TECHNOLOGY OVERVIEW

HTA
Issue 29
March 2007

Long-term Clinical and Cost-Effectiveness of Infliximab and Etanercept for Rheumatoid Arthritis

Supporting Informed Decisions
Until April 2006, the Canadian Agency for Drugs and Technologies in Health (CADTH) was known as the Canadian Coordinating Office for Health Technology Assessment (CCOHTA).


Production of this report is made possible by financial contributions from Health Canada and the governments of Alberta, British Columbia, Manitoba, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut, Ontario, Prince Edward Island, Saskatchewan, and Yukon. The Canadian Agency for Drugs and Technologies in Health takes sole responsibility for the final form and content of this report. The views expressed herein do not necessarily represent the views of Health Canada or any provincial or territorial government.

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CADTH is funded by Canadian federal, provincial, and territorial governments.

Legal Deposit – 2007
National Library of Canada
ISSN: 1203-9012 (print)
ISSN: 1481-4501 (online)
H0435 – March 2007

PUBLICATIONS MAIL AGREEMENT NO. 40026386
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Long-term Clinical and Cost-Effectiveness of Infliximab and Etanercept for Rheumatoid Arthritis

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We thank Suzanne Morphet for her assistance in creating this overview from two longer reports authored by Suarez-Almazor ME et al.

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**Technology and Condition**
Infliximab (IFX) and etanercept (ETN) are anti-tumour necrosis factor (TNF) biologic agents used in the treatment of rheumatoid arthritis (RA). RA is a chronic inflammatory disorder of unknown etiology, characterized by a chronic polyarthritis causing pain and disability, with no known cure. Most patients experience progressive functional decline. An estimated 150,000 to 300,000 Canadians have been diagnosed with RA, most often women (3:1), and most frequently in the fifth or sixth decade of life.

**Issue**
There is uncertainty about the long-term (≥12 months) clinical impact compared to traditional disease-modifying anti-rheumatic drugs (DMARDs) and whether the additional cost is justifiable. There is uncertainty about the effectiveness of using one anti-TNF agent in patients who failed by another, which agents should be used first, and whether the timing of therapeutic onset influences clinical effectiveness. There is uncertainty about the known clinical effectiveness of escalating dose.

**Methods and Results**
A systematic review of the literature was performed. One hundred and seventy-seven studies and 14 reviews provided evidence for long-term clinical impact. Twenty-nine studies provided evidence for timing of therapeutic introduction, dose escalation, and switching between IFX and ETN. Twenty-two economic evaluations were identified.

### Implications for Decision Making
- **IFX and ETN are moderately effective at one year.** The evidence suggests that IFX and ETN, when used concomitantly with methotrexate (MTX), improve surrogate and composite outcomes, such as delay in radiological progression and American College of Rheumatology improvement criteria. The long-term impact on functionality, survival, or quality of life has not been demonstrated.

- **IFX and ETN are not cost-saving.** The economic evidence suggests that ETN and IFX, when used concomitantly with MTX, is only cost-effective for the treatment of RA after the failure of other DMARDs and if society is willing to pay more than $100,000 to obtain a quality-adjusted life-year.

- **Timing therapy may improve response rates. Uncertainty remains about dose escalation and switching.** The evidence suggests that surrogate responses to IFX or ETN combined with MTX, when compared to using MTX alone, are increased in patients with longer disease duration or in those who had failed previous treatment with MTX. There is insufficient evidence to support switching between agents and the practice of dose escalation.

1 Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that affects the joints and surrounding tissue to such a degree that it can be crippling. Mortality rates are also higher among RA patients.\textsuperscript{1,2} Those with advanced RA have a reduced quality of life and a survival rate similar to those of patients with coronary artery disease and Hodgkin’s lymphoma.\textsuperscript{3}

While the clinical course of the disease varies, most patients experience flares and partial remissions with some disease activity always present.\textsuperscript{4,5} For about a third of patients, the disease is progressive with no remissions. A few will have one flare that can last for months or years, followed by a prolonged remission.\textsuperscript{4} It is estimated that between 0.5\% and 1.5\% of adults age \textgreater{}18 years old have RA.\textsuperscript{1} Women are more commonly affected than men (3:1), and although RA may appear at any age, it most frequently occurs among those in their 50s.

The etiology of RA is unknown but it has been proposed that several factors play a role, including genetics and environmental factors such as infections. Many RA patients share an association with the human leucocyte antigen HLA-DR4, implying a genetic predisposition to the disease.

Treatment for RA includes drug therapies, usually starting with non-steroidal anti-inflammatory drugs (NSAIDs).\textsuperscript{6} These reduce joint pain, stiffness, and swelling within days of beginning treatment, but there is no evidence to show that they slow destruction of the joints. The evidence does show that long-term use of NSAIDs can lead to severe and potentially fatal gastrointestinal adverse events. Approximately 16,500 patients who take NSAIDs for arthritis in the US are thought to die each year from complications.\textsuperscript{6}

Disease-modifying anti-rheumatic drugs (DMARDs) modify the natural course of RA by interfering with inflammatory and immunologic pathways.\textsuperscript{6} As a result, they have a more profound effect than NSAIDs, but it can be weeks or months before symptoms improve. Popular DMARDS include methotrexate (MTX), sulfasalazine, anti-malarials, leflunomide, gold salts, cyclosporine, and cytotoxic agents (azathioprine and cyclophosphamide). There is a trend toward using \textgeq{}2 DMARDs in combination. While not all combinations have proven to be more efficacious than one drug alone, many appear to be, especially those that include MTX.\textsuperscript{6} None of these drugs is curative, and patients fare better if they take them throughout their lives rather than use them intermittently.\textsuperscript{7}

It is important to treat patients with RA early and aggressively because structural damage, as seen in radiological erosions, often occurs during the first year of the disease. The damage is generally irreversible.

Biologic therapies offer a new approach to treating RA. They target specific cytokines or cell-signaling proteins, which are critical to the pathogenesis of the disease. Three biologic therapies have been approved for use against the cytokine known as tumour necrosis factor (TNF), which contributes to chronic joint inflammation in RA. They are etanercept (ETN, Enbrel\textsuperscript{6}; marketed by Amgen Canada), infliximab (IFX, Remicade\textsuperscript{6}; marketed by Schering Canada, Inc.), and adalimumab (ADM, Humira\textsuperscript{6}; marketed by Abbott, Canada). The technology reports on which this Overview is based evaluated the first two agents approved in Canada for patients with moderate to severe RA — IFX in 2000 and ETN in 2001 — both of which are classified as selective immunsuppressive agents.\textsuperscript{8}
IFX is a chimeric monoclonal antibody that is 30% murine and 70% human. It binds to membrane-bound and soluble TNF. IFX is administered intravenously with a recommended dose of 3 mg/kg at weeks zero, two, and six, and every eight weeks thereafter. A 100 mg vial costs $940.9

ETN is a genetically engineered fusion protein: two chains of a recombinant human p75 TNF soluble receptor are linked to the Fc domain of human IgG. ETN binds only soluble TNF. The recommended dose is 50 mg subcutaneously, weekly. A 25 mg vial is $185.64, and a 50 mg syringe injection is $353.60.10

Patients may develop a tolerance to these agents, particularly IFX, requiring an increase in dosage.11-13 As a result, it is recommended that IFX be given with MTX, to limit the development of anti-IFX antibodies that diminish its effectiveness. Most of the cost of treatment is related to the drug, so increasing the dose of IFX is expensive. Switching from one anti-TNF agent to another after the first one fails is increasingly common, but it is unknown whether this is beneficial or if adverse effects caused by one agent will recur with another one. Nor is it known whether the timing of therapeutic onset influences clinical effectiveness.

2 Objectives

This health technology assessment was published in two reports. The first report synthesized the available evidence of long-term (≥12 months) clinical benefits and harm, and the associated economic impact of anti-TNF agents in the treatment of RA compared to DMARDS. The second report examined the evidence of the clinical impact associated with timing of therapeutic introduction, dose escalation, and switching between IFX and ETN. For both reports, we performed systematic reviews of the literature, which included randomized controlled trials (RCTs), observational studies, and — in the case of the first report — economic evaluations.

To meet these objectives, six research questions were addressed.
• What is the evidence from clinical trials or observational studies of the long-term (≥12 months) benefit and harm from IFX and ETN for RA compared to standard care?
• What is the evidence of cost-effectiveness for IFX and ETN for RA compared to standard care?
• What is the clinical impact of introducing IFX or ETN as initial therapy or after failure with other drug therapies?
• What is the clinical impact of using higher doses at more frequent intervals (dose creep) versus no dose change?
• What is the dose-related clinical impact of using IFX or ETN at various stages of disease?
• Do patients who fail treatment with one anti-TNF agent respond to therapy with a different one?

3 Clinical Review Methods

Literature Search Strategy
Initially, we intended to write one systematic review covering all our objectives. Therefore, we designed a comprehensive, single-search strategy to identify published and grey literature about the safety, clinical effectiveness, cost-effectiveness, therapeutic timing, dose escalation, and switching
between IFX and ETN in the treatment of patients with RA. Given the large volume of information gathered, it became apparent at the end of the process that two reports would be better than one.

Using the DIALOG® system, we searched the MEDLINE®, EMBASE®, BIOSIS Previews®, and ToxFile databases on March 16, 2005 and updated results biweekly until September 4, 2005. We did parallel searches on PubMed and searched the 2005 (issues 1 to 3) Cochrane Library. Publication dates were unrestricted, but languages were limited to English, Spanish, French, Italian, Portuguese, and German because of the availability of translation. Searches were further restricted to studies on humans.

We used reviews published in English, mainly to identify information that we may have missed in our searches; the two exceptions were HTA reports from Denmark and Hungary,\textsuperscript{14,15} from which we gleaned information from the tables. We hand-searched the bibliographies of relevant articles, reviews, and reports for additional references, and we contacted the manufacturers of ETN (Amgen Canada) and IFX (Schering Canada, Inc.) for additional information. We cross-referenced all databases and other sources of information to eliminate duplicate citations.

**Selection Criteria**

Table 1 shows the selection criteria for each aspect of our review. Using the criteria in Table 1, two raters independently examined each study for inclusion or exclusion. A third person assisted if consensus could not be reached. After the studies were selected, one reviewer extracted data using a structured form, while a second person independently cross-checked the work.

**Strategy for Quality Assessment**

Two independent raters assessed the quality of each study. The Jadad score\textsuperscript{16} was used to assess RCTs and CCTs, while the Newcastle-Ottawa Scale\textsuperscript{17} was used to evaluate observational studies. We rated allocation concealment as adequate, inadequate, or unclear.

**Data Analysis Methods**

For RCTs, we used meta-analysis and intention-to-treat results when available. To estimate the effect size for continuous data, we used weighted mean differences (WMD) and standardized mean differences (SMD). With SMD, 0.80 is considered to be large, 0.50 moderate, and 0.20 small. We reported dichotomous data as relative benefit or absolute benefit difference for improvements in health, and as relative risk (RR) for adverse events. A chi-square test was performed to test the homogeneity of data, and a fixed-effects model was used to pool studies and get summary results. In the presence of heterogeneity, we used random effects models.

The mean and standard deviations were used when available, and if unavailable, we estimated the standard deviation from confidence intervals (CIs), if possible.

We used the following outcome measures, determined a priori for RCTs:

- American College of Rheumatology (ACR) improvement responses – ACR50 and ACR70 – shown as relative benefit and absolute benefit difference
- physical functional status, shown as WMD and SMD
- radiological scores, reported as WMD and SMD; a score of $\geq 5$ is considered to be meaningful on the van der Heijde-Sharp scale and is the smallest detectable difference apart from the differences due to reliability of readings.\textsuperscript{18,19}
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Clinical Benefit</th>
<th>Clinical Harm</th>
<th>Timing Of Therapeutic Introduction</th>
<th>Dose Escalation</th>
<th>Switching Between Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Design</strong></td>
<td>RCTs, CCTs, quasi-randomized studies, cohort studies, case-control studies</td>
<td>pharmacovigilance reports, cohort studies, case-control studies, case series, case reports</td>
<td>RCTs, CCTs, quasi-randomized studies, cohort studies, case-control studies</td>
<td>RCTs, CCTs, quasi-randomized studies, cohort studies, case-control studies, case series</td>
<td>RCT, CCT, observational study (cohort, case-control, case series)</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>RA patients</td>
<td>RA patients</td>
<td>RA Patients</td>
<td>RA patients</td>
<td>RA patients</td>
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<tr>
<td><strong>Intervention</strong></td>
<td>IFX or ETN</td>
<td>IFX or ETN</td>
<td>IFX or ETN</td>
<td>IFX or ETN</td>
<td>initially IFX or ETN, then the other</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>placebo, other therapies for RCTs and CCTs</td>
<td>placebo, other therapies for RCTs and CCTs</td>
<td>placebo, other therapies for RCTs and CCTs</td>
<td>placebo, other therapies for RCTs and CCTs</td>
<td>placebo, other therapies for RCTs and CCTs</td>
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<tr>
<td><strong>Duration of therapy and follow-up</strong></td>
<td>≥1 year (mean or average for all patients)</td>
<td>≥1 year (mean or average for all patients)</td>
<td>≥3 months</td>
<td>≥3 months</td>
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<tr>
<td><strong>Outcomes</strong></td>
<td>≥1 of DAS; ACR 50/70 or EULAR improvement criteria; health-related quality of life; swollen joint counts; radiological damage; drug terminations</td>
<td>≥1 of drug terminations, serious adverse events, total serious and specific morbidity hospitalizations, mortality</td>
<td>≥1 of DAS; ACR 50/70 or EULAR improvement criteria; health-related quality of life; radiological damage; drug terminations</td>
<td>reporting of dosing, with clear denominator (aggregated dosages reported for all patients)</td>
<td>≥1 of swollen joint counts, tender joint counts, pain, function, patient's global assessment and physician's global assessment, DAS, ACR20, ACR50, ACR70, EULAR improvement criteria, radiological damage, adverse events</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>≥30 for observational studies</td>
<td>not applicable</td>
<td>≥30 for observational studies</td>
<td>not applicable</td>
<td>≥30 for observational studies</td>
</tr>
</tbody>
</table>

ACR=American College of Rheumatology; CCT=clinical controlled trial; DAS=Disease Activity Score; ETN=etanercept; EULAR=European League Against Rheumatism; IFX=infliximab; RA=rheumatoid arthritis; RCT=randomized controlled trial.

For RCTs on clinical benefit and harm, we had a fourth outcome measure: discontinuations (all, lack of efficacy, adverse events), reported as RR. We used the Cochrane Collaboration RevMan 4.2.7 software to conduct all meta-analyses.

For our analysis of timing of therapeutic introduction, we did a subgroup analysis, categorizing all RCTs according to the duration of disease (<2 years or ≥2 years), and whether the patients had previously been treated with MTX.

For observational studies, we included those that followed up patients for at least a year and reported separate results for those on IFX or ETN, with the exception of the dose escalation and switching, evaluations for which we included studies with as little as three months of follow-up. We extracted and synthesized data without meta-analysis and tabulated results, according to the primary outcome measure, including discontinuations, ACR responses, swollen joint counts, functional status, radiological outcomes, and harm.
4 Results

Quantity of Research Available

Of the 3,620 potentially relevant citations found, 1,403 were excluded because they focused on diseases other than RA, reported on different therapies, or were laboratory studies. We obtained the remainder in full text and then excluded an additional 1,530 because of irrelevant or insufficient information, because they were abstracts from meetings or published papers, or they were commentaries. We excluded 65 articles in languages other than those that met our selection criteria and excluded 33 because the full publication could not be retrieved. After applying the other selection criteria to the remaining publications, we were left with eight HTA reports, 14 systematic review articles, 177 original publications on clinical review, and 22 original publications on economic review. Thirty original publications related to long-term clinical effectiveness, 160 had data on harm, and 22 were economic evaluations. Of the 30 on clinical benefit, nine were RCTs and 21 were observational studies. Six RCTs were relevant to the timing of therapeutic introduction, 12 observational studies related to dose escalation, and 11 publications related to switching between IFX and ETN.

Trial and Patient Characteristics

The eight health technology assessments (HTAs) were conducted in five countries between 2001 and 2006, and reported on clinical effectiveness and safety.\textsuperscript{14,15,20-25} Their literature searches spanned 1991 to 2003. Three of the eight publications were updates.

The eight systematic reviews on clinical benefit included meta-analyses, RCTs, and non-quantitative and observational studies.\textsuperscript{26-33} They had at least six months of follow-up, and the number of patients ranged from 529 to 3,907.

Of the original publications selected, four trials (in five publications)\textsuperscript{34-38} looked at IFX and two trials (in four publications)\textsuperscript{39-42} examined ETN. The number of patients in the IFX trials ranged from 20 to 1,049. Three studies had a follow-up ranging from one to two years. All four were double-blinded during the first year. Jadad quality scores ranged from three to five in the first year. Patients in all studies received an IFX dose of 3 mg/kg every eight weeks, except one in which patients received 5 mg/kg every eight weeks.\textsuperscript{37} The Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT)\textsuperscript{34,35} used doses of 3 mg/kg every four weeks, 10 mg/kg every eight weeks, and 10 mg/kg every four weeks. The Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis\textsuperscript{36} used 6 mg/kg every eight weeks. Patients in treatment and control groups in all trials received oral MTX. In two studies,\textsuperscript{34,35,37} patients had failed MTX previously, while those in the other two studies started oral MTX at the time of the trial.\textsuperscript{36,38}

In the two ETN trials, the numbers of patients were 632 and 682 (869 ETN and 445 controls). Allocation concealment was unclear in the Early Rheumatoid Arthritis (ERA) trial\textsuperscript{39} and adequate in the Trial of Etanercept and Methotrexate with Radiographic Patients Outcomes (TEMPO) study.\textsuperscript{42} Jadad scores were two and four respectively. One trial became open after the first year and had a two-year follow-up.\textsuperscript{41} Patients in both studies received 25 mg subcutaneously biweekly (biw). In ERA, a dose of 10 mg subcutaneously biw was also used. Patients in the control groups received oral MTX.

We included 21 observational studies that were cohort studies: four were retrospective, 16 were prospective, and one was both. In 10 studies, patients received IFX only. In seven studies, they
received ETN only. In four studies, the treatment was either. Several studies followed up patients who were previously involved in RCTs. Eight studies reported discontinuation rates only, five reported clinical outcomes, and eight included discontinuations and clinical outcomes. Most studies did not have control groups with patients not receiving TNF antagonists. On the Newcastle-Ottawa Scale, the studies ranged between two and nine in quality.

We included 18 pharmacovigilance reports, 34 observational studies, and 79 case series and reports on the safety of IFX and ETN. Most of the pharmacovigilance reports were from the US, with the remainder from Sweden, Spain, France, Canada, and the Netherlands. The number of cases reported ranged from three to 697, but many included diseases other than RA. Of the observational safety studies, six reported on adverse events in general, and the remainder reported on specific adverse events or complications, such as infections or autoimmunity. The case series and reports described safety issues in patients receiving IFX (71 cases) or ETN (37 cases).

**Data Analysis and Synthesis**

a) **Clinical Benefit**

The HTAs and systematic reviews showed both anti-TNF agents to be efficacious. For our synthesis of RCTs, we included the following outcomes: ACR responses, disease activity score, functional status, and radiological progression.

**ACR responses:** Anti-TNF agents have a small to moderate effect on patients’ clinical outcomes, according to the results of RCTs that lasted for \( \geq 1 \) year. At the recommended doses of 3 mg/kg for IFX+MTX and 25 mg biw for ETN+MTX, the beneficial effects were modest compared to those of MTX alone, scoring between 1.13 and 1.60 for relative ACR50 benefits. For ACR50 improvement, the numbers needed to treat at year one were seven for IFX+MTX, four for ETN+MTX, and 20 for ETN alone.

**Disease activity score:** The improvement in DAS28 scores was clinical and statistically significant for IFX+MTX and ETN+MTX, compared to MTX alone. The degree of improvement was small, often below the 0.6 cut-off for clinical relevance\(^{43}\).

**Functional status:** IFX and ETN had a modest long-term impact on patients’ functional status. The Health Assessment Questionnaire revealed statistically significant comparative results, but the size of the effects was generally small, below the 0.22 threshold used for minimal clinical significance\(^{44}\). For the SF-36 physical component, we observed a statistically significant pooled result with IFX 3 mg/kg every eight weeks, but the effect did not appear to be clinically meaningful (1.77, with an effect size of 0.15). When IFX was given in higher doses, we observed better results. The SF-36 results for ETN+MTX were neither clinically nor statistically significant.

**Radiological outcomes:** Anti-TNF agents appear to be most beneficial in slowing or halting radiological progression. Fewer than six percent of patients in the IFX groups experienced disease progression, compared to almost a third of patients receiving MTX alone. About half the IFX+MTX patients showed radiological improvement, compared to 14% in the MTX-only group. Not all statistically significant differences between treatment and control groups were found to be clinically significant. For IFX+MTX (5 mg/kg to 6 mg/kg) versus MTX, the WMD was 3.44; the minimal clinically important difference for the index used was considered to be \( \geq 5 \).\(^{19}\) The SMD was 0.44. ETN+MTX patients experienced similar results. Even though trials found no differences in clinical
outcomes between the ETN only and MTX groups, they observed a statistically significant difference favouring ETN only, but of a small magnitude (SMD effect size 0.14).

b) Harm and Persistence

Patients tolerate anti-TNF agents well in the short term, but in the long term, many discontinue treatment, raising the issue of long-term safety. Pooled results from RCTs showed that a third of patients on IFX and a fifth of patients on ETN stopped therapy by their second year of treatment.\(^{35,41}\) Observational studies also showed higher rates of discontinuation for all causes with IFX than with ETN, and rates increased with each year of treatment. Discontinuations due to lack of efficacy were similar in three IFX versus ETN studies: rates were 8% to 20% for IFX in year one and 8% in year two; rates for ETN were 5% to 18% in year one and 8% in year two.\(^{45-47}\)

Concerns about the harm associated with therapy were revealed by rates of infections, lymphomas, autoimmunity, and demyelination. While rates are low, they are serious enough to warrant consideration when evaluating potential treatment with anti-TNF agents. Once treatment begins, patients need to be monitored for these conditions. Serious complications, such as tuberculosis and autoimmune disorders, seem to be more common in IFX patients than ETN patients, but observational studies are needed to compare the two agents head-to-head.

c) Timing of Therapeutic Introduction

We focused on three therapeutic comparisons: IFX+MTX versus MTX,\(^{34-38}\) ETN+MTX versus MTX,\(^{42}\) and ETN versus MTX.\(^{39,41}\) Not all trials had two years of follow-up data, so we used one-year data, and because there were insufficient data for each dose, we pooled all IFX dosages in each RCT. We found a difference in benefit according to therapeutic timing, with significant differences favouring therapy in patients with longer duration of disease or in patients who had failed treatment with MTX. Patients in the latter group, who have not benefited from MTX alone, have the most to gain from these agents. IFX+MTX had a slight advantage over ETN+MTX. By itself, ETN had no clear advantage.

Statistically significant differences favouring anti-TNF agents were observed for patients with at least two years’ disease duration. The relative benefit (RB) of achieving ACR50 responses were 4.14 (95% CI: 2.00, 8.57) for IFX+MTX and 1.6 (95% CI: 1.35, 1.90) for ETN+MTX, compared to MTX alone. No differences were observed between ETN and MTX alone; the RB of achieving ACR50 response for ETN alone compared to MTX alone was 1.12 (95% CI: 0.91, 1.37). For patients with disease duration of <2 years, there was no ETN+MTX trial. The IFX+MTX group showed statistically significant relative differences compared to MTX [RB of achieving ACR50 of 1.53 (95% CI: 1.27, 1.84)]. The indirect comparison with patients with disease duration >2 years [4.14 (95% CI: 2.00, 8.57)] showed statistically significant greater benefit for patients with a longer duration of disease.

Using indirect comparisons, the RB of achieving ACR50 for IFX+MTX favoured patients who had previously failed MTX compared to those who were MTX naïve, with a RB of 4.26 (95% CI: 2.11, 8.62) versus 1.51 (95% CI: 1.26, 1.82). The indirect comparisons also significantly favoured IFX+MTX over ETN+MTX (4.26 and 1.60 respectively, with no overlap in 95% CIs). Comparing ETN to MTX, no statistically significant differences were observed for previously treated or treatment-naïve patients.
d) **Dose Escalation**

Increasing the dosage of IFX is common in clinical practice, by increasing individual doses or increasing the frequency of infusions. This is not the case with ETN, perhaps because it is administered subcutaneously and would cause more inconvenience to patients. Based on the findings of the ATTRACT trial\(^{34,35}\) and our pooled results for higher dosages of IFX, it appears that increased doses of IFX are more beneficial than the recommended dose of 3 mg/kg every eight weeks. Insufficient information exists to evaluate the clinical benefits or potential risk of escalating doses.

e) **Switching Between Anti-TNF Agents**

Most patients switched agents because of lack of efficacy, but some switched because of side effects or other causes. A similar number of studies reported on switching from ETN to IFX as from IFX to ETN. We could not pool the results from the 11 citations of eight studies because of differences in intervention, study population, design, and reporting. One publication found no improvement in patients switching from ETN to IFX.\(^{48}\) Most studies reported that switching worked for many. After failing one anti-TNF agent, many patients still responded to a second one. Most of the studies were small, uncontrolled case series with no random allocation or blinding of assessments.

5 **Economic Review**

**Methods**

a) **Literature Search Strategy**

We used the same search strategy as for our clinical review, but we imposed no language restrictions, and we added the Health Economics Evaluations Database to the databases searched.

b) **Selection Criteria**

We included economic evaluations in which RA was specified by the author, treatment was ETN or IFX at adequate dosages, there was a time horizon of at least six months, direct costs were estimated (not just drug costs), and there were adequate data on costs and therapeutic effects. The data extraction strategy was the same as the one used in the clinical review.

c) **Data Analysis Methods**

We extracted, tabulated, and analyzed data from each report, but did not try to pool results from original economic evaluations because of the heterogeneity in study designs. We converted currency into Canadian dollars (except for one study,\(^{25}\) which was already in Canadian currency) and inflated values to 2004 prices.

**Results**

a) **Quantity of research available**

Of the 86 citations we found on economic issues, we excluded those with insufficient data and applied our selection criteria to 33 original publications, after which, we were left with 22 economic evaluations for our review. We identified seven systematic reviews and seven technology assessment reports.
b) Study Characteristics
The HTAs are the same as those described in the clinical review. All but one had an economic analysis. The systematic reviews were done between 2001 and 2005, and at least four were funded or authored by pharmaceutical companies. Of the 22 economic evaluations, nine were cost-utility analyses, two were cost-effectiveness analyses, one was a cost-effectiveness with minimization analysis, six were cost analyses, and three were benefit analyses. One publication described a budget impact evaluation. The pharmaceutical industry funded more than half of the studies.

c) Data Analysis and Synthesis
ETN and IFX, each used concomitantly with MTX, may be a cost-effective treatment for RA after traditional DMARDS have failed, but our results are equivocal. Many economic evaluations show that the costs per quality-adjusted life-year are high, above a widely adopted threshold of $50,000. Studies from a societal perspective were more likely to find therapies to be cost-effective than those from a health care system perspective. Insufficient information exists to suggest that they may be cost-effective as initial therapy.

Three studies, all funded by industry, dominate the economic literature. The Immunex and TEMPO studies provided most of the clinical data for ETN. The former suggests that ETN is more cost-effective than non-biologic agents. The latter found that ETN+MTX is more cost-effective than either drug alone. An evaluation based on the ATTRACT study found that IFX+MTX was more cost-effective than MTX alone. HTA reports showed modest cost-effectiveness for biologic agents in most scenarios, but from a cost-utility perspective, they should be used as a last resort. No studies directly compared the cost-effectiveness of IFX versus that of ETN.

Because indirect costs play a role in determining cost-effectiveness, a social perspective is the most realistic approach. The only evaluation of ETN and IFX+MTX in the Canadian health care system — Coyle et al. — took a third-party payer’s perspective (the Ontario Ministry of Health). From this viewpoint, neither treatment was cost-effective compared to a baseline strategy of MTX followed by gold, then followed by palliative care if gold failed. The study did not account for any cost offsets due to therapeutic benefit, because evidence was limited. Had these been considered, the incremental cost-effectiveness ratio would have been more attractive, because the effect of biologic agents on indirect and direct non-medical costs is evident.

6 Limitations
Few trials examined the long-term effectiveness — beyond one or two years — of anti-TNF agents. Direct comparisons between ETN and IFX are unavailable. No comparisons had been made of biologic agents versus combined traditional therapies when we did our search, even though many patients have drugs added when one fails. Many RCTs did not follow clinical practice, often comparing patients treated with IFX or ETN with a control group of patients who had already failed MTX. Observational studies were of moderate quality, but we needed to include them to establish the long-term clinical effectiveness of IFX and ETN. In the analysis of switching between agents, studies were small, unblinded, and potentially biased. In the economic review, few studies were conducted independently of the pharmaceutical industry, which may have influenced the results. They projected long-term benefit based on short-term data (six months or a year). The clinical evidence identified in our review shows that anti-TNF agents may lose effectiveness in the long term. The economic
modelling did not consider improved radiographic progression, even though clinical data showed that is the difference between anti-TNF agents and traditional DMARDs.

**Health System Implications**

Adopting anti-TNF therapies for RA will have an impact on health budgets because demand is likely to grow with increased availability. Because IFX is administered intravenously, a large investment in outpatient facilities and training is required. This will likely decrease as more patients use the service. Because dose escalation and switching between agents is common, this can increase administrative costs and drug costs. Because ETN is self-injected, the initial costs will not be large, but neither will they decline as demand increases.

**7 Conclusion**

IFX and ETN, each used concomitantly with MTX, have moderate efficacy in the long-term treatment of RA after failure with conventional therapy. They were mostly beneficial in patients with a longer duration of disease or who had failed traditional treatment with MTX. Indirect comparisons showed a trend favouring the use of IFX+MTX over ETN+MTX and no advantage to using ETN alone over MTX. No information exists for assessing the use of IFX alone.

Dose escalation with IFX was common in clinical practice, as an increase in dosage or as an increase in the frequency of infusions. Increased doses appeared to be more beneficial than the recommended dose of 3 mg/kg every eight weeks. There was no significant increase in the dose of ETN over time.

Based on limited evidence gathered from small case series, many patients who failed one anti-TNF agent responded to the other one after switching agents.

The short-term safety profile of these anti-TNF agents is acceptable, but concerns remain about their long-term safety with respect to infections, lymphomas, autoimmunity, and demyelination.

The results of the economic review suggest that ETN and IFX, each used concomitantly with MTX, is only cost-effective as second-line therapy after failure with a traditional DMARD. There was insufficient information to suggest that these agents are cost-effective as initial therapy. Longer-term studies and economic evaluations need to account for community practice patterns, to better reflect the realistic benefits and costs of these therapies.


8 References


