

# Long-term Remission of Crohn's Disease Using Infliximab Without Human Anti-chimeric Antibody (HACA) in Absence of Anti-metabolites: A Series of Three Case Reports



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Optimal medical management of Crohn's disease has long been a challenging process. Currently, it is common practice to "stack" medications to induce remission by starting with the less toxic 5-aminosalicylic acid, then adding Azathioprine or 6-mercaptopurine and finally infliximab. Concomitant immunosuppressive therapy is employed to reduce the magnitude of the immunogenic antibody response to Infliximab, so as to enhance its medical efficacy(1). However the use of multiple agents, especially the immunomodulators, is not without its downsides such as cost, compliance, drug interactions and intrinsic toxicity of the medications. Given these concerns, it can be hypothesized whether Infliximab either alone or in combination with a less toxic first line agent could sufficiently control disease without the use of immunomodulators. Additionally, if a serial rather than random infusion method of Infliximab administration is employed, is there a lower rate of both infusion reactions and formation of HACA in the absence of immunomodulators?

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### Methods

We reviewed our Crohn's patients taking infliximab who for medical reasons could not use an anti-metabolite. Between the years 2000 to 2005, we were able to identify 3 patients from the hospital and clinics of the Kaiser Permanente Medical Center at Los Angeles who have clinically moderate/severe Crohn's disease and were placed on infliximab (1 patient) or a combination of infliximab and Mesalamine (2 patients). All were placed on the standard regimen of 5 mg/kg infusions at 0, 2, and 6 weeks with maintenance dosing every 8 weeks for 3, 4 and 2 years respectively.

### Results

All 3 patients are in remission clinically without the usage of immunomodulators. No significant side effect from infliximab, measurable level of HACA or infusion reaction was reported in any of the 3 patients.

### Conclusion

In conclusion, serial infusion of infliximab in treatment of moderate to severe Crohn's disease seems to be well tolerated within our small sample population of patients who are not taking immunomodulators. Despite the limited data, clinical remission in all of our patients suggests that infliximab, by itself or in combination with other less toxic classes of medications can achieve and maintain clinical remission in moderate to severe Crohn's disease using continual therapy rather than infusions as needed to treat flares.

## INTRODUCTION

Optimal medical management of Crohn's disease has long been a challenging process. With more classes of medications becoming readily available at the clinician's disposal, the management of Crohn's disease has changed significantly over the past decade. This is especially true with the evolution of immunomodulators and infliximab, which have had a dramatic impact on the clinical course of the disease. Currently, it is common practice to "stack" medications to induce remission starting with the less toxic 5-aminosalicylic acid and then adding an immunomodulator and finally infliximab. However, the use of multiple agents, especially the immunomodulators, is not without considerable disadvantages such as cost, compliance, drug interactions and intrinsic toxicities of the medications. These disadvantages could potentially be avoided if infliximab alone was able to sufficiently control disease as in select cases presented here.

It is currently felt that stacking medications produces an additive effect therapeutically in Crohn's disease. Also, it has been assumed that anti-metabolites are necessary to prevent the immune-mediated compromise of infliximab by formation of antibodies to infliximab (ATIs). A recent study by Baert F, et al illustrated that the magnitude of immunogenic response to infliximab was reduced with concomitant immunomodulator therapy (1). Upon examining this study protocol, it is important to note that the "on demand" infliximab therapy approach was used. All patients in this study received a series of three infusions of 5 mg/kg at weeks 0, 2 and 6 at the initiation of the study, but only those patients that had an initial response received additional treatment when they relapsed. This treatment scheme essentially "vaccinated" these patients against infliximab. Logically, upon re-treatment, or "re-challenge," of these patients with infliximab, their ATI levels would elevate and interfere with the activity of infliximab. A subsequent study by Farrell, et al found a positive correlation between ATI development and loss of response as well as increased risk of infusion reactions (2,3) This phenomenon was especially noted in patients who were treated episodically during their Crohn's flare. Patients treated with "on demand" therapy were also noted to have muted response on re-challenge. Concomitant immunomodulator therapy was used to prevent the formation of these antibodies. However, given the potential complications of immunomodulators as previously mentioned, another strategy to minimize the formation of HACA is to serially infuse patient with infliximab thus to induce immunologic tolerance in these patients. Immune tolerance with a maintenance treatment strategy was evidenced in the ACCENT I trial, where patients on maintenance therapy had significantly less ATI development (4). Furthermore, patients who developed ATIs in a maintenance regimen did not experience loss of response that is associated with antibody formation in an episodic regimen (5). Patients who were anti-

body positive did experience a 2 to 3-fold risk of infusion reaction, regardless of the treatment strategy used.

The side effects of currently available therapies are well documented. Azathioprine and 6-MP are metabolized via a competitive biochemical pathway that results in either the active agent 6-thioguanine or by a thiopurine methyltransferase (TPMT) dependent pathway into 6-methylmercaptopurine, a potentially hepatotoxic agent (6). Other potential toxicities include bone marrow suppression and the development of neoplasia after long term use (7,8). Like immunomodulators, infliximab also has had reported side effects including infusion reactions, opportunistic infections and reactivation of latent tuberculosis. Additionally, many of the immunomodulators are pregnancy category D, posing a difficult dilemma for female patients with Crohn's disease who are in their reproductive years. To date, the experience of infliximab use in pregnancy has come from The TREAT registry and a separate report of post-marketing experience. The TREAT registry was designed to monitor and assess the long-term safety of infliximab. As of 2003, no fetal malformations, differences in the rate of miscarriage or neonatal complications were reported in patients who received infliximab versus those who did not (9). Data gathered by Katz, et al reflect spontaneous reports of outcomes for women exposed to infliximab during pregnancy. These data suggest that outcomes of pregnancies associated with infliximab exposure do not differ from those of the background population (10). With FDA approval of a pregnancy category B medication label for infliximab, there have been animal studies that show no teratogenic effects, in contrast to those seen with immunomodulators. While there have been no human pregnancy studies carried out, data gathered to date suggest that the benefit of using infliximab during pregnancy may outweigh risks to the fetus and mother. Clearly, infliximab should only be given during pregnancy when it is absolutely necessary.

If anti-metabolite therapy were not essential to maintaining remission of Crohn's disease and if it were also not necessary to prevent the formation of ATIs then the treatment process would be streamlined from a variety of standpoints. Economically, a tremendous amount of time and effort has been required to moni-

tor patients on antimetabolite therapy for signs of potentially lethal side effects. By eliminating the use of Azathioprine or 6-mercaptopurine there would be no need for surveillance monitoring of 6-thioguanine, TPMT, blood counts, or liver function tests. Patient compliance also improves with a less complex medication regimen.

Given the above concerns, it can be hypothesized whether infliximab either alone or in combination with a less toxic first line agent could sufficiently control disease without the use of immunomodulators. Additionally, if a serial rather than episodic infusion method of infliximab administration is employed, is there a lower rate of both infusion reactions and formation of ATIs in the absence of immunomodulators?

### METHOD

We set out to review our Crohn's patients who are on serial infliximab infusion without receiving immunomodulators to look for their disease progression and the formation of ATIs. Between the years 2000 to 2005, we were able to identify three patients from the hospital and clinics of the Kaiser Permanente Medical Center at Los Angeles who have clinically moderate/severe Crohn's disease and were placed on infliximab (1 patient) or a combination of infliximab and mesalamine (2 patients). All were placed on the standard regimen of 5 mg/kg infusions at 0, 2, and 6 weeks with maintenance dosing every 8 weeks for 3, 4 and 2 years respectively. This regimen has been demonstrated to be effective in inducing remission in patients with refractory luminal Crohn's disease in the ACCENT I trial (11).

### RESULT

Our first patient was a 75-year-old Caucasian gentleman who was diagnosed with Crohn's disease in 1996. He was initially placed on sulfasalazine, and later switched to mesalamine. The patient underwent a surveillance colonoscopy in 1998 that showed solitary fissures and shallow ulcerations with mild edema of distal terminal ileum consistent with small bowel Crohn's disease. The mucosa of the colon appeared normal with normal vascular pattern. His disease progres-

*(continued on page 110)*

## Long-Term Remission of Crohn's Disease

### A CASE REPORT

(continued from page 108)

sively worsened, however, he was not a candidate for therapy with azathioprine or 6-MP due to chronic renal insufficiency as well as chronic medication with allopurinol for a history of gout (due to allopurinol's interference with the xanthine oxydase pathway for metabolism of 6-MP). Therapy with infliximab was started in 2002. The patient's ATI level was checked by Prometheus Laboratories (San Diego, CA), which reported negative ATI after the first infusion. The patient subsequently received serial infusions of infliximab at 8 week intervals. No infusion reaction has been documented during or post-infusion. The patient also had serial ATI levels measured in 2003 as well as 2004 which were both negative. Infliximab levels were also checked by Prometheus laboratories at the same time, and therapeutic ranges of infliximab were reported (2.8mcg/mL in 2003 then 12.9 mcg/mL in 3/2004 and 18.1 mcg/mL in 6/2004). The patient underwent a second surveillance colonoscopy in 2004—after starting infliximab—which showed normal bowel with improvement of terminal ileum ulceration. Biopsies were also taken which showed a mild increase of chronic inflammatory cells in the lamina propria without granulomas identified in the colon and rectum. Terminal ileum biopsy revealed no histopathologic alterations. Clinically, the patient is asymptomatic and has been in remission for the past 3 years.

Our second patient was a 47-year-old Filipino male who was diagnosed with Crohn's disease in 1999. At that time, esophagogastroduodenoscopy showed a few aphthous ulcers in the oropharynx with normal esophagus, stomach and duodenum. Colonoscopy revealed a great number of ulcerations from 35 mm in diameter up to 2 cm in diameter, predominately in the left colon. These lesions also had a gray-to-white flat bases with very well circumscribed margins. There was normal appearing mucosa between the ulcerations consistent with Crohn's disease. After evaluation, the patient was started on steroids and 5-aminosalicylic acid combination therapy for Crohn's disease. His clinical symptoms started to worsen during May of 1999. A second endoscopy was performed which revealed a 1 × 0.5 cm esophageal ulcer approximately 2 cm above the cardio-esophageal junction with sharp margined gray-white base. This was felt to be worsening of the patient's Crohn's disease at the

time. Meanwhile, the patient was also taking increasing doses of steroids with variable success. Steroids were therefore discontinued and azathioprine was initiated at 100 milligrams per day. The patient's oral ulcerations did not improve and additionally, his stomatitis seemed to be exacerbated by azathioprine. He was then taken off of immunomodulators due to lack of clinical response and placed on serial infliximab therapy in 2001.

The patient had an ATI level drawn prior to infusion which was undetectable. This was rechecked in 2004 after 2 years of serial infusions and again, the ATI level was undetectable. The level of infliximab was noted to be therapeutic at 26.1 mcg/mL. After 4 years of serial infliximab therapy, the patient is currently in clinical remission on infliximab and 5-aminosalicylic acid. The patient's stomatitis and his oral ulcerations have improved with cessation of azathioprine and initiation of infliximab

Our third patient was a 71-year-old Caucasian gentleman with a history of asthma who was diagnosed with ulcerative colitis-like Crohn's disease in 1995. He was initially treated with 5-aminosalicylic acid. His disease progressed in 1999 and a colonoscopy at that time showed moderate pancolitis and ileitis at the ileocecal valve. Scattered areas of flat, yellow-white based and well circumscribed small ulcerations were seen throughout the colon from the rectum to the cecum. Steroids were added at that time and subsequently, 50 mg of azathioprine was initiated in an attempt to wean the patient from steroid therapy. In 2002, the patient underwent a second colonoscopy for surveillance. This showed interval improvement from the prior study with mild differential colitis and small ulcerations in the right and left colon. While on azathioprine, the patient's clinical course was complicated by an episode of acute gouty arthritis and elevated liver enzymes, which were both thought to be related to azathioprine. Therefore, azathioprine was discontinued and infliximab therapy was initiated in 2003. After infusion of infliximab, his symptoms have gradually improved and he has been in remission after 2 years of infliximab treatment. He also had a therapeutic infliximab level and an undetectable ATI level in 2005. Interestingly, the patient's asthma also improved after discontinuing his immunomodulators.



## DISCUSSION

In our experience, serial infusion of infliximab in treatment of moderate to severe Crohn's disease seems to be well tolerated within our small sample population of patients who for various reasons were not able to receive immunomodulators. Clinical improvement in all of our patients suggests that infliximab, by itself or in combination with other less toxic classes of medications can achieve and maintain clinical remission in moderate to severe Crohn's disease. The efficacy of poly-pharmacy, patient compliance, and the possible adverse affect on patients' quality of life was recently addressed in a study evaluating the need for azathioprine in addition to olsalazine for maintenance of remission in steroid dependent ulcerative colitis. This study found no benefit with the addition of azathioprine in maintaining ulcerative colitis remission (12). This study also opened the possibility that what was traditionally thought to be standard of care in ulcerative colitis might not be warranted. At the same time, it also raised the question of whether immunomodulators are needed in Crohn's disease. Our observation with minimal "stacking" of medications in treating Crohn's disease seems to support the argument that immunomodulators might not be needed.

With serial infusions, our patients also did not show any clinically significant ATI levels or any infusion-related reactions after years of treatment without concurrent use of immunomodulators. By infusing patients with infliximab every 8 weeks after initial induction, we were able to prevent our patients from developing clinically significant ATI levels after many years of therapy. Our findings were further supported by encouraging results from Kinney, et al who also suggested that patients receiving serial infusions of infliximab were capable of maintaining their positive response. The same study also concluded that concomitant use of immunomodulators with infliximab in patients with Crohn's disease did not improve clinical response rate, dose reduction of prednisone, fistula response, or mean intervals between infliximab infusions (13).

Despite the fact that these findings are purely observational and reflect a small patient population, the implication for patient safety, compliance, cost and the future treatment of moderate to severe Crohn's disease is tremendous. These possible benefits have led to

a multi-center, controlled trial comparing infliximab treatment regimens with and without concomitant immunomodulators. The trial is now in progress. ■

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