI at 2 weeks and remission (CDAI <150)	Mild-to-moderate CD		[46]
	Placebo	8%				
	3 mg/kg	39%				
Ghosh *et al.*	Two infusion 4 weeks apart		Remission as defined by CDAI <150 at week 6	Moderate-to-severe CD (CDAI 220–450)	There was a signal for efficacy at week 8 (preset primary end point) but this was not significant. Had a statistically significant benefit at other time points	[47]
	Placebo	17%				
	3 mg/kg + placebo	20%				
	3 mg/kg + 3 mg/kg	29%				
	6 mg/kg + 6 mg/kg	16%				
ENACT-1	Week 0, 4 and 8		Response at week 10 as defined by reduction in CDAI by 70 points from baseline and remission (CDAI <150)	Moderate-to-severe CD	Did not achieve primary end point but thought to be related to high placebo response and inclusion of patients with low CRP (no active inflammation)	[48]
	Placebo	Response: 49%				
		Remission: 30%				
	300 mg	Response: 56%				
		Remission: 37%				
ENCORE	Week 0, 4 and 8		Response as defined by decrease in CDAI by 70 points from baseline at week 8 and sustained to week 12	Moderate-to-severe CD with elevated CRP	Established that this agent was effective at maintaining remission	[49]
	Placebo	32%				
	300 mg	48%				

CD: Crohn's disease; CDAI: Crohn's disease activity index; CRP: C-reactive protein; TNF: Tumor necrosis factor.

Table 2

Long-term clinical remission for monoclonal agents in Crohn's disease.

Author	Agent	Remission rate	Remission definition	Comments	Ref.
Infliximab					
Rutgeerts *et al.*		Week 48	CDAI <150 at each 4-week evaluation	Enrolled patients from Targan *et al.*'s 1997 study [12] who had a clinical response	[101]
	Placebo	19%			
	Infliximab 10 mg/kg every 8 weeks	35%			
ACCENT I	Group 1: infliximab 5 mg/kg + placebo	Week 30: 21%	CDAI <150 at week 30	Confirms that infliximab is effective at maintaining remission but there is a gradual loss of response either due to ATIs or alternate pathway of inflammation	[15]
		Week 52: 14%	Time to loss of response at week 52		
	Group 2: infliximab 5 mg/kg + 5 mg/kg (group 2	Week 30: 39%			
		Week 52: 28%			
	Group 3: infliximab 5 mg/kg + 5 mg/kg for weeks 2 and 6 and 10 mg/kg every 8 weeks	Week 30: 45%			
		Week 52: 30%			
Adalimumab					
CHARM	Week 0: 80 mg		CDAI <150 at weeks 26 and 52	Like infliximab, Humira® is effective at maintaining remission	[29]
	Week 4: 40 mg then:				
	Placebo	Week 26: 17%			
		Week 52: 12%			
	Adalimumab 40 mg every other week	Week 26: 40%			
		Week 52: 36%			
	Adalimumab 40 mg weekly	Week 26: 47%			
		Week 52: 41%			
CLASSIC II	Randomized arm:		CDAI <150 at week 56	Randomized patients were in remission after 4-week induction; open-label patients were not in remission	[27]
	Placebo	44%			
	Adalimumab 40 mg every other week	77%			
	Adalimumab 40 mg weekly	83%			
	Open label:				
	Adalimumab 40 mg every other week	46%			
Certolizumab					

Author	Agent	Remission rate	Remission definition	Comments	Ref.
PRECISE 1	Week 0, 2 and 4 and then every 4 weeks		CDAI <150 at week 6 and 26	Moderate-to-severe CD, CRP ≥10	[36]
	Placebo	10%			
	Certolizumab 400 mg	14%			
PRECISE 2	Placebo	All: 28%	Remission at week 26 and remission in the group with elevated baseline CRP	Moderate-to-severe CD	[39]
		Elevated CRP: 48%			
	Certolizumab 400 mg	All: 26%			
		Elevated CRP: 42%			
PRECISE 3	Certolizumab 400 mg every 4 weeks	41% 12 months	Remission was Harvey–Bradshaw Index <4	Continuation of patients from PRECISE 2 who received drug	[40]
		36% 18 months			
		33% 24 months			
		26% 30 months			

ATI: Antibodies to infliximab; CD: Crohn's disease; CDAI: Crohn's disease activity index; CRP: C-reactive protein.