

Monoclonal Antibody Use in Inflammatory Bowel Disease

Christopher E. Hayes, MD, and Carolina S. Cerezo, MD

CROHN'S DISEASE (CD), ULCERATIVE COLITIS (UC) and indeterminate colitis (IC) are chronic inflammatory bowel conditions usually collectively referred to as **inflammatory bowel disease (IBD)**. They appear to be the result of the interaction of genetics, the environment and microbiome of the gastrointestinal tract. The common pathway to intestinal inflammation seems to be immune dysfunction due to lack of balance between pro-inflammatory and anti-inflammatory cytokines.¹

Tumor necrosis factor alpha (TNF- α) has been identified as a key cytokine in the inflammatory cascade of IBD. TNF- α activates and sustains the inflammatory response and is responsible for activating other pro-inflammatory cytokine genes. It also promotes penetration of macrophages, lymphocytes, and neutrophils into inflamed tissues by stimulating the production of cell adhesion molecules by endothelial cells.¹

Therapeutic targets have focused on immunologic mechanisms that trigger inflammation in IBD. The use of corticosteroids, antibiotics, and anti-inflammatory agents such as **5-aminosalicylates (5-ASA)**, has improved the management of IBD patients. However, many patients become steroid dependent or resistant and refractory to other agents.

INFLIXIMAB

The treatment of moderate-severe CD was revolutionized by the advent of **monoclonal antibodies (MAB)** to key cytokines like TNF α . Infliximab (IFX) is a chimeric human/murine monoclonal IgG antibody, which binds TNF- α with high affinity and leads to loss of biological activity. The drug is delivered at initial doses of 5mg/kg in a two-hour intravenous infusion. Induction of remission is attempted with infusions at weeks zero, two, and six, with maintenance therapy doses every eight weeks thereafter if remission is achieved.² There is no evidence for further IFX therapy if remission has not been achieved after the three induction doses, known as primary non-response.

There is evidence that other monoclonal antibody agents are effective for patients who do not respond to IFX.³

Infliximab first showed promise for induction of remission in IBD in the late 1990s. One of the early landmark studies by Targan, et al demonstrated the effectiveness of a single infliximab infusion on clinical status in CD patients with moderate-severe disease who had failed steroid and 5-aminosalicylate therapy⁴. At four weeks post-infusion, 81% achieved clinical response and 33% achieved clinical remission. No difference was identified between groups receiving 5mg/kg and those receiving higher doses. This study and others led to FDA approval of IFX for adult CD in 1998. It was used off-label in pediatrics until it was formally approved for pediatric use in 2006. Infliximab was quickly identified as a rescue and then maintenance therapy for moderate-severe CD in pediatric patients with a variety of significant complications: steroid refractory or steroid dependent disease, penetrating disease (fistulas), and growth failure.⁵

Infliximab is currently indicated for use in luminal CD and fistulizing CD that is resistant to conventional therapies. While conventional therapy

is not specifically defined by the FDA, it may include 5-ASA, corticosteroids, antibiotics, solitary enteral feeding, or immunomodulation with methotrexate or **6-mercaptopurine/azathioprine (6-MP/AZA)**. As **immunomodulators (IM)** typically achieve maximal efficacy after three months of use, a minimum of three months is considered as a trial of IM therapy. Surgery is an alternative option prior to initiating IFX, especially for localized disease.⁶

The efficacy of infliximab has been demonstrated in multiple trials. Hanauer, et al showed that every 8 week maintenance therapy was effective in CD in the **ACCENT I trial (A Crohn's disease Clinical study Evaluating infliximab in a New long-term Treatment regimen)**.⁷ At 30 weeks of use, 39% of those who initially responded to IFX were still in remission. The recent, high profile **Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC)** trial found that use of IFX at 5mg/kg and given at zero, two, six, and every eight weeks thereafter achieved steroid-free remission for 44.4% of patients at 26 weeks compared to 30.6% ($p=0.009$) of patients taking azathioprine alone.⁸ The highest rate of steroid free remission (56.8%) was

Table 1: Indications for monoclonal antibody use in IBD

	*Crohn's Disease	*Ulcerative Colitis
Moderate-severe disease refractory to steroids	YES	YES
Moderate-severe disease dependent on steroids	YES	YES
Primary induction of remission for moderate-severe IBD	†YES	**NO
Maintenance of remission post response to induction therapy	YES	YES
Reduction in # of fistulizing Crohn's disease: 1. draining enterocutaneous rectovaginal fistula 2. maintaining fistula closure	YES	Not applicable

* adult and pediatric patients ** used as a "rescue" agent

† first line agent for penetrating or fistulizing Crohn's disease

Table 2. Side effects associated with monoclonal antibody: anti-TNF therapy

Side effects	Frequency#	Rate per 10,000
Infusion reaction : ie. Fever, rash, anaphylaxis	6.1%*	
Non-Hogkins Lymphoma***	Unknown	
SEER all ages		1.9
IM alone		3.6
Anti-TNF vs SEER		6.3
Anti-TNF vs IM alone		6.3
Death from lymphoma	0.067% (7/10,000)**	
Stop treatment due to adverse event	9.6% (1/10)**	
Death from sepsis	0.4% (4/1,000)**	
Tuberculosis ²⁷	0.05% (5/10,000)**	

***Siegel CA et al Clin Gastroenterol Hepatol2009

** Siegel CA. Practical Gastroenterology, 2007

* Hoentjen F. World Journal of Gastroenterology, 2009

Frequency of event from systematic analysis (annual)²⁶
SEER, Surveillance Epidemiology and End Results Registry
Anti-TNF, anti-Tumor Necrosis Factor
IM, immunomodulators

achieved at 26 weeks with combination therapy of IFX and azathioprine.

An initial debate as to whether IFX should be used for induction of remission only and periodic use thereafter or for maintenance therapy as well has been resolved in favor of long-term use for maintenance of remission.⁷ Recent findings from the Pediatric Inflammatory Bowel Disease Collaborative Research Group Registry showed that by years 1 through 3 of treatment with IFX, less than 10% of registry patients on maintenance therapy were receiving steroids.⁹ In fact, over years one, two, and three after induction with IFX, 26%, 44%, and 33%, respectively, had clinically inactive disease. The available evidence is strong that IFX is efficacious at inducing remission in CD and durable in maintaining remission.

The treatment of fistulizing Crohn's Disease has been a particular concern of gastroenterologists, given the significant morbidity associated with perirectal and intra-abdominal fistulas as well as abscess formation. Present, et al showed that infliximab yielded closure of 50% or more of draining enterocutaneous fistulas in 68% of study patients.¹⁰ The study also showed closure of all fistulas in 55% of study patients. Another pivotal study was ACCENT II (A Crohn's disease Clinical study Evaluating infliximab in a New

long-term Treatment regimen in patients with fistulizing Crohn's disease), where Lichtenstein, et al showed IFX maintenance use for fistulizing CD resulted in significantly fewer hospitalizations and surgeries.¹¹ The use of **thiopurines (6-MP/AZA)** for fistulas typically yield more modest benefit and IFX is now considered preferable for fistulizing CD.

Nearly 80% of patients with Crohn's Disease ultimately require surgical bowel resection.¹² While resections effectively palliate recalcitrant inflammation, reoperation rates for recurrent disease are significant: 10-35% at five years, 20-45% at ten years, and 45-50% at 20 years. A recent meta-analysis of clinical trials reporting on surgical outcomes from CD found a strong association between endoscopic findings of inflammation at 6 months after surgery and the clinical recurrence rate at one year after surgery.¹³ Available evidence is strong that IFX is efficacious for prevention of recurrence after surgery for CD. By controlling early recurrence of inflammation, IFX use after surgical resection may alter the natural history of the progression of CD and lower reoperation rates.

Growth failure is a common feature of uncontrolled IBD in children, and resumed growth trajectory indicates good disease control. Walters, et al showed im-

proved linear growth on IFX in a subset of chronically active CD who had growth failure despite steroid and IM use.¹⁴

While infliximab has been in use for moderate-severe Crohn's Disease since the late 1990s, strong evidence for use in ulcerative colitis has been more recent. The **Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2)** were randomized, double blind, placebo-controlled trials that studied the efficacy of IFX for induction and maintenance therapy for adults with UC.¹⁵ At eight weeks, 69% had a clinical response as compared with 37% who had received placebo. At week 54, 45% of patients had clinical response as compared with 20% who had received placebo. These important studies established IFX as efficacious for moderate-severe UC and, as in use with CD, 5mg/kg dosing was equally efficacious as higher dosing.

Given the establishment of infliximab as a powerful therapy for moderate-severe, complicated CD and UC, its proper place in the hierarchy of medical therapies for Inflammatory Bowel Disease has been a matter of debate among gastroenterologists. The more conservative approach has been so-called "step-up" therapy, in which traditional therapies are exhausted first before moving on to IFX. Initially, patients were managed nearly uniformly with 5-ASA compounds for maintenance and steroids for episodic flare-ups. If this proved unsuccessful, the addition of an immunomodulator (IM) such as 6-MP/AZA or methotrexate was then attempted first before contemplating the use of IFX.⁶

Patients with refractory disease typically started infliximab for induction and maintenance therapy while on an IM and continued use of both medications as combination therapy. One of the benefits of combination therapy was the prevention of antibody formation against IFX, which leads to drug reactions and loss of response.¹⁶ A recent trial comparing combination therapy with either IFX or an IM alone showed that combination therapy yields superior clinical outcomes.⁸

Given the evidence that infliximab and other monoclonal antibody medications are superior to more traditional IBD therapies, is generally well-tolerated, and may reduce a patient's need for surgery, there is current movement in the field of

Table 3. Monoclonal Antibody Agents Used for Inflammatory Bowel Disease

Agent	Mechanism of Action	Indication
Infliximab	Binds/inactivates TNF α , blocks inflammatory cascade	Moderate-severe IBD, refractory to conventional therapy
Adalimumab	Binds/inactivates TNF α , blocks inflammatory cascade	Moderate-severe IBD, refractory to conventional therapy; failure of infliximab therapy
Certolizumab	Binds/inactivates TNF α , blocks inflammatory cascade	Moderate-severe IBD, refractory to conventional therapy; failure of infliximab therapy
Natalizumab	Binds/inactivates integrin molecules \rightarrow prevents migration of inflammatory cells to tissue	Moderate-severe IBD, refractory to conventional therapy; failure of infliximab therapy

gastroenterology toward so-called “top-down” therapy. In other words, IFX and other monoclonal antibody agents would be utilized early in the disease course for moderate-severe disease.¹⁷

This approach is controversial largely due to our short experience with using IFX and other monoclonal antibody agents and the known serious side effects identified thus far. There is a black box warning on IFX for reactivation of tuberculosis, and this is regularly screened for prior to and throughout a patient’s course on IFX or other monoclonal antibody agents. There is a risk of infusion reactions of 6.1%.¹⁸ As anaphylaxis is a possibility, infusion of IFX is carefully monitored in the clinical setting. More common infusion reactions are fever, rash, dizziness, hypertension, myalgias or arthralgias. The overall risk of infection is between 0.3%–0.9%, the majority of which were pneumonias but sepsis, cellulitis and viral infections have also been noted. The risk of developing a serious infection while on IFX is 4.4 times that of a person not on immune suppression, and increases to 14.5 the risk when on a concomitant immune suppressive drug such as steroids or IM.¹⁸ Significantly, the risk of death from sepsis is 4/1,000 patient years (0.4%).¹⁹

The risk that gives most patients and provider pause is the risk of lymphoma. In a meta-analysis of 8905 patients representing 20,602 patient years, Siegel and colleagues reported that the risk of non-Hodgkin lymphoma with use of IM alone is 3.6/10,000 versus 6.3/10,000 with IFX

use (Table 2).¹⁹ With IFX use, the risk of dying from a lymphoma is seven per 10,000 IFX treated patient (0.067%).²⁰ These lymphomas are usually responsive to treatment. Out of the over one million patients treated with monoclonal antibody agents worldwide, 27 cases of the uniformly fatal **Hepato-Splenic T-cell Lymphoma (HSTL)** have been reported. In the 25 cases where data on 6-MP/AZA use was available, all 25 patients had exposure to these medications. These patients were not necessarily taking the two agents concomitantly.²¹ It is not known whether the risk for this exceedingly rare lymphoma lies in monoclonal antibody use, 6-MP/AZA use, or the combination. While the overall risk of these serious complications is small compared to known complications in IBD patients sick enough to warrant IFX use, the risk is significant enough to alter patients’ acceptance of the drug and in some cases alter physician prescribing patterns.

OTHER MAB USED IN THE TREATMENT OF IBD

Other monoclonal antibody agents currently approved for use in IBD are adalimumab, certolizumab, and natalizumab. Adalimumab is a fully humanized monoclonal antibody to TNF α , and is given subcutaneously on a biweekly basis. Certolizumab is a humanized antibody fragment to TNF α . Natalizumab is a monoclonal antibody against integrin molecules, which are involved in attracting inflammatory cells to tissues. None of

these have been shown to be more effective than infliximab at this time, and are usually used either after a patient has lost response to infliximab or if the medicine is not tolerated.

Adalimumab has been shown to be effective for induction and maintenance of remission in CD. In the **CLASSIC I trial (Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn’s Disease)**, rates of remission at four weeks of use were as high as 36% utilizing dosing at zero and two weeks of 160mg and 80mg, respectively.²² The CLASSIC II trial further showed that adalimumab is effective for maintenance of remission. 55 patients who had achieved remission by week four of adalimumab use were enrolled and randomized to receive either adalimumab every week, every other week, or placebo. The rates of remission at week 56 of the trial were 83%, 79%, and 44%, respectively.²³ The CHARM trial (Crohn’s trial of the fully Human antibody Adalimumab for Remission Maintenance) also showed promising evidence for adalimumab maintenance therapy for moderate-severe CD. Those who initially responded to the medicine showed continued remission at week 56 of about 40%, three times the rate of those in the placebo group.²⁴

There is evidence that adalimumab can be used effectively despite loss of response to IFX therapy. In the **RESEAT study (Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy)** in pediatric patients, of whom 95% had previously lost response to IFX therapy, clinical response by physician global assessment at three, six, and 12 months of use was 65%, 71%, and 70%, respectively. Steroid-free remission was achieved at three, six, and 12 months by 22%, 33%, and 42% of patients, respectively.²⁵

CONCLUSION

Monoclonal antibody therapies that target mediators of inflammation have shown remarkable efficacy in inducing and maintaining remission in moderate-severe IBD. They show the promise not only of clinical wellness, but also of the potential to change the natural history of IBD by postponing the need for surgery. While the preponderance of evidence to date is with the use of infliximab, further study of the

proper use of other monoclonal antibody therapies could provide for better therapeutic options and health outcomes for those with moderate-severe IBD.

Acknowledgement

We would like to extend our gratitude to Dr. Neal S. Leleiko for his guidance and support.

REFERENCES

- Owczarek D, Cibor D, Szczepanek M, Mach T. Biological therapy of inflammatory bowel disease. *Polskie Archiwum Medycyny Wewnętrznej*. 2009;119(1-2).
- Physician's Desk Reference. 59th ed. Montvale, NJ: Medical Economics. 2005.
- Sandborn WJ, Rutgeerts P, Enns R, Pollack PF, et al. Adalimumab induction therapy for Crohn's disease previously treated with infliximab: a randomized trial. *Ann Intern Med*. 2007;146:829-38.
- Targan SR, Hanauer SB, van Deventer SJH, Rutgeerts PJ, et al. A Short-Term Study of Chimeric Monoclonal Antibody cA2 to Tumor Necrosis Factor α for Crohn's Disease. *N Eng J Med*. 1997;337(15):1029-35.
- Vasiliauskas EA, Thomas DW, Schaffer S, Targan SR, et al. Collaborative Experience of Open-Label Infliximab in Refractory Pediatric Crohn's Disease. *Journal of Pediatric Gastroenterology & Nutrition*. 1999;29(4):525.
- St. Charles M, Weiss Smith SR, Beardsley R, Cross RK, et al. Gastroenterologists' Prescribing of Infliximab for Crohn's Disease: A National Study. *Inflammatory Bowel Disease*. 2009;15(10):1467-75.
- Hanauer SB, Feagan BG, Lichtenstein GR, Rutgeerts P, and the ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. *Lancet*. 2002;359(9317):1541-9.
- Colombel JF, Sandborn WJ, Reinisch W, Rutgeerts P, et al. Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease. *N Eng J Med*. 2010;362(15):1383-95.
- Hyams JS, Lerer T, Griffiths A, Markowitz J and the Pediatric Inflammatory Bowel Disease Collaborative Research Group. Long-term outcome of maintenance infliximab therapy in children with Crohn's disease. *Inflammatory Bowel Disease*. 2009;15(6):816-22.
- Present DH, Rutgeerts P, Targan S, van Deventer SJH, et al. Infliximab for the Treatment of Fistulas in Patients with Crohn's Disease. *N Eng J Med*. 1999;340: 1398-1405.
- Lichtenstein GR, Yan S, Bala M, Blank M, and Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedure in fistulizing Crohn's disease. *Gastroenterology*. 2005;128(4):862-9.
- Yamamoto T. Factors affecting recurrence after surgery for Crohn's disease. *World Journal of Gastroenterology*. 2005;11(26):3971-9.
- Yamamoto T. Prevention of recurrence after surgery for Crohn's disease: Efficacy of infliximab. *World Journal of Gastroenterology*. 2010;16(43): 5405-10.
- Walters TD, Gilman AR, Griffiths AM. Linear growth improves during infliximab therapy in

- children with chronically active severe Crohn's disease. *Inflammatory Bowel Disease*. 2007; 13(4): 424-30.
- Rutgeerts P, Sandborn WJ, Feagan BG, Colombel JF, et al. Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis. *N Eng J Med*. 2005;353(23):2462-76.
- Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Eng J Med*. 2003;348(7):601-8.
- Velayos FS, Sandborn WJ. Positioning biologic therapy for Crohn's disease and ulcerative colitis. *Current Gastroenterology Reports*. 2007;9(6): 521-7.
- Hoentjen F, Bodegraven AV. Safety of anti-tumor necrosis factor therapy in inflammatory bowel disease. *World Journal of Gastroenterology*. 2009;15(17):2067-73.
- Siegel CA, et al. *Clin Gastroenterol Hepatol*. 2009;7:874-81
- Siegel CA. Guide to Discussing the Risk of Immunomodulator and Anti-TNF Therapy with Inflammatory Bowel Disease Patients. *Practical Gastroenterology*. 2007;XXXI (11):14-24.
- Janssen Biotech, Inc. Medical Information Services, Inquiry #1-1313975908, Data on File, October 25, 2011.
- Hanauer SB, Sandborn WJ, Rutgeerts P, Pollack P, et al. Human Anti-Tumor Necrosis Factor Monoclonal Antibody (Adalimumab) in Crohn's Disease: the CLASSIC-I Trial. *Gastroenterology*. 2006;130:323-33.
- Sandborn WJ, Hanauer SB, Rutgeerts P, Pollack PF, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut*. 2007;56:1232-9.
- Colombel JF, Sandborn WJ, Rutgeerts P, Pollack PF, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132(1):52-65.

- Rosh JR, Lerer T, Markowitz J, Hyams JS, et al. Retrospective Evaluation of the Safety and Effect of Adalimumab Therapy (RESEAT) in Pediatric Crohn's Disease. *Gastroenterology*. 2009;104:3042-9.
- Siegel CA, Hur C, Korzenik JR, et al. Risks and benefits of infliximab for the treatment of Crohn's disease. *Clin Gastroenterol Hepatol*. 2006;4(8):1017-24.
- Wolfe F, Michaud K, Anderson J, et al. Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. *Arthritis Rheum*. 2004;50(2):372-9.

Disclosure of Financial Interest

The authors and/or spouses/significant others have no financial interests to disclose.

Christopher E. Hayes, MD, is a senior fellow in Pediatric Gastroenterology, Nutrition and Liver Diseases at Hasbro Children's Hospital.

Carolina S. Cerezo, MD, FAAP, is an Assistant Professor of Pediatrics (Clinical) at the Warren Alpert Medical School of Brown University and a full-time pediatric gastroenterologist at Hasbro Children's Hospital.

CORRESPONDENCE

Carolina S. Cerezo, MD, FAAP
Division of Pediatric Gastroenterology,
Nutrition and Liver Diseases
Hasbro Children's Hospital
593 Eddy Street, MPH 131
Providence, RI 02903
e-mail: Carolina_Cerezo@brown.edu

