Infliximab: A Review of its Use in the Treatment of Crohn’s Disease

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Abstract: Infliximab is a chimeric monoclonal antibody to human tumor necrosis factor alpha. While its use was developed in the treatment of rheumatologic diseases its effects on Crohn’s disease have revolutionized the management of this chronic illness. Infliximab has effects on both immune and epithelial cells leading to a reduction in gut inflammation and collagen deposition which promotes wound healing. Large randomized trials have proven efficacy of the drug in luminal and fistulizing Crohn’s disease. Over time our understanding of antibody formation and long-term tolerability of the drug have refined our use of infliximab, eliminating episodic dosing and utilizing concomitant immunomodulator therapy to improve efficacy. Questions remain regarding top-down strategies, length of therapy, cost, reduction in surgical procedures, and the determination of which patients will respond best to any strategy chosen.

Keywords: infliximab, Crohn’s disease, tumor necrosis factor, top-down
Introduction to Infliximab

Crohn’s disease is an inflammatory disorder of the gastrointestinal tract affecting nearly one million people in the United States and Europe. The disease is characterized by luminal-intestinal and extraintestinal manifestations mediated by an inflammatory cascade characterized by tumor necrosis factor alpha (TNF-alpha). The natural history of this disease is notable for a relapsing and remitting course with frequent fibrostenosis and/or fistulae often requiring surgery. Historically the disease has been treated with a variety of anti-inflammatory medications and immune modulators such as aminosalicylates and corticosteroids with mixed results. However, the advent of ‘biologic’ therapies over the past 15 years has revolutionized the treatment of this potentially devastating disorder. While numerous biologics are under evaluation for the treatment of Crohn’s disease, focusing on a variety of anti-inflammatory medications and immune modulators including tumor necrosis factor alpha, IL-12, interferon-chi, IL-6 receptors, inhibitors of adhesion molecules and growth factors, it is only infliximab (Remicade®, Centocor Incorporated, Horsham, PA, USA) that has been widely studied over the past 10 years of clinical practice.

Infliximab is a chimeric monoclonal antibody to human TNF-alpha. Initially studied in rheumatic disease, its use has now expanded to inflammatory bowel disease, ankylosing spondylitis, plaque psoriasis, rheumatoid arthritis, and acute graft versus host disease. Additionally, while its role has traditionally been for refractory Crohn’s disease, recent evidence suggests that more liberal use early in the course of disease may be beneficial in decreasing corticosteroid use as well as acquiring/maintaining clinical remissions. Questions regarding clinical setting, timing, dosing, safety, and length of therapy are frequently encountered in clinical practice. This review serves to highlight the clinical evidence for infliximab in Crohn’s disease with an emphasis on the above clinical conundrums.

Mechanism and Pharmacokinetic Profile of Infliximab

Infliximab is a chimeric IgG1 monoclonal antibody (149.1 kDa) directed against TNF-alpha. It is composed of murine variable and human constant regions and consists of approximately 75% human and 25% murine components. Infliximab has very limited cross-reactivity and binds only to human and chimpanzee TNF-alpha. Binding with high affinity to soluble and transmembrane forms of TNF-alpha it inhibits the binding of TNF-alpha with its receptors. Infliximab specifically neutralizes TNF-alpha and does not neutralize lymphotoxin. Cells expressing transmembrane bound TNF-alpha bound by infliximab can be lysed in vitro by complement or effector cells. Anti-TNF-alpha agents reduce production of chemokines and prevent up-regulation of endothelial adhesion molecules during in vitro studies.

Evidence indicates that infliximab has effects on both immune cells and epithelial cells. Specifically, monocytes and lamina propria T lymphocytes are induced to apoptosis when exposed to infliximab. These effects on lamina propria T lymphocytes are highlighted by the failure of the anti-TNF-alpha drug etanercept to improve clinical outcomes in Crohn’s disease. Investigators looking at etanercept versus infliximab function found that only the latter induced peripheral and lamina propria lymphocyte apoptosis when compared with a control antibody. Furthermore, there is suggestion that infliximab inhibition of TNF-alpha reduces gut inflammation by decreasing intestinal permeability. This permeability is likely key in the pathogenesis of Crohn’s disease. Clinically, infliximab reduces infiltration of inflammatory cells and TNF-alpha production in inflamed areas of the bowel. It has also been proposed that TNF-alpha blockade with infliximab down regulates the CD40/CD40L pathway in the mucosal microcirculation leading to an anti-inflammatory effect. This pathway could decrease interactions between the intestinal microvasculature and T cells. Finally, infliximab appears to affect fibroblast migration inhibiting collagen deposition and thereby facilitating intestinal wound-healing.

Infliximab is administered intravenously as infusions of 1–20 mg/kg over two hours. When this is done there is a linear relationship between the maximum concentration and area under the curve. Infliximab remains mostly within the vascular compartment with an apparent volume of distribution of 3–6L. Mean population elimination half-lives have been found to range from 7–18.5 days. No accumulation has been noted when dosed at every 4 to 8 week intervals. Importantly, in one study clearance
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was found to be 2.7 times higher and elimination half life was 34% lower in the presence of antibodies to infliximab (ATI). It has yet to be determined what exact serum level of infliximab is needed to exert its therapeutic effects.

Since early in the experience with infliximab it has been accepted that antibody formation to the monoclonal antibody can lead to infusion reactions and a reduction in the therapeutic efficacy over time. A number of infusion schedules have been developed for infliximab. While they were initially developed to evaluate for the greatest efficacy with respect to clinical endpoints, it emerged that certain scheduling led to increased formation of ATI. For example, in the prospective observational study of 125 patients with luminal or fistulizing Crohn’s disease by Baert et al, concentrations of infliximab and ATI were assessed before and every 4 weeks after each infusion. The patients with luminal disease received only a single dose of infliximab at 5 mg/kg, while patients with fistulizing disease received the 5 mg/kg dose at weeks 0, 2, and 6. The study cohort received an average of 3.9 infusions over a mean period of 10 months. Clinical response to infliximab was achieved in 71% of patients. 61% of patients developed detectable levels of antibody during the course of therapy while 37% of patients developed antibody concentrations greater than 8.0 mcg/mL. Those patients that received concomitant immunomodulators had a significantly lower incidence of ATI at 43% vs. 75% (P < 0.01). The presence of high antibody concentrations was associated with a shorter duration of response. Specifically, the median response was 35 days for titers greater than 8 mcg/mL versus 71 days for titers less than 8 mcg/mL (P < 0.001).

In response to the potential problem of ATI, Sandborn proposed three ‘optimization strategies’: maintenance therapy, concomitant use of immunomodulators, or infusion of corticosteroids with infliximab. In the ACCENT I trial (A Crohn’s Disease Clinical Trial Evaluating Infliximab in a New Long term Treatment Regimen) less than 10% of patients treated with maintenance infusions every 8 weeks had antibody formation versus 28% of those treated episodically. In those patients treated with episodic infusions, the rates of ATI were 38% without immunomodulators versus 16% of those on immunomodulators. When premedication with steroids was evaluated, investigators found that 26% of patients developed ATI versus 42% of placebo treated patients. Unfortunately, it remains unclear as to which immunomodulatory agents and what doses are ideal to maximize clinical efficacy, decrease antibody formation to infliximab, and minimize toxicity. While the exact regimen of concomitant immunomodulator therapy still has not been identified it is clear that clinicians should avoid drug holidays and plan for scheduled infliximab therapy.

Clinical Studies

Approval for clinical use of infliximab occurred after the typical sequence of pilot studies and controlled trials proving efficacy and safety. In May of 1998 the FDA (Food and Drug Administration) in the United States voted unanimously to approve infliximab for two indications. These indications were as a single dose for induction of remission in patients with moderate-to-severe inflammatory Crohn’s disease for whom conventional therapy was inadequate and as a three dose regimen in patients with fistulizing Crohn’s disease. As clinical evidence has grown, knowledge of dosing, timing, combination therapy, the use in stricturing disease, and the use in the peri-operative setting has evolved. A selection of critical studies is summarized in the following sections to highlight the evolution of the clinical applications of infliximab.

Induction of remission and maintenance in moderate-to-severe Crohn’s

Despite case reports of clinical activity of infliximab for Crohn’s disease in the early 1990s it was not until the first multicenter, double-blind, placebo controlled, and randomized trial by Targan et al was published in 1997 that infliximab was strongly considered for FDA approval. In Targan et al 108 patients with moderate-to-severe Crohn’s disease for at least six months were treated for 12 weeks. All patients were on oral corticosteroid therapy for eight weeks or more and had Crohn’s Disease Activity Index (CDAI) scores between 220 and 400. In the study 25 patients received placebo while 83 received either 5, 10, or 20 mg/kg of infliximab. At two weeks, only 17% of the placebo group responded, while 61% of the infliximab group demonstrated a clinical response (P < 0.001). The primary endpoint was reduction in CDAI by greater than 70 points at week four. Sixty-five percent
of the infliximab group and only 17% of placebo met this goal \((P < 0.001)\). The benefit of this single dose of infliximab waned by 12 weeks. At 12 weeks 24\% of the infliximab group were in remission versus 7\% of the placebo group \((P = 0.31)\). No significant difference was found between the different doses of infliximab.

To determine the efficacy of ongoing maintenance therapy with infliximab in Crohn’s disease patients with an initial response to the drug, Rutgeerts et al performed a study of recurring infusions at 10 mg/kg versus placebo.\(^{26}\) They took 73 patients with an initial response to infliximab at 4 weeks and gave the drug or placebo every 8 weeks through week 36. Interestingly, the difference in median time to loss of remission approached significance, over 48 weeks for drug versus 37 weeks for placebo \((P = 0.057)\). More importantly however was the finding that the proportions of remission were higher in the re-treatment arm at the end of the trial than at the 12 week evaluation. The remission rate at 12 weeks on therapy was 37.8\% and after 44 weeks it was 52.9\%. Remission rate in the placebo group at 44 weeks was only 20\% \((P = 0.013)\). This demonstrated that long term therapy may increase the numbers with response to the drug.

Data from the ACCENT I trial was released in 2002 looking at maintenance therapy following a single dose of infliximab.\(^{29}\) Three groups were randomized out of the 573 patients with CDAI scores of \(>220\) that responded by week 2 to a single infusion of infliximab 5 mg/kg at week 0. Group I received placebo on a schedule at weeks 2, 6, and then every 8 weeks until week 46. Group II received repeat infusions of 5 mg/kg of infliximab at weeks 2, 6 and then every 8 weeks until week 46. Group III received 5 mg/kg of infliximab at weeks 2 and 6 and then 10 mg/kg of infliximab every 8 weeks until week 46. The primary endpoints of the study were the proportion of patients who responded at week 2 and were in remission at week 30 \((\text{CDAI} < 150)\) and the time to loss of response up to week 54. The response rate at 2 weeks was 58\% of those who entered the study. At the week 30 Group I patients had a 21\% remission rate compared to Group II patients who had a 39\% remission rate \((P = 0.003)\) and Group III who had a 45\% remission rate \((P = 0.0002)\). At the 54 week mark Group I patients had a median time to loss of response of 19 weeks compared to Group II patients at 38 weeks and Group III patients at 54 weeks. This large trial solidified the notion that ongoing therapy was effective in obtaining and maintaining a remission.

**Fistulizing disease**

Crohn’s disease is divided into three phenotypic patterns; inflammatory, fibrostenosing, and fistulizing.\(^{27}\) The incidence of fistulae ranges from 17\% to 43\% in multiple series.\(^{28-30}\) A population-based study found that 83\% of patients with fistulae required surgery and that 23\% of the patients required a bowel resection.\(^{31}\) The development of a drug that could decrease these hospitalizations and surgeries could potentially decrease cost and morbidity.

Present et al made the key early evaluation of induction use in patients with fistulizing disease.\(^{32}\) 94 patients were randomized to either 5 mg/kg, 10 mg/kg, or placebo at 0, 2 and 6 weeks. The primary endpoint was defined as a 50\% reduction in the number of draining fistulae at baseline. While 56\% of those patients receiving 10 mg/kg met this endpoint, 68\% of those on the 5 mg/kg dose did. These results were in comparison to 26\% for the placebo group. The median fistula closure time was 3 months. Interestingly, 55\% of those receiving 5 mg/kg of infliximab and 38\% of those receiving 10 mg/kg had complete closure of all fistula compared with 13\% of those on placebo \((P = 0.001\) and \(P = 0.04\) respectively). The reason for the unequal response between the 5 mg/kg and 10 mg/kg dose has never been fully explained.

The efficacy of infliximab as maintenance therapy for patients with fistulae was examined in ACCENT II.\(^{33,34}\) In this trial, 195 patients who had at least 50\% of their fistulae closed over one month on infliximab induction with 5 mg/kg at 0, 2 and 6 weeks were randomized to receive infliximab 5 mg/kg or placebo every 8 weeks through 46 weeks of treatment. The primary efficacy endpoint was defined as the time to loss of fistula response (defined as a less than 50\% reduction from baseline in the number of draining fistulae or by the need for other medical/surgical intervention). The results demonstrated that the median time to loss of response was over 40 weeks for the infliximab maintenance group. The placebo group had a median loss of response at 14 weeks \((P < 0.001)\). Additionally, the efficacy of infliximab did not depend on the baseline number of fistulae in each patient.
Based upon these studies the use of infliximab at 5 mg/kg with induction at 0, 2, and 6 weeks followed by every 8 week maintenance therapy became the standard of care for biologic therapy of fistulizing disease. However, it is important to note that a significant proportion of patients did not respond to infliximab, regardless of dose. Specifically, 32% of patients did not respond to the 5 mg/kg of infliximab dosing at the 14 week mark. The relatively high failure rate in fistulizing and luminal Crohn’s along with frequent recurrence of fistulae ultimately led to the strategy of dose intensification.

**Dosing and timing**

In the 11 years since the FDA approved infliximab for use in Crohn’s disease there have been a number of trials designed with the purpose of refining scheduling, dosing, and timing of the drug. One of the most significant changes has been the move to scheduled treatment strategies versus single dose or episodic therapy. This move has been applied to the treatment of adults with both luminal and fistulizing Crohn’s as well as to the pediatric population.

In 2004 Rutgeerts et al performed a subgroup analysis of data from ACCENT I and determined that the efficacy of scheduled infliximab was better than episodic treatment. Specifically, CDAI scores were significantly improved in the 10 mg/kg scheduled maintenance group from weeks 10–30. Additionally, a greater proportion of scheduled patients achieved mucosal healing at week 54 (P = 0.041). It was noted that the scheduled groups had fewer hospitalizations and fewer developed ATI than those in the episodic group without an increase in side effects.

Additional subgroup analysis of ACCENT I by Rutgeerts looked specifically at dosing schedules with respect to endoscopic healing of mucosal ulcerations and led to further support for maintenance dosing. In this study the primary outcome was absence of all mucosal ulcerations during ileocolonoscopic examinations at week 10 with a secondary endpoint at week 54 or at both weeks 10 and 54. Complete mucosal healing occurred significantly more frequently with scheduled maintenance dosing compared with episodic treatment at week 10 (P = < 0.001) and week 54 (P = 0.026).

Similar data was found in studies related to fistulizing Crohn’s disease. Beyond the original work by Sands, data has been found showing decreases in hospitalizations and surgeries in maintenance therapy versus episodic dosing. In one study comparing scheduled with episodic dosing, rates of clinical remission were higher in the scheduled group and this was associated with a detectable trough serum infliximab level. Additionally, this detectable trough level was associated with a decreased C-reactive protein level and a higher rate of endoscopic improvement when compared to episodic therapy. The levels of C-reactive protein and trough levels may further be affected by concomitant immunosuppressives often used in Crohn’s treatment lending credence to the idea of top-down therapy.

**Issues with antibody formation—development of top down strategies**

Early in the use of infliximab it was apparent that patients on concomitant immunosuppressives, such as azathioprine or methotrexate, tended to have longer response durations with infliximab and improved clinical response rates. The finding that human ATI occurred and were associated with increased infusion reactions and decreased clinical response led to research on combining therapies. In 2003, Baert et al studied ATI in a cohort of 125 patients with Crohn’s disease who were treated with infliximab. ATI were detected in a total of 61% of patients. Interestingly, concentrations of ATI of 8 mcg per milliliter or greater before an infusion predicted a shorter duration of response to infliximab; 35 days versus 71 days (P < 0.001). An increased risk of infusion reactions was associated with that same level of ATI. Importantly, they found statistically significant data that concomitant immunosuppressive therapy was predictive of low titers of ATI and high concentrations of infliximab four weeks after an infusion leading to the belief that this regimen may improve therapeutic efficacy of infliximab.

While other studies have found lower levels of ATI formation, the clinical implications of ATI are appreciated. In the ACCENT I trial only 6% of patients on immunosuppressives and infliximab formed antibodies compared to 18% on infliximab alone. A post-hoc analysis of this data showed that scheduled dosing of infliximab was likely the strongest predictor of response to infliximab versus concomitant immunomodulators. This was echoed in further
studies showing that scheduled dosing led to increased serum trough concentrations of infliximab and that this predicted a higher rate of clinical remission, endoscopic improvement, and lower C-reactive protein levels. More recently Van Assche et al studied the use of ongoing combined therapy with immunosuppressives versus interruption of this combination after six months. They found that combined therapy led to increases in median infliximab trough levels and decreased C-reactive protein but no clear benefit in endoscopic resolution of Crohn’s disease or proportion of patients requiring a decrease in infliximab dosing. These potentially conflicting data have led to questions about timing of discontinuation of the immunosuppressive medications.

Knowing that patients with concomitant use of infliximab and immunomodulators seem to have improved clinical response rates, researchers developed the theory of a ‘Top-Down’ approach to Crohn’s management. This new approach was in contrast to the traditional ‘Step-Up’ therapy using corticosteroids with the later addition of an immunomodulator or biologic predicated on clinical response. The efficacy of top-down strategies had been previously proven in the treatment of rheumatic illnesses. Additionally, the use of infliximab early in the course of recently diagnosed Crohn’s patients showed promise in the pediatric literature. An initial pilot study in Germany in 2002 revealed that long-term use of 6-MP/Azathioprine after induction dosing of infliximab could prolong the closure of fistulae.

Questions remained about the use of infliximab as a bridge to long term immunosuppression therapy and if immunosuppressive use prior to infliximab predicted improved outcomes. Lemann et al evaluated infliximab in steroid refractory patients on azathioprine. In this trial those patients that received the three induction doses of infliximab with the azathioprine had a higher success rate in steroid independence at 24 weeks compared to those patients receiving placebo and azathioprine (57% vs. 29%; P = 0.003). While some experts utilized this data as a reason to use infliximab as a bridge to long term immunosuppressive therapy, many countered that it demonstrated the need for further testing with use of infliximab and immunosuppressives together over the long-term especially since the risk of ATI increases if infliximab was to be considered for use again. In 2006, Hommes et al published a trial of top-down versus step-up therapy. 133 patients with severe Crohn’s (CDAI > 220) naïve to treatment with glucocorticoids, immunosuppressives, or infliximab received 3 infusions of infliximab and azathioprine 2–2.5 mg/kg/day (top-down) versus topical budesonide or oral glucocorticosteroids 40 mg/day (step-up). The primary endpoint was remission at 6 and 12 months. They found that induction therapy was successful in 81% of the top-down group at 10 weeks versus 60% in the step-up group. Moreover, remission without resection or glucocorticoid use was seen in 60% of the top-down group versus 41% of the step-up group (P = 0.03). Interestingly, the top-down strategy had nearly 100% response to infliximab versus 60%–70% in the step up approach with significantly better control of fistulae. The early combined immunosuppression group had remission rates of 60% versus 35.9% for the controls at 26 weeks (P = 0.0062). The difference remained significant at 52 weeks with 61.5% of the top-down patients in remission versus 42.2% of the control patients. However, these results could not delineate whether it was the infliximab, azathioprine, or combination therapy that out-performed the control. Additionally, the design of this study was criticized as it allowed for episodic infusions of infliximab, a practice no longer considered standard. Moreover, clinical practice guidelines recommend starting immunosuppressives with the first course of glucocorticoids which was not done in this study and may have weakened the step-up regimen, regardless of whether or not this is commonly done in clinical practice.

These questions were ultimately addressed by two trials released in 2008. Feagan et al demonstrated that the use of infliximab and methotrexate showed no advantage in time to treatment failure at 50 weeks when compared with infliximab alone. However, this data did not have an arm to compare either regimen to methotrexate alone. The SONIC trial by Sandborn et al evaluated patients with moderate-to-severe Crohn’s disease who were naïve to immunomodulators and biologic therapies and were subsequently randomized to azathioprine monotherapy, infliximab monotherapy, or combination therapy. At 26 weeks the primary endpoint of steroid free clinical remission was achieved in significantly more patients in the combination group than either of the monotherapy
groups. In 2009 Sandborn reported his SONIC data in abstract form to 52 weeks. He found that 72% of combination therapy patients had steroid free remission versus 60.8% in the infliximab alone group or 54.7% in the azathioprine monotherapy group when evaluating only the 280 patients that continued in the extension of the original study. The advantage of combination therapy over azathioprine monotherapy was statistically significant (P = 0.01), although the difference between combination therapy and infliximab alone was not statistically significant (P = 0.065). The trial was criticized for lack of dose escalation of azathioprine as no thiopurine metabolite monitoring was performed. All patients received a fixed dose of azathioprine at 2.5 mg/kg/day.

It is important to remember that this trial was not a comparison of top-down strategies versus traditional corticosteroid based step-up strategies. In clinical practice, many physicians may elect to initiate co-therapy with both an immunomodulator and infliximab based on physician preference, severity of the patient illness, or other clinical factors deemed significant by the treating physician. However, for patients who are being initiated on infliximab and are not already taking an immunomodulator it is reasonable to use the infliximab as monotherapy based upon current evidence. In patients being started on infliximab who are already taking an immunomodulator, it may be appropriate to discontinue the immunomodulator after six months of combination therapy. Additionally, if a patient has been on combination therapy it may be reasonable to discontinue the immunomodulator and follow clinical status.

Strictures and stenoses

Strictures and stenoses of the small bowel and colon are one of the most common complications of Crohn’s disease. They are a frequent cause of obstruction leading to surgery and increased morbidity. While the pathogenesis and cascade of persistent inflammation progressing to fibrostenotic narrowing and stricture is not well delineated, it is appreciated that there often is a continuum from inflammatory stenosis to fibrotic stricture and that there may be overlap.

It has been postulated in the clinical literature that the rapid healing promoted by infliximab could lead to fibrosis in the submucosa and muscularis propria causing stricture formation. Additionally, it has been described that TNF-alpha may be anti-fibrotic and therefore inhibition of this molecule may lead to fibrosis. Initial reports early in the use of infliximab highlighted the apparent association between the medication and formation of stenoses, strictures, or obstruction. Lichtenstein found that stricturing disease rendered a higher probability of not responding to therapy with infliximab in a prospective evaluation of his first 31 patients treated with the drug. However, these early reports were all limited by small numbers of patients.

Lichtenstein et al later reviewed the ACCENT I and TREAT registry and that data resulted in a different conclusion. Multivariate analyses were used to evaluate the frequency of occurrence of stenoses, strictures, or obstruction in patients treated with infliximab. These analyses demonstrated that infliximab was not associated with these complications, while severity at time of onset, duration of disease, and new corticosteroid use were. One of the conclusions was that a possible bias existed in the early studies for patients with the most severe disease. A recent retrospective study looked at 31 patients with symptomatic strictures treated with infliximab after failure of conventional medical treatment. The conclusion of this study was that infliximab may be effective in patients with symptomatic strictures and should be considered as a rescue therapy before surgery is undertaken. Additionally, evidence from 2004 shows that infliximab is anti-fibrogenic. Conclusions from this data, case reports showing that infliximab does not worsen preexisting stenoses, and that it may actually decrease the need for surgery have led experts to recommend its use in this setting. The difficulty remains in making a clinical determination of which strictures have an inflammatory component and would benefit from medical treatment. Surgery will remain a viable option for all stricturing disease but any therapy that can decrease the need for surgery should improve overall cost and morbidity.

Surgical considerations

Despite the advances in the medical treatment of Crohn’s disease, surgery remains an important part of the treatment of the disease. It is estimated that up to 80% of Crohn’s patients will require a surgical procedure within 20 years after diagnosis. In the pre-infliximab era a rate of surgery by three years from
diagnosis was 24% with ileocecal resection being the most commonly performed surgery. Even with the liberal use of immunosuppressant medications over the 25 years before infliximab was approved, no decrease in the need for surgery was seen. It remains unfortunate that surgical resection is not curative, with 70%–90% of patients developing recurrence of their disease within one year after resection. Issues with surgical therapy and infliximab include complications associated with peri-operative use and use to prevent the early recurrence of stricturing or fistulizing disease.

A retrospective study of 270 patients who received abdominal surgery for Crohn’s disease was performed with the goal of assessing if immunosuppression or infliximab increased post-operative complications including sepsis, anastomotic leak, intra-abdominal abscess, and extra-abdominal infections. Infliximab was utilized in 52 of these patients. Results of the study indicated that early complications after elective abdominal surgery for Crohn’s disease were not associated with steroid dose, immunosuppressive therapy, or infliximab use. However, there was a non-significant trend toward increased risk between preoperative steroids and complications. Marchal et al also found that infliximab used peri-operatively did not increase the risk of complications in Crohn’s disease.

It appears that infliximab use in the peri-operative time period may actually decrease the risk of recurrence. A pilot study was performed looking at seven patients with surgical treatment for intestinal Crohn’s disease treated with infliximab given 4 and 8 weeks after surgery followed by repeated infusions at 8 week intervals. These patients were compared to 16 controls treated with mesalamine after surgery. While the mesalamine group had combined endoscopic and clinical recurrences at two years of 73%, the infliximab group had no signs or symptoms of recurrence. A more recent study by Regueiro et al prospectively studied 24 patients with ileocolonic resection and administered infliximab within 4 weeks of surgery and then at weeks 2 and 6 followed by recurrent infusions every 8 weeks for a total of 54 weeks. Endoscopic recurrence at one year was significantly lower in the infliximab group versus the placebo control (9.1% vs. 84.6%, P = 0.0006). Histologic recurrence was also significantly less in the infliximab group (27.3% vs. 84.6%, P = 0.01). Contrary to these studies is a recent retrospective look at post-surgical outcomes in patients who were on infliximab before surgery. In this study, 60 patients who were on infliximab within 3 months prior to ileocolonic resection were followed for 30 days after surgery. These patients were compared to 329 patients who did not have infliximab prior to ileocolonic surgery. On multivariate analysis of this retrospective data it was found that there was an association between infliximab use and readmission, sepsis, and intra-abdominal abscess. These results could be criticized for their retrospective data, small numbers, and potential bias for comparing patients with a more severe disease course to those with milder stricturing disease.

In a study looking at patients status post fistula drainage with seton placement it was found that 77% had short term improvement with respect to the perianal Crohn’s Disease Activity Index. Infliximab was given only as an induction with episodic re-administration based upon symptoms. In this setting long-term benefit to the perianal disease was seen in only 18% of patients. Given the current recognition of the shortcomings of episodic infliximab infusions, the question remains as to whether or not scheduled maintenance therapy could sustain or even improve upon the effects seen in the short-term follow-up in this study. Additional multi-center, randomized, controlled studies need to be performed to further delineate the potential benefits and harms of infliximab in the peri-operative setting. However, the initial data provides hope that the overall costs and morbidity associated with this illness may be better controlled with anti-TNF therapy.

Immune-mediated extra-intestinal manifestations

Extra-intestinal manifestations (EIM) of IBD occur in approximately 25% of patients. EIM are a significant source of morbidity in Crohn’s patients. EIM are divided into the immune mediated diseases of the joints, eyes, and skin versus those EIM caused by chronic inflammatory changes in the bowel such as malabsorption. Infliximab has shown efficacy in a variety of the EIM but has been best studied in immune mediated joint manifestations. That noted, there is evidence that infliximab has benefit in the immune mediated ocular and mucocutaneous manifestations of the disease as well. Data from ACCENT I
demonstrate a trend toward improvement in EIM seen in that population. Additionally, case reports and small series have shown benefit of infliximab in ankylosing spondylitis, erythema nodosum, psoriasis, uveitis, and pyoderma gangrenosum. Finally, randomized prospective data exists for the treatment of pyoderma gangrenosum, ankylosing spondylitis, psoriasis, and peripheral arthropathy.

Safety and Tolerability

Safety issues with biologic therapies have been one of the major impediments to increased use in clinical practice. Clinicians need to be aware of the safety issues and data that have been realized over the past decade. Overall, infliximab is generally well tolerated and severe side effects are no more frequent than in patients with Crohn’s disease not receiving infliximab. However, clinical trials and post-marketing surveillance have identified multiple adverse effects of infliximab to include infusion reactions, infections, malignancy, and autoimmune phenomena. Clinicians need to be aware of the potential adverse effects associated with the use of infliximab and patients should be counseled about these toxicities prior to initiating therapy.

Any adverse event occurring during or within 2 hours of an infusion is considered an acute infusion reaction. Approximately 20% of infliximab-treated patients experience infusion reactions although most symptoms are mild and can be controlled with drugs (premedication with antihistamines or steroids) or slowing the infusion rate. The most common infusion-related events are headache, nausea, fever, chills, pruritus, urticaria, chest tightness, and dyspnea. Serious infusion reactions, such as anaphylaxis, occur in less than 1% of patients receiving infliximab. Only 3% of patients experience infusion reactions that lead to discontinuation.

Delayed hypersensitivity or serum sickness—like reactions have been associated with patients who develop ATI and a prolonged interval between infusions. Patients may experience headache, fever, rash, sore throat, myalgias, polyarthralgias, edema, and dysphagia symptoms up to 14 days after an infusion. Delayed hypersensitivity reactions have been shown to occur in up to 3% of patients. The use of concomitant immune modifiers has been shown to decrease the development of ATI and may reduce the frequency of infusion reactions. Similarly, the symptoms of delayed reactions can be mitigated with steroid prophylaxis but there is typically a loss of response to therapy. Patients who experience delayed hypersensitivity reactions could potentially benefit from switching to fully human biologic therapies like adalimumab.

Infliximab has been associated with a higher overall risk of infectious complications because of the significant role that TNF-alpha has in the immune system response to infectious organisms. The infections most commonly reported are of the respiratory and urinary tract. However, the TREAT registry and a recent long-term safety review of infliximab both confirmed that the frequency of serious infections was similar in patients receiving infliximab therapy and placebo. That stated, infliximab should not be given to patients who have an active infection and it should be discontinued if a patient develops a serious infection while receiving therapy. The concomitant use of corticosteroids with infliximab treatment has been shown to be an independent predictor for serious infections and should be avoided.

Reactivation of latent tuberculosis is a well described risk of TNF-alpha inhibitor therapy. TNF-alpha inhibitors reduce the ability of macrophages to kill mycobacteria and hinder the formation of granulomas, which sequester the mycobacteria and prevent their dissemination. Therefore, screening for latent tuberculosis infection is advised in all patients before treatment with infliximab. Screening should include a careful history, a tuberculin skin test, and a chest radiograph. Individuals who have a positive tuberculin skin test must be evaluated for evidence of active tuberculosis. If active tuberculosis is identified, then patients must be treated with a full course of therapy before initiation of treatment with infliximab. Patients diagnosed with a latent tuberculosis infection (LTBI) should, if possible, complete a full course of preventive therapy prior to infliximab administration. Clinicians may choose to initiate infliximab infusions as early as 1 month after the start of the patient’s LTBI prophylaxis regimen if the patient’s clinical condition warrants it.

Crohn’s disease and long-term immunosuppressive therapy are both associated with an increased risk of developing lymphoma. Patients undergoing immunosuppressive therapy with azathioprine or
6-mercaptopurine have a greater than 4-fold increase in the risk of lymphoma. Several clinical trials have suggested a possible link between lymphoma and anti-TNF therapy, but clinical data demonstrates that patients with Crohn’s disease treated with infliximab do not have an increased risk of lymphoma. Recently published long-term safety data for infliximab also does not establish an increased risk for developing other malignancies.

Treatment with infliximab has been shown to induce the formation of antinuclear antibodies (ANA) and anti-DNA antibodies. The development of drug-induced lupus is quite rare and only occurred in 0.2% of the patients treated with infliximab in ACCENT I and II. Fortunately, the syndrome has been promptly reversible with discontinuation of treatment.

The limited clinical data currently available shows no significant difference in pregnancy outcomes of patients exposed to infliximab during pregnancy or during breastfeeding when compared to a healthy population. Physicians should be aware that the fetus may be exposed to therapeutic monoclonal antibodies when administered to pregnant patients and the long term implications on the child’s developing immune system are unknown at this time.

**Patient Focused Perspectives**

Several studies have shown that Crohn’s disease patients suffer from reduced quality of life and lower rates of employment compared to those without the disease. The costs of treatment must be weighed against the value of controlling this morbid illness. In one recent evaluation of Crohn’s patients it was found that 68% felt that their symptoms affected their work and one fourth of these patients changed jobs due to symptoms. In contrast to this, remission of disease was associated with a return to work rate of 31% versus only 16% of those who did not reach this goal. Additionally, with remission came an increase in physical and mental function and a significant decrease in hospitalizations and surgeries. Another study reviewing ACCENT I data looked at quality of life and found that infliximab maintenance therapy provided greater improvement compared with placebo after a single dose of the drug.

Remission can be difficult to attain in a certain population of patients. Those patients that have difficulty attaining remission often utilize the greatest amount of resources for hospitalizations and surgeries. Additionally, knowing that surgery accounts for the majority of hospitalizations and costs one could postulate that prevention of surgical disease could substantially decrease overall cost of therapy. In fact, infliximab has been shown to decrease annual incidence of all surgeries and overall resource use. Furthermore, fistulizing patients on infliximab have been shown to have a significant decrease in hospitalizations, surgeries, and procedures when compared to placebo.

Based upon these results, predictions were made that infliximab could lead to overall cost savings despite its relatively high cost. In fact, in a retrospective evaluation of infliximab use in the UK it was found that use led to a significant decrease in hospitalizations, surgeries, and procedures. Additionally, a net monetary savings with infliximab use was calculated. Clearly, this is an area that requires more research as there is conflicting cost data that predated the popularity of the current infliximab maintenance regimen.

Knowing that the majority of patients on infliximab in the year 2009 will be placed on long-term maintenance therapy, the issue of tolerability becomes critical. From evaluations of utilization management it is known that few infliximab patients are non-adherent with therapy. As previously discussed, long-term maintenance therapy can increase rates of remission and prevent ATI. However, in some patient questionnaires only one third of patients on infliximab felt they were benefitting from the drug despite tolerability of the medication. Furthermore, while the majority of patients on maintenance therapy continue to have response to the medication, approximately 10% per year will lose that response. Fortunately, dose intensification with either an increase to 10 mg/kg per infusion or interval reduction to every 4–6 weeks seems to regain remission in 75% of patients. This intensification will also have an impact on long-term cost issues and will need to be explored in comparison to other healthcare costs.

Finally, if a means to predict which patients respond best to infliximab existed then clinicians could restrict use to the cohort of patients that will have the greatest benefit maximizing a cost to benefit ratio. It has been theorized that a set of clinical parameters or inflammatory labs exist that...
could make this prediction with some accuracy and precision. Unfortunately, significant data has not born this suggestion out. Numerous antibodies and genetic markers have been evaluated without consistent association to disease course and relation to specific therapeutic modalities. TNF levels were tested and found to have an association with response to infliximab in fistulizing patients but this effect has not been evaluated in a large prospective fashion and is not currently used to select patients for infliximab therapy. Additionally, while speckled anti-neutrophil antibody positivity was initially found to have a better response to infliximab its use in clinical practice has not been popularized. Other serologic markers such as anti-Saccharomyces cervisiae antibodies and perinuclear anti-neutrophil cytoplasmic antibodies have been evaluated and neither could predict response to anti-TNF therapy. Patients with increased CRP levels in the setting of active inflammation likely have the best chance of responding to infliximab. When looking at clinical parameters one consistent association with response to infliximab or lack thereof is in patients who smoke. Also, one study found that young age, Crohn’s colitis, and concomitant immunosuppressive treatment were identified as independent variables favoring short-term response to infliximab. Finally, it is appreciated that external and peri-anal fistulae seem to respond better to infliximab than do other types of fistulae. However, the overall benefit seen in fistulizing patients in large trials such as ACCENT II have led to broad use in all fistulizing patients without restriction to those with peri-anal or external disease. Overall, no major society has made recommendations on limiting the use of infliximab based upon predictive factors such as smoking status or serologies. Further research on predictive models and the ethical limitations of withholding potentially beneficial therapy will be required before broad application is common.

**Conclusion, Place in Therapy**

In 2004 a review was performed looking at clinical outcomes in Crohn’s disease from 1966–2003. The researchers found no conclusive evidence for an improvement in outcome over those 37 years during which step-up therapy was standard. Infliximab has changed this paradigm over a single decade. Infliximab has proven efficacious in the majority of patients with luminal and fistulizing Crohn’s. Additionally, many patients with significant EIM of inflammatory bowel disease benefit from the drug. Furthermore, these improvements have led to a decrease in surgeries, hospitalizations, procedures, and possibly cost. Because of this the goals of therapy in Crohn’s disease have changed. Knowing that quality of life and remission is attainable in patients with moderate-to-severe disease, physicians have become more aggressive with therapy early in the course of illness. Current consensus guidelines advocate the use of infliximab in Crohn’s disease without response to traditional step-up therapy and in fistulizing disease. However, the knowledge that steroids increase the risk of serious infection, morbidity, and mortality, makes a steroid sparing strategy a secondary goal. Infliximab with or without immunomodulators allows for many patients to attain that goal. Provided the safety data on infliximab continues to support long-term use, more clinicians will become comfortable using this drug in their practice.

Over the past decade numerous changes have been made in the dosing and scheduling of the drug. For example, it is no longer considered standard of care to dose infliximab on an episodic basis. As understanding of the relationship between biologics and immunomodulators changes our usage of infliximab will also change. Further research must address which modalities can be used to predict which patient population will respond to infliximab. Additionally, data is needed that will demonstrate which patients should receive the ‘aggressive’ top-down approach to therapy and how long treatment with immunomodulators should be continued. Finally, the balance of cost versus morbidity will need to be considered in the setting of long-term maintenance therapy and dose intensification.

Clinicians will continue to consider known indications, dosing strategies, efficacy data, safety issues, cost constraints of their own medical systems, and established guidelines to help make decisions on the use of infliximab. Physicians must realize that infliximab is not a cure for Crohn’s disease and that approximately 30% of patients treated with infliximab have little or no response to the drug. Defining why this lack of response occurs and more importantly, elucidating the etiology for Crohn’s disease will remain as goals in research for decades to come.
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Disclosures
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