

Infliximab for the treatment of Crohn's disease: Review and indications for clinical use in Canada

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on the Use of Infliximab in Crohn's Disease

R Panaccione, for the Canadian Consensus Group on the Use of Infliximab in Crohn's Disease. Infliximab for the treatment of Crohn's disease: Review and indications for clinical use in Canada. Can J Gastroenterol 2001;15(6):371-375. Crohn's disease is a chronic inflammatory disorder of the gastrointestinal tract. It may affect any portion of the gastrointestinal tract from the mouth to the anus. Symptoms typically include cramping abdominal pain, diarrhea (which may be bloody) and nausea. As the severity of the illness worsens, patients may experience constant abdominal pain, vomiting, weight loss and fever. From the perspective of the patient, disease symptoms significantly impair quality of life, and interfere with their work environment and activities of daily living. Unfortunately, there is no cure for Crohn's disease. Patients experience a chronic, relapsing course characterized by recurrent flares of their disease. Conventional medical treatment of Crohn's disease includes the use of non-specific anti-inflammatory drugs (5-aminosalicylic acid agents, prednisone, budesonide), immunosuppressives (6-mercaptopurine, azathioprine, methotrexate) and antibiotics. A variable onset of action, incomplete response rates and a significant risk of adverse effects characterize current therapies. Although surgery is frequently used to treat complications or medically refractory disease, postoperative recurrence is a common problem.

Infliximab, a murine chimeric monoclonal antibody directed toward tumour necrosis factor-alpha, is a highly effective treatment of active Crohn's disease. In randomized, placebo-controlled clinical trials, 33% of patients treated with infliximab 5 mg/kg achieved remission (Crohn's Disease Activity Index score less than 150), compared with only 4% of those receiving placebo ($P < 0.001$). Additionally, infliximab is the only drug therapy shown to be effective for the treatment of fistulizing Crohn's disease. In studies done to date, infliximab appears to be well tolerated and has a favourable side effect profile.

Key Words: Crohn's disease; Inflammatory bowel disease; Infliximab

L'infliximab pour le traitement de la maladie de Crohn : Vue d'ensemble et indications de son usage clinique au Canada

RÉSUMÉ : La maladie de Crohn est une maladie inflammatoire chronique du tube digestif. Elle peut affecter toutes les portions du tractus gastro-intestinal, de la bouche à l'anus. Les symptômes sont

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habituellement des crampes, des douleurs abdominales, de la diarrhée (parfois sanguinolente) et des nausées. À mesure que la maladie s'aggrave, les patients éprouvent des douleurs abdominales constantes, des vomissements, ils perdent du poids et font de la fièvre. Du point de vue du patient, les symptômes de la maladie perturbent significativement la qualité de la vie et interfèrent avec les activités professionnelles et autres. Malheureusement, on ne connaît pas de remède contre la maladie de Crohn. Cette affection évolue en dents de scie. Le traitement classique repose, entre autre, sur des anti-inflammatoires non spécifiques (des agents contenant de l'acide 5-aminosalicylique, de la prednisone, du budésônide), des immunosuppresseurs (la 6-mercaptopurine, l'azathioprine, le méthotrexate) et des antibiotiques. Pour l'instant, ces traitements se caractérisent par un début d'action variable, une réponse

partielle et un risque significatif de réactions indésirables. Bien que la chirurgie soit souvent utilisée pour traiter les complications ou les cas réfractaires, il n'est pas rare que la maladie resurgisse après l'opération. L'infliximab, un anticorps monoclonal chimérique d'origine murine dirigé contre le facteur alpha de nécrose tumorale, est très efficace contre la maladie de Crohn évolutive. Dans le cadre d'essais cliniques randomisés, contrôlés par placebo, 33 % des patients traités au moyen de l'infliximab à raison de 5 mg/kg ont connu une rémission (indice de l'activité de la maladie de Crohn inférieur à 150), contre 4 % seulement des sujets sous placebo ($p < 0,001$). De plus, l'infliximab est le seul médicament à s'être révélé capable de fistuler la maladie de Crohn. Si l'on se fie aux études effectuées à ce jour, l'infliximab semble bien toléré et doté d'un profil d'effets secondaires favorable.

INFLIXIMAB: MECHANISM OF ACTION

Infliximab is a murine chimeric monoclonal antibody directed against human tumour necrosis factor (TNF)-alpha. Twenty-five per cent of the molecule is of murine origin. The murine component is found in the Fab portion of the antibody, which specifically recognizes human TNF- α . The remainder of the antibody (Fc portion) is a human immunoglobulin (Ig) G1 molecule. The human portion of the molecule decreases immunogenicity and preserves functional immune capacity (1).

Infliximab binds to TNF- α and neutralizes its interaction with cellular receptors. The drug binds with high affinity to TNF- α in both its soluble ($k_d=100$ pM) and transmembrane form ($k_d=46$ pM) (1), but does not interact with TNF- β – a related cytokine that shares the same receptor site (2).

Among patients with colonic Crohn's disease treated with a single infusion of infliximab, a decrease in the concentration of lamina propria TNF- α and in overall mucosal inflammation can be demonstrated (3). Binding of infliximab to transmembrane TNF- α causes cell lysis of activated T lymphocytes via complement fixation or antibody-dependent cellular toxicity (3).

INFLIXIMAB: EFFICACY IN ACTIVE CROHN'S DISEASE

The gold standard for evaluating the efficacy of a pharmacological therapy in Crohn's disease clinical trials is the Crohn's Disease Activity Index (CDAI) (4). The CDAI takes into account a variety of patient symptoms and signs, generating scores from 0 to 600, with higher scores indicating worse disease activity. Clinical remission is considered to be a CDAI score of less than 150, whereas a clinical response has been defined by various investigators as a reduction in CDAI score of 70 to 100 points.

van Dulleman and colleagues (5) first demonstrated the efficacy of infliximab in an open label study. This initial study demonstrated that patients treated with infliximab had a rapid improvement in symptoms within four weeks of receiving infliximab (mean decrease in CDAI score 178 points) (5). This improvement in symptoms was accompanied by healing of mucosal lesions endoscopically in many patients. This study was followed by a placebo controlled,

dose ranging study that showed similar results and provided data to proceed to two multicentre, randomized, double-blind, controlled trials that assessed the efficacy of infliximab further.

One hundred eight patients with active Crohn's disease were randomly assigned to one of three single-infusion dose regimens of infliximab (5, 10, 20 mg/kg) or placebo (6). Patients had moderately to severely active disease (CDAI score of 220 to 400) despite treatment with conventional therapies. The primary end point was a 70-point decrease in the CDAI score from the baseline value after four weeks (a clinically significant response). The secondary end point was the presence of a CDAI score of less than 150 (remission). The demographic characteristics of the patients were similar in the four treatment groups, and the mean baseline CDAI score was approximately 300. However, only 60% of the patients were receiving concomitant glucocorticoid therapy. At the end of the trial, a significant benefit of infliximab was shown, both in clinical response and in remission, at all drug doses. The most effective dose was 5 mg/kg; 82% of the patients in this dose group had a clinical response and 48% entered remission (6). A small proportion of patients who did not respond to an initial infusion of infliximab responded to a second infusion of 10 mg/kg four weeks later (response 34%, remission 17%).

Significant mucosal healing was once again demonstrated in the subgroup of patients receiving infliximab. Among 30 patients receiving infliximab who underwent endoscopic assessment in the study by Targan et al (6), ulcerated areas of colonic mucosa disappeared in 74% to 96% of cases (3). Mucosal healing correlated with improvement in CDAI scores.

Additional experience, based on open label studies, has been reported since the release of infliximab in the United States (7-9). These experiences are very similar from centre to centre and resemble the results of the randomized trials. Recently, the experience of the first 100 patients treated with infliximab at the Mayo Clinic was published (9). The indications for infliximab therapy were inflammatory disease (61 patients), fistulizing disease (26 patients) or both (13 patients). Patients received one to seven infusions of infliximab (5 mg/kg) for a total of 242 infusions. Fifty patients had complete response, 22 patients had partial

response and 28 patients did not respond. The median time to response was seven days (range one to 21 days). The median duration of response was 10.3 weeks (range three to 25 weeks). Ninety-five patients received concomitant treatment with immunosuppressive agents. Most importantly, steroid withdrawal was possible in 29 of 40 patients (73%) (9).

INFLIXIMAB: EFFICACY IN FISTULIZING CROHN'S DISEASE

In the second multicentre trial, the efficacy of infliximab in the treatment of patients with fistulizing Crohn's disease was reported by Present et al (10). Ninety-four patients with fistulizing Crohn's disease were randomly assigned to one of three treatment groups (placebo, or infliximab 5 or 10 mg/kg); three drug infusions were administered (at baseline, two and six weeks) over 18 weeks. Eligible patients had single or multiple draining enterocutaneous fistulae of at least three months' duration. Conventional medical treatments were maintained at a stable dose. The primary end point was a 50% or greater reduction in the number of open fistulae for at least two consecutive visits; a secondary end point was the closure of all fistulas. Sixty-two per cent of patients who received 5 mg/kg of infliximab had closure of 50% or more of their fistulas (primary end point), compared with 26% of those who received placebo ($P=0.017$). In addition, 55% had complete closure (the secondary end point), compared with only 14% in the placebo group ($P=0.001$). Ten per cent of patients treated with infliximab developed abscesses. This study demonstrated that infliximab is highly effective in the treatment of fistulizing Crohn's disease. Most importantly, infliximab is the only therapy for fistulizing disease that has been found to be effective in a randomized, controlled trial.

INFLIXIMAB: REPEATED DOSING

Rutgeerts et al (11) followed patients who had initially responded to their initial infusion of infliximab in the trial by Targan et al (6). Patients were randomly assigned to receive either infliximab 10 mg/kg every eight weeks or placebo. Continued infusion of infliximab in this group of patients led to a sustained benefit in both CDAI and Inflammatory Bowel Disease Questionnaire (IBDQ) scores. Patients randomly assigned to receive placebo had a gradual deterioration, with an increase in symptoms as measured by the CDAI and impairment of quality of life as measured by IBDQ. A large, open label experience also suggests that long term control of disease is possible with repeated infusions of infliximab 5 mg/kg (9,12). Open label experience suggests that the benefit achieved by patients with fistulizing disease can be extended by repeated infusions of infliximab (13-15) – similar to what was shown in the study by Rutgeerts et al (11) in patients without fistulae. Controlled data regarding the efficacy of 'maintenance' infusions will be available shortly with the completion of two large clinical trials in patients with active Crohn's disease and fistulizing Crohn's disease (A Crohn's Disease Clinical Trial

Evaluating Infliximab in a New Long-Term Treatment Regimen [ACCENT] I and II).

INFLIXIMAB: SAFETY AND TOLERABILITY

The safety and tolerability of infliximab have been reviewed in a variety of diseases, including Crohn's disease, ulcerative colitis, rheumatoid arthritis and sepsis. The safety experience from the clinical trials has been summarized by Hanauer (16) and includes a data set of 533 patients (199 with Crohn's disease). Patients with sepsis treated with infliximab were excluded from this analysis because of the disproportionately high incidence of morbidity and mortality in this population.

Among the 533 patients, 20% more patients who received infliximab experienced an adverse event compared with those who received placebo. Most of these adverse events were classified as mild, with the skin and gastrointestinal and respiratory systems being most affected (16,17). In Crohn's disease trials, approximately 5% of patients discontinued use of infliximab due to adverse events (18). These adverse events were usually infusion reactions or infections.

Infusion reactions, defined as any adverse event occurring during infliximab infusion or within 2 h after infusion, are relatively common (16% with infliximab compared with 6% with placebo) (18). These reactions are usually minor, with the most common being headache, nausea, light-headedness, flushing and urticaria. Dyspnea and chest pain were reported in 2% of infusions (18). Only 0.8% of patients discontinued their infusions due to an infusion reaction. It has been proposed that the concomitant administration of immunosuppressants may decrease the rate of infusion reactions, but this has not been proved. Patients who tested positive for human antichimeric antibodies (HACAs) were more likely to experience infusion reactions (18); however, the clinical significance is unknown because measurement of HACA levels is not commercially available. Most infusion reactions are easily dealt with by initially stopping the infusion and restarting at a decreased rate. Some patients may require the administration of diphenhydramine or acetaminophen. However, these reactions are not thought to be IgE mediated, and the incidence of IgE-mediated infusion reactions is thought to be extremely rare.

Delayed hypersensitivity reactions resulting in arthralgias, skin manifestations and low grade fever have been described in patients who were readministered infliximab after long intervals between infusions (16). These reactions were associated with high levels of HACA and resulted in a loss of efficacy. Premedication of patients with diphenhydramine or acetaminophen has not been shown to reduce the occurrence of these reactions.

Infectious complications related to impairment of the host response to microbial pathogens are a concern with all immunomodulatory agents. Patients receiving infliximab in clinical trials were more likely to require antibiotic therapy for infectious complications than those receiving placebo

(21% versus 11% [16,18]). Three per cent of patients treated with infliximab had serious infections compared with 2% of patients treated with placebo (16,18). More recently, several cases of mycobacteria tuberculosis (mTB) have been reported in patients treated with infliximab (data on file, Centocor Inc, USA). Thirty-three cases of mTB have been reported worldwide (19 patients receiving infliximab for Crohn's disease). Eighty-two per cent of patients were on concomitant immunosuppressive therapy. Most cases presented within six months of receiving infliximab, with 13 cases presenting as disseminated mTB. Other serious pulmonary infections such as cryptococcal pneumonia, aspergillus pneumonia and pneumocystis carinii pneumonia have also been reported (data on file, Centocor Inc, USA).

A potential association between infliximab treatment and the occurrence of lymphoma has been investigated (18,19). As of December 1998, 771 patients had received infliximab in clinical trials; six of these patients had developed lymphoproliferative disorders, two of whom had Crohn's disease (19). However, the lymphoma incidence in infliximab-treated patients with Crohn's disease (5.0 cases of lymphoma per 1000 patients with Crohn's disease) was identical to the rate observed for patients with Crohn's disease in general (5.2 cases per 1000), which suggests that there is no causal relationship between infliximab therapy and malignancy (20). Furthermore, no association between the dose of infliximab or duration of exposure, and the development of lymphoma is apparent. Additionally, all of the patients who developed lymphoma had been previously exposed to purine antimetabolites, which may have placed these individuals at greater risk.

Patients with Crohn's disease may be positive for antinuclear antibodies (ANA). However, patients with Crohn's disease treated with infliximab had an increase of 12% in their rate of ANA positivity (16). Two of these patients developed clinical signs of systemic lupus erythematosus. These signs resolved with administration of glucocorticoids (16). A similar syndrome has been well described in patients receiving other pharmacological agents such as hydralazine, procainamide and phenothiazines. These cases of medication-induced lupus did not result in any evidence of end organ damage.

The overall safety profile of infliximab is quite favourable based on the data available. Patients tolerate infliximab well, with most adverse events being mild. Questions regarding the long term safety of infliximab (especially in patients receiving repeated infusions) remain unanswered; however, preliminary long term safety data appear reasonable.

INFLIXIMAB: OTHER INFLAMMATORY BOWEL DISEASE INDICATIONS

Infliximab has been used in the treatment of ulcerative colitis. There are no conclusive data from controlled or uncontrolled studies. A preliminary phase IIa trial with infliximab has been reported (21). The study enrolled 11

hospitalized patients with severe, active, steroid-refractory ulcerative colitis. Patients were randomly assigned to receive placebo or infliximab 5 mg/kg, 10 mg/kg or 20 mg/kg. None of the placebo-treated patients (n=3) responded, whereas five of eight infliximab-treated patients benefited at two weeks, with a decrease in modified Truelove and Witt's scores. Despite this report, infliximab should not be used in patients with ulcerative colitis outside the context of a clinical trial until formal, large randomized, controlled studies are completed.

Uncontrolled data have shown that infliximab can be used successfully to treat Crohn's disease arising in an ileoanal pouch (22). Successful treatment of pyoderma gangrenosum (23), Behçet's (24), perineal cutaneous Crohn's disease (25), and both the spondylarthropathy and peripheral arthritis associated with Crohn's disease (26) has been reported.

DISCUSSION

Infliximab has proved to be a significant advance in the therapeutic armamentarium for clinicians who treat patients with Crohn's disease. Well designed, randomized, controlled trials have demonstrated benefits in patients with moderate to severe or fistulizing Crohn's disease refractory to other therapies. Furthermore, it is the only therapeutic agent that has shown efficacy in patients with fistulizing Crohn's disease in a randomized, placebo controlled clinical trial. The rapid onset of action and associated mucosal healing are therapeutically attractive and set this agent apart from more traditional therapies such as 5-acetylsalicylic acid agents, glucocorticoids and immunomodulators. The agent should be used as adjuvant therapy in patients with moderate to severe Crohn's disease who fail to respond to or cannot tolerate other therapies, and as a first-line therapy in patients with complicated fistulizing Crohn's disease.

The high drug acquisition costs associated with infliximab make patient selection an important issue. Clinicians should select patients according to the practice guidelines put forward by the Canadian Association of Gastroenterology. It is recognized that unique situations will arise that will predicate the use of infliximab outside the context of the proposed guidelines. For example, in a small group of patients, infliximab therapy may be considered as a bridge to long term immunosuppressive therapy if, in the clinical judgment of the treating physician, the patient's clinical status is likely to not improve or deteriorate while awaiting the delayed effects of immunosuppressive therapy.

The selection process should include a careful history, physical and laboratory measurements to insure that the patient does not have any contraindication to therapy with infliximab. Particular attention should be paid to any evidence of active infection, history of tuberculosis (or exposure to tuberculosis), history of malignancy, or symptoms and signs of intestinal obstruction. A careful evaluation for the presence of underlying abscess is important in patients with fistulizing Crohn's disease. Infliximab should be with-

held until appropriate therapy is instituted for any underlying abscess.

Infliximab should be administered at a site familiar with the administration of intravenous medications by staff that is well trained in dealing with infusion reactions to other medications such as chemotherapeutic agents. These infusion sites should be prepared to deal with severe adverse reactions by having appropriate access to resuscitation equipment and medications used to treat these reactions. As a larger clinical experience is achieved, infusions may ultimately take place outside of these settings.

The concomitant administration of an immunosuppressive therapy is important for several reasons. The addition of or optimization of immunosuppressive therapy should be part of the long term management plan for patients who have been selected as candidates for treatment with infliximab. Immunosuppressive therapy may decrease the incidence of infusion reactions, prolong the duration of response and protect against HACA formation. Every effort should be made to introduce the appropriate immunosuppressive agent if no contraindications exist.

Despite existing data regarding the efficacy and safety of infliximab in Crohn's disease, many unanswered questions remain. Ongoing and recently completed clinical trials will answer some important questions; however, new questions will be generated as the clinical experience with this novel agent evolves.

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