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Overview of Anti-TNF-α Drugs for Refractory Inflammatory Bowel Disease
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Overview of Anti-TNF-α Drugs for Refractory Inflammatory Bowel Disease

July 2009

We thank Suzanne Morphet for her assistance in creating this overview from a longer report authored by Assasi et al.

This overview is based on a technology report commissioned by CADTH: Nazila Assasi, Gord Blackhouse, Feng Xie, Kathryn Gaebel, John Marshall, E. Jan Irvine, Mita Giacomini, Diana Robertson, Kaitryn Campbell, Rob Hopkins, Ron Goeree [Technology report number 120]. Ottawa: Canadian Agency for Drugs and Technologies in Health, 2009.
1 Introduction

Canada has one of the highest rates of inflammatory bowel disease (IBD) in the world. An estimated 200,500 Canadians have been diagnosed with ulcerative colitis (UC) or Crohn’s disease (CD). Symptoms differ, and the etiology is unknown. Both types of IBD cause chronic inflammation of the gastrointestinal tract. In patients with UC, the inflammation is limited to the colon. CD can affect any part of the gastrointestinal tract.

Patients with IBD usually need medication to control symptoms and stay in remission. Conventional treatment includes 5-aminosalicylic acid (5 ASA) agents, steroids, immunomodulatory therapy, biological therapy, antibiotics, nutritional therapy, and sometimes surgery.

Approximately 5% of patients have refractory IBD, in which symptoms persist despite anti-inflammatory therapy. In Canada, approximately 8,500 patients have refractory IBD each year. These patients and those with severe IBD are increasingly using new biological therapies to reduce the need for hospitalization and surgery. Three biologic therapies are available. Infliximab is approved for use in specific patients with CD and UC. Adalimumab is approved for use in CD only. A third biological, etanercept, is not approved for CD or UC.

Tumour necrosis factor (TNF) is an inflammatory cytokine and mediator of intestinal inflammation. It is expressed more abundantly in people with IBD. Infliximab (Remicade, Schering Canada Inc) and adalimumab (Humira, Abbott Canada) are recombinant monoclonal antibodies that bind to human TNF-α. Both drugs induce and maintain clinical response and remission in patients with active IBD and in patients with fistulizing disease. Concerns have arisen regarding the development of antibodies that increase the risk of infusion reactions and decrease responsiveness to treatment in patients on long-term treatment with infliximab. Etanercept (Embrel, Amgen) is a recombinant fusion protein.

The cost of maintenance therapy for a patient on anti-TNF-α drugs ranges from $23,000 to $38,000 per year in Canada. Several Canadian jurisdictions do not list anti-TNF-α drugs as a general benefit. Instead, their publicly funded drug plans reimburse patients using pre-set criteria or on a case-by-case basis. As the volume of reimbursement requests grows, so does interest in developing or updating evidence-informed reimbursement criteria. Some jurisdictions may use the findings of this health technology assessment to pilot a reimbursement program.

2 Objectives

The aim of the assessment was to evaluate the comparative clinical-effectiveness of anti-TNF-α drugs in patients with CD or UC who have an inadequate response to conventional therapy (including 5-ASA derivatives, immunosuppressant drugs [azathioprine, cyclosporine, mercaptopurine, and methotrexate], and corticosteroids) and to determine the economic value of anti-TNF-α drugs compared with that of conventional therapy and surgery. The following research questions focus on patients with CD or UC.
How do anti-TNF-α drugs (adalimumab, etanercept, and infliximab) compare with each other in terms of clinical- and cost-effectiveness for adult patients with refractory CD or UC, including the luminal and fistulizing forms?

How do anti-TNF-α drugs (adalimumab, etanercept, and infliximab) compare with conventional therapy for patients with refractory CD or UC in terms of clinical- and cost-effectiveness?

What are the benefits and harms that are associated with dose escalation of anti-TNF-α drugs?

What potential exists that patients who have been treated with an anti-TNF-α drug could benefit or be harmed by switching to another anti-TNF-α drug?

What is the optimal timing of anti-TNF-α treatment (early versus later in the course of disease), and is there a group of patients who will benefit most from early aggressive treatment?

Is there a group of patients who respond to maintenance immunosuppressive therapy alone (after anti-TNF-α drug induction)?

What is the harm associated with the formation of neutralizing antibodies to these agents?

What is the effect of neutralizing antibody formation on dosing requirements?

Are there interventions that can prevent the formation of neutralizing antibodies?

What is the effect of anti-TNF-α drugs on clinical response, hospitalizations, surgery, clinical remission, and death?

3 Methods

A systematic review was undertaken to locate relevant clinical trials, cohort studies, and registries that focus on the assessment of infliximab (Remicade), adalimumab (Humira), or etanercept (Enbrel) for CD or UC.

Grey literature was identified by searching the Internet. The bibliographies and abstracts of key papers and conference proceedings were also reviewed.

Clinical and economic studies from 1995 (when anti-TNF-α drugs were starting to be approved and studied) to November 2008 were retrieved with no language restrictions.

Two reviewers independently screened studies. Clinical studies were included if they were randomized clinical trials (RCTs), non-RCTs, before-after trials, or single-arm cohort studies. The patients were adults with luminal or fistulizing CD or UC who were not responding to conventional treatment. The studies compared infliximab, adalimumab, or etanercept with each other, with placebo, or with conventional therapy.
Outcomes of interest in this assessment:

- **Clinical response** (for CD, a 70-point decrease in Crohn’s Disease Activity Index [CDAI] or a 70- to 100-point decrease and a 25% improvement from baseline; for UC, a three-point or greater decrease in Disease Activity Index [DAI] or Mayo score and a decrease in the subscore for rectal bleeding of one point or more, or an absolute subscore for rectal bleeding of 0 or 1)
- **Clinical remission** (for CD, CDAI = 150 points or CDAI is less than 150 points and it is decreased by 50 to 100 points; for UC, Mayo score is 2 or less with no individual subscore greater than 1)
- **Clinical response and remission using other instruments and definitions**
- **Hospitalization**
- **Need for dose escalation**
- **Surgery**
- **Adverse events**
- **Serious adverse events**
- **Death.**

Economic studies were included if they measured costs and effectiveness and if they met the same criteria as clinical studies in terms of population, interventions, and comparators.

One reviewer extracted all data using pre-defined forms. A second reviewer verified data. Any discrepancies were resolved through discussion. Reviewers assessed the quality of clinical trials and observational studies using the Jadad and Newcastle-Ottawa scales respectively.

To analyze clinical results, data was pooled from comparable studies and meta-analysis was performed using Review Manager 5. Because the number of studies in each meta-analysis was too small to evaluate the heterogeneity between trials, a fixed-effects model was used to pool estimates and confidence intervals. For clinical studies that were not comparable, a narrative synthesis was performed. Economic studies were analyzed using qualitative description.

**Results — Clinical**

The systematic review identified 20 relevant RCTs and 17 observational studies. The RCTs each had a parallel group design, and all scored three or higher on the Jadad scale (indicating higher quality). The observational studies consisted of four open-label single-arm trials and 13 cohort studies (seven prospective and six retrospective).

Infliximab was the intervention in eight RCTs of patients with CD, six RCTs of patients with UC, 10 observational studies of patients with CD, and one observational study of patients with UC. Adalimumab was evaluated in four RCTs and five observational studies of patients with CD. Etanercept was evaluated in one RCT of patients with CD.

The total number of patients in the RCTs of infliximab for CD was 1,091. Observational studies of infliximab for CD had 1,402 participants in total. The RCTs of adalimumab for CD had 1,477 participants in total. The observational studies had 157 participants in total. The RCT of etanercept had 43 participants with CD.
For the treatment of UC with infliximab, the RCTs had a total of 847 participants, and the one cohort study had 90 participants. For the treatment of UC with adalimumab, the one cohort had 10 participants.

**Crohn’s Disease**

Head-to-head trials comparing the anti-TNF-α drugs could not be found nor could any studies comparing these drugs to conventional therapy for refractory CD. One study did compare a combination therapy that included infliximab with conventional therapy.\(^\text{12}\)

a) **Infliximab**

In three trials, short-term regimens of infliximab to induce disease remission were studied. At the end of a 12-week trial, Targan et al. found that 24% of the patients on infliximab achieved clinical remission, compared with 8% of patients in the placebo group.\(^\text{13}\) Lemann et al. concluded that infliximab was superior to placebo for causing previously steroid-dependent patients to go into remission without steroids.\(^\text{14}\) By the end of the 52-week trial, 40% of patients on infliximab achieved remission, compared with 22% of patients on placebo. Present et al. noted that patients on 5 mg/kg or 10 mg/kg infliximab were more likely to have complete closure of their draining fistulas (55% and 38% respectively compared with 13% for placebo).\(^\text{15}\)

Three RCTs evaluated the effectiveness of long-term infliximab in keeping patients in remission. In Hanauer et al.’s ACCENT I trial, patients who responded to one dose of infliximab were then randomly assigned to receive 5 mg/kg doses or placebo at weeks 2 and 6, and 5 mg/kg doses, 10 mg/kg doses, or placebo every eight weeks thereafter.\(^\text{7}\) Those on infliximab had superior response rates at weeks 30 and 54. Sands et al. found that 42% of patients on infliximab with draining fistulas in the ACCENT II trial responded to treatment, compared with 23% of those on placebo.\(^\text{16}\) Pooled data from these two studies showed that patients on infliximab 5 mg/kg had a 2.75-times higher clinical response than did those on placebo. In a 36-week trial, Rutgeerts et al. found that 10 mg/kg infliximab was more effective than placebo to keep patients in remission.\(^\text{17}\) By week 36, 72% of patients on infliximab had maintained remission compared with 44% of the placebo group.

None of the studies reported harms or serious adverse events that were associated with dose escalation. Several studies found that most patients who lost response to 5 mg/kg infliximab regained it when they took a higher dose.\(^\text{7,18-20}\) This higher dose was usually 10 mg/kg, but some patients in the ACCENT I trial received 15 mg/kg.\(^\text{7,18}\)

Two trials evaluated the use of immunosuppressive drugs to maintain remission after it was started with infliximab.\(^\text{14,21}\) In one study, 80% of relapses occurred while patients were on maintenance therapy with azathioprine.\(^\text{14}\) The other study showed no statistically significant difference between infliximab and azathioprine in maintaining remission.\(^\text{21}\)

b) **Adalimumab**

Two RCTs with different populations, treatment doses, and outcomes evaluated adalimumab for induction therapy.\(^\text{8,22}\) Two other RCTs examined adalimumab’s performance in maintenance therapy.\(^\text{6,9}\) Sandborn et al. enrolled patients with CD who had lost response to infliximab or who had not tolerated it previously.\(^\text{22}\) By the end of the four-week GAIN trial, 21% of patients who
were treated with adalimumab (160 mg at week 0 and 80 mg at week 2) were in remission, compared with 7% on placebo. In the CLASSIC I trial, Hanauer et al. looked at three different doses of adalimumab being taken by participants who had not previously tried anti-TNF-α drugs. All patients on adalimumab had statistically significantly superior response rates (70 points or more in CDAI score) than did those on placebo. The rates of fistula remission and improvement were not statistically different between the two groups.

The CHARM trial compared two different doses of adalimumab with placebo for maintenance of response and remission in patients who had previously responded to anti-TNF-α drugs. The remission rates at weeks 26 and 56 were greater in both adalimumab groups (those taking 40 mg weekly or those taking 40 mg every other week) than in the placebo group, but they did not differ statistically. The CLASSIC II trial used the same dose formula as the CHARM trial, with similar results (the remission rates were higher in both adalimumab groups than in the placebo group).

For patients who lost response to adalimumab or whose symptoms worsened, Sandborn et al. analyzed the data from the CHARM trial and found that increasing the dose was beneficial (the 70-point and 100-point response rates were 76% and 69% respectively).

Adalimumab may be useful for patients who have lost response to infliximab or never responded to it, according to two RCTs and four observational studies. The two drugs may be effective in the reverse order. No evidence suggested that the sequence of use of anti-TNF-α drugs matters.

c) Infliximab or adalimumab for other outcomes in treating Crohn’s disease

In terms of optimal timing to start the treatment of CD using anti-TNF-α drugs, the results from three studies indicate that earlier is better for improving the rate of remission. These studies looked at infliximab, a combination of infliximab with conventional therapy, and adalimumab.

The review showed that the presence of antibodies against anti-TNF-α drugs could lower the effectiveness of these drugs. Two studies found that the level of antibodies was statistically significantly higher in patients who had lost response to infliximab. Two other studies found that patients who were treated episodically with infliximab had higher levels of antibodies than did those on scheduled therapy. Another study showed a negative relationship between the levels of antibodies to infliximab and the duration of response. West et al. showed that there was a statistically significant relationship between the presence of antibodies to adalimumab and a non-response to the drug. Concomitant immunomodulators could protect against the formation of antibodies to adalimumab and infliximab, especially in patients who receive episodic treatment. For example, in the ACCENT I trial, 16% of patients in the episodic treatment group who were on concomitant immunomodulator treatment developed antibodies, compared with 38% who were not on concomitant immunomodulator treatment.
Studies showed that the use of infliximab\textsuperscript{16,36,37} and adalimumab\textsuperscript{38} reduced the need for surgery and hospitalization. For instance, in the ACCENT II trial, patients with CD receiving infliximab for maintenance therapy experienced half the rate and duration of hospitalization than did those on placebo.\textsuperscript{37}

d) Etanercept

There was no statistically significant difference between the groups in the RCT that compared etanercept with placebo in patients with CD. By the end of the four-week trial, the clinical response rate was 30\% in both groups, and the remission rates were 13\% and 25\% in the etanercept and placebo groups respectively.\textsuperscript{39}

**Ulcerative Colitis**

No head-to-head trials compared the anti-TNF-\(\alpha\) drugs.

a) Infliximab

Five RCTs compared infliximab with placebo,\textsuperscript{40-43} and one RCT compared infliximab with methylprednisolone.\textsuperscript{44,45} Infliximab was effective in starting and maintaining a clinical response, even in patients who were resistant or refractory to conventional therapy. Infliximab was superior to placebo when the results from the ACT1\textsuperscript{40} and ACT2\textsuperscript{40} trials were pooled. There was no relationship between the efficacy of infliximab and disease duration.\textsuperscript{46} Two studies evaluated dose escalation, and neither reported harms.\textsuperscript{41,47} In the ACT1\textsuperscript{40} and ACT2 trials,\textsuperscript{40} the proportion of patients who had an infusion reaction was higher among those who had developed antibodies to infliximab. Patients on infliximab were half as likely to be hospitalized as patients on placebo in the ACT1 and ACT2 trials.\textsuperscript{48} In another study, 29\% of patients on infliximab underwent colectomy compared with 67\% of patients on placebo.\textsuperscript{42}

b) Adalimumab

One uncontrolled study evaluated adalimumab in 10 patients who had lost response or could not tolerate infliximab.\textsuperscript{49} By the end of the four-week study, three (30\%) patients had clinical improvement, and one (10\%) was in remission. The other six (60\%) had no response. All patients tolerated adalimumab with no serious adverse events observed.

c) Etanercept

No studies were identified for UC.

**Safety of Anti-TNF-\(\alpha\) Drugs in CD and UC**

Anti-TNF-\(\alpha\) drugs were associated with adverse events in nine infliximab trials,\textsuperscript{7,13,14,16,17,40,42,43} four adalimumab trials,\textsuperscript{5,8,9,22} and one etanercept trial.\textsuperscript{39} Most of the adverse events that were associated with infliximab and adalimumab were mild to moderate and included injection site reactions, headache, upper respiratory infection, nausea, fatigue, joint pain, infections, and fever. The rates of serious adverse events in patients with CD taking infliximab, adalimumab, or etanercept were 11.3\%, 5.5\%, and 4\% respectively.
Results — Economic

We found seven economic evaluations of strategies to treat CD and one of UC. The descriptions appear in Appendix 16 of the Technology Report. The primary economic evaluation included two cost-utility analyses that used Markov models to investigate treatments for patients with refractory CD or UC. In each analysis, the perspective was that of a publicly funded health care system. We used a five-year time horizon for the base-case analysis. All direct costs (hospital, physician, drugs for eligible patients) were included. The unit cost of infliximab was $952 per 100 mg vial (manufacturer’s price). The unit cost of adalimumab was assumed to be $715 per 40 mg vial (average price on three provincial formularies).

For CD, the comparators were usual care (for example, corticosteroids and other immunosuppressants); infliximab induction (5 mg/kg at weeks 0, 2, and 6) and maintenance (5 mg/kg every eight weeks); and adalimumab induction (160 mg at week 0 and 80 mg at week 2) and maintenance (40 mg every two weeks). The rates of remission and response, relapse, surgery, and hospitalization were derived from published studies. The base-case results for CD appear in Table 1.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost</th>
<th>Incremental Cost</th>
<th>QALYs</th>
<th>Incremental QALYs</th>
<th>ICUR versus Usual Care</th>
<th>ICUR Efficiency Frontier</th>
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ICUR = incremental cost-utility ratio; QALYs = quality-adjusted life-years.

For UC, the comparators were usual care, strategy B 5 mg/kg infliximab plus adalimumab, and strategy C 5 mg/kg and 10 mg/kg infliximab plus adalimumab. Clinical parameters were estimated using a fixed-effect meta-analysis of the findings from the ACT trial. The base-case results appear in Table 2.

<table>
<thead>
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<th>Strategy</th>
<th>Cost</th>
<th>Incremental Cost</th>
<th>QALYs</th>
<th>Incremental QALYs</th>
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ICUR = incremental cost-utility ratio; QALYs = quality-adjusted life-years.

Strategy B: 5 mg/kg infliximab plus adalimumab; Strategy C: 5 mg/kg and 10 mg/kg infliximab plus adalimumab.
4 Limitations

The lack of studies on adalimumab for refractory UC and on etanercept for UC and CD limited our investigation. The heterogeneity of available studies prevented the pooling of statistics. Because the primary economic analyses adopted a public health care payer perspective, indirect costs, such as loss of productivity, were not considered. Because of a lack of head-to-head evidence, differences in efficacy between adalimumab and infliximab in the economic model for CD were estimated. The treatment regimens that were used in the induction trials\textsuperscript{8,13} differ from the recommended regimens that were used in the model. The CD model was potentially weakened when dose escalation was not considered after anti-TNF failure.

5 Health System Implications

In 2008, the Crohn’s and Colitis Foundation of Canada estimated that there were 88,500 cases of UC and 112,000 cases of CD.\textsuperscript{1} Using data from public and private drug plans, total expenditures in 2008 were calculated at $35,498,642 for infliximab and $205,431 for adalimumab. Based on the increases from 2006 to 2008, an estimate of total spending on anti-TNF-α drugs from 2010 to 2011 could be $70,176,163.

6 Conclusion

Infliximab and adalimumab have shown a consistent superiority to placebo in the induction and maintenance of clinical remission and in reducing the rates of surgery and hospitalization in refractory CD. Infliximab also leads to higher response and remission rates in patients with UC, compared with placebo. There was no compelling evidence of a clinically important effect in the treatment of CD with etanercept. Although infliximab and adalimumab have been shown to provide clinical benefit, the costs associated with these treatments could be perceived as high. Furthermore, based on incremental cost-utility findings from our primary economic evaluations, adalimumab and infliximab for the treatment of IBD may not be perceived to be a cost-effective use of health care resources. Given the limited number of long-term RCTs on the effectiveness and safety and cost-effectiveness of anti-TNF-α drugs, it is appropriate to weigh the potential risks and costs when deciding whether patients with IBD should use these drugs.

7 References


11. Ndegwa SL. *Adalimumab for refractory Crohn's disease and ulcerative colitis* [ACP Brief - Spring 2007 prioritization, FINAL]. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2007.