TITLE: Infliximab for Maintenance Therapy for Treatment of Crohn’s Disease: A Review of the Clinical Effectiveness and Guidelines

DATE: 18 May 2010

CONTEXT AND POLICY ISSUES:

Therapeutic goals of Crohn’s disease are to induce clinical remission and to maintain clinical response or remission.1 Treatment choices are based on the site and extent of the disease and the severity of symptoms.1 Pharmacologic treatments include aminosalicylates, corticosteroids, immunosuppressants and the anti-tumour necrosis factor alpha (TNFα) agents, infliximab and adalimumab.1

Historically, a “step-up” approach has been recommended, with first line therapy consisting of aminosalicylates, antibiotics, or corticosteroids (i.e., budesonide); second line therapy with corticosteroids (prednisone); third line therapy with immunosuppressants (azathioprine, 6-mercaptopurine, or methotrexate); and anti-TNFα biologic agents (infliximab or adalimumab) for patients who have failed all other treatment options.2 A new treatment approach that is emerging is a top-down approach in which anti-TNFα agents and immunosuppressants are employed early in the course of the disease.1

The recommended dose of infliximab is 5 mg/kg given as an induction regimen at zero, two, and six weeks followed by a maintenance regimen of 5 mg/kg every eight weeks.3 A review article by Gisbert et al suggests that for every patient-year of infliximab treatment, more than 10% of patients will lose response to treatment.4 In the Canadian infliximab product monograph, increasing the dose to 10 mg/kg is recommended in some situations where there is incomplete response, or where response is lost at the lower dose.3

For the purposes of this HTIS report, the term “dose escalation” will be used to refer to an increase in the mg/kg dose or an increase in the frequency of administration of infliximab. This report will review the clinical effectiveness of dose escalation of infliximab in the treatment of patients with Crohn’s disease, and also review the guidelines for dose escalation.

Disclaimer: The Health Technology Inquiry Service (HTIS) is an information service for those involved in planning and providing health care in Canada. HTIS responses are based on a limited literature search and are not comprehensive, systematic reviews. The intent is to provide a list of sources and a summary of the best evidence on the topic that CADTH could identify using all reasonable efforts within the time allowed. HTIS responses should be considered along with other types of information and health care considerations. The information included in this response is not intended to replace professional medical advice, nor should it be construed as a recommendation for or against the use of a particular health technology. Readers are also cautioned that a lack of good quality evidence does not necessarily mean a lack of effectiveness particularly in the case of new and emerging health technologies, for which little information can be found, but which may in future prove to be effective. While CADTH has taken care in the preparation of the report to ensure that its contents are accurate, complete and up to date, CADTH does not make any guarantee to that effect. CADTH is not liable for any loss or damages resulting from use of the information in the report.

Copyright: This report contains CADTH copyright material. It may be copied and used for non-commercial purposes, provided that attribution is given to CADTH.

Links: This report may contain links to other information available on the websites of third parties on the Internet. CADTH does not have control over the content of such sites. Use of third party sites is governed by the owners’ own terms and conditions.
RESEARCH QUESTIONS:

1. What is the clinical effectiveness of an increased infliximab dose for maintenance therapy for treatment of Crohn’s disease?

2. What is the clinical effectiveness of a compressed dosing schedule of infliximab for maintenance therapy for the treatment of Crohn’s disease?

3. What are the evidence-based guidelines for increased dose or compressed dosing schedule of infliximab for maintenance therapy for treatment of Crohn’s disease?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 4, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2008 and May 10, 2010. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials, observational studies, and guidelines. These searches were supplemented by hand searching. Internet links were provided, where available.

This report is an update to a CADTH health technology assessment (HTA) which briefly discussed dose escalation. Studies published following the search dates of the CADTH HTA were included. In addition, North American guidelines were included.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, HTAs, systematic reviews, and meta-analyses are presented first. These are followed by observational studies and evidence-based guidelines.

SUMMARY OF FINDINGS:

The search identified one HTA, which cited several observational studies, three observational studies, and one Canadian treatment guideline which discusses infliximab dose escalation.

Health technology assessments

There were no health technology assessment reports identified whose primary goal was to study infliximab dose escalation. The CADTH HTA was a clinical and cost-effectiveness analysis on anti-TNFα drugs for refractory inflammatory bowel disease (2009). Dose escalation was not the focus of the report, but the authors did include a short section summarizing results from one randomized controlled trial and five single-arm observational studies that reported data related to infliximab dose escalation in Crohn’s disease. The studies reported data on the effects of infliximab dose increases (e.g. from 5 mg/kg to 10 mg/kg) or an increase in frequency of administration (e.g. every 8 weeks to every 4 weeks).
Infliximab for Maintenance Therapy for Treatment of Crohn’s Disease

The CADTH report concluded that most patients with Crohn’s disease re-establish response after infliximab dose escalation. However, there are significant limitations to the studies summarized in the CADTH report. None of the studies randomized patients who lost response to infliximab to dose escalation versus no dose escalation. Without this randomized comparison, definitive conclusions regarding the efficacy of dose escalation cannot be made. For example, the CADTH report included a summary of the ACCENT I study in which 573 patients were randomized to receive episodic 5 mg/kg infliximab, 5 mg/kg scheduled infliximab, or 10 mg/kg scheduled infliximab. A subgroup analysis was performed in ACCENT I patients who initially responded to infliximab, lost response, and crossed over to treatment with a higher dose (e.g. from 5 mg/kg to 10 mg/kg or from 10 mg/kg to 15 mg/kg). This analysis was like an observational study nested within a randomized controlled trial. Thirty percent (58/192) of patients lost response while in the 5 mg/kg scheduled treatment strategy group, and of these, approximately 90% reestablished response after dose escalation to 10 mg/kg. Twenty-six percent (51/193) of patients lost response while in the 10 mg/kg treatment strategy group and of these, approximately 80% reestablished response after dose escalation to 15 mg/kg. In this subgroup analysis, there was no control group of patients who continued to receive the infliximab dose that they were originally randomized to, after they lost response. For this reason, it is not possible to quantify the benefit gained by increasing the infliximab dose. The severity of symptoms of Crohn’s disease fluctuates; therefore, a control group is required to determine whether the infliximab dose increase caused patients to regain response.

The other five studies summarized in the CADTH report used observational designs and most data were collected retrospectively, with the exception of one study. The conclusions of four out of five of these studies suggested that dose escalation is effective at regaining response in patients who lost response to infliximab. The fifth trial described the prevalence of dose escalation but did not measure its impact on patient response. Three of the studies were reported in abstract form, making it difficult to appraise their quality. There was no control group in any of the studies and all studies used a before-after design. That is, response to infliximab was measured before dose escalation and after dose escalation. The definition of response to infliximab differed in these studies and for some trials there was no clear definition provided.

Observational studies

Gonzalez-Lama et al conducted a retrospective survey of 169 Crohn’s disease patients treated with infliximab and reported response to therapy in these patients. Of the 24 patients who lost response to maintenance infliximab therapy, dose was increased in 10 patients and infusion interval was shortened in five patients (details about dose and frequency were not provided). Among the 15 patients who had infliximab dose escalation, “10 achieved a good outcome that lasted for a mean of 19 weeks.”

One abstract cited in the CADTH report was subsequently published in full in 2009. This study by Schnitzler et al prospectively followed the course of 614 patients with Crohn’s disease on infliximab at a single centre with a median follow up time of 55 months. In case of loss of response, patients were given infliximab doses up to 10 mg/kg or the dosing frequency was increased up to every 4 weeks. Of the 547 subjects who initially responded, the interval between infliximab doses was reduced in 108 patients (20%) and of these, 29% (31/108) eventually returned back to an every 8 week regimen. The infliximab dose was increased from 5
mg/kg to 10 mg/kg and/or an induction regimen was re-administered to 144 patients (26%). Of these, 72% (103/144) with an increase in dose and/or a re-induction with infliximab were able to return to a 5 mg/kg dose.7

In a letter to the editor, Magro et al describe a small (N=30) retrospective study in Crohn’s disease patients on infliximab.8 They compared symptom scores between three groups. Group 1 were patients taking infliximab every 8 weeks without relapse (N=15); group 2 were patients taking infliximab every 8 weeks with clinical relapse (see group 3 for sample size); group 3 were group 2 patients after reducing the infusion interval to 6 weeks (N=15). The Harvey-Bradshaw score (an index for quantifying Crohn’s disease symptoms; higher scores indicate more severe symptoms) in group 1, 2, and 3 were 0.5, 3.7, and 0.5, respectively. The authors did not clearly state the timepoints that they used to measure the outcomes. The authors stated that there are statistically significant differences between groups 2 and 3, which appear to be a before-after comparison. They concluded that changing intervals between infliximab infusions to 6 weeks was effective, but cite several limitations including a retrospective study design and small sample size. The authors suggested that a prospective study design is required to definitively answer questions regarding dose escalation.8

The main limitation of the Gonzalez-Lama, Schnitzler, and Magro studies was that there was no true control group to allow a comparative assessment of the efficacy of dose escalation.6-8

Guidelines and recommendations

The Canadian Association of Gastroenterology published guidelines for the use of TNFα antagonist therapy in Crohn’s disease (2009).9 The guidelines are in the form of 23 statements, each of which was voted on by a consensus panel of 25 clinicians with expertise in inflammatory bowel disease. An iterative voting and feedback process was used in advance of the consensus meeting in conjunction with a systematic literature review to refine the voting statements. Each statement underwent discussion, reformulation, voting, and revision until group consensus was obtained (at least 80% agreement). The guidelines make two statements related to infliximab dose escalation:

- “For patients who have a partial response to… multiple dose induction regimens for luminal Crohn’s disease, alternative strategies (which may include dose escalation or switching to another TNF antagonist) may be considered on a case-by-case basis.”9 The grade of evidence for this statement was low (“Additional research is likely to impact both the Committee’s confidence in the estimate of the effect and change their estimate of the effect”.9) For the vote, 64% agreed strongly with the statement and 36% agreed with minor reservations.

- “During maintenance therapy with infliximab, a diminished or suboptimal response can be managed by: (i) Shortening the interval between infliximab dosing; or (ii) Increasing the dose to 10 mg/kg.”9 The grade of evidence for this statement was moderate (“Additional research is likely to add important information thereby impacting the Committee’s confidence in the estimate of the effect. In turn, this may lead to a change in the estimate of the effect.”). Eighty percent of the panel members agreed strongly with the statement and 20% agreed with minor reservations.

The evidence cited to support these statements in the Canadian guidelines are the same as those that were summarized in the CADTH report.15,16
The American College of Gastroenterology published guidelines for the management of Crohn’s disease in adults (2009). There was no specific comment on infliximab dose escalation.¹

Limitations

The main limitations of the available studies are related to their methodological deficiencies. There were no RCTs identified and most of the observational trials that were identified did not have a control group. While most of these studies reported that patients were able to regain response after infliximab dose escalation, it is not possible to attribute the regained response to infliximab because there were no prospective, adequately designed studies with a control group.

There are several issues related to dose escalation that were not addressed in the identified literature including:

- The relative effectiveness of increasing infliximab dosing frequency versus increasing the mg/kg dose.
- The risk of harm associated with infliximab dose escalation.
- The relative effectiveness of infliximab dose escalation compared with switching to another anti-TNF agent. No clinical study was identified that directly compared these strategies. A cost-effectiveness analysis was published suggesting that infliximab dose escalation results in more quality-adjusted life years compared to switch to adalimumab, but was associated with significant costs.¹⁷

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Observational studies have reported that response to infliximab is regained after the dose is increased, or dosing frequency is increased. A Canadian clinical practice guideline supports the practice of dose escalation in the event of loss of response. The CADTH HTA and current Canadian guidelines appear to be using the same studies to draw conclusions regarding the effectiveness of infliximab dose escalation in Crohn’s disease. The economic impact of infliximab dose escalation was not considered in the Canadian guidelines and this may be an issue for policy consideration since it could double drug costs. The limited information from controlled studies about infliximab dose escalation may be a consideration for decision-making.

PREPARED BY:
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439
REFERENCES:


