THE SAFETY OF ANTI-TUMOR NECROSIS FACTOR-ALPHA AGENTS USED FOR THE TREATMENT OF INFLAMMATORY BOWEL DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

GERALD SHANE McGRATH

The Safety of Anti-Tumor Necrosis Factor-alpha Agents Used for the Treatment of Inflammatory Bowel Disease: A Systematic Review and Meta-analysis.

by

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Abstract

Background. Anti-tumor necrosis factor alpha (anti-TNF-α) therapy is used to treat inflammatory bowel disease. Infrequent but serious adverse events related to these medications have occurred.

Objective. The aim of this meta-analysis is to evaluate the safety of anti-TNF-α agents in patients with inflammatory bowel disease (IBD).

Methods. Randomized trials that evaluated an anti-TNF-α agent (infliximab, adalimumab, certolizumab, etanercept, CDP 571 and onercept) for the treatment of IBD were included. The studies had to report on safety and tolerability. Trials were identified by searching electronic databases and the data were analyzed using the Cochrane review manager (RevMan 5.1) software.

Results. Twenty four studies were included in the meta-analysis. There was no statistical difference in the frequency of withdrawal due to adverse events, serious infections, death, malignancies or tuberculosis between anti-TNF-α and placebo groups. Placebo patients were more likely to experience a serious adverse event than patients treated with an anti-TNF-α agent. Patients treated with anti-TNF-α agents were more likely to develop pneumonia or experience an infusion reaction than placebo patients. There were no reports of opportunistic infections, congestive heart failure, or demyelinating disease, for any of the agents studied. However, post marketing surveillance has shown that patients are at an increased risk of opportunistic infections. Adverse events with anti-TNF-α agents were noted to occur irrespective of the indication.

Conclusion. Overall, the results of this meta-analysis demonstrate that the use of anti-TNF-α agents is safe for patients with IBD.

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Dr. Gerry Mugford
Clinical Epidemiologist
Associate Professor of Medicine
Memorial University
St. John's, NL

Dr. Brian Feagan
Professor of Medicine
University of Western Ontario
London, ON

John K. MacDonald
Managing Editor
Cochrane Inflammatory Bowel Disease
and Functional Bowel Disorders Review Group
Robarts Research Institute
London, ON

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CD	Crohn's disease
DMARDs	Disease-modifying anti-rheumatic drugs
IBD	Inflammatory bowel disease
RCT	Randomized control Trial
SAE	Serious adverse event
TB	Tuberculosis
TNF-α	Tumor necrosis factor alpha
anti-TNF-α	Anti-tumor necrosis factor alpha
TREAT	Therapy Resource, Evaluation and Assessment Tool
UC	Ulcerative colitis
95%CI	95% Confidence Interval

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Chapter 1. Background

Tumor necrosis factor-alpha (TNF-α) is a cytokine involved in systemic inflammation. It stimulates an acute phase reaction causing apoptotic cell death, cellular proliferation, differentiation and inflammation. TNF-α is synthesized initially by activated macrophages and T cells as a transmembrane precursor protein and then cleaved to release soluble TNF-α. It was originally known as cachexin, and was first described in 1975 for its ability to lyse tumors (Carswell 1975).

It is now known that the biological activity of TNF-α requires the aggregation of three monomers to form a trimeric structure, which then acts by binding to one of two types of receptors known as p55 and p75. Activation of these receptors exerts multiple effects on the immune system, including:

1. stimulation of the release of inflammatory cytokines;
2. upregulation of the expression of endothelial adhesion molecules; and
3. coordination of the migration of leukocytes to targeted organs (Roach 2002).

This immune response has long been implicated in the pathogenesis of ulcerative colitis (UC) and Crohn's disease (CD). It is also known that the pathogenesis of Inflammatory Bowel Disease (IBD) is also partly related to the dysregulation of immune responses to organisms in the intestine (Plevy 1997).

Tumor necrosis factor-alpha (TNF-α) agents represent important treatment advances in a number of inflammatory conditions. TNF-α agents offer a targeted strategy that contrasts with the nonspecific immunosuppressive agents traditionally used to treat CD and UC.

Two biologic agents, infliximab and adalimumab have been approved in Canada for the induction and maintenance of remission in Crohn's disease. Only infliximab is approved for the induction and maintenance of remission of patient's with UC. A third agent, certolizumab is approved for the treatment of CD in the United States but is not

available in Canada. CDP571, etanercept, and onercept are other TNF-α agents that have been evaluated for the treatment of IBD but shown to be ineffective.

1.1 Clinical Efficacy

These drugs are often referred to as biologic therapies or biologics because they are medically engineered antibodies that are designed to work as antagonists to specific protein molecules. Clinical trials are carried out as part of drug development to determine the efficacy, safety and adverse events associated with pharmaceuticals and other treatments. Trials that analyze biologic therapy are often divided into induction or maintenance trials depending on the duration of the study. Induction trials are carried out during an acute flare up of a condition and the main goal is to get the condition under control and induce remission. Once a chronic condition is in remission the next step is to ensure that future flares are less likely to occur. Studies that analyze medications for this purpose are classified as maintenance trials.

1.1.1 Infliximab

Infliximab is a chimeric (mouse/human) TNF-α monoclonal antibody comprised of human (75%) and murine (25%) sequences. It has a high specificity for and affinity to TNF-α and is available for treatment of moderate to severe Crohn's disease, patients with fistulizing CD as well as moderate to severe UC. Infliximab neutralizes TNF-α by inhibiting binding to its receptors and inducing the apoptosis of activated T-lymphocytes. (Lugering 1997; Lugering 2001; Van den Brande 2003).

Multiple studies have evaluated the efficacy of infliximab in patients with active Crohn's disease. The first reported trial was a single dose study carried out in 1995. It included 108 patients with moderate to severe Crohn's disease. At week four, 81 percent of patients who received infliximab at 5 mg/kg, 50 percent of patients who received 10 mg/kg, and 64 percent of patients who received 20 mg/kg had a clinical response compared to 17 percent of placebo patients (Targan 1997). Following this initial trial subsequent studies have shown that scheduled, maintenance therapy with infliximab has substantial clinical benefits in patients who have achieved remission with induction

therapy. (Feagan 2003; Hanauer 2002; Rutgeerts 1999; Rutgeerts 2004). Two randomized controlled trials have examined the efficacy of infliximab in patients with fistulizing Crohn's disease. (Present 1999; Sands 2004). These trials have shown that significantly more patients receiving infliximab as induction therapy had a reduction in the number of draining fistulas and demonstrated fistula closure as compared to placebo. There was also a statistically significant increased likelihood of a sustained response with infliximab maintenance therapy compared to placebo.

The two largest trials to investigate infliximab for the treatment of UC (ACT 1 and ACT 2) focused on patients with persistently active UC despite treatment with glucocorticoids, immunosuppressants or aminosalycilates (Rutgeerts 2005). In ACT 1 patients who received infliximab had a clinical remission rate of 34 percent (5mg/kg) versus 16 percent in the placebo group. The clinical remission rates were similar in ACT 2 at 36 percent for the infliximab group (5mg/kg) compared with 11 percent in the placebo group.

1.1.2 Adalimumab

Adalimumab is a fully human monoclonal TNF-α antibody. Four pivotal studies have been conducted to evaluate the efficacy of adalimumab as induction and maintenance therapy of CD. The CLASSIC-I trial included patients with moderate to severely active CD disease despite conventional therapy. Patients were randomly assigned to placebo or adalimumab at three different induction doses (40mg/20mg, 80mg/40mg, 160mg/80mg). Remission at four weeks was achieved significantly more often in patients receiving the induction dose of 160mg followed by 80mg compared with placebo: 36 versus 12 percent respectively (Hanauer 2006). The CLASSIC-II trial was a continuation of CLASSIC-I. Fifty-five patients who were in remission at week four of the CLASSIC-I trial were re-randomized to three treatment groups: placebo, adalimumab 40 mg every other week or 40 mg weekly for 56 weeks. Of the randomized patients, remission at week 56 was seen in 79 percent of adalimumab 40 mg every other week, 83 percent of 40 mg weekly, and 44 percent of those treated with placebo (Sandborn 2007a).

The "CHARM" trial examined the efficacy of adalimumab for long term maintenance in 854 patients with active disease despite concomitant therapies. All patients received open label induction therapy with adalimumab (80 mg at week zero and 40 mg at week two) and were then randomized to maintenance treatment with adalimumab versus placebo (Colombel 2007). At week 56, remission rates in the 40 mg every other week (36 percent) and 40 mg weekly groups (41 percent) were significantly higher than with placebo (12 percent). The GAIN study was a randomized trial that compared adalimumab to placebo for the induction of remission of CD in patients previously treated with infliximab. Three hundred and one patients completed the trial. In the adalimumab group 21% of patients achieved remission compared to 7% of those in the placebo group (Sandborn 2007b).

1.1.3 Certolizumab

Certolizumab is a humanized monoclonal antibody linked to polyethylene glycol that neutralizes TNF-α. Polyethylene glycol increases the plasma half-life and may possibly reduce antigenicity as well. This agent is commercially available in the United States for the treatment of CD but is not yet available in Canada.

PRECISE 1 was one of the largest studies of certolizumab (Sandborn 2007c). It was a randomized placebo controlled trial that included 662 patients with moderate-to-severe Crohn's disease. Patients received certolizumab pegol or placebo at weeks 0, 2, 4 and then every four weeks. At week 6 and 26 response rates were significantly higher in the certolizumab group (35 versus 27 and 23 versus 16 percent, respectively). PRECISE 2 was a second randomized trial that included 668 patients with moderate-to-severe CD who were randomly assigned to certolizumab or placebo (Schreiber 2007). Those who responded over this initial six week phase were randomly assigned to continue certolizumab or receive placebo for 26 weeks. Four hundred twenty eight patients (64 percent) had a response during the initial six week period and were continued in the trial. Maintenance of response was also higher in the active treatment group (63 versus 36 percent) at week 26 compared to placebo ($P<0.001$).

1.1.4 Other Agents

Three other anti-TNF-α agents have been studied for the treatment of IBD. CDP571 is a humanized monoclonal IgG4 antibody with specificity for TNF-α. It has been prepared by grafting the complementary determining regions from a rodent antibody onto a human antibody (Stephen 1995). Five randomized studies have been conducted with CDP571 for the treatment of CD (Feagan 2005; Feagan 2006; Sandborn 2001a; Sandborn 2004; Stack 1997). These studies have had mixed results. Overall CDP571 is well tolerated and may have some efficacy in the short term but long term it does not appear to be effective.

Etanercept is a genetically engineered fusion protein. It consists of two identical chains of the recombinant tumor necrosis factor receptor p75 monomer fused with the Fc domain of human IgG1. This allows it to bind and inactivate TNF-α (Mohler 1993). Etanercept is a very effective and safe agent for the treatment of rheumatoid arthritis; unfortunately it is ineffective for the treatment of CD (Sandborn 2001b).

The final anti-TNF-α agent studied is onercept. It is a soluble human p55 TNF-α receptor antibody produced by recombinant DNA technology. It neutralizes TNF-α by forming a high affinity antibody antigen complex. It is well tolerated with a favorable safety profile but was not effective for treating active CD (Trinchard-Lugan 2001).

1.2 Adverse Events

All of the anti-TNF-α agents studied are generally well tolerated, however a number of adverse events have been associated with the use of these agents. Most of these adverse events are minor, however some are quite serious and even fatal. Some of the most common adverse events are infections (Colombel 2004; Crawford 2008; Curtis 2007; Lichtenstein 2006; Ljung 2004). Patients who are suspected of having any active infection prior to initiation of an anti-TNF-α agent therapy need to be adequately treated prior to initiating therapy. Any infection could worsen if an anti-TNF-α agent is used while the infection is present. Therapy should also be held in patients who develop a serious infection (Orlando 2008). Serious infections including pneumonia, cellulitis, skin

ulceration, urinary tract infection, and abdominal abscesses have been reported (Colombel 2004; Lichtenstein 2006; Ljung 2004). More serious and even fatal infections, including sepsis (Colombel 2004; Ljung 2004), disseminated tuberculosis (Keane 2001), histoplasmosis (Lee 2002), *Pneumocystis carinii* pneumonia (Seddik 2004), and aspergillosis (Tsiodras 2008) have also been reported with the use of these drugs.

Acute infusion reactions have also been described following anti-TNF-α therapy (Colombel 2004; Ljung 2004). Infusion reactions are characterized by nonspecific symptoms such as dyspnea, hypotension, and/or urticaria. Infusion reactions are typically mild and treated by reducing the infusion rate and administration of acetaminophen and/or antihistamines. Epinephrine or corticosteroids may be required for severe infusion reactions. Delayed hypersensitivity-like infusion reactions have also been observed from three days up to two weeks following the first or second reinfusion. These reactions often occur in patients with long intervals between doses and manifest with myalgia, rash, fever, arthralgia and pruritus. In rare situations patients may even develop anaphylaxis with hypotension, wheezing, and hives. Localized injection site reactions have been reported with subcutaneously injected anti-TNF-α agents (Paltiel 2008). Drug induced lupus has also been reported with the use of anti-TNF-α agents (Colombel 2004; Ljung 2004; Benucci 2008; Mañosa 2008; Spillane 2007; de Bandt 2005; Elkayam 2004). The exact frequency of the development of these adverse events has been variable. This is due in part to how the adverse events were categorized, reported and whether they were attributed to these drugs. The purpose of this meta-analysis is to evaluate the safety profile of anti-TNF-α agents used in patients with IBD.

Chapter 2. Methods

2.1 Objectives

The primary objective of this review was to assess the safety of anti-TNF-α agents used for the treatment of inflammatory bowel disease.

2.2 Criteria for Considering Studies

Randomized controlled trials comparing anti-TNF-α agents with placebo were considered for inclusion. The participants in the studies included patients within specified age ranges with UC or CD diagnosed by a combination of clinical, radiographic, endoscopic and histologic criteria. In each of the included studies the participants were randomized to either anti-TNF-α agents or placebo. Standard medications for the treatment of inflammatory bowel disease were allowed. The studies had to report on safety and tolerability in order to be included. Trials were identified by searching electronic databases.

2.3 Outcome Measures

The primary outcome measure of this meta-analysis was the incidence of serious adverse events while on therapy with either an anti-TNF-α agent or placebo. Other safety outcomes of interest included: withdrawal due to adverse events, death, malignancies (including lymphoma), serious infections (e.g. tuberculosis, pneumonia, abscess formation), infusion reactions and injection site reactions. Extremely rare events including opportunistic infections, drug induced lupus, congestive heart failure and demyelinating syndromes were also analyzed. All outcome measures were expressed as a percentage of the patients' randomized (intention to treat analysis).

2.3.1 Specific Outcomes

An adverse event is defined by the US Food and Drug Administration (FDA) as any undesirable experience associated with the use of a medical product in a patient. For the purposes of this meta-analysis the following specific rates were analyzed:

1. Serious adverse events (SAEs)
    - the total number of serious adverse events were recorded for each of the anti-TNF-α agents and placebo groups.
    - the FDA defines a serious adverse event as any undesirable experience associated with the use of a medical product in a patient that results in death, hospitalization, disability, a congenital anomaly or is life threatening.
2. Withdrawals due to adverse events
    - the total number of withdrawals due to adverse events were recorded for each of the anti-TNF-α agents and placebo groups.
3. Death
    - the total number of deaths were recorded for each of the anti-TNF-α agents and placebo groups.
4. Malignancy
    - the total number of malignancies were recorded for each of the anti-TNF-α agents and placebo groups.
5. Serious infections
    - the total number of serious infections were recorded for each of the anti-TNF-α agents and placebo groups.
    - the types of infections recorded as serious included those infections associated with death, hospitalization, and the use of intravenous antibiotics.

6. Tuberculosis (TB)
    - TB reactivation, miliary or cavitary TB of the lung or any other body organ were extracted as a single case of TB.
    - the total number of cases of TB were recorded for each of the anti-TNF-α agents and placebo groups.
7. Pneumonia
    - the total number of cases of pneumonia were recorded for each of the anti-TNF-α agents and placebo groups.
8. Abscess
    - the total number of cases of an abscess were recorded for each of the anti-TNF-α agents and placebo groups.
9. Infusion reactions
    - for intravenous medications, the total number of infusion reactions were recorded for each of the anti-TNF-α agents and placebo groups.
10. Injection site reactions
    - for subcutaneous medications, the total number of injection site reactions were recorded for each of the anti-TNF-α agents and placebo groups.
11. Neurologic side effects, fungal and opportunistic infections were also recorded when they occurred.

Some patients also withdraw from IBD trials if their symptoms flare during the study period. From the standpoint of a clinical trial this could result from a lack of treatment in a placebo group or alternatively a lack of efficacy in a treatment group. In either situation this is recorded as an adverse outcome and in some cases results in withdrawal from the study. This does not only occur in IBD trials. Similar observations have been noted in trials of anti-TNF-α agents for the treatment of rheumatoid arthritis and psoriasis.

2.4 Post Marketing Surveillance

Before any drug can be marketed in Canada, efficacy and safety must be established. Rigorous well designed clinical trials are required to generate these data. These trials often have small numbers of participants and last for a short period of time. The participants have to meet strict inclusion and exclusion criteria and thus represent highly selected individuals who differ from those in a community practice. For these reasons uncommon adverse events may not be detected during a clinical trial.

Post marketing surveillance or pharmacovigilance is defined by the World Health Organization as "the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (Harmark 2008)." This information can be ascertained by various means including spontaneous reporting, intensive monitoring and database studies. It is a vital component of pharmaceutical evaluation because it is impossible to determine all side effects of a drug based on clinical trials. A review of post marketing surveillance data regarding anti-TNF-α agents was conducted as part of this review. The data were obtained from relevant post marketing publications identified via a literature search. The data from these studies were then summarized and estimates of adverse events were determined.

2.5 Search Methods

A computer assisted search of the Cochrane Central Register of Controlled Trials, the Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Review Group Specialized Trials Register and the on-line databases MEDLINE and EMBASE was performed to identify relevant publications between 1966 and November 2010. The medical subject heading (MeSH) terms "Crohn's disease" or "Colitis, Ulcerative" or "Inflammatory Bowel Disease", and "anti tumor necrosis factor" or "infliximab" or "monoclonal antibody cA2" or "Remicade" or "CDP571" or "etanercept" or "onercept" or

"adalimumab" or "humira" or "d2e7" or "CDP870" or "certolizumab" or "cimzia" were used to perform key word searches of each database. Manual searches of reference lists from potentially relevant papers were performed in order to identify additional studies that may have been missed using the computer-assisted search strategy.
Abstracts from meetings were not included because this meta-analysis aimed to quantify adverse events which are usually considered secondary endpoints and thus not routinely mentioned in abstracts.

2.6 Data Collection and Analysis

2.6.1 Study Selection

All publications identified by the search strategy were assessed and relevant studies were selected according to the inclusion criteria. The methodological quality of the included studies was assessed using the Cochrane risk of bias tool (Higgins 2008). Factors assessed included:

1) sequence generation
    - was the allocation sequence adequately generated?
2) allocation sequence concealment
    - was allocation adequately concealed prior to randomization?
3) blinding
    - was knowledge of the allocated intervention adequately prevented during the study?
4) incomplete outcome data
    - were incomplete outcome data adequately addressed?
5) selective outcome reporting
    - are reports of the study free of suggestion of selective outcome reporting?
6) other potential sources of bias
    - was the study apparently free of other problems that could put it at a high risk of bias?

A judgment of 'Yes' indicates a low risk of bias, 'No' indicates a higher risk of bias and unclear indicates an unclear risk of bias. All trials included in this analysis were randomized, double blind, placebo controlled trials and were deemed to be of a high quality and at low risk for bias (Appendix A).

2.6.2 Data Extraction

Data were extracted using a prespecified data extraction form (Appendix A). Each trial was assessed for its methodological quality according the criteria specified above. To ascertain the validity of eligible studies, data were extracted independently by John K. MacDonald, the managing editor of the Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Review Group and Gerald S. McGrath. Comparison of the data was carried out and any disagreement was resolved by consensus.

The raw data were then analyzed using Review Manager (RevMan 5.1). All data were analyzed on an intention-to-treat basis. Data were extracted from the original research articles and converted into 2x2 tables. The presence of significant heterogeneity among studies was assessed using the chi-square test.

For pooled data, summary test statistics were derived using the relative risk and 95% confidence intervals. A fixed effects model was used for pooling of data. The definitions of adverse events, including serious adverse events were set by the authors of each paper, and the data were combined for this analysis only if the definitions were sufficiently similar.

Chapter 3. Literature Review

3.1 Literature Search

The search for randomized trials identified 352 potentially eligible articles. (Figure 1: Flow chart for included studies). Twenty four placebo-controlled, randomized trials of anti-TNF-α agents in adults with IBD fulfilled the inclusion criteria and were included in the meta-analysis of safety. There were 328 excluded articles which included clinical reviews, retrospective studies, preliminary results, trials with no placebo group, subgroup analyses and duplicate publications of RCTs.

3.2 Description of Included Studies

Ten studies in this analysis were trials that included infliximab. The first published study, TARGAN 1997, was a multicenter, double-blind, placebo-controlled induction trial of infliximab in 108 patients and lasted 12 weeks. Participants had moderate-to-severe CD and adverse events were recorded at the time of infusion and weeks 2, 4, 8 and 12.

The next study, RUTGEERTS 1999 was a randomized, double-blind, placebo-controlled trial of infliximab in 73 patients. It lasted 36 weeks and safety evaluations were based on changes in clinical, laboratory, physical examinations and the incidence of adverse events that patients experienced.

PRESENT 1999 was a randomized multicenter double-blind, placebo-controlled trial of infliximab in 94 patients with fistulizing CD that lasted 6 weeks. All patients were evaluated for safety and adverse events during this study.

HANAUER 2002 conducted the ACCENT 1 trial which was a randomized double-blind, placebo-controlled trial of infliximab as maintenance therapy in 573 patients with active Crohn's. Over a 46 week period safety analysis and the incidence of adverse events were recorded.

Sands 2004 conducted a randomized, double blind, placebo controlled, infliximab maintenance trial for fistulizing Crohn's disease. The study enrolled 282 patients and lasted 54 weeks and adverse events were ascertained.

Lemann 2006 conducted a randomized, double-blind, placebo-controlled trial of infliximab in steroid-dependent CD in 113 patients. During this 52 week trial adverse events were recorded at each visit and were classified according to severity and likelihood of relationship to study medication.

Probert 2003 conducted a double-blind, randomized, placebo controlled trial in the treatment of glucocorticoid resistant UC in 42 patients. The study lasted 6 weeks and serious adverse events were recorded during the study period and for 30 days after completion of the trial.

Jarneot 2005 conducted a double-blind, randomized placebo controlled trial in the treatment of UC in 45 patients refractory to medical therapy over three months. General side effects were assessed in both placebo and infliximab groups.

Rutgeerts 2005 reported the results of the Active UC Trials 1 and 2 (ACT 1 and ACT 2, respectively). These were both randomized, double blind, placebo controlled trials that evaluated the efficacy of infliximab for induction and maintenance therapy for UC. ACT1 lasted 54 weeks and enrolled 364 patients while ACT 2 enrolled 364 patients and lasted 30 weeks. Both studies conducted safety evaluations.

Four randomized controlled trials of adalimumab for the treatment of inflammatory bowel disease were included in the meta-analysis. Colombel 2007 was a randomized, double-blind, placebo-controlled trial of 778 patients that lasted 60 weeks. Efficacy and safety data were assessed every 2 weeks for the first 8 weeks followed by every 4 weeks until the trial was completed.

Hanauer 2006 was a randomized, double-blind, placebo-controlled trial that evaluated the efficacy of adalimumab induction therapy in 299 patients with CD over 4 weeks. At each study visit adverse events were recorded and safety assessments conducted.

Sandborn 2007A evaluated the long term efficacy and safety of adalimumab maintenance therapy in Crohn's disease. It was a randomized, double-blind, placebo-controlled trial that included 276 patients and lasted 56 weeks. Efficacy and safety data were assessed every 2 weeks for the first 8 weeks followed by every 4 weeks until week 56.

Sandborn 2007B was a randomized, double-blind, placebo-controlled trial that evaluated the effectiveness of adalimumab in 325 patients with CD who had lost response or were intolerant of infliximab. The trial lasted 4 weeks and adverse events were recorded through queries, observations by site personnel and patient report.

Certolizumab pegol is a pegylated anti-TNF-α agent and four studies involving this agent were included in this analysis. Winter 2004 was a randomized, double-blind, placebo-controlled trial that included 92 patients with moderate-to-severe CD who were followed over a 12-week period. Patients were randomized to certolizumab versus placebo and monitored for adverse events at each visit.

Schreiber 2005 conducted a 12 week phase II randomized, double-blind, placebo-controlled trial involving 292 patients. These patients received subcutaneous certolizumab or placebo and adverse events were monitored for throughout the study and recorded by the investigator.

Schreiber 2007 reported on a randomized, double-blind, placebo-controlled trial involving 668 patients that lasted 24 weeks. The efficacy of certolizumab pegol maintenance therapy versus placebo in adults with moderate-to-severe CD was assessed. Clinical assessments and adverse event data were recorded every 2 weeks for the first 8 weeks followed by every 4 weeks until study completion.

Sandborn 2007C was a randomized, double-blind, placebo-controlled trial, which evaluated the efficacy of certolizumab in 660 adults with moderate-to-severe Crohn's disease. The trial was 26 weeks and safety data were assessed during every clinic visit.

Sandborn 2001B reported on etanercept. It was a randomized, double-blind placebo controlled trial. Forty-three patients with moderate-to-severe CD were enrolled in this 8-week trial. All adverse events were recorded and graded according to prespecified criteria.

Stack 1997 tested the hypothesis that CDP571, a genetically engineered antibody to TNF-α, was effective in the treatment of Crohn's disease. His group conducted a randomized, double-blind placebo-controlled trial with 31 patients. Over the 8 week duration of the study patients were monitored for adverse events.

Feagan 2005 was a randomized, double-blind placebo controlled trial of CDP571 verses placebo. Seventy-one patients were followed for 16 weeks for response and the occurrence of adverse events.

Feagan 2006 was a similar but longer study that was also a randomized, double-blind placebo-controlled trial of CDP571 verses placebo in 269 patients with corticosteroid-dependent CD over 32 weeks. Adverse events were assessed at each study visit along with a physical examination, fistula evaluation, quality of life assessment and laboratory tests.

Sandborn 2001A reported on a randomized, double-blind placebo controlled trial in 159 patients with moderate-to-severe Crohn's disease. The 24-week trial evaluated response and adverse events to prespecified criteria.

Sandborn 2004 also evaluated CDP571. This randomized, double-blind placebo controlled trial of 396 patients lasted 24 weeks and adverse events were recorded.

Rutgeerts 2006 was a randomized, double-blind, placebo-controlled, dose-ranging trial that evaluated the efficacy of onercept in 207 patients with Crohn's disease. Safety outcomes including changes in physical examination, vital signs, laboratory values and the incidence and severity of adverse events were monitored during the study.

3.3 Description of Excluded Studies

A total of nine studies were excluded. Sands 2001 was the first study that evaluated the effect of infliximab on UC. They reported the experience of 11 patients enrolled in a double-blind, placebo-controlled clinical trial of infliximab for severe, active steroid-refractory UC. The study was never completed as a result of slow enrollment. Thus safety data was incomplete and is was excluded.

Baldassano 2003 studied infliximab in a pediatric population. It was excluded because it was a small open label study and was not placebo controlled. Farrell 2003 initially conducted a prospective study to evaluate clinical response to infliximab. However all patients received infliximab and there was no placebo group, thus the study was not included.

Armuzzi 2004 studied infliximab as a treatment of steroid-dependent UC. This study was excluded because it was an open label study. Likewise Ochsenkuhn 2004 was a randomized pilot study of infliximab for acute steroid-refractory UC that was not placebo controlled and thus it was excluded.

Hyams 2007 also studied infliximab administered to pediatric patients and was not included because it lacked a placebo arm. Likewise Schröder 2006 was excluded because it was an open label study and all patients received infliximab. The studies by Sands 2007 and Van Assche 2008 were not included because patients in both the active and control arm received infliximab.

Chapter 4. Data Analysis

Twenty-four trials involving 6395 patients were included. All of these trials included a safety analysis. There were 4074 patients in the anti-TNF-α groups and 2321 patients in the control groups.

4.1 Serious Adverse Events

In the overall analysis, there was a small difference in the frequency of serious adverse events between the anti-TNF-α (n=419) and control groups (n=284): 10.7% versus 12.9%, respectively. The risk ratio for a serious adverse event was 0.83, 95% CI (0.72, 0.95) for anti-TNF-α drugs compared to placebo (Figure 2). In subgroup analysis, infliximab and adalimumab had slightly fewer serious adverse events than control with a risk ratio of 0.77, 95% CI (0.64, 0.93) and 0.53, 95% CI (0.37, 0.77) respectively. There was no statistically significant difference in the frequency of serious adverse events between anti-TNF-α and control groups for patients treated with certolizumab: risk ratio of 1.24, 95% CI (0.86, 1.78), CDP 571: risk ratio of 1.04, 95% CI (0.72, 1.51), etanercept: risk ratio of 0.43, 95% CI (0.04, 4.44), and onercept: risk ratio of 1.09, 95% CI (0.13, 9.04).

4.2 Withdrawal due to Adverse Events

In overall analysis, there was no difference in the frequency of withdrawal due to adverse events between anti-TNF-α (n=318) and control groups (n=197): 8.2% versus 9.1%, respectively. The risk ratio was 0.87, 95% CI (0.73, 1.04) for withdrawal due to an adverse event (Figure 3). In subgroup analysis, adalimumab had significantly fewer withdrawals due to adverse events than control with a risk ratio of 0.50, 95% CI (0.33, 0.75). There was no statistically significant difference in the frequency of withdrawal due to adverse events between anti-TNF-α and control groups for patients treated with the other anti-TNF-α agents: infliximab: risk ratio of 1.19, 95% CI (0.82, 1.72), certolizumab:

risk ratio of 0.85, 95% CI (0.62, 1.15), CDP 571: risk ratio of 1.00, 95% CI (0.70, 1.45), etanercept: risk ratio of 4.38, 95% CI (0.22, 86.08), and onercept: risk ratio of 0.51, 95% CI (0.14, 1.87).

4.3 Deaths

There was a small difference in the frequency of death between anti-TNF-α (n=7) and control groups (n = 1): 0.21% versus 0.05% respectively, which was not statistically significant. The risk ratio was 2.03, 95% CI (0.58, 7.07) for the anti-TNF-α drugs versus placebo (Figure 4). In subgroup analysis, there was no difference in the frequency of death between anti-TNF-α agents and control arms in clinical trials involving infliximab, adalimumab, certolizumab, or CDP571. There were no deaths reported in randomized trials involving adalimumab, etanercept or onercept.

4.4 Malignancies

In overall analysis, there was no statistically significant difference in the frequency of malignancies between anti-TNF-α (n=12) and control groups (n=9): 0.35% versus 0.46% respectively. The risk ratio was 0.72; 95% CI (0.34, 1.53) for the anti-TNF-α drugs versus placebo (Figure 5). In subgroup analysis, there was a statistically significant difference between adalimumab and placebo: two malignancies were reported in patients receiving placebo and none for those receiving adalimumab. Otherwise there was no difference in the frequency of malignancies between anti-TNF-α and control groups involving infliximab, certolizumab, or CDP571. There were no malignancies reported in randomized trials involving etanercept or onercept.

4.5 Serious Infections

In overall analysis, there was no difference in the frequency of serious infections between anti-TNF-α (n = 97) and control groups (n = 53): 2.4% versus 2.3%

respectively. The risk ratio was 1.00 with a 95% CI (0.71, 1.39) for the anti-TNF-α drugs versus placebo (Figure 6). No individual anti-TNF-α medications were found to be statistically different than control groups in subgroup analysis. The risk ratio for infliximab was 0.86, 95% CI (0.54, 1.37), adalimumab was 0.69, 95% CI (0.34, 1.40), certolizumab was 2.30, 95% CI (0.92, 5.78) and CDP571 was 1.35, 95% CI (0.46, 4.00).

4.6 Tuberculosis

In overall analysis, there was a slight difference in the frequency of tuberculosis between anti-TNF-α (n = 3) and control groups (n = 0): 0.13% versus 0 respectively. The risk ratio was 1.89, 95% CI (0.31, 11.69) for the anti-TNF-α drugs versus placebo and this was not statistically significant (Figure 7). In subgroup analysis, there was no difference in the frequency of tuberculosis between anti-TNF-α and control groups for infliximab or certolizumab.

4.7 Pneumonia

The frequency of pneumonia was higher in the anti-TNF-α (n = 13) group versus control groups (n = 1): 0.8% versus 0.1%. However, the risk ratio was 2.54, 95% CI (0.75, 8.59) for the anti-TNF-α drugs versus placebo (Figure 8). This was not a statistically significant difference but clearly there was a tendency towards patients treated with anti-TNF-α to develop pneumonia more frequently than patients treated with placebo. In subgroup analysis, there was no difference in the frequency of pneumonia between anti-TNF-α and control groups for infliximab, adalimumab or certolizumab.

4.8 Abscess

There was no difference in the frequency of abscess formation between anti-TNF-α (n=55) and control groups (n=45): 2.1% versus 2.6% respectively. The risk ratio was 0.93, 95% CI (0.63, 1.37) for the anti-TNF-α drugs versus placebo. (Figure 9) In

subgroup analysis, there was no difference in the frequency of abscess between anti-TNF-α and control arms in clinical trials involving infliximab, adalimumab, certolizumab, or CDP571.

4.9 Infusion Reaction

Infliximab and CDP571 are agents that are infused. There was a difference in the frequency of infusion reactions between anti-TNF-α (n=276) and control groups (n=103), 15.3% versus 10.0% respectively. The risk ratio was 1.50, 95% CI (1.21, 1.86) for the anti-TNF-α drugs versus placebo. (Figure 10) In subgroup analysis, infliximab had a risk ratio of 1.47; 95% CI (1.11, 1.93). There was also a difference for CDP 571 with a risk ratio of 1.57; 95% CI (1.12, 2.50) compared to placebo.

4.10 Injection Site Reaction

In overall analysis, there was no difference in the frequency of injection site reactions between anti-TNF-α (n=199) and control groups (n=113), 9.39% versus 9.49% respectively. The risk ratio was 0.91, 95% CI (0.71, 1.18) for the anti-TNF-α drugs versus placebo. (Figure 11) In subgroup analysis, there was no difference in the frequency of injection site reactions for etanercept or onercept. There were actually more injection reactions noted for patients who received placebo compared with certolizumab with 4.7% versus 13.0% respectively. The risk ratio was 0.37, 95% CI (0.25, 0.56). In the case of adalimumab 11.9% patients experienced an injection reaction compared to 6.2% of those receiving control. The risk ratio was 1.79, 95% CI: (1.22, 2.63).

4.11 Other Events

There were no reports of opportunistic infections, congestive heart failure or demyelinating disease for any of the agents studied. There was one reported case of

drug induced lupus. This occurred in a patient receiving infliximab. Studies involving Certolizumab and CDP571 also measured this outcome but reported no cases.

4.12 Heterogenity

The presence of heterogeneity among studies was assessed using the chi-square test of homogeneity and a fixed-effect model. Statistically significant heterogeneity was found for withdrawal due to adverse events and injection site reactions (P=0.003 and P<0.00001, respectively).

On review of these individual analyses it was found that statistical heterogeneity was present because of one particular trial. Hanauer 2002 had 45 withdrawals from the 385 patients in the infliximab group and only 5 withdrawals from 188 patients in the placebo group. These proportions were different from the other trials with infliximab. Further analysis revealed this trial accounted for all of the heterogeneity.

The other outcome with heterogeneity was injection site reaction. Two of the certolizumab studies accounted for this result. The studies Sandborn 2007C and Schreiber 2007 had less injections reactions in patients who received certolizumab compared to control. There were also proportionately less injection reactions for certolizumab in these studies compared to the third certolizumab study, Schreiber 2005 and all of the adalimumab studies.

4.13 Bias

Funnel plots in which the treatment effects from individual studies on the horizontal axis are plotted against a measure of study precision on the vertical axis are used to detect publication bias in meta-analysis. In the absence of bias the graph resembles a symmetrical inverted funnel. This occurs because the treatment effect estimates from smaller studies scatter more widely at the bottom of the graph and the spread narrows

with increasing precision among larger studies. If there is publication bias because smaller studies which show no statistically significant effects remain unpublished then the funnel plot will appear asymmetrical.

For this analysis a funnel plot of trials performed for the primary outcome, serious adverse reaction was symmetrical, suggesting the absence of publication bias (Figure 12).

4.14 PRISMA

This meta-analysis was conducted and reported in accordance with "The PRISMA Statement: Preferred Reporting Items for Systematic Reviews and Meta-Analyses." (Mohler 2009) Appendix C includes a checklist that outlines the topics that encompass the PRISMA requirements and outlines the corresponding sections in this document.

Chapter 5. Post Marketing Surveillance

The first post marketing surveillance data published regarding the use of anti-TNF-α agents in patients with inflammatory bowel disease was a retrospective cohort study from the Mayo clinic (Colombel 2004). It evaluated the short and long-term safety of infliximab. This group reviewed the medical records of 500 consecutive patients who received a median of 3 infusions of infliximab and had a median follow-up of 17 months. They calculated an intrinsic likelihood (imputability) score to determine the likelihood of a causal relationship to infliximab for each adverse event. Overall forty-three patients (8.6%) experienced a serious adverse event and thirty of these events were felt to be related to infliximab. The most commonly reported events were infections which occurred in 48 patients and 41 (8.2%) of these were attributed to infliximab. Twenty patients had a serious infection: fatal sepsis (2), pneumonia (8), viral infections (6), abdominal abscesses (2), cellulitis (1), and histoplasmosis (1). Three of nine reported malignancies were possibly related to infliximab. Five deaths occurred which were possibly related to infliximab. Acute infusion reactions occurred in 19 of 500 patients (3.8%) and serum sickness-like disease was attributed to infliximab in 14 patients (2.8%). Three patients developed drug-induced lupus and one patient developed a new demyelinating disorder.

Shortly after the Mayo review a European study was also published that analyzed serious adverse events associated with infliximab (Seiderer 2004). This group retrospectively analyzed the charts of 100 patients for acute and sub-acute adverse events. Their results were based on data from 322 infusions. Generally infliximab therapy was well tolerated and no deaths, malignancies, autoimmune diseases, tuberculosis, neurologic or cardiac adverse events were reported. Only 10 patients experienced adverse events: 2 patients suffered an acute infusion reaction, 1 developed serum sickness, 4 patients had a bacterial or viral infection and one 1 developed pancytopenia.

A similar analysis was also conducted in Sweden (Ljung 2004). A cohort of 217 IBD patients treated with a mean of 2.6 infliximab infusions between 1999 and 2001 were assessed for adverse events. Forty-two severe adverse events were registered in 41 patients. Three patients developed lymphoma which was fatal in two, opportunistic infections occurred in two patients (one was fatal), and two patients with severe attacks of IBD died due to sepsis (one with CD, one postoperatively with UC). One additional patient with UC died from a pulmonary embolism after colectomy. The authors concluded that Infliximab was efficacious however they noted that adverse events were an issue in elderly patients with severe attacks of IBD.

The TREAT (Crohn's Therapy Resource, Evaluation and Assessment Tool) registry has enrolled thousands of patients who have been treated with infliximab and other therapies (Lichtenstein 2006). One of the goals of this database is to assess the long-term safety of these medications. Lichtenstein 2006 has published data regarding 6,290 patients enrolled in the registry. Infliximab was given to 3,179 patients representing 5,519 patient-years of follow up and 3,111 patients received other therapies representing 6,123 patient-years of follow up. The mortality rates were similar for infliximab- and non-infliximab-treated patients (0.53 per 100 patient-years compared to 0.43 patient-years; relative risk, 1.24; 95% CI, 0.73-2.10). Multivariate logistic regression analysis determined that serious infections were most likely due to the development of moderate to severe CD (HR 2.46, $P<0.001$) and the use of prednisone or narcotics more than doubled the risk of a serious infection ($P<0.001$). Prednisone was also associated with an increased risk of mortality (odds ratio [OR], 2.10; 95% CI (1.15-3.83); $P=0.016$). The group also found that about 3.3% of infliximab infusions resulted in an infusion reaction. However, only 0.08% of reactions were serious. There was no difference in deaths between the two groups.

A Spanish group carried out a multicenter retrospective survey of all 169 CD patients treated with infliximab at 8 University hospitals (Gonzalez-Lama 2008). The patients were followed for an average of 28 months and safety data was one of the parameters analyzed. This analysis included data from 1,355 infliximab infusions. Infusion reactions

occurred in 17 patients (1.2% of the infusions). Only one case was a severe infusion reaction the remaining 16 were mild. Other minor adverse events occurred in 26% of the patients and were the cause of treatment withdrawal in 7 patients (4.1%).

Fiddler 2009 conducted a study involving 734 patients with IBD who were followed for a median of 58 months. This cohort consisted of patients who were treated over a 14-year period. The group also evaluated 666 control patients not treated with infliximab for adverse events. One hundred twelve serious adverse events occurred in 93 patients (13%) treated with infliximab compared to 157 serious adverse events in 126 (19%) control patients with an odds ratio of 1.33, 95% CI (0.56, 3.00), p=0.45. There was no difference between the two groups in mortality, malignancies and infection rate. TB was the most serious infection that occurred in two patients receiving infliximab. Interestingly two of these patients had a negative skin test whereas none of the 16 patients with a positive skin test who received prophylaxis developed TB. The only significant independent risk factor for infections in patients treated with infliximab was concomitant treatment with steroids with an odds ratio of 2.69, 95% CI (1.18, 6.12), P=0.018.

The Leuven group conducted a similar large observational study that assessed the long-term use of infliximab in 614 consecutive patients with CD (Schnitzler 2009). These patients had a median follow-up of 55 months. Withdrawal due to adverse events occurred in about 12.8% of patients and 6% developed delayed infusion reactions. Three patients died while on treatment: one developed *Aspergillus* infection, one sudden death occurred and one patient developed pancreatic cancer. They also found there was a greater need for hospitalizations and surgery in the patients that received episodic treatment with infliximab. Patients in the regularly scheduled group were also more likely than those in the episodic group to discontinue steroids.

A Hungarian study recently reported the nationwide, multicenter experience with infliximab therapy for CD (Mineller 2009). Over a 6-year-period this group treated 363 patients with infliximab. Adverse events included 34 allergic reactions (9.4%), 17 delayed type hypersensitivity (4.7%), 16 infections (4.4%), and 3 malignancies (0.8%).

Another small study examined the induction and maintenance responses to infliximab in an outpatient inflammatory bowel disease clinic (Teshima 2009). This Canadian group conducted a retrospective chart review and they also analyzed for adverse events. Fifteen of 117 patients (12.8%) reported nine infusion reactions, four serum sickness-like reactions, one rash and one infection. No serious infections, malignancies or neurological adverse events were encountered.

Two hundred ninety-seven consecutive patients with CD treated with infliximab at the Beth Israel Deaconess Medical Center were reviewed for adverse events (Hamzaoglu 2010). This group of patients received a total of 1794 infusions with a median of 4 infusions per patient. Forty-four patients (15%) experienced a serious adverse event. Eighteen patients (6%) had an acute infusion reaction resulting in respiratory problems in 10 patients (3%), an anaphylactoid reaction in one patient (0.3%) and serum sickness in one patient (0.3%). Three patients (1%) developed drug-induced lupus and one patient developed a possible new demyelinating disorder. Eight patients (2.7%) developed a serious infection, all of whom were on concurrent immunosuppressants and one of these infections resulted in fatal sepsis. Six patients (2%) developed malignancies including two lymphomas and two skin cancers.

Zabana 2010 evaluated the long-term safety profile of infliximab over a nine year period with a median of five infusions per patient. All IBD patients treated with infliximab were registered and adverse outcomes recorded. One hundred fifty-two patients with a median of five infliximab infusions were included. Thirteen percent had an infusion reaction, twenty patients had a viral or bacterial infection and two patients developed neoplasia. This was over a median of one hundred forty two infusions. Overall the rate of serious adverse events was less than 10%.

A review regarding the safety of infliximab in a cohort of 120 pediatric patients under the age of 17 was published in 2011 (Cromb 2011). The median duration of follow up was 32 months. This cohort of patients included 50 (42%) who received episodic treatment and 70 (58%) who received maintenance therapy. Infliximab efficacy was defined as

those still responding to infliximab at their last visit and those who stopped infliximab while in remission. The infliximab failure group included patients who stopped due to adverse events and nonresponders. The risk of surgery was reduced (p=0.009) in the infliximab group and lower in patients with scheduled therapy compared to episodic therapy (p=0.03). Patients in the infliximab group also had significant catch-up growth (p=0.04), while those who failed infliximab did not. The conclusion was that long-term infliximab use resulted in a lower rate of surgery and improved catch-up in growth, especially when receiving scheduled therapy. Hyams et al. also assessed the long-term effects of maintenance infliximab therapy in 60 children (Hyams 2011). Six children had serious infections, the most common being upper respiratory infections.

Lees 2009 reviewed 202 patients who received anti-TNF-α agents (adalimumab and infliximab) in Edinburgh from 1999 to 2007. The most common adverse events reported were infections. A total of 42 patients experienced at least one infection. A total of 6 malignancies, 3 hematological and 3 bronchogenic lung cancers were reported. Four of these occurred 20 months or longer after the last infliximab infusion. The other two were diagnosed within 4 to 8 weeks of the last infusion.

Adalimumab was approved for use in Canada during 2007 thus there is not as much clinical experience with it. Recently, publications have reported post marketing data on this agent. Nichita et al. assessed the long-term effectiveness and safety of adalimumab in a multicenter cohort of 55 patients over a three year period (Nichita 2010). Only a few minor adverse events were reported and adalimumab was well tolerated in patients with moderate-to-severe CD, demonstrating sustained long-term efficacy.

The Scottish Society of Gastroenterology also evaluated the efficacy and safety of adalimumab (Ho 2009). They identified and followed up on the clinical outcomes of patients with CD treated with adalimumab over a 4-year period (2004 to 2008). Ninety eight patients received adalimumab and there was over 100 patient years of follow-up recorded. Overall eight had nonfatal serious adverse events. However there were two

case fatalities: one patient developed sepsis following perforation and another had disseminated colorectal cancer.

Swoger 2010 reviewed 118 patients who were prescribed adalimumab for CD between January 2003 and June 2007. Sixty-four patients (54%) experienced a total of 117 adverse events and thirteen of these patients (11%) experienced 15 serious adverse events. A total of 16 patients (14%) discontinued adalimumab due to an adverse event.

5.1 Temporal Trends Based on Post Marketing Surveillance

The temporal developments of adverse events were analyzed as part of this review. The initial data from the Treat registry were combined with the post marketing data and a pooled estimate was calculated for four specific outcomes: death, malignancy, serious infections and tuberculosis (Table 1). Likewise the five year Treat data were used in combination with the post marketing data to determine a pooled estimate for these outcomes.

The combined post marketing surveillance data are presented in Table 1. Based on this information the overall risk of death was 6.6 per 1000 patients. When the initial Treat data and five year Treat data were included this number increased to 7.7 and 17.2 respectively. A similar temporal increase was seen with respect to the risk of malignancy and serious infections. The corresponding combined post marketing data showed an increase from 13.5 to 18.0 cases of malignancy per 1000 patients and the overall risk of serious infection went from 33.5 to 72.1. It is interesting to note that the risk of developing tuberculosis was constant over time.

The development of adverse events associated with Anti-TNF-α agents appears to increase over time. Table 1 also shows the rates of each of these events based on the meta-analyses. The risk of death was 2.0 (events per 1000 patients), malignancy 4.0 and serious infection 24. It is no surprise that the results from the meta-analysis are

much lower than those from the post marketing data. The results obtained from the post marketing studies cover a longer duration of time; up to 5 years in the case of the Treat data. The information in the meta-analysis is based on randomized trials that ranged in durations from 4 to 56 weeks. The post marketing data also contains information on a broad range of patients with Crohn's disease. This group of patients were not subject to the strict inclusion and exclusion criteria that was applied to the group of patients included in the data from randomized trials.

Chapter 6. Discussion

Patients with IBD have a tendency toward a variety of co-morbidities. Compared with healthy individuals in the general population, they are known to have an increased risk of infection, TB, solid tumors, lymphoma, and demyelinating disorders (Marehbian 2009). The rates of these conditions have been shown to be higher in patients with poorly controlled disease. Regimens used to treat moderate-to-severe IBD have also been associated with an increased risk of some of these adverse events. As a result physicians have often limited the use of certain drugs to treat IBD. Anti-TNF-α agents are a relatively new pharmacological class of drugs that are very effective for treating IBD but fall into this category.

The safety profile of anti-TNF-α agents is a timely issue because the use and indications for these drugs are rapidly increasing. Safety data available from 24 controlled trials of up to 60 weeks in duration for CD and UC were included in this meta-analysis. This study specifically evaluated the safety outcomes of anti-TNF-α therapy in IBD to determine the risk of adverse outcomes associated with these drugs.

Our analysis included 6395 patients and it revealed that there was no statistically significant difference between anti-TNF-α therapy and placebo with respect to increased risk of serious adverse event, withdrawal due to an adverse event, death, or malignancy. Subgroup analysis for infliximab, certolizumab, CDP571, etanercept and onercept revealed no difference between these agents and control. However placebo treated patients in the adalimumab studies did have a slightly increased risk of having a serious adverse event and withdrawal due to an adverse event (Colombel 2007). This occurred because exacerbation of Crohn's disease, was the most common serious adverse event affecting 32.2% of placebo patients and only 19.1% of patients treated with adalimumab. This was also the most common reason for withdrawal from the study for patients in the placebo group.

Regarding overall safety, the results of this meta-analysis did not show a statistically significant difference between anti-TNF-α therapy and placebo with respect to mortality, serious infection, or malignancy. However these results need to be interpreted with caution. The risk ratio was 2.03 for mortality from anti-TNF-α drugs compared to placebo and the mortality rate was 0.21% for anti-TNF-α drugs versus 0.05% in the control group. Thus there was a tendency to increased mortality even though the result was not statistically significant.

Perhaps the most pertinent clinical concern with the use of biological agents is the risk of serious infections. Our analysis revealed no statistically significant difference between anti-TNF-α and placebo for serious infection, tuberculosis, pneumonia or abscess. Subgroup analysis for each of these parameters also revealed no statistically significant difference with any of the pharmacological agents included in this analysis. However the risk ratio was 2.3 for a serious infection with the use of certolizumab. This indicates that there was a tendency for patients to develop serious infections with this medication. Although the result was not statistically significant this is noteworthy from a clinical standpoint.

Other authors have found similar results when analyzing the risk of developing a serious infection in patients with IBD who have been treated with anti-TNF-α agents (Colombel 2004; Curtis 2007; Lichtenstein 2006; Ljung 2004). It has been noted that the baseline risk of serious infection is much higher in IBD than other autoimmune conditions. Since IBD is a chronic disorder that involves a breakdown of the mucosal barrier of the gut, patients are at increased risk of abscess formation, sepsis and perianal disease (Lichtenstein 2006; Orlando 2008). Patients with other inflammatory and autoimmune conditions are not as vulnerable to infection as patients with IBD.

There were three cases of tuberculosis reported in patients treated with anti-TNF-α agents and none in the placebo group. The risk ratio was 1.89 and this was not statistically significant. However from a clinical standpoint it is concerning that three patients developed tuberculosis since these patients were each screened with a chest

x-ray and TB skin test prior to initiating therapy with an anti-TNF-α agent. This raises the question as to whether TB skin testing is adequate screening prior to commencing therapy with an anti-TNF-α agent.

Both upper and lower respiratory tract infections have been recognized as a complication of therapy with anti-TNF-α agents (Colombel 2004; Crawford 2008; Curtis 2007; Ljung 2004; Lichtenstein 2006; Orlando 2008). This study specifically analyzed pneumonia and the risk ratio for the development of pneumonia was 2.54 for patients treated with an anti-TNF-α agent compared to placebo. Although this was not a statistically significant result the frequency of pneumonia was 0.8% for the anti-TNF-α group compared to 0.1% for placebo. Since this is a clinically relevant result, physicians and patients on these agents need to be vigilant with respect to symptoms suggesting a respiratory tract infection.

Two anti-TNF-α agents are infused: infliximab and CDP571 and there were slightly more infusion reactions with these agents compared to placebo. This is an expected result. Nurses and physicians closely monitor patients in clinical settings where these agents are given and protocols are in place to deal with reactions. The remainder of the anti-TNF-α agents are given via injection and overall there was no difference for injection site reactions compared with placebo. Subgroup analysis did reveal adalimumab caused more injection site reactions than placebo; these were localized reactions and are monitored for in clinical practice and treated accordingly.

6.1 Biologic Use and Modern Medicine

Biologic agents or "biologics" refer to a class of therapeutic agents that are produced by means of biological processes involving recombinant DNA technology. These medications have had a profound impact on many medical fields, primarily rheumatology, oncology, dermatology and gastroenterology. In each of these disciplines, biologics have added major therapeutic options for the treatment of many diseases. Some of these conditions had no effective therapies or previously existing

therapies were clearly inadequate. Biologic medications usually fall into one of three categories:

1. Substances identical or nearly identical to the body's own signaling proteins. Examples are the blood-production stimulating protein erythropoietin, growth hormone, or biosynthetic human insulin.
2. Monoclonal antibodies. These are custom-designed antibodies similar to those that the immune system uses to fight off bacteria and viruses. They are made specifically to counteract or block a given substance in the body, or to target a specific cell type.
3. Receptor constructs. These are fusion proteins based on a naturally-occurring receptor linked to an immunoglobulin frame. These agents block the receptor thereby reducing the inflammatory cascade.

Patients who receive certain biologic therapies are at an increased risk for adverse events including infection and malignancy. However, when standard therapies are ineffective, biologic therapies may offer an effective alternative despite the increased risk.

6.1.1 Combination Therapy

Another long standing issue is whether combination therapy with immunosuppressive agents or steroids may also have an impact on the long term safety profile of these medications. The concern of combination therapy with infliximab and azathioprine was addressed by the SONIC trial (Colombel 2010). This study had three treatment arms: azathioprine (an immunosuppressant) alone, infliximab alone and azathioprine in combination with infliximab. It was not included in our analysis because it was not placebo controlled. One of the endpoints addressed in this study was the occurrence of adverse events.

The results of this trial revealed that the percentage of patients with any adverse event was the same across all three treatment arms. However 26.7% of patients in the

azathioprine group developed a serious adverse event compared to 23.9% for the infliximab group and 15.1% for the combination group. Withdrawal from the study was highest in the azathioprine arm at 26.1%, while it was 20.7% for combination therapy and 17.8% for the infliximab group.

The risk of serious infection has also been a major concern with the use of combination therapy. The SONIC trial found that the rate of serious infection was 3.9% for the combination group, 4.9% for the infliximab group and 5.6% for the azathioprine group. The corresponding results for any infection were 41.9%, 46.0% and 45.3% respectively. Based on the results of this well organized randomized control trial is appears that the combination of azathioprine and infliximab is safe.

6.1.2 Treat Registry

Another valuable source of information on biologics is the Treat (Crohn's Therapy Resource, Evaluation and Assessment Tool) registry (Lichtenstein 2006). The participants in this cohort study are still being followed and data regarding their health status is being recorded. Five years ago based on TREAT data Lichenstein published a report assessing the safety of immunosuppressants and infliximab used for the treatment of Crohn's disease. At that point in time, data were available for 3,179 patients who had received infliximab. The analysis involved 5,519 patient-years of follow up or 1.7 years per patient receiving infliximab. They found that mortality rates were similar for infliximab and non-infliximab treated patients, that serious infections were most likely due to the development of moderate to severe Crohn's disease, the use of prednisone or the use of narcotics. Prednisone was also associated with an increased mortality risk.

The group analyzing the TREAT registry has recently reported data based on approximately five years of follow-up on 6273 patients at Digestive Disease Week 2011. Lichenstein 2011 reported data on 6273 patients with an average follow-up of 5.2 years. His group found that the mortality rates were similar for infliximab and non-infliximab

treated patients at 0.56 and 0.62 deaths per 100 patient years respectively. With respect to serious infections the risk factors were the same as the initial findings of the Treat registry with one difference. The updated results revealed that infliximab was associated with an increased risk of serious infections. Prednisone use and narcotics were associated with an increased risk of mortality and serious infection.

6.1.3 Reviews of Biologic Agents used for IBD

There have been three smaller meta-analyses of biologic therapies for the treatment of inflammatory bowel disease that have reported results regarding adverse events.

Peyrin-Biroulet 2008 conducted the first reported meta-analysis of placebo-controlled trials to evaluate the safety and efficacy of anti-TNF-α agents for Crohn's disease. The review analyzed 21 studies enrolling 5356 individuals, with 3341 patients in the anti-TNF-α groups and 2015 patients in the control groups. In their overall analysis Peyrin-Biroulet found no statistically significant difference in the frequency of death between anti-TNF-α and control groups (0.21% versus 0.05%). In subgroup analysis, Peyrin-Biroulet also found no statistically significant difference in the frequency of death between anti-TNF-α and control arms for induction trials or maintenance trials. Our results found a similar frequency of death between anti-TNF-α and control groups (0.21% versus 0.04%, respectively; and a RR 2.03, 95% CI (0.58, 7.07).

With respect to malignancies Peyrin-Biroulet found no difference in the frequency between anti-TNF-α and control groups (0.24% vs. 0.39%). Our results were similar with the frequency of malignancy between anti-TNF-α and control groups (0.35% versus 0.46%, respectively; and a RR 0.72, 95% CI, 0.34-1.53). Peyrin-Biroulet also found no difference in the frequency of serious infections between anti-TNF-α and control groups (2.09% vs. 2.13%). The results reported in our analysis were similar with no difference between the frequency of serious infections between anti-TNF-α and control groups (2.37% versus 2.31%, respectively; RR 1.00, 95% CI (0.71-1.39).

Another small meta-analysis of randomized control trials provided a comprehensive review of the efficacy and safety of certolizumab in Crohn's disease. (Shao 2009) For this safety analysis 1313 patients who had received continuous treatment with certolizumab 400 mg were included. They concluded there was no apparent relationship between certolizumab exposure and the following adverse events: malignancies, lymphoma, tuberculosis and death. The only exception was with the development of infections. The risk of infection increased with longer duration of exposure in both certolizumab-treated (47.5% (≥4 weeks duration) vs. 60.6% (≥6 months duration)) and placebo-treated (31.7% (≥4 weeks) vs. 40.7% (≥6 months)) patients. The subgroup analysis for our meta-analysis found a trend for patients treated with certolizumab to development clinically relevant infections and the temporal analysis revealed that the risk of infection increased with the duration of treatment.

A third meta-analysis (Siegel 2009) was reported that specifically addressed the risk of lymphoma associated with the combination of an anti-TNF-α and an immunomodulator. There is a concern that the combination of these drugs might increase the risk of lymphoma. In particular, some case reports of a particularly rare and aggressive form of hepatosplenic T-cell lymphoma have been associated with combination therapy. (Thai 2010) Siegel's meta-analysis was performed to determine the rate of non Hodgkin's lymphoma (NHL) in adult CD patients receiving dual therapy. The final report included twenty-six studies involving 8905 patients and 21,178 patient-years of follow-up. The analysis contained a variety of studies including nine randomized trials, three cohort studies and 14 case series.

Patients on combined therapy were compared to a population-based registry and to a population of CD patients treated with immunomodulators. Among anti-TNF-α treated subjects, 13 cases of NHL were reported (6.1 per 10,000 patient-years) and the majority of these patients had previous immunomodulator exposure. Compared with the expected rate of NHL (1.9 per 10,000 patient-years), anti-TNF-α treated subjects had an elevated risk (standardized incidence ratio, 3.23; 95% confidence interval, 1.5-6.9). When CD patients treated with anti-TNF-α were compared with CD patients treated

with only immunomodulators (4 cases of NHL per 10,000 patient-years), the standardized incidence ratio was 1.7 (95% confidence interval, 0.5-7.1). This indicates a slightly increased risk of lymphoma attributable to these agents.

The results from our meta-analysis included trials that reported two cases of lymphoma. (Sandborn 2007a, Rutgeerts 1999) Both of these cases were included in the meta-analysis by Siegel. His meta-analysis included more episodes of lymphoma because it also included cohort studies and case series. In particular he included data from the Treat registry as well as the study by LJUNG 2004. These two cohorts included a total of nine patients who developed lymphoma. In the post marketing analysis we conducted we also found that the cases of lymphoma reported after anti-TNF-α agents entered the marketplace increased. Essentially both this review and Siegel's meta-analysis have similar results: the number of case of lymphoma during randomized control trials is low and it slightly increases with the extended use of these drugs once they are in widespread use.

6.1.4 Cochrane Collaboration on Biological Agents

Recently the Cochrane collaboration published a systematic review regarding the adverse effects of biologics. This group explored the adverse effects of numerous biological agents including anti-TNF-α agents, interleukin (IL)-1 agent, IL-6 agent, anti-CD28 (abatacept), and anti-B cell therapy in patients with any disease condition except HIV (Singh 2011).

The analysis included 163 randomized controlled trials with 50,010 participants. They also analyzed a further 46 open-label extension studies which enrolled 11,954 participants. When all biologic agents were grouped and compared to control, the rates of serious adverse events, serious infections, lymphoma, and congestive heart failure were not significantly different. They did find that there was a higher rate of withdrawals due to adverse events and tuberculosis reactivation, associated with the use of biologics.

The Cochrane review also found that certolizumab pegol was associated with a significantly higher risk of serious infections compared to control treatment. The odds ratio was 3.51, 95% CI (1.59, 7.79). The results of our meta-analysis, which looked at only patients with inflammatory bowel disease, found that there was no difference in the frequency of serious infections between anti-TNF-α and control groups. The risk ratio was 1.00 with a 95% CI (0.71, 1.39) for the anti-TNF-α drugs compared to placebo. Also, no individual anti-TNF-α medications were found to be statistically different than control groups with respect to the development of serious infections. However, the individual risk ratio for certolizumab was 2.30, 95% CI (0.92, 5.78). The risk ratio calculated for infliximab was 0.86, 95% CI (0.54, 1.37), adalimumab was 0.69, 95% CI (0.34, 1.40), and CDP571 was 1.35, 95% CI (0.46, 4.00). This trend for certolizumab to be associated with more serious infections is something that requires further examination. If certolizumab causes more serious infections this would be a major concern and might affect how this agent is prescribed. If all other adverse events are comparable, agents with a lower risk of infection, especially serious infection, should be prescribed first.

The Cochrane review of all biologics found that infliximab was associated with a statistically significant increased likelihood of withdrawal due to adverse effects compared to control (OR 2.04, 95% CI 1.43 to 2.91). The other biologics were not significantly different from control. Our analysis looked at this outcome and the overall risk ratio for all anti-TNF-α agents was 0.87, 95% CI (0.73, 1.04). In subgroup analysis there was no difference for infliximab and the risk ratio was 1.19, 95% CI (0.82, 1.72). The findings are different but this can easily be explained by the fact that patients with different conditions may have varying reasons for withdrawing from a study. The Cochrane meta-analysis also included many more patients and thus had more statistical power to detect a difference.

Overall, the results of the Cochrane review of biologics for all conditions were similar to this review of anti-TNF-α agents used for inflammatory bowel disease: generally these

agents are safe but prescribers must be vigilant and monitor for adverse events and serious infections.

6.1.5 Biologic Agents used for Rheumatoid Arthritis

Rheumatoid arthritis is an inflammatory arthritis that affects 0.5% to 1.0% of adults in Western countries (Kvien 2004). It results in joint inflammation and destruction which leads to major decrements in quality of life (Odegard 2005) and disability (Yelin 2007). There are similarities in the pathogenesis of rheumatoid arthritis and Crohn's disease. Specifically, dysregulation of T-helper cell subsets and specific cytokines which influence the development and perpetuation of systemic inflammation are involved in the pathogenesis of inflammation in both these conditions.

Biologic therapies are used for the treatment of rheumatoid arthritis. These agents target either the down regulation of proinflammatory responses or the up regulation of anti-inflammatory cytokine production. Several biologics are currently approved for the treatment of rheumatoid arthritis in Canada. Their use has revolutionized the treatment of this condition and they dramatically inhibit the progression of joint damage. These medications include anti-TNF-α agents, anti-interleukin-1 therapy, anti-CD28 therapy and anti–B-cell therapy. Biologics are generally recommended for patients with rheumatoid arthritis who have a suboptimal response or intolerance to traditional anti-rheumatic drugs: the treatment of CD also follows a similar step up process.

Rheumatologists share the same concerns as gastroenterologists with respect to the adverse event profiles of these agents. One of the first systematic reviews to address the topic of safety and biologics in the treatment of rheumatoid arthritis was conducted by Bongartz 2006. His group assessed the extent to which anti-TNF-α therapies increased the risk of serious infections and malignancies in patients with rheumatoid arthritis. They conducted a meta-analysis to derive estimates of these adverse events. This group analyzed nine trials and obtained data on 3493 patients who received infliximab or adalimumab and 1512 patients who received placebo. The pooled odds

ratio for malignancy was 3.3, 95% CI (1.2, 9.1) and for serious infection was 2.0, 95% CI (1.3, 3.1). Another meta-analysis was conducted to compare the benefits and safety of 6 biologics (abatacept, adalimumab, anakinra, etanercept, infliximab and rituximab) in patients with rheumatoid arthritis (Singh 2009). They found that withdrawals related to adverse events were significantly higher among patients taking adalimumab, OR 1.54, 95% CI (1.12, 2.12), anakinra OR 1.67, 95% CI (1.22, 2.29) and infliximab OR 2.21, 95% CI (1.28, 3.82) compared to placebo. The other agents studied etanercept, rituximab and abatacept did not result in increased withdrawal compared to placebo. Likewise, the results for anti-TNF-α agents used to treat CD found that none of these agents resulted in increased withdrawals compared to placebo. The risk ratio from Crohn's studies for withdrawal due to adverse events was 0.87, 95% CI (0.73, 1.04).

This group's analysis also compared biologics and withdrawal from therapy. They found significantly lower rates of withdrawals because of adverse events with etanercept than with adalimumab, anakinra or infliximab (Lee 2008). Unfortunately, etanercept was not an effective treatment for inflammatory bowel disease.

Another systematic review was conducted that analyzed randomized clinical trials which compared intravenous administration of infliximab to placebo in patients with rheumatoid arthritis (Wiens 2009). This review also included a meta-analysis to assess the efficacy and the safety of infliximab use and withdrawals due to adverse events or lack of efficacy. Seven trials comprising 2,129 patients met the inclusion criteria. The following results were found:

1. serious adverse events: relative risk 1.12, 95% CI (0.90, 1.41)
2. withdrawals due to adverse events: relative risk 2.05, 95% CI (1.33, 3.16)
3. deaths: relative risk 0.71, 95% CI (0.11, 4.85)
4. malignancy: relative risk 1.64, 95% CI (0.30, 8.89)
5. serious infections: relative risk 0.96, 95% CI (0.39, 2.38)
6. infusion reactions: relative risk 1.97, 95% CI (1.12, 3.45)
7. infection: relative risk 1.21, 95% CI (0.99, 1.49)
8. any adverse events: relative risk 0.83, 95% CI (0.64, 1.08).

Results are available for the first six variables from our meta-analysis. The ratios were ascertained from subgroup analysis regarding infliximab for the treatment of inflammatory bowel disease:

1. serious adverse events: relative risk 0.77, 95% CI (0.64, 0.93)
2. withdrawals due to adverse events: relative risk 1.19, 95% CI (0.82, 1.72)
3. deaths: relative risk 1.99, 95% CI (0.44, 8.99)
4. malignancy: relative risk 1.05, 95% CI (0.32, 3.41)
5. serious infections: relative risk 0.86, 95% CI (0.54, 1.37)
6. infusion reactions: relative risk 1.47, 95% CI (1.11, 1.93).

These results are very similar and it is reassuring to see that there is consistency in the adverse event profile of infliximab for two different medical conditions.

A similar review was conducted regarding the use of adalimumab for the treatment of rheumatoid arthritis (Wiens 2010). This review also included a meta-analysis to assess the efficacy and the safety of adalimumab use and withdrawals due to adverse events or lack of efficacy. Eight studies met the inclusion criteria, comprising 2,692 patients. This meta-analysis of safety revealed the following results:

1. serious adverse events: relative risk 0.98, 95% CI (0.67, 1.43)
2. withdrawals due to adverse events: relative risk 1.56, 95% CI (1.04, 2.35)
3. deaths: relative risk 2.52, 95% CI (0.72, 8.86)
4. malignancy: relative risk 0.55, 95% CI (0.14, 2.11)
5. serious infections: relative risk 2.22, 95% CI (0.83, 5.99).

The corresponding results for adalimumab from our meta-analysis are:

1. serious adverse events: relative risk 0.77, 95% CI (0.64, 0.93)
2. withdrawals due to adverse events: relative risk 0.50, 95% CI (0.33, 0.75)
3. deaths: relative risk 1.99, 95% CI (0.44, 8.99)
4. malignancy: relative risk 0.08, 95% CI (0.01, 0.71)
5. serious infections: relative risk 0.69, 95% CI (0.34, 1.40).

These results were similar with the exception of withdrawal due to adverse events. As mentioned earlier there was an aberrancy noted in the withdrawals in the adalimumab trials because of the high number of withdrawals due to a flare up of Crohn's disease.

6.1.6 Biologic Agents used for Psoriasis

Psoriasis is one of the most common immune-mediated disorders affecting about 2 to 3% of the general population (Griffiths 2007). It is a chronic incurable autoimmune skin condition that has remarkable costs because it causes substantial problems in everyday life, work limitations and productivity loss (de Korte 2004; Javitz 2002; Naldi 2004; Schmitt 2006; Stern 2004). Several recent studies have suggested that patients with psoriasis have an increased risk for cardiovascular disease, depressive illness, liver disease and a decreased life expectancy (Gelfand 2006; Gelfand 2007; Kremers 2007; Mallbris 2004; Schmitt 2007). T-cells and TNF-α play a central role in the pathogenesis of psoriasis. Currently, three biologic anti-TNF-α agents: infliximab (Chaudhari 2001), etanercept (Leonardi 2003), and adalimumab (Menter 2008), and two T-cell agents: efalizumab (Gordon 2003) and alefacept (Ellis 2001) are approved for chronic plaque psoriasis.

Schmitt 2008 conducted a meta-analysis of all published randomized controlled trials of biologic and nonbiologic systemic treatments approved for moderate to severe plaque psoriasis to determine their comparative efficacy and tolerability. Overall, 24 randomized trials including 9,384 patients with chronic plaque psoriasis met the inclusion criteria. This group found similar incidence rates of withdrawals due to adverse events for all drugs used to treat psoriasis: 1.3% for infliximab, 1.2% for cyclosporine and efalizumab, 0.5% for etanercept and 0.3% for adalimumab. With respect to reactions the pooled monthly incidence rate of infusion reactions was 2.6% for infliximab while the incidence rate of injection site reactions was 4.8% in patients treated with etanercept. The most commonly reported infections were upper respiratory tract with a monthly incidence rate of 1.8% in patients treated with adalimumab (Menter 2008).

A German group conducted a similar systematic review and meta-analysis of all randomized controlled trials in which biologics for the treatment of psoriasis were examined (Zhang 2009). Secondary endpoints of this analysis were the monthly incidences of study withdrawals and adverse events. They obtained data on 8,057 patients and found that the monthly incidence rates of withdrawals due to adverse events were 1.2% for infliximab, 0.5% for etanercept, 1.0% for efalizumab, and 0.5% for adalimumab. They did not report on other adverse events.

Psoriatic arthritis is a seronegative inflammatory arthropathy that complicates about 30% of patients with psoriasis. It is also treated with disease-modifying anti-rheumatic drugs (DMARDs) as well as biological agents. A meta-analysis of 18 studies assessing various agents used to treat psoriatic arthritis was conducted (Ravindran 2008). In total 11 studies assessing DMARD monotherapy, one study assessed DMARD combinations, five studied anti-TNF-α agents and one studied another biologic agent, alefacept. Overall anti-TNF-α agents showed the largest treatment effect sizes and they had the best efficacy-to-toxicity ratio. Toxicity leading to withdrawal was more common among the other agents studied: leflunomide, gold salts and sulfasalazine.

Overall, the results for psoriasis and psoriatic arthritis are similar to the results found for IBD. In both conditions the most commonly reported adverse events were infections. Respiratory tract infections were by far the most frequently seen infection.

6.1.7 Infliximab Safety in Outpatients

Duscharme et al. recently addressed the issue of the safety of infliximab administration in community clinics outside the hospital environment. Most publications describing acute adverse drug reactions have been limited to the hospital environment or within the confines of clinical trials (Duscharme 2010). Since these patients are preselected and do not represent the full spectrum of patients receiving infliximab the risk of adverse events and infusion reactions is likely not the same in the community setting.

Duscharme's goal was to evaluate the safety of infliximab across all types of patients in a community setting. This group conducted a retrospective chart review on the infusion reaction rate seen in patients treated with infliximab in community infusion clinics from December 1, 2006 to April 15, 2008 throughout Ontario. Results were obtained from multiple infusion clinics across Ontario. These clinics all followed standardized infliximab infusion and monitoring protocols and these protocols were in place for more than six years. The patients were followed by community specialists and were diagnosed with UC, Crohn's disease, rheumatoid arthritis, ankylosing spondylitis, psoriasis or uveitis.

On the day of the infusion patients were initially seen by a nurse and underwent an assessment prior to initiating infliximab. During the infusion, vital signs were monitored and recorded every 30 minutes and then monitored for one hour post infusion. The patients were asked to seek medical attention should any adverse event occur after discharge. A total of 3161 patients received 20,976 infliximab infusions during the time frame analyzed. Acute adverse drug reactions that occurred during the infusion or within twenty four hours of the infusion were included. Most reactions that occurred after this would have been seen by private family physicians or in the emergency room and unfortunately were not accessible.

Five hundred twenty-four acute adverse drug reactions occurred in 353 patients (11.2%). Two hundred sixty-three reactions were classified as mild (1.3% of all infusions and 233 were moderate (1.1% of all infusions). Twenty-eight reactions were severe representing about 1 out of 1000 infusions. Seven patients required transfer to a hospital emergency room but none were admitted. The group also noted that the number of infusion reactions did not vary according to age or diagnosis.

With respect to our meta-analysis, a subgroup analysis revealed that 160 out of 1125 patients who received infliximab (14.2%) had an infusion reaction. The majority of these were mild reactions but some were delayed infusion reactions. It should also be noted that 24 out of 689 patients receiving placebo (3.4%) developed an infusion reaction. The risk of infusion reaction attributable to infliximab from the combined data of the clinical

trials is 10.8%. This number is very similar to that found by Duscharme et al. This would indicate that the risk of an infusion reaction in a real life setting is comparable to the results of clinical trials and meta-analyses.

6.1.8 Adalimumab Safety in Outpatients

Adalimumab has been studied for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, psoriasis and juvenile idiopathic arthritis. An analysis of 19,041 patients in 36 global clinical trials was carried out to determine the safety of adalimumab, the stability of serious adverse event rates over time and compare the safety of adalimumab in psoriatic arthritis, ankylosing spondylitis, Crohn's disease, psoriasis and juvenile idiopathic arthritis within the context of the established safety profile in rheumatoid arthritis (Burmester 2009). A secondary outcome was an assessment of the number of malignancies and mortality rates.

The results revealed that the cumulative serious adverse events rates from 2002, 2004, 2005 and 2006 were found to be comparable to 2007:

- serious infections (4.6–5.1 versus 4.7/100 patient-years)
- tuberculosis (0.22–0.28 versus 0.29/100 patient-years)
- lymphomas (0.10–0.21 versus 0.12/100 patient-years)
- demyelinating disease (0.05–0.08 versus 0.05/100 patient-years)
- lupus-like syndrome (0.05–0.10 versus 0.07/100 patient years).

Serious infections were the most commonly reported adverse event. It was interesting to note that the greatest rates of serious infections were observed for patients with rheumatoid arthritis and Crohn's disease. The most commonly reported serious infections were pneumonia and abscess. These results are similar to the findings of our meta-analysis where serious infections were the most commonly reported serious adverse event.

Tuberculosis was rare and rates were similar across all diseases. The most commonly reported opportunistic infections were oral candidiasis, followed by six cases of histoplasmosis; three cases of cytomegalovirus infections and two cases each of coccidioidomycosis and nocardiosis. There was one case each of toxoplasmosis, listeriosis, aspergilloma, Pneumocystis infection, esophageal candidiasis and candida sepsis. These infections occurred in patients with CD and rheumatoid arthritis. Opportunistic infections were infrequently reported among patients with other immune-mediated inflammatory diseases. These data support our post marketing surveillance data analysis which revealed that opportunistic infections occur in patients with Crohn's disease. These infections were not reported to the same degree during randomized trials and can be quite serious.

The adalimumab review also found the risk of malignancies was not increased when compared with the general population. However risks associated with long-term use were not evaluated. The review did find the number of cases of lymphoma in patients with rheumatoid arthritis to be significantly greater than that expected for the general population. However patients with rheumatoid arthritis have an inherent twofold increased risk of developing lymphomas irrespective of therapy compared with the general population (Baecklund 2006; Gridley 1993; Mellemkjaer 1996). Our meta-analysis showed no increased risk of malignancy but this is a rare long term adverse outcome that may manifest at a later date.

6.2 Temporal Comparison of Adverse Events

As part of this analysis the initial data from the Treat registry were combined with the post marketing data and a pooled estimate was determined for four specific outcomes: death, malignancy, serious infections and tuberculosis. The meta-analysis determined that the probability of death was 2 per 1000 patients. Based on post marketing data combined with TREAT results this estimate increased to 7.7 and 17.2 based on the 1.7 and 5 year respectively. The five year data from the Treat registry found no difference between patients treated with infliximab and those treated with other agents. It is no

surprise that the results from the meta-analysis are much lower than either the 1.7 or 5 year data because the analysis is based on randomized trials that ranged in durations from 4 to 56 weeks.

Likewise the data for the development of malignancy showed a temporal increase. The results of the meta-analysis revealed 4.0 cases per 1000 patients and this increased to a pooled estimate of 13.5 cases for the 1.7 year TREAT data and post marketing data. The estimate increased further to 18.0 when the 5 year Treat data were included. It is important to note that over time the risk of malignancy increases while patients are taking anti-TNF-α drugs. However, once again the five year data from the Treat registry shows that for patients with CD on other therapies this is also true. In fact other studies have shown that patients with IBD are at an increased risk of malignancy even if no medications are taken (Bernstein 2001).

From a clinicians perspective serious infections are always a major concern with biologic use and are the most common serious adverse event. The combination of 5 year post marketing data showed the rate to be 72.1 per 1000 patients. The rate from the meta-analysis was 24 and this is lower due to the short time frame of the included studies. According to the TREAT data serious infections also occur frequently in patients with CD treated with any pharmaceutical. In fact, Crohn's patients have a higher baseline risk of infection than the general population.

Opportunistic infections can occur with the use of anti-TNF-α agents. The reactivation of latent tuberculosis is a major complication with the use of these agents. Screening for tuberculosis prior to initiating infliximab is currently the standard of care. The results of this study found that the rate of development of tuberculosis did not increase over time. This means that patients who develop tuberculosis generally do so early in the course of treatment with an anti-TNF-α agent. Also, patients who developed tuberculosis often had a negative skin test and chest X-ray prior to commencing therapy. It should also be noted that patients with positive skin tests who received adequate prophylaxis did not develop tuberculosis.

The rate of development of TB was constant at approximately one per 1000 patients. However this would still seem high in light of the fact screening for this condition is carried out prior to starting therapy. It is well recognized that the use of tuberculin skin testing for patients with CD and UC is controversial. This is due to the high rate of false-negative results in patients receiving immunosuppressive treatment (Connell 2006). Quantiferon is a new method for detecting latent tuberculosis. It is an interferon gamma release assay that has a greater sensitivity and specificity for tuberculosis than tuberculin skin testing. Since these interferon-gamma release assays are more reliable than tuberculin skin tests they are being utilized by some physicians prior to commencing an anti-TNF-α agent (Bocchino 2008).

6.3 Post Marketing Surveillance in Canada

Before any drug can be marketed in Canada, efficacy and safety must be established. Rigorous well designed clinical trials are required to generate these data. These trials often have small numbers of patients, last for a short period of time and often include highly selected participants who differ from those in a standard practice. The people in these trials frequently do not have the co-morbidities which may exist in the population the drug will eventually be prescribed to. The participants in trials may also be more compliant and more likely to seek medical attention when adverse events arise.

Since all possible adverse events of a drug cannot be determined based on clinical trials, it is essential that drugs continue to be investigated after they have entered the market in order to ascertain long term safety and efficacy data. This post marketing surveillance can further refine, confirm or deny the safety of a drug. However, post marketing surveillance is only useful if it is carried out in a manner which allows information to be obtained on large numbers of individuals who have a wide variety of medical conditions. Concerns have been raised regarding the lack of an appropriate process for evaluating newly approved pharmaceuticals and therapeutics. This is a worldwide problem and also a major clinical concern in Canada (Laupacis 2003).

One of the strengths of this analysis is that post marketing surveillance data were included. A total of 16 different post marketing sources were reviewed. Most of the reports were fairly large with a few hundred patients but the TREAT registry is a substantial resource and contains information regarding 6290 patients. The most interesting finding of the post marketing surveillance data was the number of reports of opportunistic infections: one case of *Listeria* (Lichtenstein 2006), two cases of *Pneumocystis carini* (Lichtenstein 2006, Ljung 2004), three cases of *Aspergillus* infection (Armuzzi 2004; Miheller 2009; Ochsenkühn 2008), one case of histoplasmosis (Colombel 2004) and multiple cases of herpes zoster (Armuzzi 2004; Jarnerot 2005; Miheller 2009; Ochsenkühn 2008; Sands 2007; Seiderer 2004) and tuberculosis (Miheller 2009). In contrast, no cases of opportunistic fungal infections were noted during the clinical trials. These fungal infections can be quite serious and even fatal.

There is a paucity of data regarding the risk of fungal infections during anti-TNF-α therapy. The Mayo clinic has reviewed this topic and found that the majority of patients (98%) who experienced fungal infections were also on concomitant immunosuppressive therapy (Tsiodras 2008). It was also noted that the risk of these infections dramatically increases when anti-TNF-α therapy is combined with corticosteroids or thiopurine therapy (Toruner 2008). The most common pathogens were those causing histoplasmosis (30%), candidiasis (23%), and aspergillosis (23%). Overall the Mayo clinic has also reported that the risk of opportunistic infections in IBD patients treated with infliximab to be 0.3%. It is noteworthy that invasive fungal infections were not noted during the clinical trials but were detected by post marketing surveillance.

6.3.1 Improving Post Marketing Surveillance

Post marketing information can be gathered in various ways but usually it is obtained from administrative databases, patient registries, surveys or reports from clinicians or patients. However problems exist with each of these methods. These limitations include under-reporting, incomplete data, poor quality data and difficulty demonstrating a causal relationship between an exposure and an adverse event. Regulatory authorities in

Canada have expressed a vital need for pharmacoepidemiological data on long-term efficacy, safety, and cost-effectiveness of new drugs in relation to the standard of care (Barr 2004).

Spontaneous reporting systems have been created by various regulatory agencies such as Health Canada and the Food and Drug Administration in the United States. These have become the primary method of collecting post marketing information on drug safety. The purpose of these reporting systems is the early detection of rare and serious drug reactions. It allows physicians, pharmacists and patients to report suspected reactions (van Grootheest 2004a, van Grootheest 2004b, van Grootheest 2005). The main problem with this approach is the potential for selective reporting and underreporting (Eland 2009). In one review article the magnitude of underreporting in spontaneous reporting systems was determined to be more than 94% (Hazell 2006). Chronic underreporting can lead to the false conclusion that risk is absent. Selective reporting of risks may also give a false impression of a risk that does not exist.

Various approaches have been devised in an attempt to improve post marketing surveillance for biologics. In Alberta, the Rheumatoid Arthritis Pharmacovigilance Program and Outcomes Research in Therapeutics (RAPPORT) Team, has developed a registry to assess the outcomes of biological therapies used in patients with rheumatoid arthritis (Barr 2004). This team has developed a systematic approach to collecting data on the effectiveness, adverse events and cost-effectiveness of biologics for the treatment of rheumatoid arthritis in Alberta. It is a collaborative venture between academia, government payers, and industry.

All patients in Alberta using biologic therapies to treat rheumatoid arthritis and who wish to receive public coverage are required to become a part of the RAPPORT registry. Data collected includes demographics, co-morbid conditions, quality of life measures, measures of health care resource use, and medication history. This registry allows for the surveillance of the effectiveness of therapy and adverse events. The program is

funded by industry but is administered by government and operates at arms length from industry.

A similar undertaking could be used to monitor patients with IBD. The information gathered would be of greater value if such an endeavor were conducted on a national level. This would further expand the pool of participants allowing very rare events to be captured. An even greater initiative could be to include all patients on anti-TNF-α agents, irrespective of diagnosis. Since Canada has a relatively small population, a uniform medical system and one of the highest rates of IBD in the world, a nationwide registry of IBD patients on biologics could enable us to become an international leader in pharmacosurveillance. Similar initiatives have occurred in Sweden (van Vollenhoven 2003), Spain (Gomez-Reino 2003), and the United Kingdom (Silman 2003) for biologic use in patients with rheumatoid arthritis.

Provincial drug plans, hospital databases and third party payer administered programs are other rich sources of data. These resources could be used to provide details on patients who have IBD. Drug databases could be cross referenced with the diagnosis to determine who is at risk and who should be monitored. These patients could then be observed closely for the development of adverse events. Unfortunately, despite the existence of these drug databases they have been underutilized for this purpose. One other potential problem is variability between provinces in terms of coverage and data collected. This means that pooling of this information could be difficult.

Patient registries are sometimes implemented by manufacturers to monitor certain medications. These databases offer the opportunity to monitor patients for serious adverse drug reactions and may help reduce exposure to high-risk drugs. Access to the data contained in such registries is often limited by the pharmaceutical companies. Timely access may be difficult and opportunities for replication by others can be restricted.

As mentioned earlier, the TREAT registry has been established for patients with CD (Lichtenstein 2006). It is a prospective, observational, multicenter endeavour that has focused on clinical, economic, and adverse events associated with the treatment of Crohn's disease. Physicians manage patients as they would under normal practice conditions and there is no predefined schedule of visits or medical procedures. Data regarding disease severity, medication use and adverse events were collected on a semi-annual basis by physicians (Silman 2003).

Currently there is no clear consensus on the 'best' way to carry out post marketing surveillance in Canada. The optimal strategy would appear to involve obtaining population-level data on a national level and allowing relatively open access so that it could be easily monitored for validity and reliability. It is critical that post marketing surveillance meets the following criteria:

1. scientific rigor in evaluating clinically-meaningful outcomes;
2. collection of population-level data;
3. timely and relatively easy access to data;
4. independent assessment;
5. sustainable research groups with relevant expertise;
6. affordability;
7. transparency (Carleton 2005).

In the future post marketing surveillance must be able to identify new safety issues without delay. If this does not happen patients' confidence in drugs will be eroded as serious adverse events occur and are publicized. As we move forward, methods to identify patients at risk of developing an adverse drug reaction need to be developed. Any future endeavours need to use patients as a source of information. This approach would be consistent with the growing trend of patient involvement in drug safety.

6.3.2 Monitoring for Adverse Events

There is considerable debate regarding the appropriate procedure for determining a reliable estimate for the risk of adverse effects (Ioannidis 2006). A diverse range of

study designs including randomized controlled trials, cohort or case-control studies can be used to record adverse events. Randomized controlled trials yield unbiased outcome estimates of treatment effect but due to the short timeframe of these studies adverse event data can be inaccurate (Levine 1994; Meade 1997; Papanikolaou 2006). Many reviews have found that randomized trials fail to provide adequate adverse event data and the information provided is often poor (Cuervo 2003; Ethgen 2005; Ioannidis 2001a; Ioannidis 2006; Ioannidis 1998; Nuovo 2007; Papanikolaou 2004). These trials are designed and powered to explore efficacy not adverse events which are less likely to occur than treatment effect (Aagaard 2009; Clarke 2006; Henry 1999; Hughes 2007; Kaufman 2000; Lee 2008; Vandenbroucke 2004). Also, randomized trials often have rigid exclusion criteria that may exclude patients at high risk of adverse effects and those with potential drug interactions (Ahmad 2003; Chou 2005; Gutterman 2004; Hyrich 2005; Mittmann 1999; Ravaud 2005; Vandenbroucke 2006).

Post marketing surveillance is another strategy for the detection of adverse events. The data are usually collected from observational or retrospective studies, but these sources are afflicted by an increased risk of bias and confounding. Nevertheless, observational data may be the only available source of information for particular adverse effects (Jacob 2000; Psaty 1999; Skegg 2001). Like randomized controlled trials these observational studies are another potential source of adverse event data to be used in a meta-analysis. However there is the potential for discrepancy between the pooled estimates depending on what type of study is used.

It is well recognized that differences in treatment effect between randomized trials and observational studies exist (Britton 1998; Concato 2000; Ioannidis 2001b; Oliver 2010; Shikata 2006). Likewise there are many examples of both agreement and disagreement in the reported risk of adverse events between randomized controlled trials and observational studies (Berlin 1999; Jick 1998; McPherson 2004; Ray 2003). There are many reasons why the results between pooled observational data and meta-analysis could differ. Randomized controlled trials have a strict methodological evaluation compared to observational cohorts. Randomized controlled trials may record a higher

incidence of adverse effects because of closer monitoring of patients and more thorough recording. Observational studies are longer and more likely to detect rare adverse outcomes. Trials are also more likely to be conducted in line with regulatory requirements and this will affect the recording of adverse events (Ofman 2002). Depending on the source of the data the conclusions of the meta-analysis could be different.

There is considerable debate and controversy as to the relative merits of using randomized controlled trial data as opposed to observational data from systematic reviews to determine the overall rate of adverse events. One group actually examined the estimates of harm from meta-analyses of randomized study designs and compared them to estimates from meta-analyses of similar observational studies. This meta-analysis of meta-analyses aimed to assess the level of agreement or disagreement in the estimates of harm derived from meta-analysis of RCTs as compared to meta-analysis of observational studies (Golder 2011). This group carried out searches in ten databases in addition to reference checking, contacting experts, citation searches, and hand-searching key journals, conference proceedings, and web sites to identify studies. A pooled relative measure of an adverse effect (odds ratio or risk ratio) from randomized trials was directly compared with the pooled estimate for the same adverse effect arising from observational studies. The pooled ratio of odds ratios of RCTs compared to observational studies was estimated to be 1.03, 95% CI (0.93, 1.15). In terms of statistical significance, for 37 of 58 studies (64%), the results agreed. Thus 64% of the time both studies showing a significant increase, significant decrease or no significant difference. This evidence indicates that systematic reviews of adverse effects should not be restricted to specific study types. Their conclusion was that there was no difference on average in the risk estimate of adverse effects of an intervention derived from a meta-analysis of randomized trials versus a meta-analysis of observational studies.

6.4 Limitations of this Study

As with any meta-analysis, these results need to be interpreted with caution and there are limitations to this data. Clinical trials might contain patients which are not representative of clinical practice. Also many of these trials are short in duration ranging from 4 to 56 weeks whereas in clinical practice most patients will be on these drugs for many years. Follow-up might not be long enough for some rare long term adverse events to be detected. As well, some uncommon severe complications might only occur in patients receiving combination therapy with both anti-TNF-α and immunosuppressive agents.

Publication bias was assessed. This form of bias usually refers to the non-publication of trials which show no evidence of efficacy. The funnel plot was symmetrical suggesting the absence of publication bias. However, given that the purpose of this meta-analysis was to assess for adverse events this may not be an appropriate measure. From our perspective, publication bias would be important if rare side effects were not reported. This is certainly a concern from the standpoint of our review and was addressed by a post-marketing review. By conducting this we did find that the randomized trials were not long enough to capture serious rare adverse events such as invasive fungal infections.

The data presented regarding the pooled estimates of the post marketing data has a number of limitations as well. When comparing the pooled results from different observational study designs it is important to consider confounding factors. For instance, different medications were prescribed, some patients did not receive a complete induction therapy, maintenance therapy was observed for different durations, concomitant medications differed, as did demographics. Based on this it might be expected that the magnitude of any adverse events recorded would be significantly different. However this was not the case. Slight increases were seen as patients were on these agents long term. This is expected since the longer you are on any pharmaceutical the more likely you are to develop an adverse outcome.

Chapter 7. Conclusion

The results of this meta-analysis demonstrate that anti-TNF-α agents are safe for patients with inflammatory bowel disease not responding to conventional treatment with steroids, mesalamine or immunosuppressants. However, these patients must be monitored closely for the development of infections, malignancy and other autoimmune conditions. From this review, it is clear that rigorous, independent and timely post marketing surveillance must continue to be carried out regarding biological agents since certain extremely rare side effects may not yet be detected. Overall, the information in this analysis will serve to reassure many clinicians and patients that anti-TNF-α agents are safe in patients who have failed standard medical therapy. However, serious adverse events can occur and need to be monitored.

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Figures

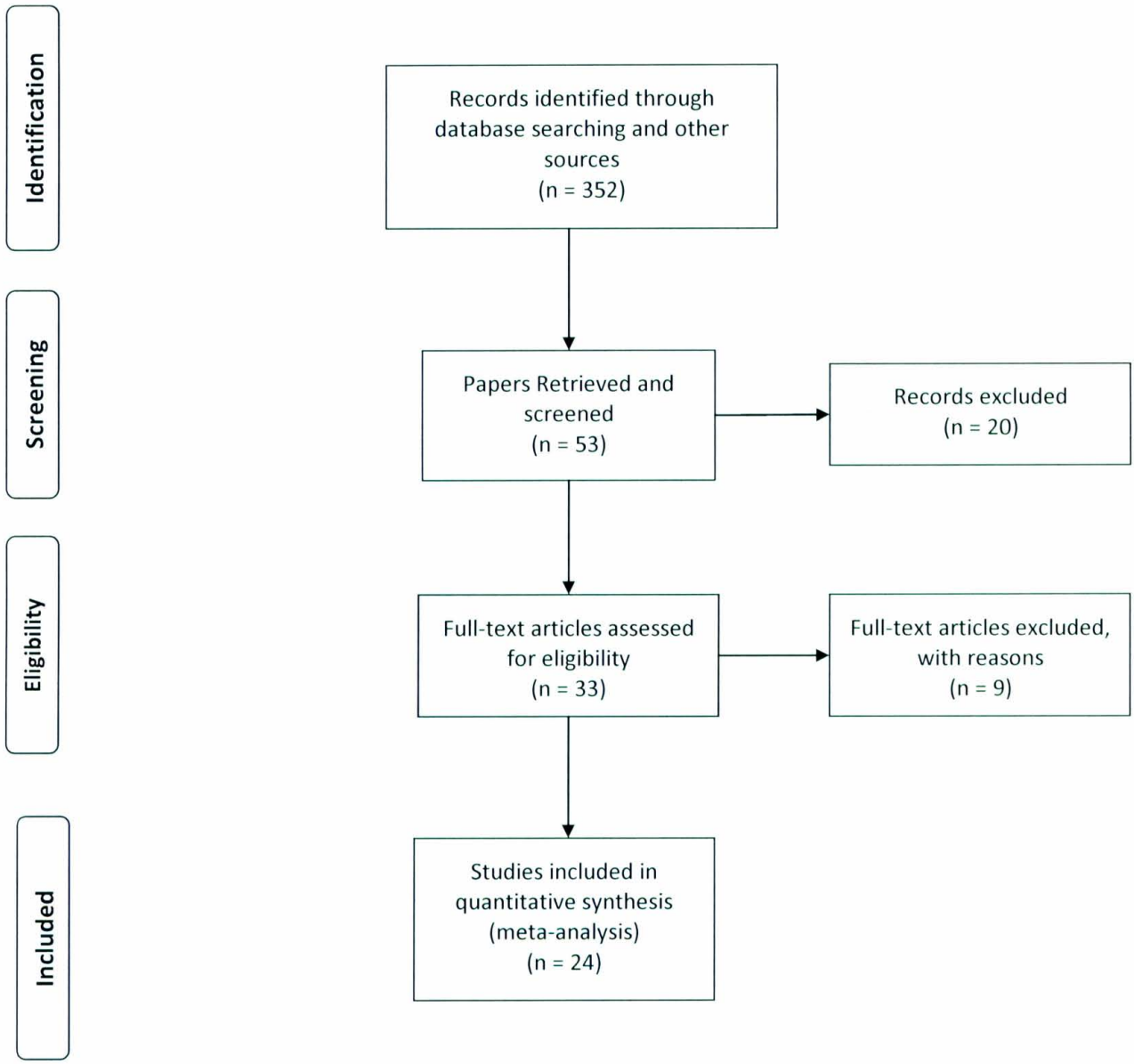

Figure 1. Flow chart for included studies.

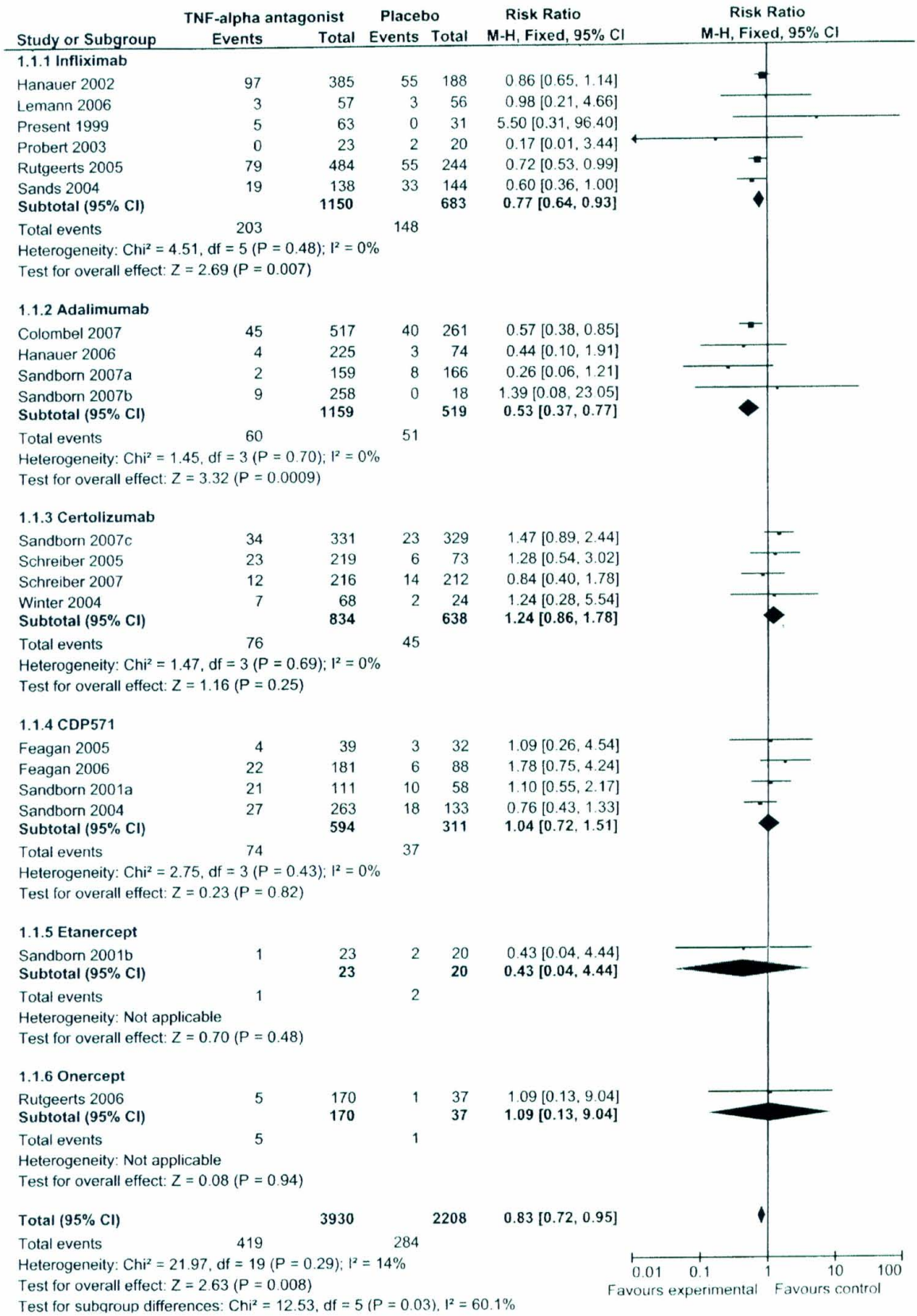

Figure 2. Serious Adverse Events

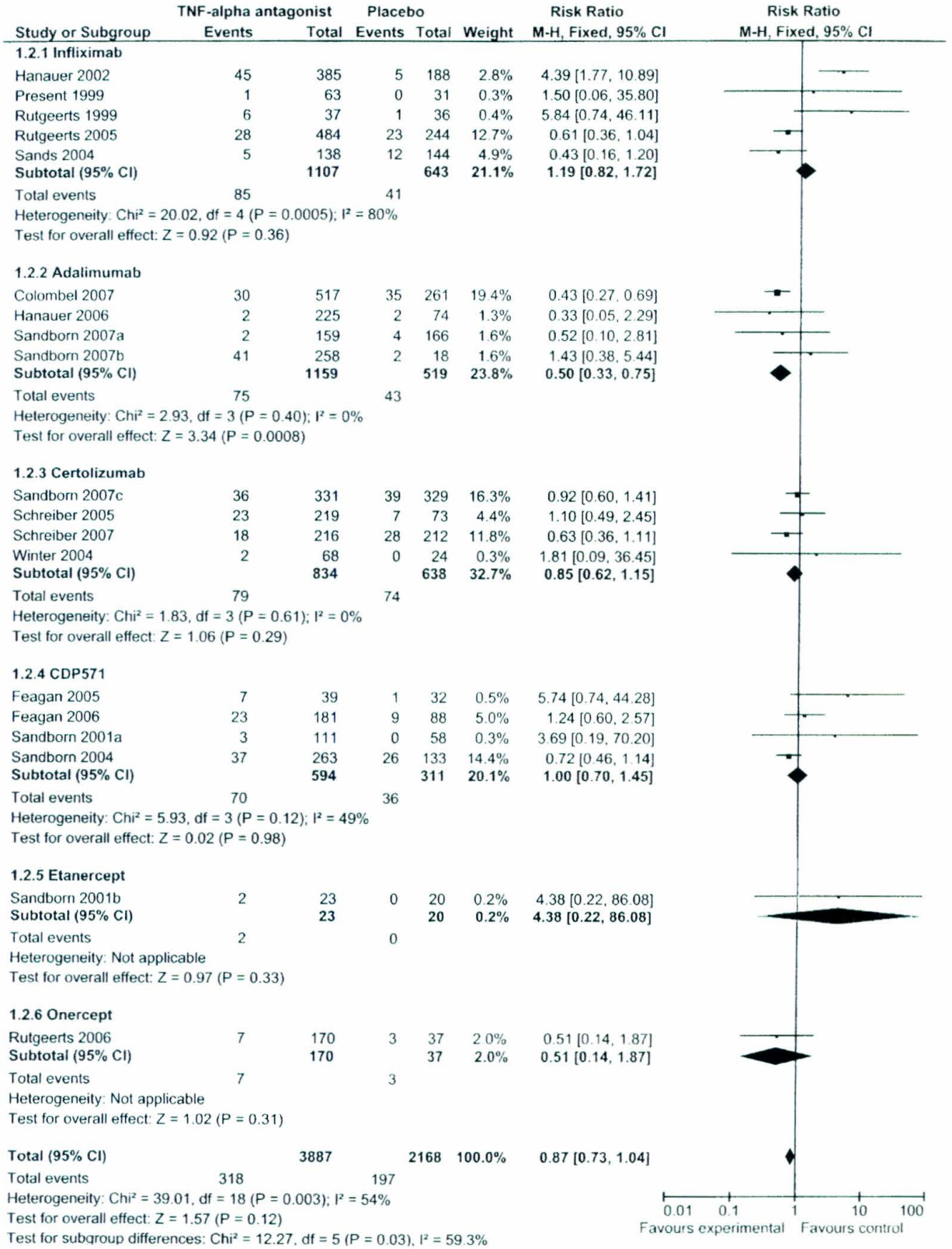

Figure 3. Withdrawal due to Adverse Events

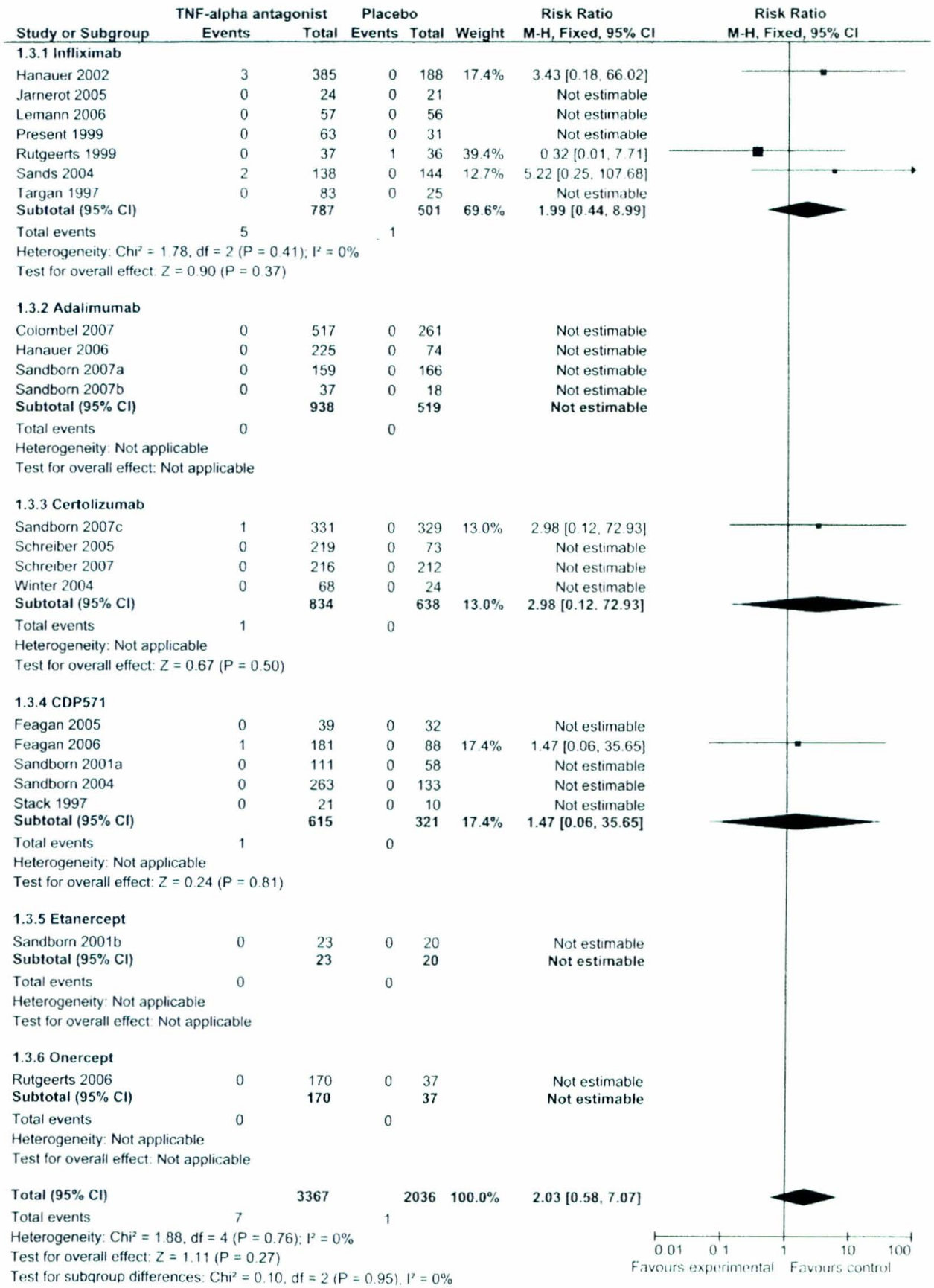

Figure 4. Deaths

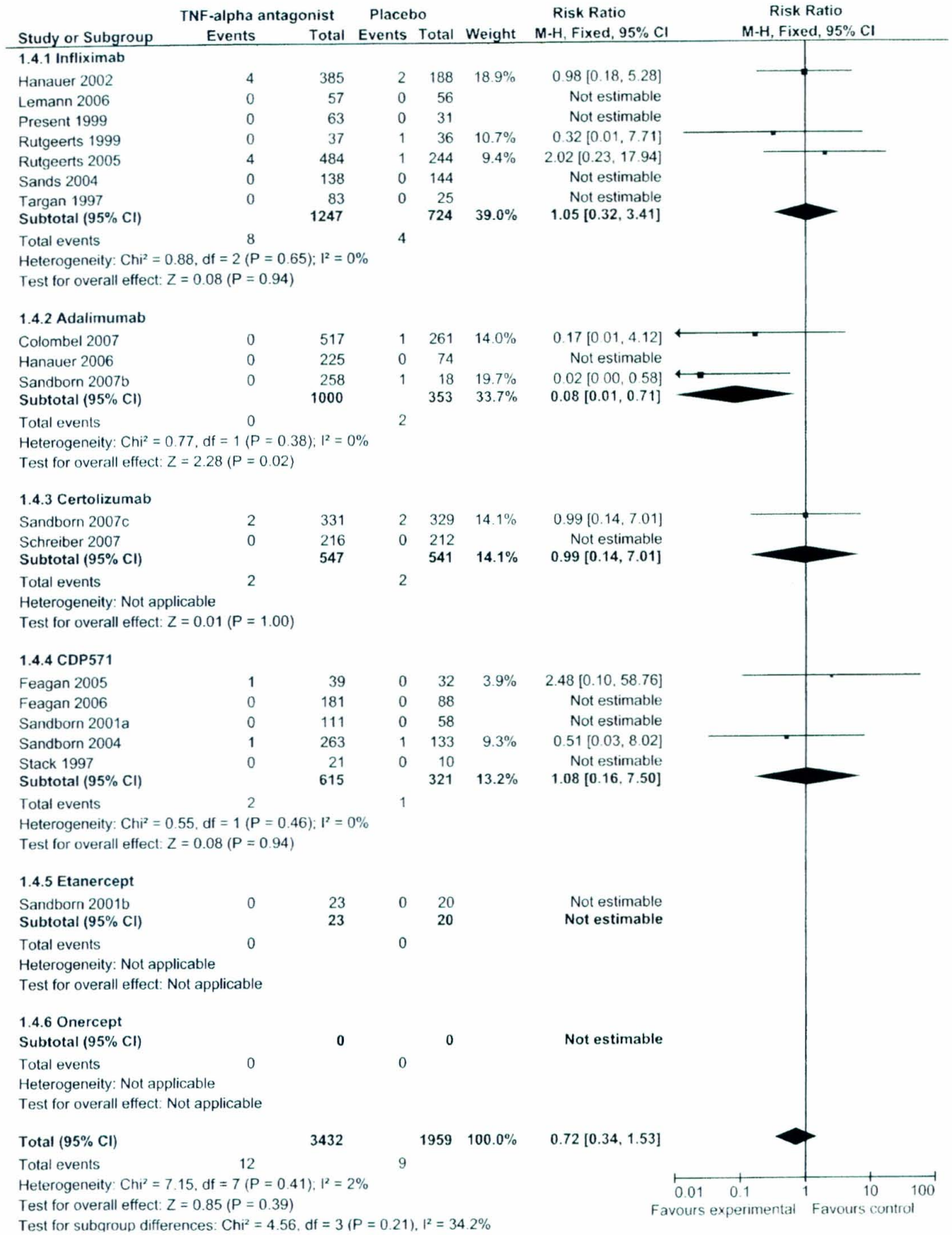

Figure 5. Malignancies

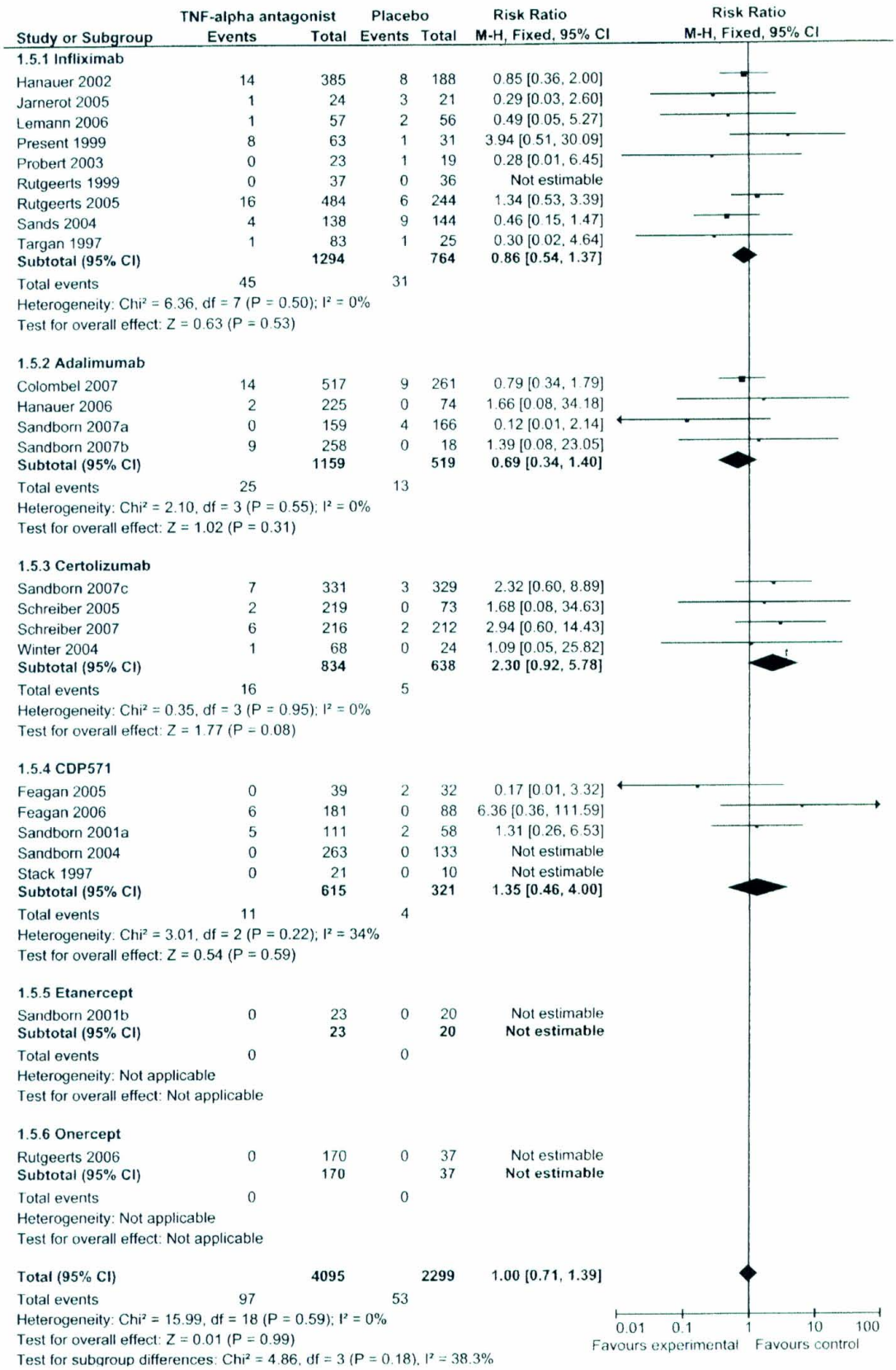

Figure 6. Serious Infections

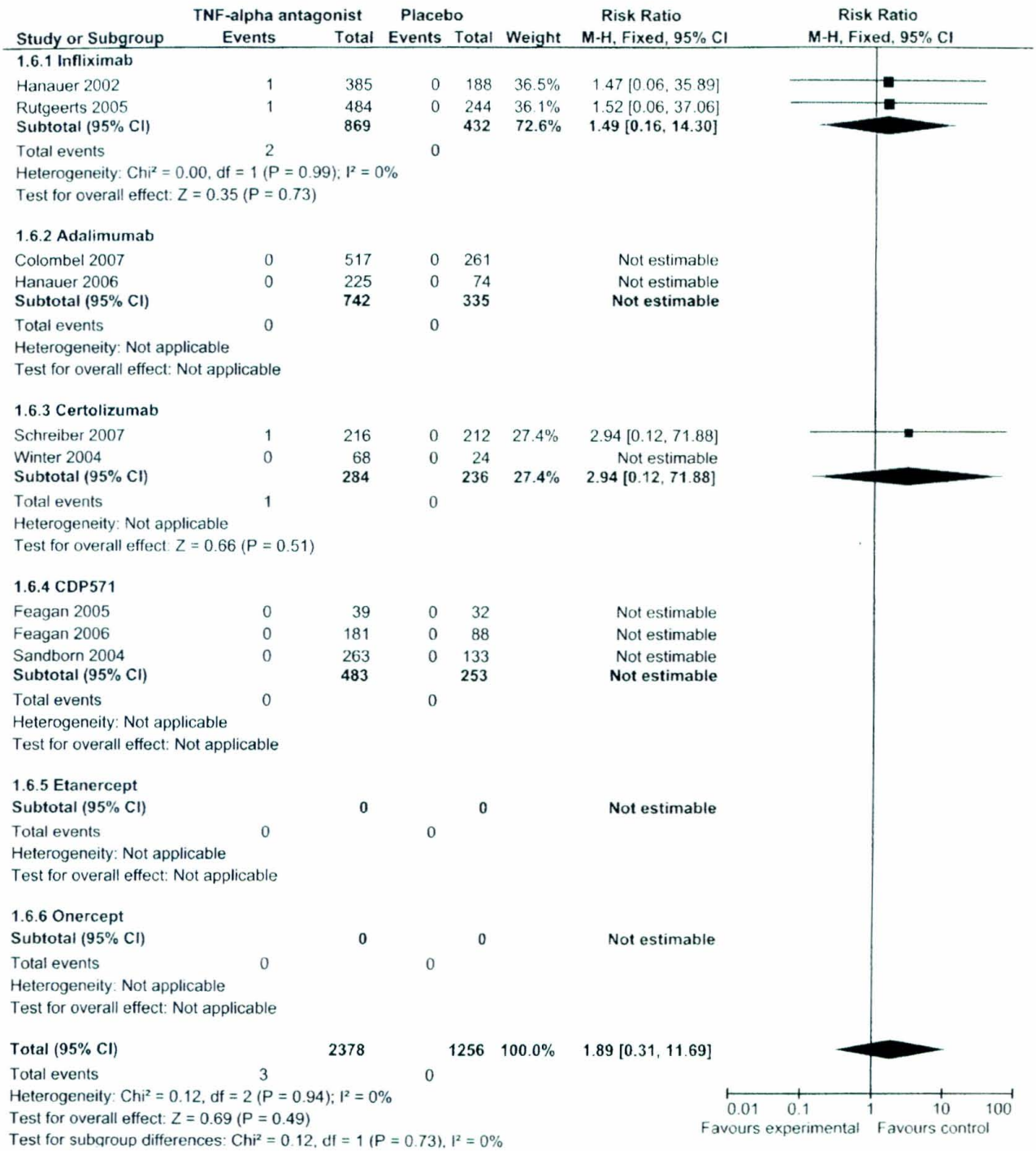

Figure 7. Tuberculosis

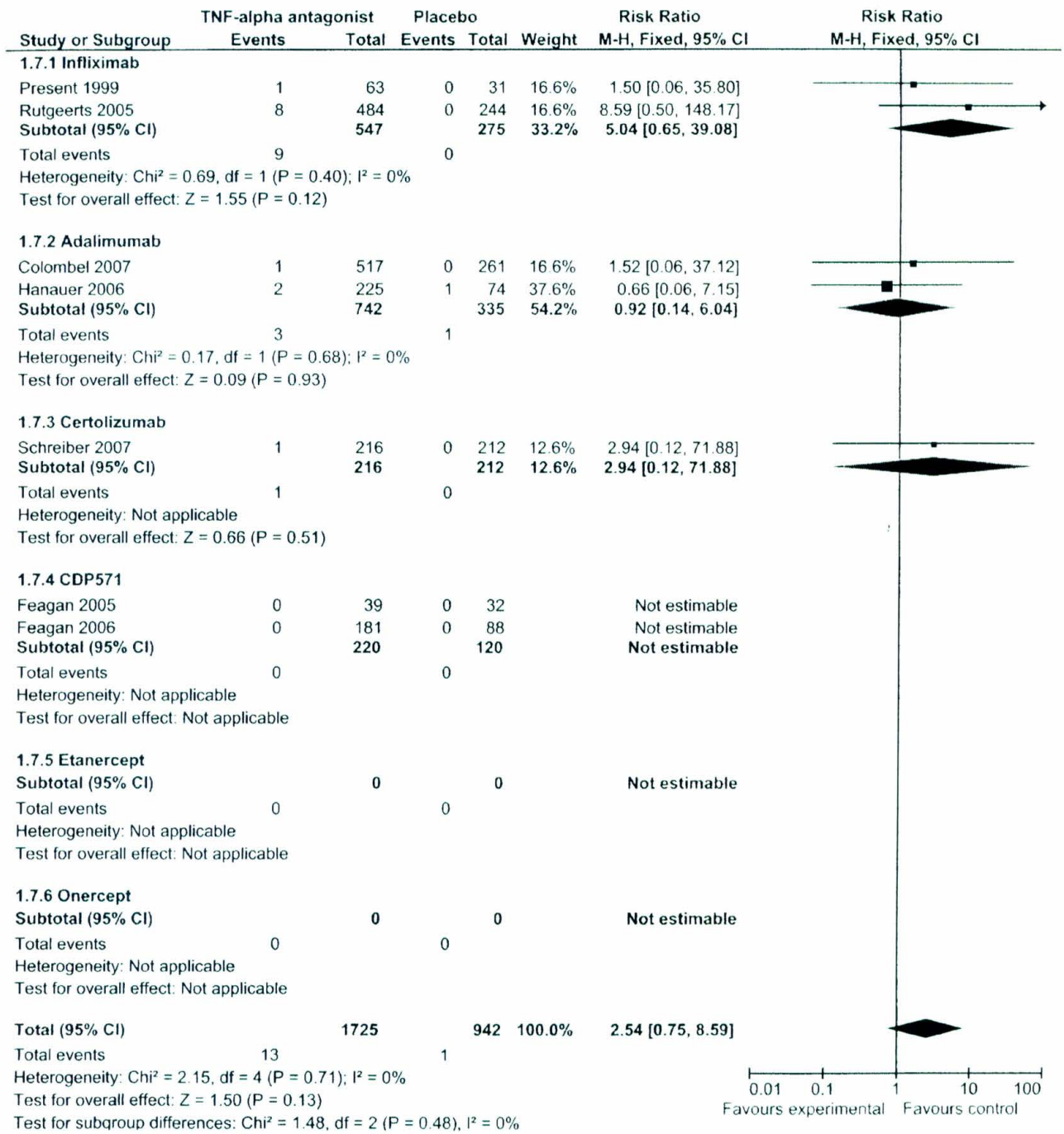

Figure 8. Pneumonia

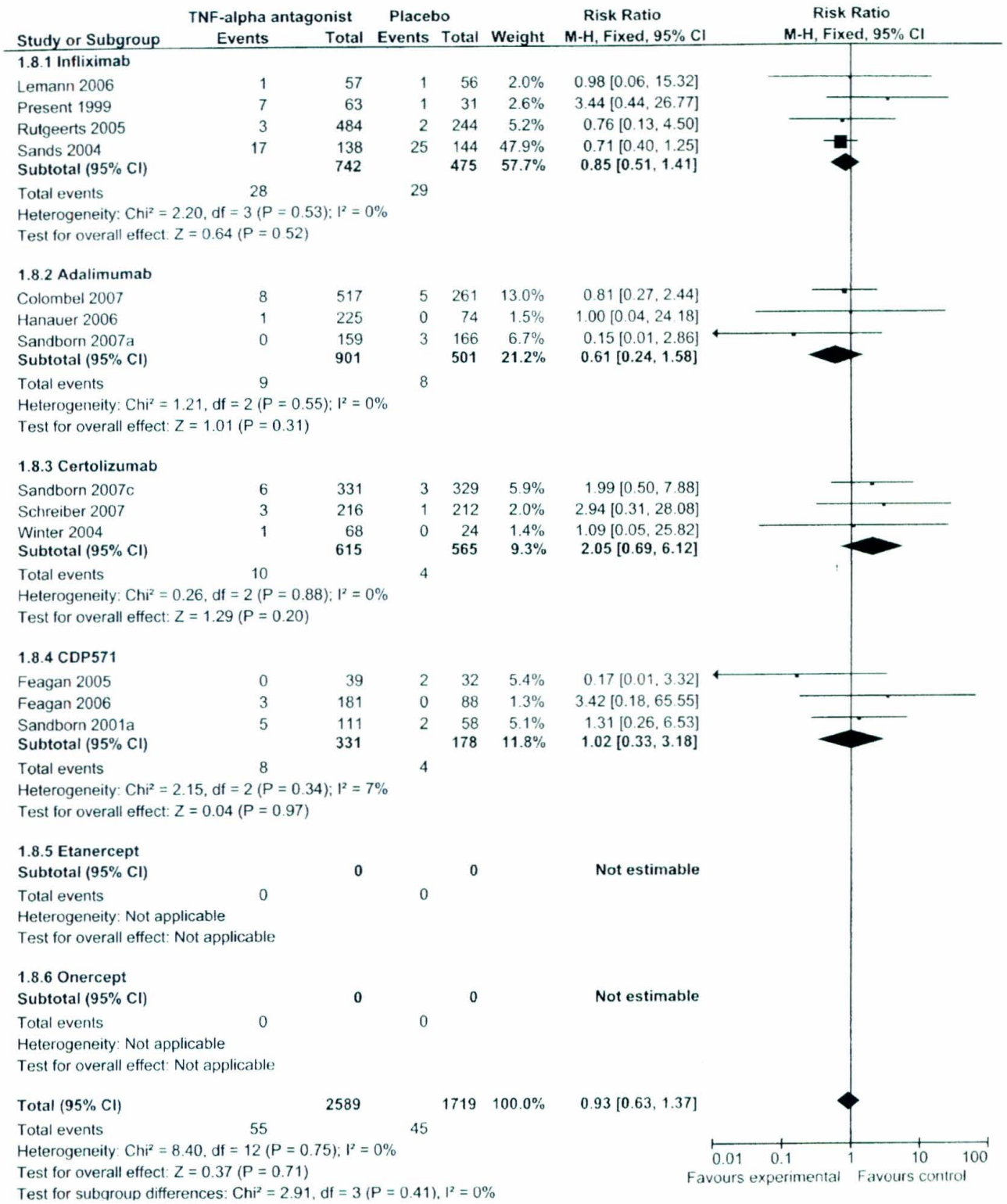

Figure 9. Abscess

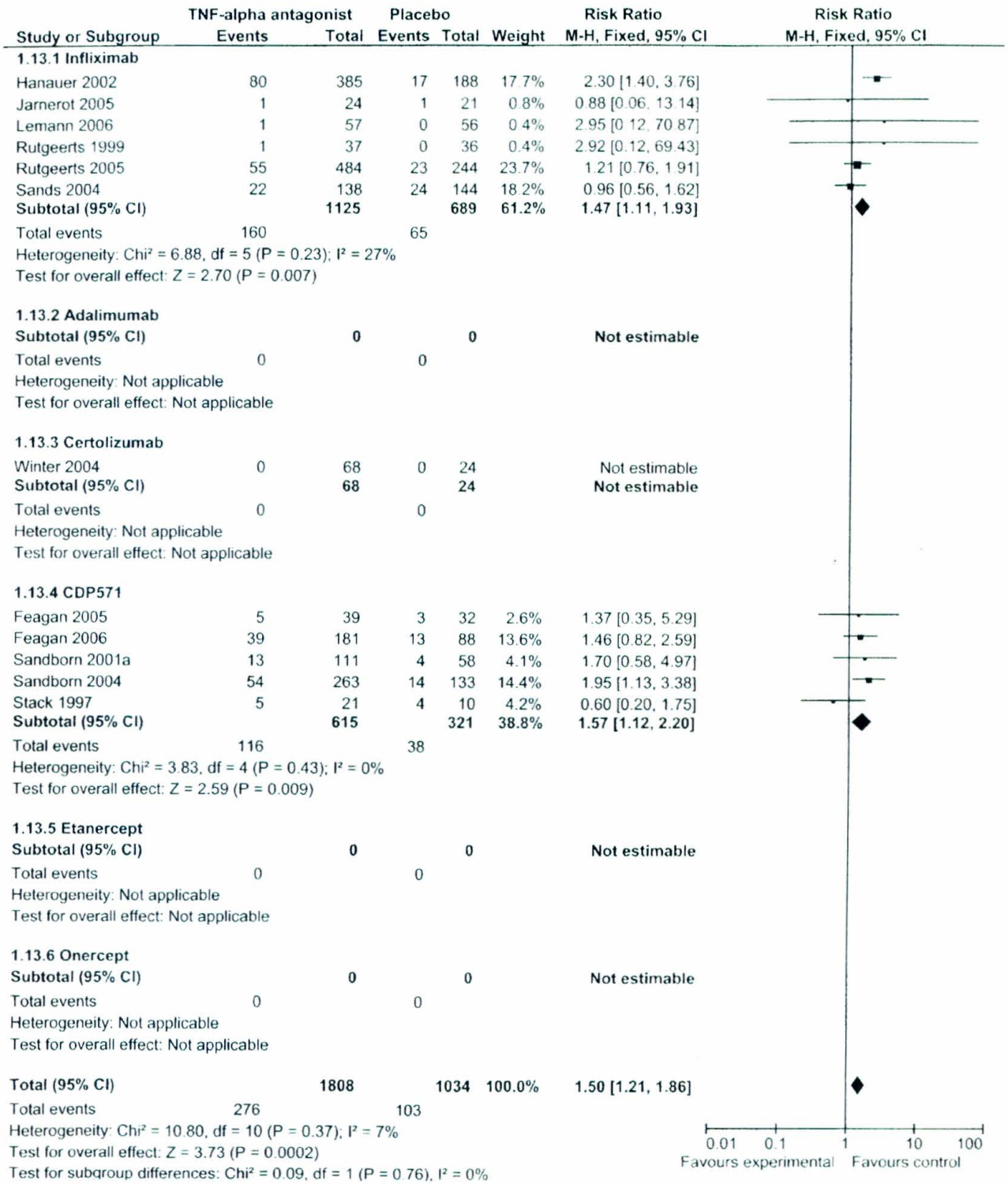

Figure 10. Infusion Reaction

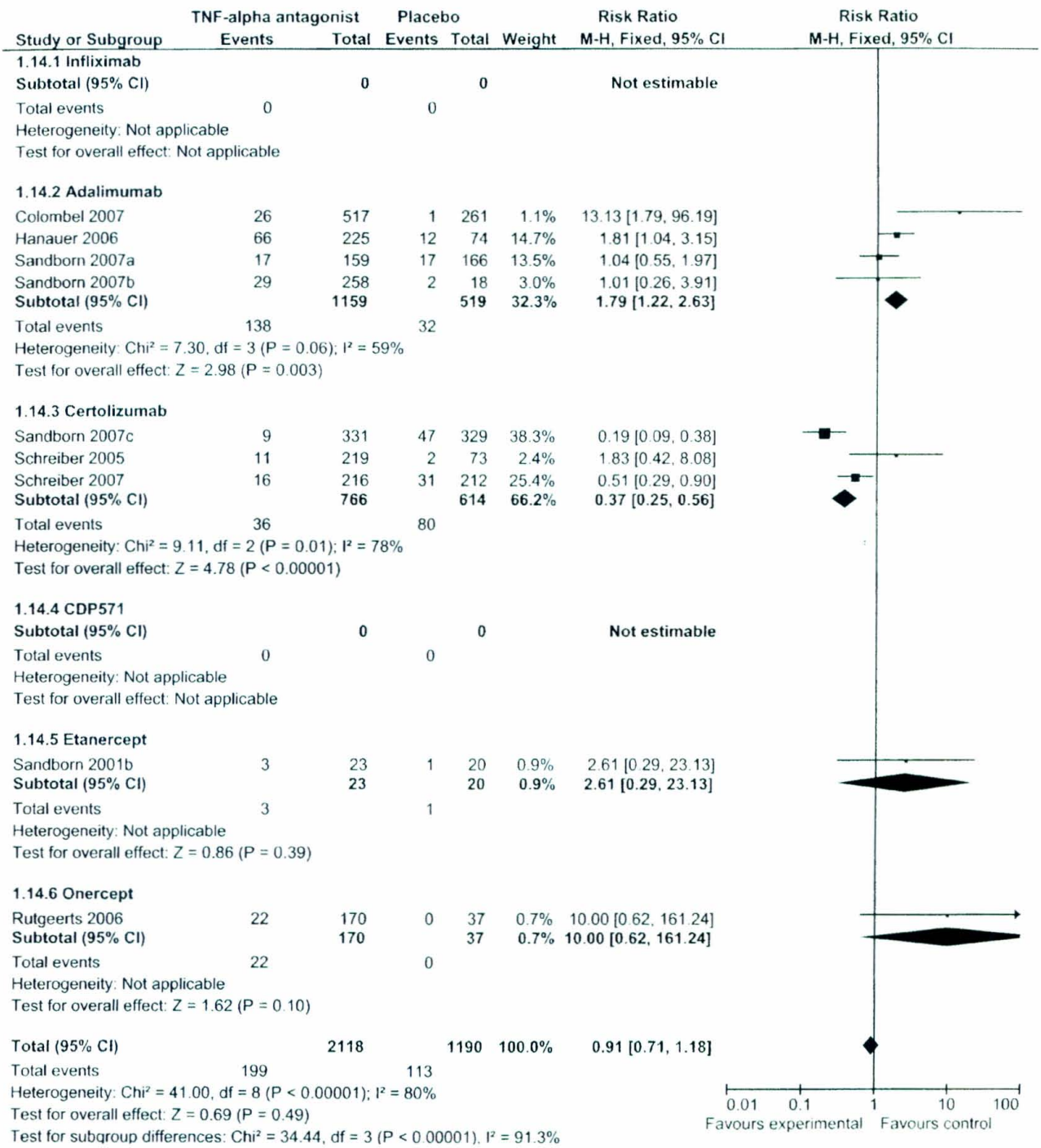

Figure 11. Injection Site Reaction

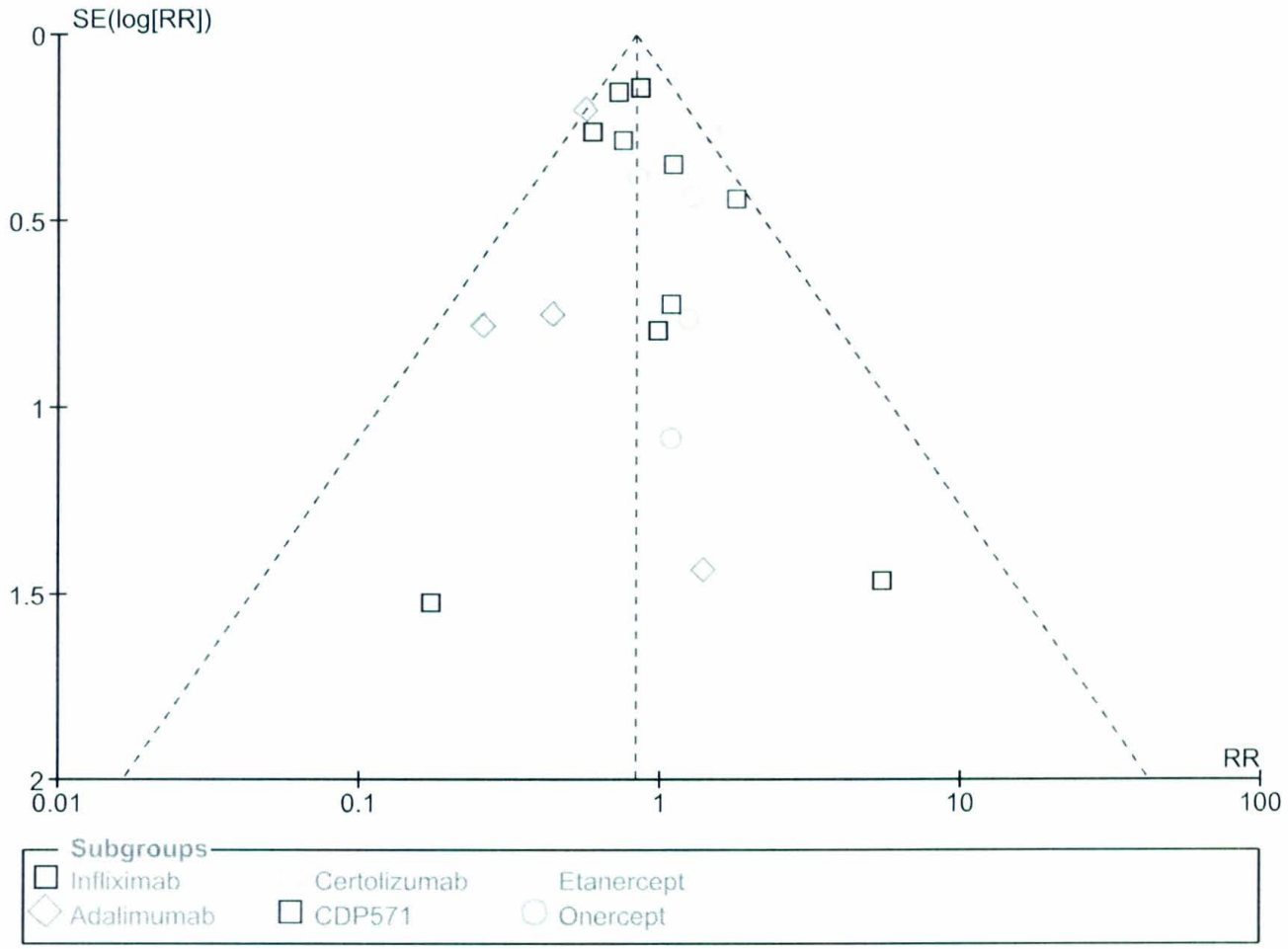

Figure 12. Funnel Plot of Serious Adverse Events

Table

Table 1. Temporal Association of Adverse Events.

	Results of Meta-analysis (events/ 1000 patients)	**Post Marketting Data** (events/1000 patients)		
		Excluding Treat data	Including 1.7 yr TREAT data	Including 5 yr TREAT data
Death	2.0	6.6	7.7	17.2
Malignancy	4.0	13.5	13.5	18.0
Serious Infections	24	41.0	33.5	72.1
Tuberculosis	1.3	2	1.0	1.1

Table 1. Temporal Comparison of Adverse Events

Appendix A: Data Extraction

Data Extraction Tool

Risk of Bias Tool

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title:

Treatment Studied:

Dose:

Inclusion Criteria:

Exclusion Criteria

Duration of Treatment:
Randomized: Yes/No
Placebo Controlled: Yes/No
Blinding: Yes/No
Allocation concealment: Yes/No

Adverse Events

Variable	**Plb**	**Treatment**
Adverse events		
Serious Adverse Events		
Adverse events leading to discontinuation		
Death		
Malignancy		
Serious Infections		
TB		
Pneumonia		
Abscess		
Infusion Reactions		
Injection site reactions		
Other/Notes		

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Colombel 2007	+	+	+	?	+	+
Colombel 2010	+	+	+	+	+	+
Feagan 2005	+	+	+	+	+	+
Feagan 2006	+	+	+	+	+	+
Hanauer 2002	+	+	+	+	+	+
Hanauer 2006	+	+	+	+	+	+
Jarnerot 2005	+	+	+	+	+	+
Lemann 2006	+	+	+	+	+	+
Present 1999	?	+	+	+	+	+
Probert 2003	?	+	+	+	+	+
Rutgeerts 1999	?	+	+	+	+	+
Rutgeerts 2005	+	+	?	?	+	+
Rutgeerts 2006	+	+	+	+	+	+
Sandborn 2001a	+	+	+	+	+	+
Sandborn 2001b	+	+	?	+	+	+
Sandborn 2004	+	+	?	+	+	+
Sandborn 2007a	+	+	+	+	+	+
Sandborn 2007b	+	+	+	+	+	+
Sandborn 2007c	+	+	?	+	+	+
Sands 2004	+	?	+	+	+	+
Schreiber 2005	+	+	?	+	+	+
Schreiber 2007	+	+	?	+	+	+
Stack 1997	?	+	?	+	+	+
Targan 1997	?	+	+	+	+	+
Winter 2004	?	?	?	+	+	+

Risk of Bias Tool (Higgins 2008)

Appendix B: Data Extraction – Included Studies

A1. Adalimumab

A2. CDP 571

A3. Certolizumab

A4. Etanercept

A5. Infliximab

A6. Onercept

A1. Adalimumab

Hanauer 2006

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Human anti–tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I Trial. Hanauer SB, Sandborn WJ, Rutgeerts P. et al. Gastroenterology 2006;130:323-33.

Treatment Studied: Adalimumab.

Dose: Weeks 0 and 2 with 40 mg/20 mg, 80 mg/40 mg, or 160 mg/80 mg or placebo.

Inclusion Criteria:

- men and women;
- 18–75 years of age;
- Crohn's disease for at least 4 months;
- CDAI score of 220–450 points;
- radiologic or endoscopic studies were required to confirm the diagnosis of Crohn's disease;
- concurrent therapies for Crohn's disease, including 5-aminosalicylates, prednisone (≤20 mg/day), budesonide (≤9 mg/day), azathioprine, 6-mercaptopurine, methotrexate, and antibiotics, were permitted at stable dosages;
- female patients with childbearing potential were required to use a highly effective form of birth control;
- all patients were required to have adequate cardiac, renal, and hepatic function.

Exclusion Criteria

- history of malignancy;
- history of active tuberculosis, listeriosis, or HIV;
- ulcerative colitis;
- symptomatic obstructive strictures;
- underwent surgical bowel resection within 6 months;
- an ostomy;
- underwent extensive bowel resection (>100 cm) or had short bowel syndrome;
- total parenteral nutrition;
- received investigational chemical agents within 30 days;
- received investigational biologic therapy within 4 months;
- received antibiotic treatment within 3 weeks for infections not related to Crohn's disease;
- pregnant;
- breast-feeding;
- clinically significant drug or alcohol abuse within 1 year;
- poorly controlled medical conditions;
- previously received infliximab or any other anti-TNF therapy;
- received enema therapy within 2 weeks;
- received cyclosporine or tacrolimus within 8 weeks;
- positive *Clostridium difficile* stool assay;
- clinically significant deviations in prespecified laboratory parameters.

Duration of Treatment:	4 weeks
Randomized:	Yes
Placebo Controlled:	Yes
Blinding:	Yes
Allocation concealment:	Yes

Adverse Events

Variable	Plb (n = 74)	ADA 40/20 (n = 74)	ADA 80/40 (n = 75)	ADA 160/80 (n = 76)
Adverse events, # (%)	55 (74)	50 (68)	51 (68)	57 (75)
Adverse events leading to discontinuation	2 (3)	1 (1)	1 (1)	0 (0)
Adverse events				
Abdominal tenderness	1 (1)	1 (1)	0 (0)	4 (5)
Crohn's disease aggravated	4 (5)	2 (3)	3 (4)	2 (3)
Crohn's disease	2 (3)	4 (5)	2 (3)	3 (4)
Nausea	1 (1)	5 (7)	4 (5)	6 (8)
Flatulence	3 (4)	2 (3)	2 (3)	4 (5)
Nasopharyngitis	1 (1)	2 (3)	4 (5)	4 (5)
Pharyngitis	2 (3)	1 (1)	1 (1)	5 (7)
Headache	4 (5)	3 (4)	4 (5)	7 (9)
Infections	12 (16)	8 (10)	13(17)	16(21)
Pneumonia	1 (1)	0	0	2 (3)
Serious adverse events	3 (4)	0 (0)	1 (1)	3 (4)
Serious infections	0 (0)	0 (0)	0 (0)	2 (3)
Perianal abscess	0 (0)	0 (0)	0 (0)	1 (1)
Pneumonia (SAE)	0 (0)	0 (0)	0 (0)	1 (1)
Lymphoma	0 (0)	0 (0)	0 (0)	0 (0)
TB	0 (0)	0 (0)	0 (0)	0 (0)
Injection site reactions	12 (16)	19 (26)	18 (24)	29 (38)
Injection site burning	6 (8)	9 (12)	8 (11)	11 (15)
Injection site pain	6 (8)	6 (8)	4 (5)	6 (8)
Injection site rx nonspecific	0 (0)	3 (4)	5 (7)	6 (8)
Injection site erythema	0 (0)	1 (1)	0 (0)	3 (4)
Injection site bruising	0 (0)	0 (0)	1 (1)	2 (3)
Injection site pruritus	0 (0)	0 (0)	0 (0)	2 (3)

Colombel 2007

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: The CHARM trial. Colombel JF, Sandborn WJ, Rutgeerts P, et al., Gastroenterolgy 2007;132:52–65.

Treatment Studied: Adalimumab.

Dose:

- adalimumab 80 mg (week 0) followed by 40 mg (week 2);
- at week 4, patients were stratified by response (decrease in Crohn's Disease Activity Index >70 points from baseline) and randomized to double-blind treatment with placebo, adalimumab 40 mg every other week (eow), or adalimumab 40 mg weekly through week 56.

Inclusion Criteria:

- men and women 18–75 years;
- known CD of at least 4 months' duration (radiologic/endoscopic confirmation required);
- Crohn's Disease Activity Index (CDAI) score of 220–450 points
- Concurrent therapies: stable dosages (for at least 4 weeks before screening) of azathioprine, 6-mercaptopurine, methotrexate, 5-aminosalicylates, sulfasalazine, oral mesalamine, and CD-related antibiotics;
- stable dosages (for at least 2 weeks before screening) of prednisone (30 mg/day or equivalent) or budesonide (9 mg/day) (patients could not be on both prednisone and budesonide);
- patients who had received infliximab or any TNF antagonist other than adalimumab more than 12 weeks before screening could be enrolled provided that they did not exhibit initial nonresponse to the agent (ie, no clinical response to first injection as judged by the investigator);
- female patients of childbearing potential were required to use an effective form of birth control.

Exclusion Criteria:

- ulcerative colitis;
- symptomatic obstructive disease;
- bowel resection within the past 6 months;
- an ostomy;
- extensive small bowel resection (as determined by the investigator);
- short bowel syndrome;
- currently receiving total parenteral nutrition;
- a history of cancer;
- a history of *Listeria or HIV;*
- central nervous system demyelinating disease;
- untreated tuberculosis;
- received investigational chemical agents within 30 days;
- investigational biologic therapy within 3 months before screening;
- received antibiotic treatment for non-CD–related infections within 3 weeks before screening;
- pregnant or breast-feeding;
- significant drug or alcohol abuse within the past year;

- poorly controlled medical conditions;
- received treatment with adalimumab or participated in an adalimumab clinical study;
- had received enema therapy within 2 weeks before screening;
- had received cyclosporine, mycophenolate mofetil, or tacrolimus within 8 weeks of screening;
- had a positive *Clostridium difficile* stool assay;
- clinically significant deviations in prespecified laboratory parameters.

Duration of Treatment:	56 weeks
Duration of Study:	July 2003 to September 2005.
Randomized:	Yes
Placebo Controlled:	Yes
Blinding:	Yes
Allocation concealment:	Blinded

Adverse Events

	Induction	Placebo	ADA 40 q2wk	ADA 40 qwk
Adverse events	507 (59.4)	221 (84.7)	231 (88.8)	220 (85.6)
Adverse events leading to discontinuation of study drug (Flare of CD)	54 (6.3)	35 (13.4) (7.7)	18 (6.9) (1.9)	12 (4.7) (1.2)
Adverse events				
CD flare		84 (32.2)	51 (19.6)	48 (18.7)
Arthralgia		23 (8.8)	27 (10.4)	34 (13.2)
Nasopharyngitis		18 (6.9)	29 (11.2)	31 (12.1)
Headache	51 (6.0)	15 (5.7)	25 (9.6)	30 (11.7)
Nausea	45 (5.3)	16 (6.1)	19 (7.3)	22 (8.6)
Fatigue		6 (2.3)	11 (4.2)	20 (7.8)
Abdominal pain		17 (6.5)	20 (7.7)	19 (7.4)
Pyrexia		14 (5.4)	14 (5.4)	17 (6.6)
Upper respiratory tract infection		16 (6.1)	12 (4.6)	16 (6.2)
Injection site reaction		1 (0.4)	11 (4.2)	15 (5.8)
Urinary tract infection		4 (1.5)	11 (4.2)	15 (5.8)
Influenza		13 (5.0)	14 (5.4)	13 (5.1)
Diarrhea		15 (5.7)	10 (3.8)	12 (4.7)
Pharyngolaryngeal pain		14 (5.4)	11 (4.2)	7 (2.7)
Serious adverse events	45 (5.3)	40 (15.3)	24 (9.2)	21 (8.2)
Infectious adverse events	130 (15.2)	96 (36.8)	120 (46.2)	114 (44.4)
Serious infectious adverse events	10 (1.2)	9 (3.4)	7 (2.7)	7 (2.7)
Selected injection site reactions				
Bruising	1 (0.1)	2 (0.8)	6 (2.3)	2 (0.8)
Erythema	7 (0.8)	0	7 (2.7)	3 (1.2)
Hemorrhage	4 (0.5)	2 (0.8)	5 (1.9)	0
Irritation	39 (4.6)	2 (0.8)	10 (3.8)	7 (2.7)
Pain	41 (4.8)	2 (0.8)	5 (1.9)	4 (1.6)
Pruritus	2 (0.2)	0	3 (1.2)	2 (0.8)
Reaction	17 (2.0)	1 (0.4)	11 (4.2)	15 (5.8)

Adverse Events (cont.)

	Induction	Placebo	ADA 40 q2wk	ADA 40 qwk
Infections and infestations	10 (1.2)	9 (3.4)	7 (2.7)	7 (2.7)
Abscess	7 (0.8)	5 (1.9)	3 (1.2)	5 (1.9)
Tuberculosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other opportunistic infections	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Wound infection, sepsis, postop inf.	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Cancer (Breast)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Multiple sclerosis	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Serum sickness	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Death (PE)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Sandborn 2007A

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Ann Intern Med. 2007;146(12):829-38.

Treatment Studied: Adalimumab.

Dose: 160mg followed by 80 mg in 2 weeks.

Inclusion Criteria:

- men and women 18 to 75 yrs;
- Crohn disease for at least 4 months;
- moderately to severely active;
- CDAI score of 220 - 450 points;
- radiologic or endoscopic evidence to confirm the presence of CD;
- intolerant of infliximab or must have previously responded to infliximab and then lost response;
- concurrent therapies, including stable dosages of 5-aminosalicylates, prednisone (<=40 mg/d), budesonide (<=9 mg/d), azathioprine, 6-mercaptopurine, methotrexate, and antibiotics, were permitted.

Exclusion Criteria:

- primary nonresponse to infliximab;
- received infliximab or another TNF antagonist within the past 8 weeks;
- previously received adalimumab;
- participated in an adalimumab clinical trial;
- patients who changed dosages or discontinued azathioprine, 6-mercaptopurine, or methotrexate treatment within 12 weeks of screening;
- patients who changed dosages or discontinued 5-aminosalicylates, mesalamine, or sulfasalazine treatment within 4 weeks of screening;
- prednisone;
- short bowel syndrome;
- symptomatic stricture;
- bowel resection within the past 6 months;
- ostomy or ileoanal pouch;
- total parenteral nutrition;
- pts who had received antibiotic treatment for infections not related to Crohn disease within 3 wks;
- untreated tuberculosis;
- demyelinating disorders;
- pregnant;
- breast-feeding;
- significant drug or alcohol abuse;
- abnormal results on electrocardiography; or elevated concentrations of aspartate or alanine aminotransferase, total bilirubin or serum creatinine.

Duration of Treatment:	4-week
Duration of Study:	November 2004 to December 2005
Randomized:	Yes
Placebo Controlled:	Yes
Blinding:	Yes
Allocation concealment:	Yes

Adverse Events

Variable	Placebo Group (n = 166)	Adalimumab Group (n = 159)
Adverse Events	121 (73)	91 (57)
Abdominal pain	12 (7)	9 (6)
Arthralgia	3 (2)	9 (6)
Headache	12 (7)	8 (5)
Injection-site irritation	7 (4)	8 (5)
Fatigue	9 (5)	7 (4)
Crohn disease	15 (9)	2 (1)
Injection-site reactions	17 (10)	17 (11)
Injection-site–related events		
Bruising	1 (0.6)	3 (2)
Erythema	0 (0)	1 (0.6)
Hemorrhage	0 (0)	1 (0.6)
Irritation	7 (4)	8 (5)
Pain	4 (2)	1 (0.6)
Pruritus	0 (0)	1 (0.6)
Injection-site reaction	6 (4)	5 (3)
Adverse events causing discontinuation	4 (2)	2 (1)
Serious adverse events	8 (5) 3 - abscess 1 - sepsis 2 - CD 2 - abd pain	2 (1) 2 - dehydration
Infections	39 (24)	26 (16)
Serious infections	4 (2)	0 (0)
Abdominal abscess	1 (0.6)	0 (0)
Pelvic abscess	1 (0.6)	0 (0)
Perianal abscess	1 (0.6)	0 (0)
Staphylococcal sepsis	1 (0.6)	0 (0)

Sandborn 2007B

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Sandborn WJ, Hanauer SB, Rutgeerts PJ, et al. Gut. 2007;56(9):1232-9.

Treatment Studied: Adalimumab.

Dose: open-label adalimumab 40 mg at weeks 0 and 2;

55 patients in remission at both weeks 0 and 4 were re-randomised to adalimumab 40 mg every other week, 40 mg weekly, or placebo for 56 weeks.

Patients not in remission at both weeks 0 and 4 were enrolled in an open-label arm and received adalimumab 40 mg every other week.

Inclusion Criteria

- men and women;
- 18–75 years of age;
- crohn's disease for at least 4 months;
- CDAI score of 220–450 points, inclusive;
- radiologic or endoscopic studies were required to confirm the diagnosis of Crohn's disease;
- concurrent therapies for Crohn's disease, including 5-aminosalicylates, prednisone (≤20 mg/day), budesonide (≤9 mg/day), azathioprine, 6-MP, methotrexate, and antibiotics, were permitted at stable dosages;
- female patients with childbearing potential were required to use a highly effective form of birth control;
- adequate cardiac, renal, and hepatic function.

Exclusion Criteria

- history of malignancy;
- history of active tuberculosis, listeriosis, or HIV;
- ulcerative colitis;
- symptomatic obstructive strictures;
- underwent surgical bowel resection within 6 months;
- an ostomy;
- underwent extensive bowel resection (>100 cm) or had short bowel syndrome;
- total parenteral nutrition;
- received investigational chemical agents within 30 days;
- received investigational biologic therapy within 4 months;
- received antibiotic treatment within 3 weeks for infections not related to Crohn's disease;
- pregnant or breast-feeding;
- clinically significant drug or alcohol abuse within 1 year;
- poorly controlled medical conditions;
- previously received infliximab or any other anti-TNF therapy;
- received enema therapy within 2 weeks;
- received cyclosporine or tacrolimus within 8 weeks;
- positive *Clostridium difficile* stool assay;
- clinically significant deviations in prespecified laboratory parameters.

Duration of Treatment:	56 weeks
Duration of Study:	28 August 2002 and 12 January 2005
Randomized:	Yes
Placebo Controlled:	Yes
Blinding:	Yes
Allocation concealment:	Yes
Patients:	276 patients from CLASSIC I enrolled in CLASSIC II

Adverse Events

Variable	**Randomised cohort**		**Patients who received open-label treatment or stopped at wk 4**		
	Placebo (n = 18)	**Adalimumab 40 mg Eow (n = 19)**	**Adalimumab 40 mg weekly (n = 18)**	**Adalimumab 40 mg EOW (n = 221)**	**Total (n = 276)**
Adverse events	18 (100)	15 (79)	14 (78)	207 (94)	254 (92)
Adverse events leading to withdrawal	2 (11)	1 (5)	1 (6)	39 (18)	43 (16)
Nasopharyngitis	7 (39)	5 (26)	2 (11)	37 (17)	51 (19)
CD	5 (28)	4 (21)	2 (11)	48 (22)	59 (21)
Sinusitis	1 (6)	4 (21)	1 (6)	20 (9)	26 (9)
Injection-site RXN	2 (12)	1 (5)	0 (0)	26 (12)	29 (12)
Rx-emergent infectious adverse events	15 (83)	14 (74)	6 (33)	127 (58)	162 (59)
Malignancies	1 (5)	0 (0)	0 (0)	0 (0)	1 (0.4)
Serious adverse events	2 (11)	1 (5)	0 (0)	37 (17)	40 (15)
Serious infections	0 (0)	0 (0)	0 (0)	9 (4)	0 (0)

No demyelination
No CHF
No Lupus

A2. CDP 571

Stack 1997

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Randomised controlled trial of CDP571 antibody to tumour necrosis factor-alpha in Crohn's disease. Stack WA, Mann SD, Roy AJ et al. Lancet. 1997;349:521-4.

Treatment Studied: CDP571

Dose: CDP571 5mg/kg x 1 dose

Inclusion Criteria:

- aged 18-80 years;
- mild to moderately active Crohn's disease;
- Crohn's disease activity index between 150-400;
- a firm diagnosis of Crohn's disease previously made on a combination of radiological and histological criteria was required.

Exclusion Criteria:

- treatment with metronidazole, sodium cromoglycate, or cyclosporin within the previous 3 months;
- positive stool culture for enteric pathogens;
- perforation or significant obstructive symptoms;
- history of asthma;
- pregnancy.

Duration of Treatment: 8 weeks
Randomized: Yes
Placebo Controlled: Yes
Blinding: Yes
Allocation concealment: ?

Adverse Events

5/ 21 patients receiving CDP571 reported mild adverse reactions on the day of infusion

- Dizziness
- abdominal pain
- increased flatus
-

4/10 placebo recipients experienced similar symptoms.

1.8 adverse drug reactions per patient for those receiving placebo.

2.05 adverse drug reactions per patient for those receiving CDP571.

Of these 0.01 per patient (placebo) and 0.14 per patient (CDP571) were probably related to treatment.

In 7 patients, there was a small but significant and sustained rise in antibodies directed against CDP571.

Sandborn 2001A

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: An engineered human antibody to TNF (CDP571) for active Crohn's disease: a randomized double-blind placebo-controlled trial. Sandborn WJ, Feagan BG, Hanauer SB, et al. Gastroenterology. 2001; 120:1330-8.

Treatment Studied: CDP571

Dose: 10mg/kg or 20mg/kg q8 or 12wk

Inclusion Criteria:

- at least 18 years;
- moderate to severe Crohn's disease CDAI 220–450;
- Crohn's disease based on radiological, endoscopic, or histological evidence.

Exclusion Criteria:

- an ileostomy or colostomy
- serious intercurrent infection
- other clinically important active diseases (such a renal or hepatic disease)
- those with bowel perforation, fixed stenosis at endoscopy or by radiographic study within 6 months
- obstructive symptoms within 3 months (unless imaging studies showed the absence of significant mechanical obstruction)
- small bowel resection >100 cm;
- more than the right colon resected;
- history of cancer other than cervical dysplasia or basal cell carcinoma within 5 years, dysplasia of the colon within 5 years
- clinically significant hematologic or biochemical values
- pregnant or breast-feeding women
- multiple drug allergies
- positive stool culture for enteric pathogens
- recent drug or alcohol abuse
- known hepatitis or human immunodeficiency virus

Duration of Treatment: 24 weeks
Duration of Study: June 1998 and June 1999
Randomized: Yes
Placebo Controlled: Yes
Blinding: Yes
Allocation concealment: Yes

Adverse Events

Variable	No of patients (%)	
	Placebo (n = 58)	**CDP571 (n = 111)**
No. of adverse events	133	367
Pts with adverse events	40 (69%)	96 (87%)
Pts with serious adverse events	10 (17%)	21 (19%)
Pts with severe adverse events	12 (21%)	26 (23%)
Most frequent adverse events (#events)		
Abdominal pain	11 (19%)	12 (11%)
Asthenia	2 (3%)	7 (6%)
Fever	2 (3%)	7 (6%)
Flu syndrome	4 (7%)	10 (9%)
Headache	6 (10%)	20 (18%)
Infection	6 (10%)	16 (14%)
Body pain	6 (10%)	9 (8%)
Ileitis	7 (12%)	12 (11%)
Liver function test abnormality	1 (2%)	6 (5%)
Nausea	9 (16%)	16 (14%)
Vomiting	5 (9%)	7 (6%)
Depression	1 (2%)	6 (5%)
Dizziness	5 (9%)	10 (9%)
Insomnia	0 (0%)	7 (6%)
Pruritus	0 (0%)	6 (5%)
Rash	0 (0%)	6 (5%)
Adverse events potentially associated with anti-TNF antibody therapy (no. of patients with events)		
Infusion reaction	4 (7%)	13 (12%)
Abscess	2 (3%)	5 (5%)
Infection	6 (10%)	16 (14%)
Anti–double-stranded DNA present	0 (0%)	2 (2%)
Antinuclear antibody present	2 (3%)	4 (4%)
Anticardiolipin antibody present	2 (3%)	3 (3%)
Lupus syndrome	0 (0%)	0 (0%)
Lymphoma	0 (0%)	0 (0%)
Anti-idiotype antibody to CDP571	0 (0%)	8 (7%)

Sandborn 2004

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: CDP571, a humanised monoclonal antibody to tumour necrosis factor alpha, for moderate to severe Crohn's disease: a randomised, double blind, placebo controlled trial. Sandborn WJ, Feagan BG, Radford-Smith G, et al. Gut 2004 Oct;53(10):1485-93.

Treatment Studied: CDP571

Dose: 10mg/kg q8wk

Inclusion Criteria:

- at least 18 years;
- moderate to severe Crohn's disease CDAI 220–450;
- Crohn's disease based on radiological, endoscopic, or histological evidence.

Exclusion Criteria:

- infection of a fistula;
- abscess;
- ulcerative colitis;
- bowel perforation;
- evidence of non-inflammatory obstruction within the six months prior to study entry (fixed stenosis at endoscopy or radiography);
- obstructive symptoms due to significant mechanical obstruction within the three months prior to study entry;
- small bowel resection >100 cm;
- more than the right colon resected;
- a functional colostomy;
- an ileostomy;
- current infection with enteric pathogens;
- serious intercurrent infection;
- other clinically important active disease (such as renal or hepatic disease) within the 3 months prior to entry;
- current or previous malignancy (other than carcinoma of the cervix or basal cell carcinoma successfully treated 5 years prior to study entry);
- current or previous bowel dysplasia within the five years prior to study screening;
- clinically important allergies or multiple drug allergies;
- drug or alcohol abuse;
- significant abnormal haematology or biochemical values at study entry;
- history of or concurrent tuberculosis, hepatitis, or human immunodeficiency virus;
- pregnant and lactating women were ineligible.

Duration of Treatment: 24 weeks
Duration of Study: 18 January 2001 and 15 May 2002.
Randomized: Yes
Placebo Controlled: Yes
Blinding: Yes
Allocation concealment: Yes

Adverse Events

Variable	No of patients (%)	
	CDP571 (n = 133)	**Placebo (n = 263)**
Adverse Events	96 (72.2)	200 (76.0)
Serious Adverse Events	18 (13.5)	27 (10.3)
Withdrawal due to Adverse Events	26 (19.5)	37 (14.1)
Deaths	0 (0)	0 (0)
Patients with severe AEs	22 (16.5)	46 (17.5)
Patients with probably drug related AEs	3 (2.3)	17 (6.5)
Patients with definitely drug related AEs	1 (0.8)	8 (3.0)
Infections and infestations	39 (29.3)	77 (29.3)
Headache	20 (15.0)	32 (12.2)
Crohn's disease aggravated	14 (10.5)	22 (8.4)
Nausea	8 (6.0)	20 (7.6)
Nasopharyngitis	7 (5.3)	19 (7.2)
Abdominal pain	6 (4.5)	17 (6.5)
Arthralgia	8 (6.0)	13 (4.9)
Vomiting	10 (7.5)	10 (3.8)
Pyrexia	7 (5.3)	10 (3.8)
Cough	8 (6.0)	7 (2.7)
Rectal Cancer	0	1 (0.38)
Cervical Cancer	1 (0.75)	0
Patients with AEs occurring within 2 hrs of the start of the infusion		
Any	14 (10.5)	54 (20.5)
Hypersensitivity	0 (0)	7 (2.7)
Dizziness	1 (0.8)	5 (1.9)
Dermatitis	0 (0)	4 (1.5)
Headache	4 (3.0)	2 (0.8)

Feagan 2005

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: A randomized, double-blind, placebo-controlled trial of CDP571, a humanized monoclonal antibody to tumour necrosis factor-alpha, in patients with corticosteroid-dependent Crohn's disease. Feagan BG, Sandborn WJ, Baker JP, et al. Aliment Pharmacol Ther. 2005;21:373-384.

Treatment Studied: CDP571

Dose: CDP571 10mg/kg q8wk

Inclusion Criteria:

- at least 18 years;
- Crohn's Disease Activity Index (CDAI) score less than or equal to 150 points (indicating remission);
- corticosteroid therapy with prednisolone or prednisone 15–40 mg/day or budesonide 9 mg/day to control symptoms for at least 8 weeks;
- at least one unsuccessful attempt to discontinue prednisolone, prednisone or budesonide therapy (defined as worsening symptoms within 30 days) within 8 weeks of study entry;
- a stable corticosteroid dose (except during attempted withdrawal) for at least 2 weeks prior to screening.

Exclusion Criteria:

- use of broad-spectrum antibiotics, mycophenolate mofetil, cyclosporin or sodium cromoglycate within 1 month of screening;
- ulcerative colitis;
- extensive bowel resection (>100 cm of the small intestine);
- extended right hemicolectomy;
- a stoma;
- obstructive symptoms;
- radiographic evidence of fixed, noninflammatory bowel obstruction within the 6 months prior to study entry;
- history of bowel perforation;
- critical illness;
- active infections (including enteric pathogens);
- multiple drug allergies;
- other significant medical conditions (including malignancy, except carcinoma of the cervix or basal cell carcinoma of the skin);
- current or previous bowel dysplasia within 5 years;
- significant abnormal haematology or biochemical values at study entry;
- history of hepatitis or human immunodeficiency virus;
- pregnancy or lactation;
- previous treatment with infliximab or other anti-TNF-a therapy (except CDP571);
- experimental immunomodulatory antibodies, cytokines or drugs (within the preceding 3 months);
- participation in any other clinical trial (within the preceding 1 month);
- intravenous corticosteroids or corticotrophin (within 1 month);
- corticosteroid treatment for other diseases (except topical hydrocortisone or inhaled corticosteroids for pulmonary disease) within the preceding 6 months; discontinued antimetabolite therapy within the preceding month.

Duration of Treatment:	16 weeks
Duration of Study:	4 June 1998 and 10 November 1999.
Randomized:	Yes
Placebo Controlled:	Yes
Blinding:	Yes
Allocation concealed:	Yes

Adverse Events

Variable	**No. of patients (%)**	
	Placebo (n = 32)	**CDP571 10 mg/kg (n = 39)**
Number of adverse events	112	177
Patients with adverse events	25 (78.1)	35 (89.7)
Patients with serious adverse events	3 (9.4)	4 (10.3)
Patients withdrawn due to adverse events	1 (3.1)	7 (17.9)
Deaths	0	0
Patients with severe adverse events	7 (21.9)	8 (20.5)
Patients with possibly, probably or definitely drug-related adverse events	17 (53.1%)	24 (61.5%)
Flu syndrome	5 (15.6)	2 (5.1)
Asthenia	5 (15.6)	0
Abdominal pain	4 (12.5)	5 (12.8)
Headache	4 (12.5)	5 (12.8)
Vasodilation	1 (3.1)	4 (10.3)
Dizziness	3 (9.4)	4 (10.3)
Antinuclear antibody	3 (9.4)	3 (7.7)
Diarrhoea	1 (3.1)	3 (7.7)
Nausea	0	3 (7.7)
Dry skin	0	3 (7.7)
Abscess	2 (6.3)	0
Infection	1 (3.1)	2 (5.1)
Pain	0	2 (5.1)

FEAGAN 2006

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: CDP571, a humanized monoclonal antibody to tumour necrosis factor-alpha, for steroid-dependent Crohn's disease: A randomized, double-blind, placebo-controlled trial. Feagan BG, Sandborn WJ, Lichtenstein G, et al. Aliment Pharmacol Ther. 2006;3: 617-628.

Treatment Studied: CDP571

Dose: CDP571 10mg/kg q8wk

Inclusion Criteria:

- at least 18 years;
- steroid-dependent Crohn's disease defined as: (i) the requirement for steroid treatment with prednisolone or prednisone (15–40 mg/day), or budesonide (9 mg/day) for at least 8 weeks (although the dose could have been temporarily reduced during an attempt at steroid withdrawal), with a stable dose for at least 2 weeks prior to study entry; (ii) an unsuccessful attempt to decrease or discontinue steroid treatment, owing to disease flare within 30 days of the attempt, on at least one occasion in the 8 weeks prior to study entry;
- all patients had a baseline score of 150 points on the Crohn's Disease Activity Index (CDAI);
- the diagnosis of Crohn's disease was made using radiological,
- endoscopical, or histological evidence.

Exclusion Criteria:

- infection of a fistula (abscess);
- ulcerative colitis;
- bowel perforation;
- evidence of a non-inflammatory obstruction (within 6 months);
- obstructive symptoms owing to significant mechanical obstruction (within 3 months);
- small bowel resection >100 cm and/or more than the right colon resected
- colostomy;
- ileostomy;
- infectious enteritis;
- other serious infection;
- clinically important chronic disease in the 3 months before study entry;
- history of blood dyscrasia (pancytopenia or aplastic anaemia);
- demyelinating disease;
- current or previous malignancy other than successfully treated carcinoma of the cervix or basal cell carcinoma (> 5 years prior to entry);
- current or previous bowel dysplasia (5 years before screening);
- clinically important allergies;
- multiple drug allergies;
- drug or alcohol abuse;
- significant abnormal haematology or biochemical values;
- concurrent tuberculosis,hepatitis, or HIV;
- pregnant and lactating women.

Duration of Treatment:	32 weeks
Duration of Study:	30 Nov 2000 and 13 May 2002.
Randomized:	Yes
Placebo Controlled:	Yes
Blinding:	Yes
Allocation concealment:	Yes

Adverse Events

Variable	**No. of patients (%)** **Placebo (n = 88)**	**CDP571 (n = 181)**
Patients with adverse events	62 (70.5)	128 (70.7)
Patients with serious adverse events	6 (6.8)	22 (12.2)
Patients with severe adverse events	9 (10.2)	32 (17.7)
Patients with possibly, probably, or definitely drug-related AEs	37 (42.0)	76 (42)
Patients with AEs leading to withdrawal	9 (10.2)	23 (12.7)
Deaths	0 (0)	1 (0.6)
AEs possibly or probably related to treatment		
Crohn's disease aggravated	12 (13.6)	34 (18.8)
Headache	11 (12.5)	30 (16.6)
Nausea	4 (4.5)	16 (8.8)
Arthralgia	3 (3.4)	16 (8.8)
Abdominal pain	3 (3.4)	14 (7.7)
Dermatitis	6 (6.8)	12 (6.6)
Sore throat	2 (2.3)	11 (6.1)
Pyrexia	3 (3.4)	9 (5.0)
Viral infection	6 (6.8)	8 (4.4)
Upper respiratory tract infection	6 (6.8)	7 (3.9)
Nasopharyngitis	6 (6.8)	6 (3.3)
Back pain	6 (6.8)	6 (3.3)
Urinary tract infection	7 (8.0)	5 (2.8)
Patients with AE occurring within 2h - Any	13 (14.8)	39 (22.8)
Hypersensitivity	0	7 (3.9)
Urinary tract infection	2 (2.3)	4 (2.2)
Headache	2 (2.3)	2 (1.1)
Chest tightness	0	2 (1.1)
Flushing	0	2 (1.1)
Hypertension	0	2 (1.1)
Nausea	0	2 (1.1)
Taste disturbance	0	2 (1.1)
Urticaria	0	2 (1.1)
Any infection	32 (36.4)	57 (31.5)
Urinary tract infection	7 (8.0)	5 (2.8)
Viral infection	6 (6.8)	8 (4.4)
Upper respiratory tract infection	6 (6.8)	7 (3.9)
Nasopharyngitis	6 (6.8)	6 (3.3)
Sinusitis	0	7 (3.9)
Influenza	4 (4.5)	1 (0.6)
Abdominal abscesses	0	2 (1.2)
Skin/subcutaneous tissue abscess	0	1 (0.6)
Scrotal infection	0	1 (0.6)
Escherichia coli sepsis	0	1 (0.6)

A3. Certolizumab

Winter 2004

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Intravenous CDP870, a PEGylated Fab' fragment of a humanized antitumour necrosis factor antibody, in patients with moderate-to-severe Crohn's disease: an exploratory study. Winter TA, Wright J, Ghosh S, et al. Aliment Pharmacol Ther 2004;20:1337-46.

Treatment Studied: Certolizumab (CDP870)

Dose: CDP870 (1.25, 5, 10 or 20 mg/kg body weight diluted with normal saline to a fixed volume (100 mL)

Inclusion Criteria

- at least 18 years;
- clinical diagnosis of moderate-to-severe CD, confirmed by radiological, endoscopic or histological evidence;
- Crohn's Disease Activity Index (CDAI) score of 220–450 points;
- permitted to receive concomitant medication, provided the dose had been stable prior to the start of the study;
- for the following durations: 8 weeks for azathioprine, methotrexate and mercaptopurine (6-mercaptopurine);
- 4 weeks for long-term antibiotics, sulfasalazine (sulphasalazine), mesalazine, olsalazine, pentasa or similar analogues; 2 weeks for corticosteroids and topical anorectal treatments. Concomitant medications also had to be stable during the 12-week study period.

Exclusion Criteria

- fistula;
- abcess;
- ulcerative colitis;
- bowel perforation;
- obstruction or history of obstructive symptoms;
- extensive bowel resection (> 100 cm of small bowel and/or more than the right side of the colon resected);
- a functional colostomy or ileostomy;
- a positive stool result for enteric pathogens;
- previous treatment or participation in a clinical trial with anti-TNF therapy within 12 weeks of screening;
- previous history of serious infection or tuberculosis;
- clinically significant abnormal haematological or biochemistry values;
- any other medical conditions considered by the investigator to warrant exclusion.

Duration of Treatment:	12 weeks
Duration of Study:	September 2001 and April 2002
Randomized:	Yes
Placebo Controlled:	Yes
Blinding:	Yes
Allocation concealment:	Yes

Adverse Events

	Placebo (n=24)	CDP870 1.25 (mg/kg) (n=2)	CDP870 5(mg/kg) (n=26)	CDP870 10 (mg/kg) (n=17)	CDP870 20(mg/kg) (n=23)	CDP870 All doses (n=68)
Any AEs	15 (62.5)	1 (50.0)	17 (65.4)	11 (64.7)	14 (60.9)	43 (63.2)
Serious AEs	2 (8.3)	0 (0.0)	1 (3.8)	1 (5.9)	5 (21.7)	7 (10.3)
AEs leading to Withdrawals	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	1 (4.3)	2 (2.9)
AEs unrelated to treatment	6 (25.0)	1 (50.0)	7 (26.9)	6 (35.3)	12 (52.2)	26 (38.2)
Aggravated CD	1 (4.2)					3 (4.4)
Rash	1 (4.2)					0
Abdominal Pain	0					2 (2.9)
Intestinal Obs.	0					2 (2.9)
Drug Overdose	0					1 (1.5)
Urinary Tract Infection	0 (0)					7 (10.3)
Nasopharyngitis	1 (4.2)					4 (5.9)
Perianal Abscess	0					1 (1.5)

No TB, death, lupus. No infusion reactions.

Schreiber 2005

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: CDP870 Crohn's Disease Study Group. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. Schreiber S, Rutgeerts P, Fedorak R, et al. Gastroenterology. 2005;129:807-18.

Treatment Studied: Certolizumab

Dose: 100mg, 200mg & 400mg

Inclusion Criteria:

- at least 18 years old;
- clinical diagnosis of Crohn's disease;
- confirmed by radiologic, endoscopic, or histologic evidence;
- patients had moderate to severe disease with 220–450 points on the CDAI.

Exclusion Criteria:

- suspected or diagnosed abscess;
- a bowel perforation or evidence of noninflammatory obstruction during the prior 6 months;
- extensive bowel resection;
- colostomy or ileostomy;
- positive stool culture for enteric pathogens;
- tuberculosis;
- treatment for Crohn's disease with sodium cromoglycate, mycophenolate, or cyclosporin within 4 weeks;
- other anti-TNF therapy with a biologic agent within 12 weeks of screening;
- patients were also excluded from the study if they had been treated previously with any anti-TNF agent and either had experienced an infusion reaction that was suspected or confirmed to be associated with an immune response;
- primary nonresponder;
- participation in another clinical trial with certolizumab;
- involved in any other clinical drug trial within the 4 weeks before screening.

Duration of Treatment: 12 weeks
Duration of Study: February 15, 2001, and March 12, 2002
Randomized: Yes
Placebo Controlled: Yes
Blinding: full blinding was not possible because certolizumab and placebo did not have the same color or viscosity
Allocation concealment: ?No

Adverse Events

	Placebo (n= 73)	CTZ 100 mg (n= 74)	CTZ 200 mg (n = 72)	CTZ 400 mg (n= 73)
Nasopharyngitis	3 (4.1)	9 (12.2)	7 (9.7)	4 (5.5)
Influenza	3 (4.1)	4 (5.4)	3 (4.2)	1 (1.4)
Fungal infection	0	2 (2.7)	1 (1.4)	2 (2.7)
Sinusitis NOS	3 (4.1)	2 (2.7)	2 (2.8)	0
Gastroenteritis *E coli/Camp*	0	1 (1.4)	1 (1.4)	1 (1.4)
Bronchitis	2 (2.7)	2 (2.7)	1 (1.4)	0
UTI	5 (6.8)	1 (1.4)	1 (1.4)	0
Pharyngitis	0	0	0	2 (2.7)
Herpes zoster	0	0	1 (1.4)	1 (1.4)
Herpes simplex	1 (1.4)	1 (1.4)	0	1 (1.4)
URTI	1 (1.4)	1 (1.4)	0	1 (1.4)
Vaginosis	1 (1.4)	0	2 (2.8)	0
Oral candidiasis	1 (1.4)	0	1 (1.4)	0
Abscess	0	2 (2.7)	0	0
Tooth abscess	1 (1.4)	2 (2.7)	0	0
Injection Site RXN	2 (2.7)	5 (6.8)	4 (5.6)	2 (2.7)
Weeks 13–20				
Nasopharyngitis	4 (5.5)	4 (5.4)	3 (4.2)	3 (4.1)
Sinusitis	0	1 (1.4)	2 (2.8)	0
Bronchitis	0	1 (1.4)	1 (1.4)	0
Gastrointestinal infection NOS	1 (1.4)	0	0	1 (1.4)
Influenza	2 (2.7)	0	1 (1.4)	0
GI NOS	2 (2.7)	0	0	0
Weeks 0–12				
Any AE	51 (69.9)	57 (77.0)	55 (76.4)	48 (65.8)
Serious AE	6 (8.2)	7 (9.5)	10 (13.9)	6 (8.2)
AE leading to withdrawal	7 (9.6)	9 (12.2)	7 (9.7)	7 (9.6)
Relationship to study medication				
Unrelated	42 (57.5)	43 (58.1)	44 (61.1)	37 (50.7)
Possible	34 (46.6)	35 (47.3)	41 (56.9)	27 (37.0)
Probable	3 (4.1)	4 (5.4)	7 (9.7)	3 (4.1)
Definite	1 (1.4)	2 (2.7)	3 (4.2)	0 (0.0)
Weeks 13–20				
Any AE	37 (50.7)	28 (37.8)	31 (43.1)	26 (35.6)
Serious AE	11 (15.1)	1 (1.4)	3 (4.2)	4 (5.5)
AE leading to withdrawal	0	0	0	0
Relationship to study Medication				
Unrelated	34 (46.6)	24 (32.4)	25 (34.7)	21 (28.8)
Possible	7 (9.6)	5 (6.8)	9 (12.5)	9 (12.3)
Probable	0	0	0	0
Definite	0	0	0	0

Other Side Effects (Text)

	Placebo	CTZ
Headache	16.4%	13.2%
Aggravation CD	13.7%	11.9%
Nausea	5.5%	11.4%
Nasopharyngitis	4.1%	9.1%
Dizziness	4.1%	6.4%
Arthalgia	2.7%	5.9%
Abd Pain	5.5%	5.9%
Pharyngolaryngeal Pain	5.5%	5.0%
Pyrexia	4.1%	5.0%
Infection	17 (23.3%)	58 (26.5%)

Schreiber 2007

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Maintenance Therapy with Certolizumab Pegol for Crohn's Disease (Precise 2) Schreiber S, Khaliq-Kareemi M, Lawrence IC, et al. N Engl J Med 2007;357:239-50.

Treatment Studied: Certolizumab pegol or placebo subcutaneously.

Dose:

- 400 mg at weeks 0, 2, and 4 and then every 4 weeks;
- at week 6 patients were stratified according to their baseline C-reactive protein level and were randomly assigned to receive 400 mg of certolizumab pegol or placebo every 4 weeks through week 24, with follow-up through week 26.

Inclusion Criteria:

- active Crohn's disease for at least 3 months;
- CDAI: 220 to 450;
- patients could receive concomitant therapy with stable doses of 5-aminosalicylates, prednisolone or its equivalent (30 mg per day or less), azathioprine, 6-mercaptopurine, methotrexate, or antibiotics.

Exclusion Criteria:

- short-bowel syndrome;
- ostomy;
- obstructive symptoms with strictures;
- abscess;
- history of TB (positive results on chest radiography or the purified-protein-derivative tuberculin skin test);
- demyelinating disease;
- cancer;
- any anti-TNF agent within the previous 3 months;
- severe hypersensitivity reaction to another TNF antagonist;
- a lack of response to the first dose of another TNF antagonist.

Duration of Treatment: 24 weeks
Duration of Study: February 2004 until May 2005
Randomized: Yes
Placebo Controlled: Yes
Blinding: Yes
Allocation concealment: Yes

Adverse Events

	CTZ (Wk 0–6) (n = 668)	CTZ Main (Wk 6–26) (n = 212)	Placebo (n = 216)
Any	392 (59)	143 (67)	140 (65)
Headache	84 (13)	14 (7)	15 (7)
Nasopharyngitis	25 (4)	8 (4)	12 (6)
Cough	5 (<1)	2 (<1)	12 (6)
CD (exacerbation)	36 (5)	25 (12)	9 (4)
Pain (injection site)	8 (1)	11 (5)	1 (<1)
Related to study drug (as determined by PI)	161 (24)	58 (27)	49 (23)
Any local rx to injection	13 (2)	31 (15)	6 (3)
Serious adverse events	47 (7)	14 (7)	12 (6)
Infection or infestation	12 (2)	2 (<1)	6 (3)
Abdominal abscess	4 (<1)	1 (<1)	0
Perianal abscess	4 (<1)	0	1 (<1)
Perineal abscess	0	0	2 (<1)
Bacteremia	0	1 (<1)	0
Otitis media	0	1 (<1)	0
Pneumonia	0	0	1 (<1)
Pyelonephritis	0	0	1 (<1)
Tuberculosis	0	0	1 (<1)
Viral gastroenteritis	1 (<1)	0	0
Infection	1 (<1)	0	0
Lobar pneumonia	1 (<1)	0	0
Pelvic inflammatory ds.	1 (<1)	0	0
Any GI disorder	29 (4)	9 (4)	4 (2)
Obstructive events	7 (1)	1 (<1)	0
Abdominal pain	1 (<1)	1 (<1)	2 (<1)
Exacerbation of CD	19 (3)	5 (2)	1 (<1)
Diarrhea	1 (<1)	0	1 (<1)
Other	1 (<1)	2 (2)	0
Blood and lymphatic -system disorder	1 (<1)	0	1 (<1)
Iron-deficiency anemia	0	0	1 (<1)
Anemia	1 (<1)	0	0
Immune-system disorders	1 (<1)	1 (<1)	0
Benign, malignant, or unspecified neoplasm (including cysts and polyps)	1 (<1)	0	0
Leading to withdrawal	51 (8)	28 (13)	18 (8)
Leading to death	1 (<1)	0	0

* 1 Death in CTZ group was an accidental fentanyl overdose

Sandborn 2007C

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Certolizumab Pegol for the Treatment of Crohn's Disease (Precise 1) Sandborn WJ, Feagan BG, Stoinov S, et al. N Engl J Med 2007;357:228-238.

Treatment Studied: Certolizumab pegol or placebo subcutaneously

Dose: 400 mg at weeks 0, 2, and 4 and then every 4 weeks.

Inclusion Criteria:

- active Crohn's disease for at least 3 months;
- CDAI: 220 to 450;
- Patients could receive concomitant therapy with stable doses of 5-aminosalicylates, prednisolone or its equivalent (30 mg per day or less), azathioprine, 6-mercaptopurine, methotrexate, or antibiotics.

Exclusion Criteria:

- short-bowel syndrome;
- ostomy;
- obstructive symptoms with strictures;
- abscess;
- hx TB (positive results on chest radiography or the purified- protein-derivative tuberculin skin test);
- demyelinating disease;
- cancer were not eligible;
- any anti-TNF agent within the previous 3 months;
- severe hypersensitivity reaction to another TNF antagonist;
- a lack of response to the first dose of another TNF antagonist.

Duration of Treatment: 26-week
Duration of Study: December 2003 and May 2005
Randomized: Yes
Placebo Controlled: Yes
Blinding: Yes
Allocation concealment: Blinded

Adverse Events

	Placebo Group (N = 329)	Certolizumab Group (N = 331)
Any adverse event	260 (79)	269 (81)
Headache	54 (16)	60 (18)
Nasopharyngitis	27 (8)	44 (13)
Abdominal pain	37 (11)	37 (11)
Exacerbation of CD	37 (11)	33 (10)
Nausea	27 (8)	26 (8)
Urinary tract infection	17 (5)	25 (8)
Arthralgia	16 (5)	22 (7)
Pyrexia	22 (7)	21 (6)
Vomiting	11 (3)	18 (5)
Back pain	17 (5)	9 (3)
Injection-site pain	23 (7)	4 (1)
Event related to study drug	120 (36)	108 (33)
Any injection-site reaction	47 (14)	9 (3)
Serious adverse events	23 (7)	34 (10)
Infection	3 (<1)	7 (2)
Abscess		
Perianal	2 (<1)	4 (1)
Muscle	0	1 (<1)
Limb	0	1 (<1)
Any	1 (<1)	0
Gastroenteritis	0	1 (<1)
Urinary tract infection	0	1 (<1)
Neoplasm		
and polyps)	2 (<1)	2 (<1)
Metastatic lung cancer	0	1 (<1)
Rectal cancer	0	1 (<1)
Cervical carcinoma	0	1 (<1)
Hodgkin's disease	1 (<1)	0
Adverse events leading to withdrawal from study	39 (12)	36 (11)
Adverse events leading to death*	0	1 (<1)

* 1 Death in CTZ group was a 22 yo Myocardial Infarction/ Met Lung Cancer

A4. Etanercept

Sandborn 2001B

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Etanercept for Active Crohn's Disease: A Randomized, Double-Blind, Placebo-Controlled Trial. Sandborn WJ, Hanauer SB, Katz S, et al. Gastroenterology 2001; 121:1088–1094.

Treatment Studied: Etanercept

Dose: 25 mg or placebo twice weekly.

Inclusion Criteria:

- at least 12 years of age;
- moderately to severely active Crohn's disease;
- CDAI: 220-450;
- CD confirmed by radiologic, endoscopic, or histologic criteria.

Exclusion Criteria:

- ileostomy;
- colostomy;
- immediate need for surgery for active gastrointestinal bleeding, peritonitis, intestinal obstruction, or intra-abdominal or pancreatic abscess requiring surgical drainage;
- those with local or systemic infection (including septic lesions in the perianal region those with symptoms of bowel obstruction within the preceding 6 months confirmed with objective radiographic or endoscopic evidence of a stricture with resulting obstruction (dilation of the bowel proximal to the stricture on barium or an inability to traverse the stricture at endoscopy), which had not been surgically corrected;
- a planned inpatient hospitalization during the study;
- other clinically important active diseases (such as renal or hepatic disease);
- an active fistula to the vagina or bladder;
- a history of cancer within 5 years, dysplasia of the colon within 5 years, or clinically significant hematological or biochemical values were also ineligible;
- pregnant or breast-feeding women;
- history of drug or alcohol abuse within 6 months.

Duration of Treatment: 8 weeks
Duration of Study: September 1999 and May 2000
Randomized: Yes
Placebo Controlled: Yes
Blinding: Yes
Allocation concealment: Yes

Adverse Events

Variable	Placebo (n = 20)	Etanercept (n = 23)
No. of adverse events	19	34
No. of pts with adverse events	10 (50%)	17 (74%)
No. of pts with serious adverse events	2 (10%)	1 (4%)
No. of pts with severe adverse events	3 (15%)	1 (4%)
Most frequent AE (no. of events)		
Headache	1 (5%)	3 (13%)
New injection site reactions	1 (5%)	3 (13%)
Asthenia	0 (0%)	2 (9%)
Abdominal pain	2 (10%)	0 (0%)
Mild anemia	0 (0%)	2 (9%)
Skin disorders	0 (0%)	2 (9%)

A5. Infliximab

Targan 1997

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: A Short term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for crohn's disease. Targan SR, Hanauer SB, van Deventer SJ, et al. N Engl J Med. 1997;337(15):1029-35.

Treatment Studied: a single dose of either placebo or 5 mg of cA2 per kilogram of body weight, 10 mg of cA2 per kilogram, or 20 mg of cA2 per kilogram IV.

Inclusion Criteria:

- Crohn's disease for six months;
- CDAI between 220 – 400;
- concomitant medications allowed: mesalamine for eight or more weeks, with stable dose. A maximum of 40 mg of corticosteroids per day for eight or more weeks, with the dose remaining stable during the two weeks before screening; and mercaptopurine or azathioprine for six or more months, with the dose remaining stable during the eight weeks before screening.

Exclusion Criteria:

- if they had received treatment with cyclosporine, methotrexate, or experimental agents within three months before screening;
- symptomatic stenosis or ileal strictures;
- proctocolectomy or total colectomy;
- stoma;
- a history of allergy to murine proteins;
- prior treatment with murine, chimeric, or humanized monoclonal antibodies; or treatment with parenteral corticosteroids or corticotropin within four weeks before screening.

Duration of Treatment: 2 hours
Duration of Study: June 21, 1995 - March 12, 1996
Randomized: Yes
Placebo Controlled: Yes
Blinding: Yes
Allocation concealment: Yes

Adverse Events

	Placebo (n=25)	One Dose of cA2 (n=102)	Two doses of cA2 (n=29)
Adverse effect — no. of patients (%)			
Any adverse effect	15 (60)	76 (75)	23 (79)
Headache	5 (20)	19 (19)	3 (10)
Nausea	2 (8)	11 (11)	5 (17)
Upper respiratory tract infection	3 (12)	8 (8)	4 (14)
Fatigue	1 (4)	6 (6)	3 (10)
Myalgia	1 (4)	4 (4)	3 (10)
Rhinitis	1 (4)	3 (3)	3 (10)
Pain	0	4 (4)	3 (10)
Pruritus	1 (4)	1 (1)	4 (14)
Chest pain	1 (4)	2 (2)	3 (10)
Vomiting	0	2 (2)	3 (10)
Dyspnea	0	1 (1)	3 (10)

Present 1999

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title:	Infliximab for the treatment of fistulas in patient's with Crohn's disease. Present DH, Rutgeerts P, Targan S, et al. N Engl J Med. 1999;340(18):1398-405.
Treatment Studied:	Infliximab
Dose:	5 mg/kg of infliximab or 10 mg/kg

Inclusion Criteria

- 18 to 65 years of age;
- single or multiple draining abdominal or perianal fistulas of at least three months duration;
- Crohn's confirmed by radiography, endoscopy, or pathological examination;
- patients could receive concomitant therapy: acceptable regimens were aminosalicylates at a dosage that had been stable for more than four weeks before screening; oral corticosteroids at a dosage of 40 mg or less per day that had been stable for more than three weeks; methotrexate given for at least three months at a dosage that had been stable for more than four weeks; azathioprine or mercaptopurine given for at least six months at a dosage that had been stable for more than eight weeks; and antibiotics at a dosage that had been stable for more than four weeks;
- if patients were not currently receiving treatment with any of these medications, they had to have discontinued therapy at least four weeks before enrollment.

Exclusion Criteria

- cyclosporine
- treatment with investigational agents
- treatment with an antiTNF within three months before enrollment;
- complications of Crohn's disease, such as current strictures or abscesses;
- presence of a stoma created less than six months before enrollment;
- a history of allergy to murine proteins;
- previous treatment with infliximab.

Duration of Treatment:	Doses given 0, 2, 6 weeks
Duration of Study:	May 30 through October 1, 1996
Randomized:	Yes
Placebo Controlled:	Yes
Blinding:	Yes
Allocation concealment:	Yes

Adverse Events

Event	Placebo (n=31)	Infliximab 5 mg/kg (n=31)	Infliximab 10 mg/kg (n=32)	Infliximab 5 or 10 mg/kg (n=63)
Headache	7 (23)	5 (16)	6 (19)	11 (17)
Abscess	1 (3)	2 (6)	5 (16)	7 (11)
URTI	2 (6)	1 (3)	5 (16)	6 (10)
Fatigue	2 (6)	2 (6)	4 (12)	6 (10)
SAE	0	1 (3)	4 (12)	5 (8)
Discontinued (SE)	0	0	1 (3)	0
Pneumonia	0	0	1 (3)	0
Obstruction	0	0	1 (3)	0
Arm Abscess	0	0	1 (3)	0
Anal Abscess	0	0	1 (3)	0
Urethral Obs	0	1 (3)	0	0
Infusion Reaction (Within 2 hrs)	0	0	0	4 (6)
DSDNA	0	0	0	8 (13)

Rutgeerts 1999

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (Infliximab) to maintain remission in Crohn's disease. Rutgeerts P, D'Haens G, Targan S, et al. Gastroenterology. 1999;117(4):761-9.

Treatment Studied: Infliximab

Dose: 10 mg/kg infliximab given every 8 weeks

Inclusion Criteria:

- Crohn's disease for six months;
- CDAI between 220 – 400;
- concomitant medications allowed: mesalamine for eight or more weeks, with stable dose. A maximum of 40 mg of corticosteroids per day for eight or more weeks, with the dose remaining stable during the two weeks before screening; and mercaptopurine or azathioprine for six or more months, with the dose remaining stable during the eight weeks before screening;
- in addition, patients who had not responded to aminosalicylates, 6-mercaptopurine, azathioprine, methotrexate, or cyclosporine were eligible for the study.

Exclusion Criteria:

- symptomatic stenosis or ileal strictures;
- proctocolectomy or total colectomy;
- stoma;
- a history of allergy to murine proteins;
- prior treatment with murine, chimeric, or humanized monoclonal antibodies; or treatment with parenteral corticosteroids or corticotropin within four weeks before screening.

Duration of Treatment:	36 weeks
Duration of Study:	?
Randomized:	Yes
Placebo Controlled:	Yes
Blinding:	Yes
Allocation concealment	?

Adverse Events

	Placebo Retreatment (n=36)	**Infliximab (10 mg/kg) Retreatment (n= 37)**
Adverse events (# patients)	35 (97.2)	35 (94.6)
Withdrawal because of AE	1 (2.8)	6 (16.7)
Adverse events, n (%)		
URTI	6 (16.7)	9 (24.3)
Headache	4 (11.1)	6 (16.2)
Abdominal pain	5 (13.9)	5 (13.5)
Nausea	3 (8.3)	7 (18.9)
Fever	5 (13.9)	4 (10.8)
Bronchitis	3 (8.3)	6 (16.2)
Pharyngitis	1 (2.8)	7 (18.9)
Lymphoma	1 (2.8)	0
Anti ds DNA	2 (1 Lupus)	0

Hanauer 2002

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Lancet. 2002;359:1541-9.

Treatment Studied: Infliximab

Dose: 5 mg/kg IV infusion of infliximab at week 0.

After assessment of response at week 2, patients were randomly assigned repeat infusions of placebo at weeks 2 and 6 and then every 8 weeks thereafter until week 46 (group I), repeat infusions of 5 mg/kg infliximab at the same timepoints (group II), or 5 mg/kg infliximab at weeks 2 and 6 followed by 10 mg/kg (group III).

Inclusion Criteria:

- men and women;
- 18–75 years of age;
- Crohn's disease for at least 3 months;
- CDAI score of 220–400 points;
- concurrent therapies for Crohn's disease, including 5-aminosalicylates or antibiotics (constant dose for 4 weeks before the screening visit); corticosteroids (prednisone, prednisolone, or budesonide) at the equivalent of 40 mg per day of prednisone or less (stable dose for 3 weeks); azathioprine and 6-mercaptopurine (stable dose for 8 weeks); or methotrexate (stable dose for 6 weeks).

Exclusion Criteria:

- previous treatment with infliximab or any other agent targeted at TNF.

Duration of Treatment: 46 weeks
Duration of Study: Feb 26, 1999 - March 15, 2001.
Randomized: Yes
Placebo Controlled: Yes
Blinding: Yes
Allocation concealment: Yes

Adverse Events

	Group I (n = 188)	Group II (n = 193)	Group III (n = 192)	Total (n = 573)
Adverse events leading to discontinuation of study agent	5 (3)	29 (15)	16 (8)	50 (9)
Serious adverse events				
All events	55 (29)	54 (28)	43 (22)	152 (27)
Reasonably related	13 (7)	15 (8)	11 (6)	39 (7)
Infections				
Infection requiring antimicrobial rx	70 (37)	64 (33)	52 (27)	186 (32)
Serious infection	8 (4)	8 (4)	6 (3)	22 (4)
Intestinal stenosis	6 (3)	3 (2)	5 (3)	14 (2)
Infusion reactions	17 (9)	44 (23)	36 (19)	97 (17)
Serum-sickness-like reactions	3 (2)	5 (3)	6 (3)	14 (2)
TB		1		1
Death (sepsis from obstruction)		1 (<1)		1
Malignancy	2	3	1	6
ANA & Anti DNA	19 (11)	123 (34)	363 (56)	

Probert 2003

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: A randomised controlled trial. Probert CS, Hearing SD, Schreiber S, et al. Gut. 2003;52(7):998-1002.

Treatment Studied: Infliximab

Dose: 5 mg/kg body weight or placebo at week 0 and a second identical infusion at week 2

Inclusion Criteria:

- age 18 years or older;
- established diagnosis of UC;
- failed to respond to conventional treatment with glucocorticoids;
- not in need of urgent colectomy;
- patients had to have received conventional treatment with at least 30 mg prednisolone (or equivalent) for at least one week for relapse, but still had clinical activity that qualified for inclusion in the study;
- ulcerative colitis symptom score (UCSS) of 6 or more;
- a sigmoidoscopy score of at least 2 on the Baron scale;
- biopsy taken showing histological changes of acute ulcerative colitis.

Exclusion Criteria:

- fulminant disease likely to require colectomy;
- pregnant or planning a pregnancy during or within six months of the trial;
- cyclosporine;
- any investigational drug within three months of enrolment;
- those who had commenced treatment (within the last three months) with 6-mercaptopurine or azathioprine were also excluded;
- stable dose of 6-mercaptopurine or azathioprine for more than three months were not excluded;
- any patient with a gastrointestinal infection was excluded;
- known serious infections (such as hepatitis, pneumonia, pyelonephritis, or an opportunistic infection);
- in the previous three months;
- past or current colorectal dysplasia;
- malignancy;
- Crohn's disease;
- prior intestinal resection;
- appendicectomy;
- presence of a stoma were also exclusion criteria.

Duration of Treatment: 6 weeks
Randomized: Yes
Placebo Controlled: Yes
Blinding: Yes

Adverse Events

Placebo group Two serious adverse events
One patient suffered septic complications.
Disease exacerbation and spontaneous perforation

All other serious adverse events were rated as mild and were not significantly different in frequency between infliximab and placebo treated patients.

No significant infusion reactions were seen.

Sands 2004

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Infliximab Maintenance Therapy for Fistulizing Crohn's Disease. Sands BE, Anderson FH, Bernstein CN et al. N Engl J Med. 2004;350:876-85.

Treatment Studied: Infliximab

Dose: 5mg/kg (0, 2, 6 then q8wk)

Inclusion Criteria:

- men and women;
- 18 years of age or older;
- Crohn's disease who had had single or multiple draining fistulas;
- perianal fistulas and enterocutaneous fistulas for at least three months;
- women with rectovagina fistulas were included if they had at least one other enterocutaneous draining fistula;
- setons were permitted at screening but were required to be removed by week 2. Concurrent therapies for Crohn's disease, including stable doses of 5-aminosalicylates, oral corticosteroids, azathioprine, mercaptopurine, mycophenolate mofetil, methotrexate,and antibiotics, were permitted.

Exclusion Criteria:

- stricture;
- abscess;
- previously been treated with infliximab.

Duration of Treatment: 54 weeks
Duration of Study: January 21, 2000 - October 17, 2001
Randomized: Yes
Placebo Controlled: Yes
Blinding: Yes
Allocation concealment: Yes

Adverse Events

Variable	Placebo (N=144)	Infliximab (N=138)
Adverse events leading to discontinuation of study agent	12 (8)	5 (4)
Serious adverse events		
All events	33 (23)	19 (14)
Reasonably related events	9 (6)	3 (2)
Infections		
Infections requiring antimicrobial treatment	39 (27)	47 (34)
Serious infections	9 (6)	4 (3)
New fistula-related abscesses	25 (17)	17 (12)
Infusion reactions	24 (17)	22 (16)
During induction	11 (8)	9 (7)
During maintenance	4 (3)	13 (9)
During treatment after crossover	14 (23)	3 (9)
Death	0	0
Cancer	0	0

Jarnerot 2005

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Infliximab as Rescue Therapy in Severe to Moderately Severe Ulcerative Colitis: A Randomized, Placebo-Controlled Study. Jarnerot G, Hertervig E, Friis-Liby I, et al. Gastroenterology 2005;128:1805–1811.

Treatment Studied: Infliximab

Dose: 5 mg/kg

Inclusion Criteria:

- age 18–75 years a diagnosis;
- certain or probable UC;
- exclusion of an infectious cause;
- a severe or moderately severe attack of UC according to the Seo index;
- fulminant colitis index >= 8.0 on day 3 or a Seo index on day 5, 6, or 7 that was compatible;
- with a severe or moderately severe attack of UC that was not responding to corticosteroid treatment.

Exclusion Criteria:

- pregnancy or planned pregnancy in the next 12 months;
- active breast-feeding;
- known or probable Crohn's colitis, infectious colitis;
- ongoing infection such as an abscess;
- central line infection;
- febrile urinary tract infection;
- active tuberculosis or exposure to tuberculosis;
- multiple sclerosis;
- malignancy;
- heart failure or treated heart failure;
- earlier treatment with infliximab or another antibody;
- another disease according to the investigator's judgment;
- psychiatric disease;
- alcoholism or anything else whereby the patient was judged incapable of completing the trial

Duration of Treatment: 1 dose given
Duration of Study: July 2001 and the last in January 2004
Randomized: Yes
Placebo Controlled: Yes
Blinding: Yes

Adverse Events

Infliximab

Central line sepsis (n = 1)
Arthralgia, knee joints (n = 2)
Upper respiratory infection (n = 2)
Pneumothorax when adopting central venous line (n = 1)
Discrete exanthema (?antibiotic related) (n = 1)
Pruritus during infusion (n = 1)
Perspiration (n = 1)
Long-lasting bleeding from rectal stump (n = 1)
Ileus 48 days after infusion (n = 1)
Nausea, vomiting, abnormal liver tests, pneumonia (n = 1)
Reflux, oral candidiasis (n = 1)

Placebo

Exanthema (?antibiotic related) (n = 2)
Epigastralgia, reflux, abnormal liver tests 50 days after infusion, probably azathioprine (n = 1)
Headache, 38.5°C 14 days after infusion (n = 1)
Ptosis, right eyelid, 32 days after infusion (n = 1)
Dermal sensations during infusion (n = 1)
Arthralgia 90 days after infusion (n = 1)
Cardiac pacemaker 111 days after infusion (n = 1)
Reoperation due to septic complication—referable to rectal stump (n = 3)
High fever, CRP >200 5 days after surgery, rectum flushed, normalization (n = 1)
Urinary tract infection, fever, antibiotics (n = 1)

Rutgeerts 2005

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Infliximab for Induction and Maintenance Therapy for Ulcerative Colitis. Rutgeerts P, Sandborn WJ, Feagan BG, et al. N Engl J Med. 2005;353:2462-76.

Treatment Studied: Infliximab

Dose: 5mg/kg

Inclusion Criteria:

- ulcerative colitis;
- MAYO score: 6 to 12 points;
- moderate-to-severe active disease on sigmoidoscopy (Mayo endoscopic subscore of at least 2)
- concurrent treatment with corticosteroids alone or in combination with azathioprine or mercaptopurine in ACT 1;
- concurrent treatment with corticosteroids alone or in combination with azathioprine or mercaptopurine and medications containing 5-ASA in ACT 2;
- concurrent therapy was not required at enrollment for patients in ACT 1 and ACT 2 who had had no response to corticosteroids within the preceding 18 months or who could not tolerate corticosteroids, patients in either study who had had no response to azathioprine or mercaptopurine within the preceding 5 years or who could not tolerate these drugs;
- in ACT 2 patients who had had no response to medications containing 5-aminosalicylates within the preceding 18 months or who could not tolerate such drugs;
- rectally administered corticosteroids or medications containing 5-aminosalicylates were not permitted within two weeks before screening.

Exclusion Criteria:

- positive tuberculin skin tests;
- diagnosis of indeterminate colitis, Crohn's disease, or clinical findings suggestive of Crohn's disease (i.e., fistula or granulomas on biopsy);
- patients previously exposed to infliximab or any other anti-TNF agent.

Duration of Treatment: ACT 1: 54 week
ACT 2: 30 week

Duration of Study: March 2002 and March 2005
Randomized: Yes
Placebo Controlled: Yes
Blinding: Yes
Allocation concealment: Yes

Adverse Events

Variable	ACT 1 (through Week 54)			ACT 2 (through Week 30)		
	Placebo (N=121)	IFX 5 mg (N=121)	IFX10 mg (N=122)	PLB (N=123)	IFX 5 mg (N=121)	IFX 10 mg (N=120)
Any adverse event	103 (85.1)	106 (87.6)	111 (91.0)	90 (73.2)	99 (81.8)	96 (80.0)
Adverse events ≥10%						
Worsening UC	40 (33.1)	23 (19.0)	26 (21.3)	20 (16.3)	11 (9.1)	12 (10.0)
Abd pain	16 (13.2)	11 (9.1)	21 (17.2)	14 (11.4)	10 (8.3)	13 (10.8)
Nausea	14 (11.6)	14 (11.6)	17 (13.9)	9 (7.3)	6 (5.0)	10 (8.3)
URTI	28 (23.1)	20 (16.5)	29 (23.8)	14 (11.4)	16 (13.2)	14 (11.7)
Pharyngitis	10 (8.3)	12 (9.9)	14 (11.5)	3 (2.4)	7 (5.8)	9 (7.5)
Sinusitis	4 (3.3)	8 (6.6)	16 (13.1)	7 (5.7)	11 (9.1)	7 (5.8)
Pain	19 (15.7)	14 (11.6)	14 (11.5)	11 (8.9)	9 (7.4)	12 (10.0)
Rash	16 (13.2)	14 (11.6)	7 (5.7)	3 (2.4)	2 (1.7)	5 (4.2)
Arthralgia	18 (14.9)	21 (17.4)	21 (17.2)	6 (4.9)	16 (13.2)	10 (8.3)
Headache	27 (22.3)	22 (18.2)	18 (14.8)	18 (14.6)	19 (15.7)	26 (21.7)
Fever	10 (8.3)	14 (11.6)	12 (9.8)	12 (9.8)	13 (10.7)	9 (7.5)
Anemia	12 (9.9)	4 (3.3)	9 (7.4)	13 (10.6)	6 (5.0)	2 (1.7)
Fatigue	11 (9.1)	14 (11.6)	14 (11.5)	6 (4.9)	6 (5.0)	14 (11.7)
Adverse events of particular interest						
Fungal dermatitis	8 (6.6)	1 (0.8)	3 (2.5)	0	0	1 (0.8)
Pneumonia	0	2 (1.7)	4 (3.3)	0	0	2 (1.7)
Varicella–zoster infection	1 (0.8)	1 (0.8)	0	0	1 (0.8)	0
Herpes zoster	0	1 (0.8)	0	1 (0.8)	2 (1.7)	1 (0.8)
Adverse events leading to discontinuation	11 (9.1)	10 (8.3)	11 (9.0)	12 (9.8)	2 (1.7)	5 (4.2)
Serious adverse events	31 (25.6)	26 (21.5)	29 (23.8)	24 (19.5)	13 (10.7)	11 (9.2)
Infections	47 (38.8)	53 (43.8)	60 (49.2)	29 (23.6)	33 (27.3)	34 (28.3)
Infections requiring antimicrobial treatment	25 (20.7)	39 (32.2)	43 (35.2)	15 (12.2)	18 (14.9)	17 (14.2)
Serious infections	5 (4.1)	3 (2.5)	8 (6.6)	1 (0.8)	2 (1.7)	3 (2.5)
Bacterial infection	1 (0.8)	0	0	0	0	0
URTI	1 (0.8)	0	0	0	0	0
Pneumonia	0	0	3 (2.5)	0	0	0
Tuberculosis	0	0	1 (0.8)	0	0	0
Abscess	1 (0.8)	0	2 (1.6)	1 (0.8)	0	1 (0.8)
Pharyngitis	1 (0.8)	0	1 (0.8)	0	0	0
Gastroenteritis	0	1 (0.8)	1 (0.8)	0	1 (0.8)	0
Earache	0	0	0	0	1 (0.8)	0
Fever	0	0	1 (0.8)	0	1 (0.8)	0
Vaginitis	0	0	0	0	0	1 (0.8)
Appendicitis	0	1 (0.8)	0	0	0	0
Colitis	0	0	1 (0.8)	0	0	0
Surgical-wound infection	1 (0.8)	0	1 (0.8)	0	0	1 (0.8)
Pancreatitis	0	1 (0.8)	0	0	0	0
Pleurisy	0	0	1 (0.8)	0	0	0
Sinusitis	1 (0.8)	0	0	0	0	0
Cancer	0	2 (1-prostate) (1-colon)	1 (Basal)	1 (Basal)	1 (Rectal)	0
Optic Neuritis	0	1	0	0	0	0
Acute infusion reaction (any adverse event occurring ≤2 hr after start of infusion)	13 (10.7)	12 (9.9)	15 (12.3)	10 (8.1)	14 (11.6)	14 (11.7)
Possible delayed hypersensitivity reactions — no. of patients (%)	2 (1.7)	2 (1.7)	0	0	0	1 (0.8)

Lemann 2006

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: A randomized placebo-controlled trial.(GETAID) Lémann M, Mary JY, Duclos B, et al. Gastroenterology. 2006;130:1054-61.

Treatment Studied: Infliximab

Dose: Infliximab 5 mg/kg or placebo at weeks 0, 2, and 6.

Inclusion Criteria:

- at least 18 years old;
- luminal steroid-dependent CD;
- diagnosis based on established clinical, endoscopic, radiologic, and histologic criteria;
- Steroid dependency: (1) prednisone had to be given for at least 6 months at a dosage 10 mg/day or more, with no interruption for more than 2 months within the past 6 months; (2) at least 2 clinical luminal relapses when tapering of steroids had been attempted, leading to an increase in the dose to more than 10 mg/day; and (3) the last attempt for steroid tapering had to be within the past 6 months. At baseline, patients had to be treated with prednisone 10 mg/day or more.
- AZA/6-MP status at baseline (1) those in the naive stratum who did not receive AZA/6-MP in the past 2 years or (2) those in the failure stratum who still had clinically active disease (Crohn's Disease Activity Index [CDAI] >= 150) despite receiving AZA/6-MP for more than 6 months at a stable and appropriate dose (2–3 mg/kg/day for AZA and 1–1.5 mg/kg/day for 6-MP).
- Adequate birth control.

Exclusion Criteria

- contraindication to AZA/6-MP or to infliximab;
- treatment with an immunosuppressive drug other than AZA/6-MP in the past 6 months;
- previous use of infliximab or other anti–tumor necrosis factor;
- previous use of thalidomide;
- concomitant treatment with aminosalicylates, budesonide, topical steroids, or artificial nutrition;
- symptomatic stricture;
- intra-abdominal abscess or infection;
- severe sepsis within the past 3 months;
- tuberculosis;
- history of Hepatitis B or C;
- human immunodeficiency virus infection;
- liver failure;
- pregnancy;
- breast-feeding;
- participation in pharmaceutical research within the past 3 months.

Duration of Treatment:	52 weeks
Duration of Study:	June 2000 to May 2002
Randomized:	Yes
Placebo Controlled:	Yes
Blinding:	Yes
Allocation concealment:	Yes

Adverse Events

	Infliximab (n=57)	**Placebo (n=56)**
At Least One Event	29 (51%)	28 (50%)
Total # Events	79	66
Mild	39	27
Moderate	36	30
Severe	4	9
Pts with at least 1 serious AE	3	3
Infections	18	16
Upper respiratory tract	8	11
Dental	2	1
Otitis	0	1
Cutaneous	3	1
Herpes virus	2	0
Urinary tract	1	1
Intestinal	1	0
Perianal abscess	0	1
Pelvic abscess	1	0
Arthralgia, myalgia	8	13
Abdominal pain, diarrhea	9	5
Nausea or vomiting	10	3
Headache	6	4
Cutaneous rash, pruritus	5	7
Fatigue	5	2
Reaction to infusion	2	0
Fever	1	4
Increase of liver enzymes	1	0
Pancreatitis	0	2
Miscellaneous	14	10

A6. Onercept

Rutgeerts 2006.

Data Extraction Form: The safety of TNF-alpha inhibitors used for the treatment of IBD

Title: Onercept for moderate-to-severe Crohn's disease: a randomized, double-blind, placebo-controlled trial. Rutgeerts P, Sandborn WJ, Fedorak RN, et al. Clin Gastroenterol Hepatol. 2006;4:888-93.

Treatment Studied: Onercept.

Dose: Onercept 10, 25, 25 or 50 mg TIW.

Inclusion Criteria:

- active CD with a CDAI between 250 and 400;
- patients with acute active Crohn's disease (AACD) were required to have received no glucocorticoid treatment for 4 weeks and no immunosuppressants for 3 months before the start of the study;
- patients with chronic active Crohn's disease (CACD) were defined as those with active disease despite treatment with oral glucocorticoids and/or immunosuppressants in the 3 months before the start of the study;
- a white cell count of 3.5 x 10^9/L or more;
- a neutrophil count of 1.5 x 10^9/L or more;
- a platelet count of 100 x 10^9/L or more;
- a hemoglobin level of 8.5 g/dL or more;
- maintenance treatment with oral sulfasalazine or mesalamine derivatives in the 4 weeks before the study was allowed.

Exclusion Criteria:

- prior treatment with cytokines, anticytokines, intercellular adhesion molecule 1, antisense oligonucleotide or anti-CD4;
- inadequate liver or renal function;
- symptoms of stenosis regarded as mainly noninflammatory;
- presence of a stoma;
- history of small-bowel resection;
- active infection;
- history of cancer;
- need for emergency surgery;
- elective surgery planned during the study.

Duration of Treatment: 8 weeks
Duration of Study: November 2001 to February 2003
Randomized: Yes
Placebo Controlled: Yes
Blinding: Yes
Allocation concealment: Yes

Adverse Events

	Plb (n=37)	ON10 (n=44)	ON25 (n=42)	ON35 (n=42)	ON 50 (n=42)
At least 1 AE	26 (70.3%)	31 (70.5%)	28 (66.7%)	30 (71.4%)	32(76.2%)
Drug-related AE	19 (51.4%)	25 (56.8%)	22 (52.4%)	27 (64.3%)	25 (59.5%)
Adverse event possibly related to anti-TNF	12 (32.4%)	11 (25.0%)	14 (33.3%)	12 (28.6%)	16 (38.1%)
Injection site erythema	0	2 (4.5%)	4 (9.5%)	9 (21.4%)	7 (16.7%)
Withdraw	3 (8.1%)	3 (6.8%)	0	2 (4.8%)	2 (4.8%)
Serious AE	1(2.7%)	1 (2.3%)	1 (2.4%)	3 (7.1%)	0
Antibodies	0	2 (4.9%)	1 (2.4%)	4 (9.8%)	6 (14.3%)

Appendix C: PRISMA Checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Cover
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	(ii)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7-9
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7-9
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	11-12
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	10
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	10
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	11
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	12 Appendix A
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	11-12

PRISMA 2009 Checklist

[illegible]	[illegible]	[illegible]	[illegible]
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	13
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix B
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	73-87
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	18-21
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	21-22
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	24-30
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	31-55
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	56
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	57
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Not Applicable

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097