Title: Infliximab versus Adalimumab for Patients with Moderate to Severe Ulcerative Colitis: A Clinical and Cost Effectiveness Review

Date: 03 March 2008

Context and policy issues:

Ulcerative colitis (UC) is a form of inflammatory bowel disease. Its cause is unknown but hereditary, infectious and immunologic factors have been proposed as possible causes. UC results in inflammation of the inner lining of the colon and the rectum. Symptoms range from mild to severe, including persistent diarrhea, abdominal pain, rectal bleeding, fever, and weight loss. In 2000, there were approximately 4,600 new incident cases of UC in Canada and the prevalence was estimated to be 63,000, or 200 out of 100,000 people.

Treatments for UC include anti-inflammatory drugs (eg sulfasalazine, mesalamine, corticosteroids), and immune system suppressors (azathioprine, cyclosporine, infliximab, adalimumab). Other medications may provide relief of symptoms (nicotine patches, anti-diarrheals, laxatives, pain relievers, iron supplements). If diet, lifestyle changes, drug therapy or other treatments are not successful, surgery may be used. This often means removal of the colon (colectomy) or the colon and rectum (proctocolectomy).

Infliximab (Remicade® by Schering) and adalimumab (Humira® by Abbott) are both biologics that act as tumour necrosis factor (TNF) alpha inhibitors. Infliximab is a chimeric (mouse-human) monoclonal antibody administered by intravenous infusion. Adalimumab is a recombinant human monoclonal antibody administered by subcutaneous injection. It is typically used for adults and children with moderate to severe UC who do not respond to or cannot tolerate other treatments. Adalimumab is currently at the experimental and investigational stage for treatment of UC. The development of an attenuated response or intolerance over time is a significant problem in UC patients treated with infliximab. Adalimumab might be a suitable alternative for patients who are refractory or immunogenic to infliximab. A review of recent evidence may shed light on the clinical and cost effectiveness of infliximab and adalimumab.
Research questions:

1. What is the clinical efficacy of infliximab versus adalimumab for treating patients with moderate to severe ulcerative colitis?

2. What is the cost effectiveness of infliximab versus adalimumab for treating patients with moderate to severe ulcerative colitis?

Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 1, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and February 2008, and are limited to English language publications only. Filters were applied to limit the retrieval to systematic reviews/health technology assessments, randomized controlled trials, observational studies, guidelines and economic studies.

There was sufficient evidence for infliximab identified in the systematic reviews and RCTS. However, observational studies were included for adalimumab due to the lack of systematic review and RCT evidence.

Summary of findings:

Health technology assessments

A new and emerging technology briefing on infliximab for UC by the National Horizon Scanning Centre of the University of Birmingham, UK, was retrieved. It referred to the two phase III trials (ACT 1 and ACT 2) that demonstrated infliximab met its primary and secondary endpoints of clinical response, clinical remission and mucosal healing in patients with moderate to severe active UC who were unresponsive to at least one standard therapy. It also referred to the Jarnerot study that demonstrated that a single infusion of infliximab is effective at three months in acutely ill in-patients with fulminant UC refractory to intravenous steroids.

The Birmingham report identified no cost effectiveness studies for infliximab in UC treatment. They noted that anti-TNF agents can be associated with the development of serious opportunistic infections including tuberculosis. They also noted that the number of infusions required for maximum benefit and long-term response is uncertain, as is the number of patients in the UK who might receive infliximab for UC. This makes the overall cost impact difficult to estimate. They suggested treatment with infliximab might lead to a net savings due to a possible reduction in hospitalization and surgical procedures. Since infliximab is already used in the treatment of Crohn’s disease, they felt minimal additional training of healthcare professionals would be required.

Systematic reviews and meta-analyses

Three systematic reviews were retrieved, all on infliximab (Lawson, Gisbert, Rahimi). The most comprehensive was by Lawson. It included five RCTs on infliximab versus placebo as well as two RCTs on infliximab versus corticosteroids. The other two systematic reviews covered the same five RCTs that Lawson did for the infliximab versus...
placebo group. Since the three systematic reviews covered essentially the same ground, and since the Lawson study was the most comprehensive, we will focus on it.

For the Lawson systematic review selected papers had to be RCTs in which patients with active UC were randomly allocated to receive a TNF alpha blocking agent in the treatment arm, and a placebo or another treatment in the comparison arm. The main outcome measure was the occurrence of remission as defined by the primary studies. Dichotomous variables relative risk (RR) and 95% confidence intervals (CI) were calculated based on the fixed effects model. Lawson found that in patients with moderate to severe UC whose disease was refractory to conventional treatment using corticosteroids and/or immunosuppressive agents, infliximab (at three intravenous infusions at 0, 2, and 6 weeks) was more effective than placebo in inducing clinical remission; inducing endoscopic remission; and in inducing clinical response at eight weeks. A single infusion of infliximab was also more effective than placebo in reducing the need for colectomy within 90 days after infusion. The results of the Lawson meta-analysis are summarized in Table 1.

Table 1: Infliximab Meta-analysis Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Clinical remission</td>
<td>3.22</td>
<td>2.18 to 4.76</td>
</tr>
<tr>
<td>Endoscopic remission</td>
<td>1.88</td>
<td>1.54 to 2.28</td>
</tr>
<tr>
<td>Clinical response</td>
<td>1.99</td>
<td>1.65 to 2.41</td>
</tr>
<tr>
<td>Colectomy</td>
<td>0.44</td>
<td>0.22 to 0.87</td>
</tr>
</tbody>
</table>

Lawson concluded that for the patient group studied, infliximab is effective in inducing clinical remission, inducing clinical response, promoting mucosal healing, and reducing the need for colectomy, at least in the short term. Serious adverse events attributable to infliximab were not common in the included studies. However, the authors advised physicians to be aware of and be prepared to deal with potential adverse events such as anaphylactic reactions and infections. The authors did not find evidence to support the use of other TNF alpha inhibitors in acute UC. Table 2 summarizes the RCTs included in the Lawson systematic review.

Table 2: Summary of RCTs Included in the Lawson Systematic Review

<table>
<thead>
<tr>
<th>RCT</th>
<th>Sample size, Study duration</th>
<th>Key conclusions</th>
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<tbody>
<tr>
<td>Infliximab versus placebo</td>
<td></td>
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<tr>
<td>Rutgeerts 2005 ACT1⁹</td>
<td>364 patients 54 weeks</td>
<td>Data from the ACT 1 and ACT 2 clinical trials showed that infliximab met its primary and secondary endpoints of clinical response, clinical remission and mucosal healing.</td>
</tr>
<tr>
<td>Rutgeerts 2005 ACT2⁹</td>
<td>364 patients 30 weeks</td>
<td>Data from the ACT 1 and ACT 2 clinical trials showed that infliximab met its primary and secondary endpoints of clinical response, clinical remission and mucosal healing.</td>
</tr>
<tr>
<td>Janerot 2005¹⁰</td>
<td>45 patients 3 months</td>
<td>Infliximab is an effective and safe rescue therapy in patients experiencing an acute severe or moderately severe attack of UC not responding to conventional treatment.</td>
</tr>
</tbody>
</table>
### Key conclusions

<table>
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<tr>
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</tr>
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<tbody>
<tr>
<td>Probert 2003(^{15})</td>
<td>43 patients 6 weeks</td>
<td>The data do not support the use of infliximab in the management of moderately active glucocorticoid resistant UC.</td>
</tr>
<tr>
<td>Sands 2001(^{14})</td>
<td>11 patients 2 weeks</td>
<td>The small number of patients in this clinical trial precludes a definitive statement about the response to infliximab. A larger RCT is indicated to confirm the impression of benefit and to define the magnitude of the clinical response.</td>
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**Infliximab versus corticosteroids**

<table>
<thead>
<tr>
<th>RCT</th>
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<th>Key conclusions</th>
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</thead>
<tbody>
<tr>
<td>Armuzzi 2004(^{17})</td>
<td>20 patients 32 weeks</td>
<td>Infliximab seems to be as effective as steroids (methylprednisolone) in the management of moderate to severe steroid-dependent UC. Preliminary data suggest the potential efficacy of repeated treatment with infliximab for short-term maintenance of remission and steroid withdrawal in glucocorticoid-dependent UC.</td>
</tr>
<tr>
<td>Ochsenkuhn 2004(^{16})</td>
<td>13 patients 13 weeks</td>
<td>There was no statistically significant difference between infliximab versus prednisolone in the treatment of acute moderate or severe UC. Larger controlled trials are needed.</td>
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ACT=Active Ulcerative Colitis Trials  
UC=Ulcerative colitis

Another systematic review by Rahimi\(^{13}\) analyzed the same five infliximab versus placebo RCTs as the Lawson\(^{11}\) study, and came to similar conclusions. Results of the meta-analysis were presented as odds ratios (OR) rather than relative risk as in Lawson. The OR for clinical remission was 3.24 (95% CI 1.6 to 6.57). The OR for clinical response was 3.93 (95% CI 2.84 to 5.45). The study concluded that infliximab is effective in inducing response and remission in patients with UC when administered in combination with corticosteroids.

The third systematic review was done by Gisbert,\(^{12}\) again using the same five infliximab versus placebo RCTs in a meta-analysis. It also included the Armuzzi\(^{17}\) and Ochsenkuhn\(^{16}\) RCTs included by Lawson, comparing infliximab to corticosteroids, but these results were not able to be pooled. The results showed an advantage (P<0.001) of infliximab in all endpoints (short or long-term response or remission). ORs were from 2.7 to 4.6, and number-needed-to-treat (NNT) was from 3 to 5. Similar infliximab response was found independent of indication (steroid-refractory or non-steroid-refractory) or the dose (5 or 10 mg/kg). Adverse effects were reported in 83% of the infliximab and 75% of the placebo-treated patients (OR=1.52 95%CI 1.03 to 2.24). The number needed to harm was 14. The study concluded that infliximab is more effective than placebo for the treatment of moderate to severe UC, achieving clinical remission in 40% of patients at about 9 months of follow-up. They also concluded that further studies are needed to confirm the long-term efficacy of infliximab in UC.

**Randomized controlled trials**

Impairment of health-related quality of life (HRQL) is an important factor in patients with moderate to severe UC.\(^{18,19}\) A follow-up study to the ACT1 and ACT2 clinical trials was retrieved which addresses this issue (Feagan\(^{20}\)). Data from the pooled 728 patients in the two trials was
analyzed. Changes in Inflammatory Bowel Disease Questionnaire (IBDQ) and Medical Outcomes Study 36-Item Short Form Health Survey physical and mental component summary (PCS and MCS respectively) scores were used. Baseline scores indicated substantial impairment in HRQL. Improvement at week eight in the total IBDQ score was significantly greater in the infliximab 5 mg/kg (P<0.001) and 10 mg/kg (P<0.001) groups compared with the placebo group. Improvement at week eight was also significantly greater in the infliximab 5 mg/kg and 10 mg/kg groups for PCS and MCS compared with placebo (P<0.01 for all comparisons). Continued benefit was seen at weeks 30 and 54 with infliximab maintenance therapy (P<0.001 for all comparisons). The study concluded that infliximab therapy substantially improved HRQL in patients with UC, and this benefit was sustained through one year with maintenance infliximab therapy.

Observational studies

A study by Peyrin-Biroulet was the only study retrieved on the clinical response to adalimumab. A four week open-label study was undertaken to assess the subcutaneous administration of adalimumab as induction therapy in patients with UC who had an attenuated response to infliximab or had become intolerant to it. The ten patients in the study received a loading dose of 160 mg of adalimumab at week zero, followed by 80 mg at week two. Four of the ten patients benefited from adalimumab therapy. One achieved remission, and three had clinical improvement at week four. Of the six patients who had no response to adalimumab, two subsequently underwent colectomy. Of the six patients with severe UC at baseline, none achieved remission and only one patient had clinical improvement at week four. The study concluded that the small advantage of adalimumab in patients who have mild to moderate UC and have reduced response or intolerance to infliximab needs to be confirmed in randomized, double-blind, placebo-controlled trials.

Economic studies

No economic evaluations of infliximab or adalimumab were retrieved. One article that remotely touched on economic issues was found. Brown describes study findings presented at the American College of Gastroenterology meeting, suggesting infliximab can reduce the average number of hospitalizations per year for UC by about 50%. The lead investigator was William Sandborn of the Mayo Clinic in Rochester Minnesota. Sandborn’s analysis of data from the ACT1 trial showed that the average number of hospitalizations per 100 patients fell from 22 to 12 at year one with infliximab use (p=0.061). Also, infliximab use was associated with an increase in the time to first hospitalization (p=0.032). The study also included an analysis of data from ACT1 and ACT2 showing infliximab was associated with a drop in the proportion of UC hospitalizations involving the use of high-dose corticosteroids.

Guidelines and dosing recommendations

MIMS (monthly index of medical specialties) provides medical information to Australian healthcare professionals. It lists infliximab for moderately severe to severe active UC in patients who have had an inadequate response to conventional therapy. The dosage for UC is 5 mg/kg given as intravenous infusion over a two hour period followed by an additional 5 mg/kg infusion dose at two and six weeks after the first infusion, then every eight weeks after that. If patients have not responded to the initial three treatment infusion regimen at weeks zero, two and six weeks, they recommended careful consideration be given before persisting with further treatment.
The Lawson review\textsuperscript{11} found infliximab is indicated in patients with moderate to severe UC whose disease is resistant to conventional therapy using corticosteroids and/or immunosuppressive agents. It recommended a dose of 5 mg/kg for these patients but felt there is insufficient evidence to provide recommendations on the ideal dosing schedule. The authors did not find that infliximab is indicated for UC patients on corticosteroids who are not steroid refractory.

The American Gastroenterological Association\textsuperscript{23} recommends 5 mg/kg of infliximab infused over two hours in an induction regimen of three doses at weeks zero, two and six, followed by maintenance therapy every eight weeks in patients who respond. In the case of no response to three infusions, they do not recommend further treatment with infliximab. They felt an attempt to withdraw or taper any concomitant corticosteroid therapy is sensible in patients who achieve remission with infliximab.

Canadian guidelines on the use of infliximab in UC are currently under development and will be published in the Canadian Journal of Gastroenterology (primary author Richard Fedorak, Edmonton).

No guidelines or dosing recommendations for the use of adalimumab for UC were retrieved.

**Limitations:**

Key limitations in the current evidence base on infliximab and adalimumab were identified in this review. There are no head-to-head trials of infliximab versus adalimumab. Moreover, to date there are no RCTs on adalimumab. The Lawson systematic review\textsuperscript{11} had anti-TNF agents as the intervention of interest, and did not mention the use of adalimumab. A search for RCTs subsequent to the included systematic reviews did not return any adalimumab RCTs. A search of the observational studies returned only one study on adalimumab – an open-label case series of ten patients without a control group. The economic evidence is equally sparse. No cost effectiveness studies comparing infliximab to adalimumab were found. In fact, no cost effectiveness studies at all were returned. One study touched remotely on economic issues by analyzing data from the ACT1 and ACT2 trials on hospitalizations of the infliximab groups versus the placebo groups.

Regarding the quality of the studies included for review, the three systematic reviews\textsuperscript{11-13} appear to be of good quality, and were consistent in the RCTs that they included in their placebo and corticosteroid comparator groups. The Lawson\textsuperscript{11} study was published as a Cochrane review. Not being restricted to the same page limitations as the other two, it had the most comprehensive presentation of methodology and results.

Lawson\textsuperscript{11} notes that the earlier small RCTs in the systematic review did not demonstrate a statistically significant difference between infliximab and placebo for the induction of remission, and commented that these studies probably lacked adequate statistical power to allow detection of a difference. The more recent larger RCTs clearly demonstrated a benefit for infliximab. Lawson found that allocation concealment was unclear in Armuzzi\textsuperscript{17} and Sands\textsuperscript{14} but was adequate for the other five studies in the systematic review. Lawson also noted the absence of proper randomized controlled trials on the effectiveness of infliximab in the paediatric population.

The Peyrin-Biroulet observational study on adalimumab\textsuperscript{8} was limited in that it is an open-label case series without a control group. The economic analysis by Sandborn reported in Brown\textsuperscript{21}
looked only at effects on hospitalization and did not provide a complete analysis of the trade-offs between costs and benefits of infliximab therapy.

CADTH is currently undertaking a full technology report on adalimumab for refractory Crohn’s disease and UC. It will include a clinical review and an economic evaluation, and will help to fill some of the gaps in evidence mentioned above. Publication is expected in the fall of 2008.

Conclusions and implications for decision or policy making:

Currently, the limited clinical evidence does not allow conclusions to be drawn about the relative clinical efficacy of infliximab versus adalimumab. Adalimumab is currently at an investigational stage as a treatment for UC. The limited observational evidence considered adalimumab as an option for patients not responding well to infliximab, and not as a direct comparator to it. Similarly, the limited economic evidence does not allow conclusions to be drawn about the relative cost effectiveness of infliximab versus adalimumab. We can say that in comparison with placebo, there is good evidence that infliximab is an effective treatment for patients with moderate to severe UC. In direct comparison to corticosteroids, infliximab appears to have similar but not superior efficacy. Relative to placebo, infliximab adds benefit in terms of improved health-related quality of life. With regard to hospitalization, infliximab has the potential benefit of reducing the rate of hospitalization, and reducing the time to first hospitalization, relative to placebo.

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References:


