

Canadian Association of Gastroenterology Clinical Practice Guidelines: The use of infliximab in Crohn's disease

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RESEARCH OF PUBLISHED EVIDENCE

These guidelines are presented as a follow-up to the original Canadian Association of Gastroenterology Clinical Practice Guidelines: The use of infliximab in Crohn's disease, published in the *Canadian Journal of Gastroenterology* (1). The original guidelines represented publications between 1998 and 2000. The current guidelines have been updated to reflect knowledge gained from two pivotal randomized clinical trials, with the use of infliximab in the maintenance of inflammatory Crohn's disease in remission (2) and in the maintenance of fistulous Crohn's disease in remission (3).

MEDLINE was searched using the following key words: "tumor necrosis factor (TNF) and Crohn's disease", "TNF and ulcerative colitis", "TNF and intestinal inflammation", "TNF and colitis", "anti-TNF therapy" and "infliximab". In addition, abstracts of the 2000 to 2003 annual meetings of the American Gastroenterological Association (published in *Gastroenterology*) and the 2000 to 2003 annual United European Federation of Gastroenterological Societies Annual Meeting (published in *Gut*) were searched for the following key words: "TNF" and "infliximab".

Abstracts were only admitted as evidence if the necessary details were given in the abstract to perform the grading for the degree of evidence (as outlined below), or if the studies were known in sufficient detail to the experts through availability of detailed official study reports or other documents to perform such grading.

GOALS OF THE GUIDELINES

These recommendations are intended to provide clinicians with a consensus-based document that will provide rational and optimal guidelines for the use of the anti-TNF monoclonal antibody infliximab in patients with inflammatory and fistulizing Crohn's disease.

VALIDITY OF THE GUIDELINES

The present guidelines acknowledge the unique nature of each clinical encounter and practice setting, and allow practitioners and their patients to choose other options when appropriate.

An update through a consensus meeting is planned for the first half of 2006. It is assumed that the therapeutic use of anti-TNF agents will be influenced by continued large, randomized clinical studies.

QUALITY OF THE EVIDENCE

The guidelines were developed following the recommendations outlined by Marshall (4). The following categories were used to grade the statements in the guidelines (according to the guidelines of the Agency for Health Care Policy and Research):

- Ia Evidence obtained from the meta-analysis of randomized, controlled trials.
- Ib Evidence obtained through one or more randomized, controlled trials.
- IIa Evidence obtained through a well-designed, controlled study without randomization.
- IIb Evidence obtained through another type of well-designed, experimental study (eg, from multiple time series or from dramatic results in uncontrolled experiments).
- III Evidence obtained through a well-designed, non-experimental study (eg, descriptive studies which include comparative, correlation and case studies).
- IV Evidence obtained from opinions of respected authorities, and based on clinical experience, descriptive studies, or reports of expert committees.

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QUALITY OF THE GUIDELINES

Guidelines deduced from published evidence and/or from expert opinions were graded according to the recommendations of the Agency for Health Care Policy and Research. The following grading system was used:

- A** Based on at least one randomized, controlled trial (evidence categories Ia or Ib).
- B** Based on clinical studies without randomization (evidence categories IIa, IIb or III).
- C** Based on expert committees, opinions or experiences (evidence category IV).

The evidence is graded separately for the adult and pediatric population based on the best available evidence at the time of the consensus.

TARGET POPULATION

These clinical practice guidelines are directed at specialists who treat adult or pediatric patients with Crohn's disease.

GUIDELINES

A. Indications

1. Moderate to severe Crohn's disease:
 - a. Infliximab is indicated for patients who demonstrate continuing symptoms, despite the optimal use of conventional therapies with glucocorticoids and an adequate trial of immunosuppressive therapy (6-mercaptopurine, azathioprine or methotrexate) (Adult level of evidence A; Pediatric level of evidence B) (2,3,5-25).
 - b. Infliximab is indicated for patients who are unable to tolerate conventional therapy, including glucocorticoids and immunosuppressive therapy (Adult level of evidence C; Pediatric level of evidence C) (5,8,10,15).
2. Fistulizing Crohn's disease:
 - a. Infliximab is indicated for patients with symptomatic enterocutaneous and perianal fistulae (Adult level of evidence A; Pediatric level of evidence B) (3,6,26-31), enterovaginal fistulae (Adult level of evidence C; Pediatric level of evidence C), or enterovesical fistulae (Adult level of evidence C; Pediatric level of evidence C) (32).

B. Initial dosing

There is evidence to suggest that initial dosing with three infusions, at weeks 0, 2 and 6, results in higher remission and response (by approximately 15%) at 14 weeks than dosing at weeks 0 and 14 (33). Studies need to be conducted to determine if similar efficacy, but with improved cost effectiveness, could be achieved with infusions at week 0 and week 8.

1. Moderate to severe Crohn's disease:
 - a. Initial dose is one intravenous infusion of infliximab (5 mg/kg) (Adult level of evidence A; Pediatric level of evidence B) (2,5).
 - b. Patients with an inadequate response within two weeks may be considered for treatment with a second

5 mg/kg dose (Adult level of evidence C; Pediatric level of evidence C) (2,5,33).

Some experts would use an initial dose of three intravenous infusions of infliximab (5 mg/kg) at weeks 0, 2 and 6 (Adult level of evidence A; Pediatric level of evidence B) (2,33).

- c. Patients with an inadequate response to a second 5 mg/kg infusion, may respond to dose escalation of 10 mg/kg (Adult level of evidence B; Pediatric level of evidence C) (2,7,33).
 - d. Patients who do not respond to the above induction regimen should no longer receive infliximab for this indication (Adult level of evidence A; Pediatric level of evidence B) (2,3,33).
2. Fistulizing Crohn's disease:
 - a. Initial dose is three intravenous infusions of infliximab (5 mg/kg) at weeks 0, 2 and 6 (Adult level of evidence A; Pediatric level of evidence C) (3,6,26-32).
 - b. Patients who do not have an adequate response to three infusions should no longer receive infliximab for this indication (Adult level of evidence A; Pediatric level of evidence B) (2,3,33).

C. Concomitant therapy

There is sufficient evidence to suggest that patients receiving infliximab should receive concomitant immunosuppressant therapy to reduce the formation of antibodies to infliximab, decrease the likelihood of infusion reactions, and possibly increase overall response.

1. Patients with Crohn's disease who require therapy with infliximab should receive concomitant immunosuppressive therapy (eg, 6-mercaptopurine, azathioprine or methotrexate) if no contraindications exist, even if the patient has failed to respond to these medications in the past (Adult level of evidence B; Pediatric level of evidence C) (34-43).
2. Administration of hydrocortisone sodium succinate (Solu-Cortef, Pfizer, Canada) (200 mg) intravenously, 30 min before infusion of infliximab, reduces the incidence of antibodies to infliximab and increases measurable infliximab levels in serum (Adult level of evidence A; Pediatric level of evidence C) (40,44).
3. Corticosteroids should be tapered and discontinued. For patients who are unable to discontinue corticosteroids, the role of infliximab in long-term management should be reassessed (Adult level of evidence C; Pediatric level of evidence C).

D. Maintenance dosing

1. Moderate to severe Crohn's disease:
 - a. Regular repeat dosing every eight weeks is effective in maintaining clinical response after an induction regimen (Adult level of evidence A; Pediatric level of evidence B) (2,7,33).

- b. In patients with recurrence of symptoms following an initial infliximab-induced response or remission, therapy with infliximab (5 mg/kg) intravenously is effective in re-establishing and maintaining remission (Adult level of evidence B; Pediatric level of evidence C) (2,7,33).
 - c. Patients who have lost response during the maintenance dosing with 5 mg/kg may regain response if the dosing is increased to 10 mg/kg or the infusion intervals are shortened (Adult level of evidence B; Pediatric level of evidence C) (7,33).
2. Fistulizing Crohn's disease:
- a. Regular repeat dosing every eight weeks is effective in maintaining clinical response after an induction regimen (Adult level of evidence A; Pediatric level of evidence C) (3).
 - b. In patients with recurrence of symptoms following an initial infliximab-induced response or remission, therapy with infliximab (5 mg/kg) intravenously may be effective in re-establishing and maintaining remission (Adult level of evidence B; Pediatric level of evidence C) (3).
 - c. Patients who have lost response during the maintenance dosing (5 mg/kg) may regain response if the dosing is increased to 10 mg/kg or if infusion intervals are shortened (Adult level of evidence B; Pediatric level of evidence C) (3).

E. Precautions and safety

1. Infliximab should not be administered to the following patients:
 - a. Patients with known hypersensitivity to any murine proteins or other component of the product (Adult and pediatric level of evidence C) (34).
 - b. Patients with known active infection (viral, tuberculosis, bacterial or atypical) (Adult and pediatric level of evidence B) (2,3,45).
 - c. Patients with class III/IV congestive heart failure or central nervous system demyelinating syndromes (Adult and pediatric level of evidence B) (45-48).
2. Infliximab should be administered with caution to the following patients:
 - a. Patients with fistulizing Crohn's disease in whom an underlying abscess cannot be excluded. An abscess should be drained and infection controlled before infliximab is started (Adult and pediatric level of evidence C) (15,30,31).
 - b. Patients with intestinal obstructive symptoms or documented fibrotic intestinal narrowing (Adult and pediatric level of evidence C) (14,16-18,20,22,23).
 - c. Patients with inactive ('latent') tuberculosis. If suspected, appropriate consultation should be sought before infliximab treatment is started (Adult and pediatric level of evidence C) (45,49).
 - d. Patients with current or previous malignancy (Adult and pediatric level of evidence C) (45).

- e. Females who are pregnant, lactating, or are not willing to use appropriate birth control during infliximab therapy (Adult and pediatric level of evidence C) (45).

F. Potential indications

Infliximab has also been shown to be beneficial in the following clinical situations associated with inflammatory bowel disease:

1. Hospitalized patients with moderately severe or fistulizing Crohn's disease where a rapid onset of action is desired (Adult and pediatric level of evidence C) (35).
2. As a bridge to immunosuppressants which may take eight to 24 weeks to be effective (Adult and pediatric level of evidence C) (35).
3. Steroid dependent Crohn's disease (Adult and pediatric level of evidence B) (2,8).
4. Other manifestations of Crohn's disease (orofacial Crohn's disease, esophageal Crohn's disease, metastatic Crohn's disease, Crohn's disease of the ileoanal pouch, ankylosing spondylitis, erythema nodosum, pyoderma gangrenosum or refractory inflammatory bowel disease arthropathy) (Adult and pediatric level of evidence C) (50-54).

G. Use of infliximab in children and adolescents

In the management of pediatric Crohn's disease, efficacy of pharmacological therapies (eg, azathioprine/6-mercaptopurine) has generally been extrapolated from adult studies long before it has been specifically confirmed in younger patients (55). It is reasonable to apply the foregoing guidelines concerning indications for infliximab, dosing regimens, concomitant medications and precautions to the treatment of children and adolescents with Crohn's disease. Although Grade A evidence from specifically pediatric trials has hitherto been lacking, clinical experience with infliximab use in children and adolescents (8-12,19,21) is supportive of the now substantial adult clinical trial data. A pediatric randomized clinical trial comparing two maintenance dosing regimens is underway; until these data are available, it is reasonable to follow the above described dosing recommendations for pediatric patients.

H. Acute management of infusion reactions

Infusion reactions can occur during intravenous administration of infliximab. During the infusion the patients' vital signs should be monitored every 30 min.

If there is a prior history of an infusion-related reaction the vital signs should be monitored every 10 min during the first 30 min and then every 30 min thereafter. In this case, premedication could also be considered (diphenhydramine 25 mg to 50 mg orally and/or acetaminophen 500 mg to 650 mg orally and/or hydrocortisone 100 mg intravenously).

If an infusion reaction should occur the infusion should be slowed or stopped depending on the severity. When stopped, the intravenous access should be maintained with 154 mM sodium chloride at 250 mL/h, and the following management strategies assessed (49,56-60):

1. Itching and/or rash without respiratory difficulty:
 - a. Incidence; 3% to 6% of patients.
 - b. Administer diphenhydramine 50 mg intravenously and acetaminophen 500 mg to 650 mg orally; and
 - c. Resume infusion at one-half initial infusion rate once reaction has cleared.
2. Itching and/or rash with respiratory difficulty:
 - a. Incidence; 1% to 2% of patients.
 - b. Administer diphenhydramine 50 mg intravenously and acetaminophen 500 mg to 650 mg orally;
 - c. Start oxygen 2 L/min to 5 L/min;
 - d. Consider hydrocortisone 100 mg intravenously if symptoms persist despite diphenhydramine; and
 - e. Consider restarting the infusion only if the severity of the reaction has been mild, there has been complete resolution of symptoms and the patient has normal vital signs.
3. Anaphylactic reaction:
 - a. Incidence; rare.
 - b. Start oxygen 2 L/min to 5 L/min;
 - c. Administer adrenaline 1:1000 0.3 mL intravenously and diphenhydramine 50 mg intravenously;
 - d. Consider hydrocortisone 100 mg intravenously to prevent biphasic anaphylaxis; and
 - e. Do not restart the infusion.

DISCLOSURE OF POTENTIAL CONFLICT OF INTEREST: No, I do not have any industry or government relationships to report: IR, DS (regarding Schering and Roche), CNW, EW, MZ.

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CANADIAN ASSOCIATION OF GASTROENTEROLOGY PRACTICE GUIDELINE DISCLAIMER: This clinical practice guideline has been developed by the authors on behalf of the Canadian Association of Gastroenterology (CAG) to outline the clinical approach to management problems regarding training issues. After preparation by the authors and based on a review of the literature, each guideline is extensively reviewed by the CAG Practice Affairs Committee (composed of practitioners from across Canada). Changes are made, and once the guideline is felt to be appropriate, it is then circulated for further review by recognized Canadian experts and then amended further. The guideline is presented to the CAG Governing Board for further review and final approval. This later step occurred during CDDW March 2004. Finally, the guideline is posted on the CAG web site for input by the CAG membership at large (March 22 to April 27, 2004). Practice guidelines are intended to give an understanding of a clinical problem, and outline one or more preferred approaches to investigation and management of the problem. While practice guidelines are intended to be useful to all physicians, it is recognized that specialists may rely less on practice guidelines than those in a more general practice. These guidelines are intended to give a practical approach to a problem based on the current literature, but are not intended to be state-of-the-art reviews with extensive references. Practice guidelines are developed to be of assistance to practicing clinicians and are not intended to be the only approach to the management of clinical problems, nor are they intended to be considered as a 'standard of care'. The CAG Practice Affairs Committee recognizes that clinical circumstances may, at times, justify an approach different from that outlined in a practice guideline. It is also recognized that new developments in medical research and clinical practice may require subsequent changes to the practice guideline.

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