

A Pilot Study of Adalimumab in Infliximab-Allergic Patients

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Abstract: The anti-TNF- α antibody infliximab (Remicade) is highly effective in the treatment of Crohn's disease. A subset of patients experience allergic reactions as a result of antibodies to infliximab (ATIs). The purpose of the current study is to describe the safety and efficacy of adalimumab (Humira) in patients previously allergic or intolerant to infliximab. Adalimumab is an anti-TNF- α agent containing only human peptide sequences. Seven patients have been treated with adalimumab who had experienced immediate- or delayed-hypersensitivity reactions to infliximab and one with infliximab-induced lupus. Except for injection site discomfort, adalimumab was well tolerated without signs or symptoms of allergic reactions. One patient who had previously received pooled human immunoglobulin developed a pruritic rash after each dose of adalimumab. Patients with active disease who had previously experienced a robust response to infliximab responded to adalimumab as reflected by an improvement in Harvey-Bradshaw index and inflammatory markers. Based on these preliminary data, adalimumab may be a safe and effective substitute for infliximab-allergic patients. Individuals who have been exposed to human antibodies may be sensitized to other human antibodies such as adalimumab.

Key Words: adalimumab, Crohn's disease, delayed-type hypersensitivity, immediate-type hypersensitivity, infliximab

(*Inflamm Bowel Dis* 2004;10:333–338)

Infliximab (Remicade), a chimeric monoclonal antibody against TNF- α , is the only biological therapy currently approved for the treatment of Crohn's disease (CD). Infliximab is highly efficacious in patients with inflammatory¹ and fistulizing CD² and is approved for both induction and maintenance of remission in patients with CD.³ Infliximab is a genetically en-

gineered antibody consisting of 25% murine sequences in the variable region of the antibody (Centocor data on file). In published clinical trials, 17% to 21% of patients treated with infliximab^{1,4} and up to 60% of patients in open-label series⁵ develop antibodies against infliximab (antibodies to infliximab, or ATIs). ATIs result in immediate-type hypersensitivity reactions characterized by shortness of breath, chest tightness, hypotension, and flushing during or immediately after an infusion, whereas delayed-type hypersensitivity reactions are characterized by rash, arthritis/arthritis, myalgia, and fevers occurring 2 to 10 days after an infusion.⁵ ATIs are believed to be directed against the murine sequences in infliximab and to be specific to infliximab—not other chimeric antibodies. In an open-label study, patients allergic to infliximab were given CDP571, a humanized anti-TNF- α antibody (Ab) containing 5% murine peptide sequences, and did not experience allergic symptoms. Other than allergic reactions, anti-TNF agents including infliximab have been associated with drug-induced lupus.⁶ More than 50% of patients receiving infliximab become antinuclear antibody (ANA)-positive, but less than 2% develop manifestations of drug-induced lupus. Patients who were ANA-positive were more likely to have significantly elevated ATI titers than ANA-negative patients; however, there was no temporal relationship between the development of ANAs and time to ATI formation.⁶

Adalimumab is a recombinant human monoclonal IgG1 antibody containing only human peptide sequences. Adalimumab binds TNF- α and neutralizes its function by blocking the interaction between TNF and its cell surface receptor. Therefore, adalimumab appears to have a similar mechanism of action to infliximab. Currently, adalimumab is approved for the treatment of rheumatoid arthritis (RA). It has been evaluated in more than 2330 subjects in clinical trials for longer than 36 months. The efficacy and safety of adalimumab in RA was assessed in four double-blind, randomized controlled trials. These trials demonstrated that adalimumab was effective in reducing tender and swollen joints and improving global disease activity.⁷ Treatment with adalimumab was also shown to decrease acute phase reactants and markers of inflammation. Given the similarity in the mechanism of action of infliximab, it is predicted that adalimumab will be effective in the treat-

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Supported by the Inflammatory Bowel Disease Translational Research Fund and the Feintech Family Chair in Inflammatory Bowel Disease.

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ment of Crohn's disease. The efficacy of adalimumab in the treatment of Crohn's disease is currently being investigated in a multicenter study of infliximab-naïve patients. The aim of this study was to assess the safety and efficacy of adalimumab in patients who had a previous allergic reaction or lupus-like reaction to infliximab. We hypothesized that patients with a previous allergic reaction to infliximab or drug-induced lupus would not experience a similar reaction to adalimumab. Our results suggest that adalimumab can safely be administered to infliximab-allergic or intolerant patients. The results of our study have important therapeutic implications for a subset of patients for whom alternative anti-TNF therapies have not been available.

PATIENTS AND METHODS

This is an 8-week, single-center study of patients with Crohn's disease who received adalimumab for treatment of their disease. This study was approved by the Cedars-Sinai Medical Center Institutional Review Board. Patients were considered for adalimumab therapy if they had a diagnosis of Crohn's disease and were experiencing symptoms of moderate to severe active disease, were steroid-dependent and failed standard immunomodulators, or were experiencing draining fistula despite concomitant medical therapy. All patients in the current study had a documented adverse reaction to infliximab that prevented ongoing use of this therapy. All patients were given intravenous diphenhydramine prior to infliximab administration. Adverse reactions included immediate-type hypersensitivity (ITH) reactions characterized as chest tightness, shortness of breath, light-headedness, flushing, hypotension, fevers, rigors, or rash during infusion or within 2 hours of infusion that necessitated decreasing the rate or cessation of infusion and administration of additional antihistamines, corticosteroids, epinephrine, or a combination thereof. Delayed-type hypersensitivity (DTH) reactions were characterized by development of fever, arthralgias, arthritis, myalgia, rash, or combination thereof generally within 2 to 10 days after infusion of infliximab. Drug-induced lupus was defined by a positive ANA, malar rash, and arthralgias. Subjects with a history of cancer or lymphoproliferative disease or history of active infection including tuberculosis, listeria, or human immunodeficiency virus were excluded from anti-TNF therapy.

Patients with active luminal disease were treated with subcutaneous injection of 80 mg of adalimumab followed by 40 mg every 2 weeks similar to the dosing schedule used for the ongoing clinical trial of adalimumab in infliximab-naïve CD patients. The first and second injections of adalimumab were administered by medical staff at an on-site infusion facility, and patients were monitored for 2 hours following administration for adverse reactions. The remainder were administered by the patient or at our outpatient IBD clinic. An adverse event was defined as any untoward event that occurred during or after administration of adalimumab including hypotension,

shortness of breath, joint swelling or late reactions, that is, rash, arthralgias, myalgias and fatigue. All adverse events were documented and assessed by the investigators. Concomitant treatment with immunosuppressive or immunomodulatory agents were used as indicated to control disease. Excluded therapies included cyclosporin A, tacrolimus (FK506), and other investigational therapies.

Patients were evaluated before their initial dose of adalimumab and every 2 weeks for a total of 8 weeks duration. Baseline evaluations consisted of detailed history and physical examination, PPD placement, and laboratory work including hematology and baseline chemistries and biological markers of inflammation including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). All patients were PPD negative. In patient 2 with a previous lupus-like reaction to infliximab and patient 1 with a possible lupus-like reaction to adalimumab, ANAs and antibodies to double-stranded DNA (anti-dsDNA) were also performed. Serum obtained at baseline was assessed for antibodies to infliximab (ATI or human anti-chimeric antibodies; HACA) in coded fashion by Prometheus Laboratories (San Diego, CA, USA).

Follow up evaluations consisted of a brief examination and symptom and allergy assessment. Crohn's disease activity was monitored by patient diary, Harvey-Bradshaw index,⁸ and biochemical markers of inflammation as stated above. Clinical activity was followed using the Harvey-Bradshaw score.

Ethical Considerations

This study was approved by the Cedars-Sinai Medical Center Institutional Review Board. Patients provided informed consent to permit the collection of clinical and immunologic data concerning the treatment of their inflammatory bowel disease. No external funding was used for this study.

RESULTS

A total of seven Crohn's disease patients were treated with adalimumab between April and September of 2003. Their disease characteristics are described in Table 1. In general, these patients had used multiple immunomodulators, including experimental therapies, in the past. All patients experienced an adverse reaction to infliximab that was deemed a contraindication to further use of this therapy. These adverse reactions occurred in spite of the routine use of intravenous diphenhydramine and oral acetaminophen prior to infliximab infusions and in certain cases intravenous corticosteroids. The nature of the adverse reactions to infliximab are delineated in Table 2. The minimum number of previous infliximab infusions was 2 and the maximum number was 10. Only one patient, patient 1, had received three induction doses and every-8-week doses in conjunction with an immunomodulator. The rest had longer intervals between infusions and/or were intolerant to standard immunomodulators. All patients were considered to have been responders to infliximab by the treating

TABLE 1. Baseline Patient Demographics

Patient	Age	Smoking History	Duration of Disease (yrs)	Disease Location	Fistula	Concomitant Medications	Infliximab Dosing Schedule and Concurrent Immunomodulator Use	Prior Medications
1	27	No	6	Ileocolitis	No	Prednisone	Infusions 7/99 and 5/00 Concurrent Mycophenolate during infliximab (6-MP and 6-TG caused hyperthermia; MTX caused alopecia)	Prednisone Cipro Flagyl Budesonide Methotrexate 6TG 6MP Rowasa Enemas Asacol mycophenolate Mofetil
2	48	No	12	Duodenitis/pancolitis	No	Prednisone	0, 2, 6 week induction and q8 week dosing for 7 infusions Concurrent AZA	Prednisone Colozal Thalidomide MTX Asacol 6MP/AZA 6TG Budesonide Cyclosporine
3	49	Yes	29	Duodenitis/pancolitis	Yes	None	4 infusions (for perianal fistulas): 2/02, 4/02, 7/02 then 2/03 Concurrent prednisone	Pentasa Prednisone Cipro Flagyl
4	54	Former	17	Ileocolitis	No	None	3 infusions: 10/98, 1/99, 6/99 Concurrent prednisone (6-MP pancreatitis; 6-TG pancytopenia; MTX early hepatic fibrosis)	Prednisone Thalidomide MTX Asacol 6MP 6TG Budesonide Cyclosporine mycophenolate Mofetil Tacrolimus Natalizumab
5	24	No	3	Colitis	No	None	Infusions as needed beginning 10/99; total 8 infusions Concurrent 6-MP for first 4 infusions; discontinued 6-MP because of fatigue	6MP Cipro Flagyl Prednisone Cyclosporine Asacol 6TG
6	19	No	6	Ileocolitis	No	None	0, 2, 6 week induction 2/01; remission until 9/01, resumed q8 week infusions with anaphylactoid reaction on 3/02 (8th infusion) 6-MP and AZA caused vomiting	Prednisone Pentasa Colozal 6-MP/AZA
7	32	No	4	Enteritis	No	None	2 infusions 12/99 and 1/00 Concurrent prednisone (6-MP-hepatotoxicity; 6-TG discontinued because of risk of hepatotoxicity; MTX refractory)	6-MP 6TG Cyclosporine Budesonide Cyclophosphamide Prednisone Tacrolimus Methotrexate Pentasa

6-MP, 6-mercaptopurine; AZA, azathioprine; 6TG, thioguanine; MTX, methotrexate.

TABLE 2. Adverse Reactions to Infliximab and Adalimumab and ATI/HACA Levels Prior to Treatment with Adalimumab

Patient	AE to Infliximab	ATI/HACA ($\mu\text{g/mL}$)	AE to Adalimumab
1	ITH	11.49	Facial rash, pruritis
2	DLE	14.83	No reaction
3	DTH	9.88	Dizziness
4	ITH	<1.69	No reaction
5	ITH	4.53	Sinusitis
6	ITH	7.94	Rhinitis
7	ITH	<1.69	No reaction

AE, adverse reaction; ITH, immediate-type hypersensitivity reaction (ie, shortness of breath, lightheadedness, hypotension, flushing, fever, or rash during or 2 hours following infusion); DTH, delayed-type hypersensitivity reaction (ie, worsening fever, arthralgia, arthritis or rash 2 to 10 days following infusion); DLE, drug induced lupus erythematosus; HACA, human antichimeric antibody; ATI, antibody to infliximab.

clinician except one. This patient (patient 4) developed an anaphylactoid reaction early during the second infusion of infliximab with hypotension and hypoxia requiring transfer to the intensive care unit, and her clinical response could not be evaluated. Patient 2 was felt to have drug-induced lupus based on the presence of a positive ANA, positive anti-dsDNA, and the development of a migratory rash and migratory arthritis. These symptoms continued in spite of cessation of infliximab therapy and are similar to the signs and symptoms previously described for autoimmunity associated with infliximab therapy.⁶

The most common indication for administration of adalimumab was active luminal disease. Median Harvey-Bradshaw index was 13 at study entry. Of the six patients with elevated Harvey-Bradshaw scores at study entry, five of the six had a drop in Harvey-Bradshaw scores; median Harvey-Bradshaw score after treatment period was 5 (Fig. 1A). Quantitative CRPs and ESRs performed at Cedars-Sinai Medical Center were available for six patients (Fig. 1B). ESR was elevated in the majority of patients at baseline and mirrored the clinical response to adalimumab therapy. CRP was greater than 1 mg/dL in two patients and decreased to normal following adalimumab in both. One patient had concurrent fistulae although this was not the primary reason for administration of adalimumab. In this patient, his fistula drainage became minimal and his perianal pain score decreased from 8/10 to 2/10. Patient 1 had a severe flare of Crohn's colitis prior to adalimumab administration necessitating hospitalization for intravenous corticosteroids and was discharged on high-dose corticosteroids, prednisolone 36 mg/day. She received corticosteroids for 10 days prior to her first dose of adalimumab. This patient received adalimumab to permit taper of her steroids. By week 8, she was able to taper off the prednisolone while main-

taining her remission. Patients were started on 80 mg subcutaneously at the first dose and then continued on 40 mg every 2 weeks. In three patients, 40 mg of adalimumab was insufficient to maintain the clinical response until the next dose. These patients were given 40 mg every week (patient 3), 80 mg every 2 weeks (patient 2), or 80 mg every week (patient 5) (Fig. 2).

In general, adalimumab was well tolerated without evidence of immediate or delayed-type hypersensitivity reactions (Table 2). The most frequent adverse event was injection-site reaction characterized by erythema and discomfort lasting less than 24 hours. One patient (patient 1) developed a new facial rash after the first dose of adalimumab, which recurred with subsequent doses and necessitated discontinuation of adalimumab. Her ANA tests have been negative after adalimumab. This patient's previous allergic reaction to infliximab had been shortness of breath during an infusion without a rash. The patient with drug-induced lupus after infliximab continued to experience symptoms of lupus that were not aggravated by adalimumab. ANA and anti-dsDNA levels also did not change following adalimumab.

DISCUSSION

Biological therapy with the anti-TNF- α Ab infliximab has proven effective in both inducing and maintaining remission in severe Crohn's disease refractory to standard medical therapy with corticosteroids and immunomodulatory agents.

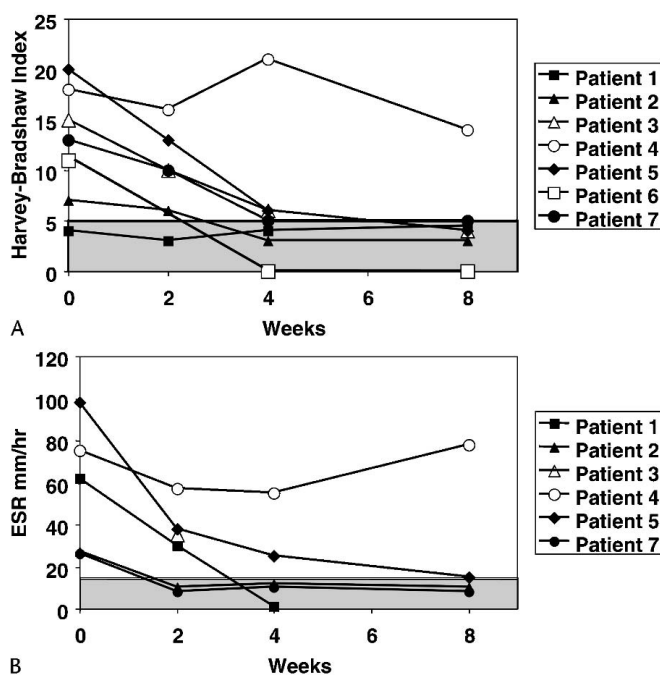


FIGURE 1. Response to adalimumab as measured by (A) Harvey-Bradshaw score, (B) erythrocyte sedimentation rate (ESR). A Harvey-Bradshaw score of less than 5 correlates with remission.¹³ Upper limit of normal for ESR is 15 mm.

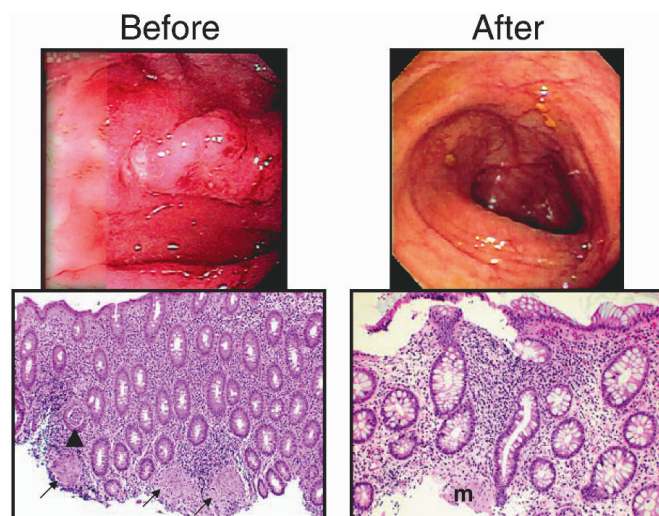


FIGURE 2. Endoscopic and histologic changes in a patient before and 8 weeks after therapy with adalimumab. Patient 5 had a flexible sigmoidoscopy performed prior to the initiation of adalimumab, which demonstrated severe inflammatory changes including deep ulcerations, aphthoid-type ulcerations, erythema, edema, and friability starting at the recto-sigmoid junction, which precluded a full colonoscopic evaluation (Fig. 2, left panels). Endoscopic biopsy of the colonic mucosa prior to treatment demonstrates expansion of the lamina propria by dense lymphoplasmacytic infiltrate and significant loss of epithelial mucin. In addition, the lower lamina propria contains three histiocytic granulomas (arrows), and there is a destructive crypt abscess (arrowhead). After 8 weeks of adalimumab therapy, this patient had a dramatic improvement in the endoscopic and microscopic appearance (Fig. 2, right panels). Endoscopic full-thickness biopsy of the colonic mucosa demonstrates a marked reduction of the inflammation within the lamina propria accompanied by restoration of the normal epithelial mucin. No granulomas or crypt abscesses are noted. The maximum activity consisted of the rare, isolated focus of mild cryptitis. A small portion of the muscularis mucosae (m) is included in the biopsy.

Unfortunately, clinical trials and open-label clinical experience have demonstrated that a significant number of patients develop immediate- and delayed-type hypersensitivity reactions to infliximab precluding its continued use in these patients.⁵ For patients with serious allergies to infliximab, there are no alternative anti-TNF agents currently approved for use in Crohn's disease.

Adalimumab is a genetically engineered IgG1 monoclonal antibody similar to infliximab. Its principal advantages over infliximab are that it is fully humanized and can be administered subcutaneously.⁷ In this study, we describe our experience using adalimumab in patients with allergic reactions to infliximab or infliximab-induced lupus. Most patients in this study had elevated levels of ATIs identified in their serum prior to administration of adalimumab. These findings are consistent with documented studies that have revealed a strong

correlation between the presence of ATIs and the occurrence of infusion reactions.⁵ In the others, ATI levels may have decreased over time.

Because adalimumab contains only human peptide sequences, we hypothesized that patients allergic to infliximab would not be allergic to adalimumab. Our results show that adalimumab was well tolerated in most patients. One of seven patients, however, developed a new rash following administration of adalimumab. This patient has a history of immune-mediated thrombocytopenic purpura treated with many courses of intravenous immune globulin. It is plausible that repeated exposure to pooled human immunoglobulins sensitized this patient to a human antibody such as adalimumab. Conversely, a subset of patients allergic to infliximab may express antibodies against the human IgG1 sequences in the Ab rather than the murine component. The ATI assay used in this study measures serum antibodies to any part of the infliximab molecule, both murine and human IgG1 sequences. The one patient in our study with infliximab-induced lupus has not had any worsening of the lupus or change in ANA or anti-dsDNA titers with adalimumab. A randomized, placebo-controlled trial of adalimumab in rheumatoid arthritis patients did not find an increase in conversion to ANA-positivity in adalimumab-treated patients,⁷ whereas infliximab-treated patients have a high rate of conversion to ANA-positivity in both rheumatoid arthritis⁹ and Crohn's disease.^{6,10} Larger studies and long-term data will be needed to ascertain whether adalimumab will result in drug-induced lupus. These data suggest that adalimumab may have utility in infliximab-allergic or -intolerant patients. Larger studies are required to quantify the frequency of allergic reactions to adalimumab in patients with Crohn's disease. As with the initial open-label experience with infliximab,^{11,12} adalimumab appears to be effective in the treatment of Crohn's disease. This may be especially true when one selects patients who previously had robust responses to infliximab. The ongoing randomized, placebo-controlled trial of adalimumab in infliximab-naïve patients will determine the efficacy of adalimumab in the treatment of Crohn's disease and the optimal dosing schedule in Crohn's disease. Until that time, clinicians faced with infliximab-allergic patients may consider using adalimumab as an alternative anti-TNF agent.

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