

Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease (Review)

Behm BW, Bickston SJ



**THE COCHRANE
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

<http://www.thecochranelibrary.com>



TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	4
DISCUSSION	10
AUTHORS' CONCLUSIONS	11
ACKNOWLEDGEMENTS	11
REFERENCES	12
CHARACTERISTICS OF STUDIES	14
DATA AND ANALYSES	20
Analysis 1.1. Comparison 1 Infliximab versus placebo, Outcome 1 Clinical Remission.	21
Analysis 1.2. Comparison 1 Infliximab versus placebo, Outcome 2 Clinical Response.	21
Analysis 1.3. Comparison 1 Infliximab versus placebo, Outcome 3 Steroid Sparing.	22
Analysis 1.4. Comparison 1 Infliximab versus placebo, Outcome 4 Fistula Healing.	22
Analysis 2.1. Comparison 2 Adalimumab versus placebo, Outcome 1 Clinical Remission.	23
Analysis 2.2. Comparison 2 Adalimumab versus placebo, Outcome 2 Clinical Response.	23
Analysis 2.3. Comparison 2 Adalimumab versus placebo, Outcome 3 Steroid Sparing.	24
Analysis 3.1. Comparison 3 CDP571 versus placebo, Outcome 1 Clinical Remission.	24
Analysis 3.2. Comparison 3 CDP571 versus placebo, Outcome 2 Clinical Response.	25
Analysis 3.3. Comparison 3 CDP571 versus placebo, Outcome 3 Steroid Sparing.	25
Analysis 4.1. Comparison 4 Certolizumab versus placebo, Outcome 1 Clinical Remission.	26
Analysis 4.2. Comparison 4 Certolizumab versus placebo, Outcome 2 Clinical Response.	26
WHAT'S NEW	26
HISTORY	27
CONTRIBUTIONS OF AUTHORS	27
DECLARATIONS OF INTEREST	27
INDEX TERMS	27

[Intervention Review]

Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease

Brian W Behm¹, Stephen J Bickston¹

¹UVA Digestive Health Center of Excellence, University of Virginia Health Systems, Charlottesville, USA

Contact address: Stephen J Bickston, UVA Digestive Health Center of Excellence, University of Virginia Health Systems, 800708 UVAHS, Charlottesville, VA, 22908, USA. sjb8n@virginia.edu. (Editorial group: Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Group.)

Cochrane Database of Systematic Reviews, Issue 1, 2009 (Status in this issue: *Unchanged*)

Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

DOI: 10.1002/14651858.CD006893

This version first published online: 23 January 2008 in Issue 1, 2008.

Last assessed as up-to-date: 2 October 2007. (Help document - [Dates and Statuses](#) explained)

This record should be cited as: Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD006893. DOI: 10.1002/14651858.CD006893.

ABSTRACT

Background

Crohn's disease may be refractory to conventional treatments including corticosteroids and immunosuppressives. Recent studies suggest TNF- α blocking agents may be effective in maintaining remission in Crohn's disease.

Objectives

To conduct a systematic review of the evidence for the effectiveness of TNF- α blocking agents in the maintenance of remission in patients with Crohn's disease.

Search strategy

MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and the IBD/FBD Review Group Specialized Trials Register were searched for relevant studies published between 1966-2007. Manual searches of references from potentially relevant papers were performed to identify additional studies. Experts in the field and study authors were contacted to identify unpublished data.

Selection criteria

Randomized controlled trials involving patients ≥ 18 years with Crohn's disease who had a clinical response or clinical remission with a TNF- α blocking agent, or patients with Crohn's disease in remission but unable to wean corticosteroids, who were then randomized to maintenance of remission with a TNF- α blocking agent or placebo

Data collection and analysis

Two independent authors performed data extraction and assessment of the methodological quality of each trial. Outcome measures reported in the primary studies included clinical remission, clinical response, and steroid-sparing effects.

Main results

Nine studies met all inclusion criteria. Four different anti-TNF- α agents were evaluated (infliximab in 3 studies, CDP571 in 3 studies, adalimumab in 2 studies, and certolizumab in 1 study). There is evidence from three randomized controlled trials that infliximab maintains clinical remission (RR 2.50; 95% CI 1.64 to 3.80), maintains clinical response (RR 1.66; 95% CI 1.00 to 2.76), has corticosteroid-sparing effects (RR 3.13; 95% CI 1.25 to 7.81), and maintains fistula healing (RR 1.87; 95% CI 1.15 to 3.04) in patients

with Crohn's disease with a response to infliximab induction therapy. There were no significant differences in remission rates between infliximab doses of 5 mg/kg or 10 mg/kg. There is evidence that adalimumab maintains clinical remission, clinical response, and has corticosteroid-sparing effects in patients with Crohn's disease who have responded or entered remission with adalimumab induction therapy. There were no significant differences in remission rates between adalimumab 40 mg weekly or every other week. There is evidence from one randomized controlled trial that certolizumab pegol maintains clinical remission (RR 1.68; 95% CI 1.30 to 2.16) and maintains clinical response (RR 1.74; 95% CI 1.41 to 2.13) in patients who have responded to certolizumab induction therapy. There is no evidence to support the use of CDP571 for the maintenance of remission in Crohn's disease.

Authors' conclusions

Infliximab 5 mg/kg or 10 mg/kg, given every 8 weeks, is effective for the maintenance of remission and maintenance of fistula healing in patients who have responded to infliximab induction therapy. Adalimumab 40 mg weekly or every other week is effective for the maintenance of remission in patients who have responded to adalimumab induction therapy. Certolizumab pegol 400 mg every 4 weeks is effective for the maintenance of remission in patients who have responded to certolizumab induction therapy. No comparative trials have evaluated the relative efficacy of these agents. Adverse events are similar in the infliximab, adalimumab, and certolizumab groups compared with placebo, but study size and duration generally are insufficient to allow an adequate assessment of serious adverse events associated with long-term use.

PLAIN LANGUAGE SUMMARY

Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease

Crohn's disease is a chronic inflammatory disease of the intestines. Crohn's disease frequently occurs in the lower part of the small intestine (the ileum), however it can affect any part of the digestive tract, from the mouth to the anus. The most common symptoms of Crohn's disease are abdominal pain, often in the lower right region of the abdomen, and diarrhea. TNF is a molecule secreted by white blood cells that increases inflammation. High levels of TNF-alpha have been associated with the development of intestinal inflammation in Crohn's disease. TNF-alpha blocking agents (infliximab, adalimumab, certolizumab pegol and CDP571) bind with TNF-alpha molecules thereby neutralizing the biological activity of TNF-alpha resulting in the healing of intestinal inflammation. All four molecules are synthetic antibodies that bind TNF. Infliximab (Remicade) is an antibody of mouse origin that has been humanized, as is CDP571. Adalimumab (Humira) is an antibody of human origin. Certolizumab is a humanized antibody fragment that is complexed with polyethylene glycol to extend the length of time the drug is in the body. Nine studies were reviewed. The studies compared TNF-alpha blocking agents with placebo (inactive intravenous infusions or injections) and found that infliximab, adalimumab, and certolizumab pegol were effective in maintaining remission in patients with Crohn's disease who respond to induction therapy with these agents. There is no evidence that CDP571 is an effective maintenance therapy. The TNF-alpha blocking agents appear to be safe for patients with Crohn's disease with equal numbers of patients receiving TNF-alpha blocking agents or placebo reporting side effects such as headache, abdominal pain, nausea, and pain at injection site. There were some serious side effects reported with the use of these agents including infections such as tuberculosis. However, patients can be screened for inactive tuberculosis prior to treatment with TNF-alpha. A link between long term treatment with TNF-alpha blocking agents and cancer is possible but not proven. Data obtained from observational studies including the Crohn's Therapy, Resource, Evaluation and Assessment Tool (TREAT) registry show no increased risk of cancer with the use of TNF-alpha blocking agents in patients with inflammatory bowel disease. The current evidence suggests that the TNF-alpha blocking agents infliximab, adalimumab, and certolizumab pegol are effective maintenance therapy in Crohn's disease. However, the use of these medications needs to be weighed against the potential risk of serious side effects, particularly infection.

BACKGROUND

Crohn's disease is a chronic inflammatory condition involving the gastrointestinal tract that is characterized by recurrent exacerbations and remissions. The cause and cure of Crohn's disease remains unknown, with current therapies aimed at inducing and maintaining remission, improving quality of life, and minimizing adverse events of medical therapy. At this time, there is no consensus on what constitutes optimal therapy for Crohn's disease. There is evidence from randomized controlled trials that the immunosuppressives methotrexate and azathioprine/6-mercaptopurine are effective for the maintenance of remission in Crohn's disease (Feagan 2000; Pearson 1998). However, patients may not respond or may not be able to tolerate conventional therapy with these medications.

Tumor necrosis factor-alpha (TNF- α) is a proinflammatory cytokine that has been shown to have important immunomodulatory properties in animals and humans. Studies have shown increased TNF- α levels in the serum and intestinal mucosa of patients with Crohn's disease (Reimund 1996; Breese 1994; Komatsu 2001). Initial evaluation of the TNF- α blocking agent infliximab found that infliximab reduces disease activity in patients with active Crohn's disease (van Dulleman 1995), and there is now evidence from several randomized controlled trials that TNF- α blocking agents are effective induction agents for active Crohn's disease (Targan 1997; Schreiber 2005a; Hanauer 2006). A recent Cochrane systematic review found that infliximab is effective for inducing remission in patients with Crohn's disease (Akobeng 2003). Several studies have been published assessing TNF- α blocking agents for the maintenance of remission of Crohn's disease. A systematic review evaluating the use of anti-TNF- α agents for the maintenance of remission in Crohn's disease is indicated.

OBJECTIVES

To conduct a systematic review to evaluate the effectiveness of TNF- α blocking agents in the maintenance of remission in patients with Crohn's disease.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials comparing TNF- α antibody with placebo or control medication.

Types of participants

Patients greater than 17 years of age with refractory or steroid-dependent Crohn's disease as defined by conventional clinical, radiographic and endoscopic criteria. Patients were categorized as

having active Crohn's disease (defined as Crohn's disease activity index [CDAI] > 150) with a response to induction therapy with an anti TNF- α agent in the presence or absence of concomitant steroid or immunosuppressive therapy, and patients with Crohn's disease (either active or in remission) that were unable to wean corticosteroids in the presence or absence of immunosuppressives.

Types of interventions

TNF- α antibody versus placebo or control medication.

Types of outcome measures

The primary outcome measure is the number of patients maintaining clinical remission, expressed as a percentage of total patients randomized (intention to treat analysis). Secondary outcomes include 1) clinical response rates as defined by the primary studies, 2) the proportion of patients who maintain clinical remission and are able to discontinue corticosteroids, 3) disease-specific quality of life, and 4) the incidence and type of adverse events.

Search methods for identification of studies

A computer-assisted search of MEDLINE (1966-July 2007), EMBASE (1966-July 2007), the Cochrane Central Register of Controlled Trials, and the Cochrane Inflammatory Bowel Disease Specialized Trial Register was performed. MEDLINE (via PUBMED) was searched using the following search strategy:

```
#41 Search #22 AND #40
#40 Search #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR
#36 OR #37 OR #38 OR #39
#39 Search research design [MESH TERMS]
#38 Search single-blind method [MESH TERMS]
#37 Search double-blind method [MESH TERMS]
#36 Search placebos [MESH TERMS]
#35 Search clinical protocols [MESH TERMS]
#34 Search clinical trials [MESH TERMS]
#33 Search random allocation [MESH TERMS]
#32 Search randomized controlled trials [MESH TERMS]
#31 Search Controlled Clinical trials [MESH FORMS]
#30 Search #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR
#29
#29 Search research OR design
#28 Search efficacy OR effective*
#27 Search random allocation
#26 Search blind OR placebo
#25 Search clinical trial
#24 Search random*
#23 Search randomized controlled trial OR randomised controlled
trial
#22 Search #8 AND #21
#21 Search #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR
#15 OR #16 OR #17 OR #18 OR #19 OR #20
#20 Search etanercept
#19 Search onercept
#18 Search adalimumab OR d2e7
```

#17 Search cdp870 OR certolizumab
 #16 Search cdp571
 #15 Search infliximab OR monoclonal antibody cA2 OR remicade
 #14 Search anti TNF antibody OR anti TNF alpha antibody
 #13 Search anti TNF OR anti TNF alpha
 #12 Search anti tumour necrosis factor antibody OR anti tumor necrosis factor antibody
 #11 Search anti tumour necrosis factor alpha antibody OR anti tumor necrosis factor alpha antibody
 #10 Search anti tumour necrosis factor alpha OR anti tumor necrosis factor alpha
 #9 Search anti tumour necrosis factor OR anti tumor necrosis factor
 #8 Search #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
 #7 Search inflammatory bowel disease [MESH FORMS]
 #6 Search inflammatory bowel disease
 #5 Search ileitis [MESH FORMS]
 #4 Search ileitis
 #3 Search regional enteritis
 #2 Search crohn disease [MESH FORMS]
 #1 Search crohn* disease

Similar search strategies were used to search the other electronic databases listed above.

Manual searches to identify key conference abstracts from 1995 onwards were performed [i.e. Gastroenterology (American Gastroenterological Association); Gut (British Society of Gastroenterology); American Journal of Gastroenterology (American College of Gastroenterology)]. References from recent reviews and published articles were searched to identify additional citations. Unpublished data from on-going trials was identified by correspondence with authors and experts in the field. The manufacturers of infliximab, adalimumab, and certolizumab were contacted for additional information.

Data collection and analysis

Selection criteria

Randomized controlled trials involving patients with Crohn's disease who had a clinical response or clinical remission with a TNF- α blocking agent, or patients with Crohn's disease in remission but unable to wean corticosteroids, who were then randomized to maintenance of remission with a TNF- α blocking agent.

Data collection and analysis

Both authors (BWB and SJB) independently reviewed full texts and assessed eligibility of the trials based on the inclusion criteria described above. The methodological quality of selected trials was assessed by the two authors using the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006) and the Jadad scale (Jadad 1996).

The criteria described in the Cochrane Handbook are summarized below:

A. adequate allocation concealment;

B. allocation concealment unclear; and

C. inadequate allocation concealment.

The Jadad scale is a validated five point scoring system that measures several factors that impact on trial quality. The scale is defined below:

a. was the study described as randomized? (yes = 1, no = 0)

b. was the method of randomization well described and appropriate? (yes = 1, no = 0)

c. was the study described as double-blind? (yes = 1, no = 0)

d. was the double blinding well described and appropriate? (yes = 1, no = 0)

e. were withdrawals and dropouts described? (yes = 1, no = 0)

One point was deducted if the described method of randomization or blinding was inappropriate.

Disagreement among authors on the methodological quality of the selected studies was resolved by consensus. Publication bias was assessed by examining the authors and institutions involved, journal of publication, funding sources, and the affiliation of authors with manufacturers.

Two authors independently extracted data and results from relevant studies and entered data into a pre-defined data extraction form. The extracted data included patient demographics such as age, disease distribution, disease duration, and concomitant medications, the type of disease activity scoring instrument used, treatment and control modalities, the number of patients randomized into each treatment group, the number of patients maintaining remission and stopping steroids, the duration of treatment and follow up, and the number of patients lost to follow up. In cases where data was not available from the published reports, attempts were made to obtain data by contacting the author.

Statistical analysis

Data were analyzed using Review Manager (RevMan 4.2.9). All data were analyzed on an intention-to-treat basis. Study heterogeneity was assessed using the chi-square test, with significance regarded as a P value = 0.10. The results were expressed as the relative risk (RR) and 95% confidence intervals (CI) for dichotomous outcomes. The relative risk was calculated using a fixed effects model when statistical heterogeneity was not present. A random effects model was used to calculate the relative risk when heterogeneity was present. Study data relating to secondary outcomes (e.g. adverse events) were described qualitatively. The definitions of clinical remission and clinical improvement were set by the authors of each paper, and the data were combined for analysis only if these definitions were sufficiently similar, as determined by consensus.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

The search strategy identified 27 randomized controlled trials on the use of anti TNF- α antibodies in Crohn's disease. Eleven studies (Stack 1997; Targan 1997; D'haens 1999; Present 1999; Sandborn 2001b; Winter 2004; Schreiber 2005a; Hanauer 2006; Lemann 2006; Rutgeerts 2006b; Sandborn 2007a) were excluded because they described the use of TNF- α blocking agents for the induction of remission in Crohn's disease. One study evaluating infliximab was excluded because only children were evaluated (Hyams 2007). One study evaluating certolizumab pegol (Sandborn 2007c) was excluded because it reported combined induction and maintenance data and it was not possible to completely evaluate maintenance therapy in clinical responders based on the published data. Five studies (Feagan 2003; Rutgeerts 2004; Geboes 2005; Lichtenstein 2005; Rutgeerts 2006a) were excluded as primary studies because they were subgroup analyses of included trials. The remaining nine randomized controlled trials that were identified (Rutgeerts 1999; Sandborn 2001a; Hanauer 2002; Sandborn 2004; Sands 2004; Feagan 2006; Colombel 2007; Sandborn 2007b; Schreiber 2007) satisfied all inclusion criteria and were included in the review.

STUDIES EVALUATING INFLIXIMAB

Three randomized controlled trials evaluating infliximab for the maintenance of remission in Crohn's disease were identified. All three studies used the CDAI to assess clinical disease activity and used the IBDQ to assess disease-related quality of life. However, there were differences in study populations and study design, including infliximab dosing, frequency of infusions, study duration, and definitions of clinical response. Rutgeerts 1999 evaluated patients with a clinical response to a single infusion of infliximab 10 mg/kg or placebo, who were then randomized to infliximab 10 mg/kg or placebo every 8 weeks until week 44. Hanauer 2002 evaluated patients with a clinical response to a single dose of infliximab 5 mg/kg, who were then randomized one of three arms: placebo at week 2 and 6 and then every 8 weeks thereafter, infliximab 5 mg/kg at week 2 and 6, then 5 mg/kg every 8 weeks thereafter, or infliximab 5 mg/kg at week 2 and 6, then 10 mg/kg every 8 weeks thereafter until week 54. Sands 2004 evaluated patients with fistulizing Crohn's disease who received open-label infliximab 5 mg/kg at weeks 0, 2, and 6. Responders were then given either infliximab 5 mg/kg or placebo every 8 weeks until week 54. This study was evaluated separately from the other two because of differences in patient population. Safety evaluations were reported for all three trials.

Rutgeerts 1999

Rutgeerts et al. conducted a randomized double-blind, placebo-controlled comparison of infliximab versus placebo in patients with active Crohn's disease. Patients with active Crohn's disease (CDAI 220 to 400) were given a single dose of infliximab 10 mg/kg or placebo. Patients who had a clinical response (CDAI reduction ≥ 70 from baseline) to the initial infusion were randomized to infliximab 10 mg/kg or placebo every 8 weeks until week 44. Seventeen patients were randomized to infliximab 10 mg/kg (n =

37) or placebo (n = 36). The primary study outcome was the number of patients who maintained a clinical response to infliximab or placebo over the study duration. Secondary outcomes included the number of patients maintaining a clinical remission (defined as a CDAI < 150) at each 4-week evaluation and the proportion of patients who discontinued because of lack of efficacy. All patients were evaluated for safety. Disease-related quality of life was assessed by the IBDQ. Corticosteroid-sparing was not assessed. Patients in the placebo arm who developed increased disease activity were not eligible to cross over to open-label infliximab therapy.

Hanauer 2002

In this study, 573 patients with Crohn's disease were enrolled in a randomized double-blind placebo-controlled trial to assess the benefit of maintenance infliximab therapy in patients with active Crohn's disease who had responded to a single infusion of infliximab. Patients with active Crohn's disease (CDAI 220 to 400) were recruited from 55 centers in North America, Europe, and Israel and received a 5 mg/kg intravenous infusion of infliximab at week 0. Clinical response to infliximab was defined as a reduction in CDAI of ≥ 70 and at least a 25% reduction in total CDAI score at week 2. After assessing response at week 2, patients were assigned to one of three treatment arms: repeat infusions of placebo at weeks 2 and 6, then every 8 weeks thereafter until week 48, or infliximab 5 mg/kg at weeks 2 and 6, followed by either 5 mg/kg or 10 mg/kg every 8 weeks thereafter. The co-primary endpoints were the time to loss of response up to week 54 in the patients who had responded to an initial dose of infliximab, and the proportion of week 2 responders that were in remission (CDAI < 150) at week 30. Secondary endpoints included the assessment of infliximab corticosteroid-sparing effects and an assessment of infliximab safety. The IBDQ was used to assess health-related quality of life. At week 14, patients who initially responded to infliximab but then worsened were eligible to cross over to active episodic treatment, comprised of 5, 10, or 15 mg/kg infliximab on an as-needed basis.

Sands 2004

In this study, 306 patients with Crohn's disease with one or more draining abdominal or perineal fistulas were enrolled in a randomized, double-blind, placebo-controlled trial. CDAI scores were not part of the study inclusion or exclusion criteria. Patients were given infliximab 5 mg/kg on weeks 0, 2, and 6 and were then randomly assigned to receive either placebo or 5 mg/kg of infliximab intravenously every 8 weeks. Patients were followed to week 54. The primary outcome was the time to loss of response among patients with an initial response to the induction regimen of infliximab at week 14; response was defined as a reduction in the number of draining fistulas of at least 50 percent from baseline. Secondary outcomes included the proportion of patients who maintained a clinical response to infliximab or placebo, defined as a reduction in baseline CDAI of 220 or greater by at least 25 percent and 70 points, and change in IBDQ. Adverse events were recorded at each study visit. Corticosteroid-sparing was not assessed. Starting

at week 22, patients who had a loss of response were eligible to cross over to 5 mg/kg from the placebo arm, or 10 mg/kg from the 5 mg/kg treatment arm.

STUDIES EVALUATING ADALIMUMAB

Two randomized controlled trials evaluating adalimumab for the maintenance of remission in Crohn's disease were identified ([Colombel 2007](#); [Sandborn 2007b](#)) and included in the review.

[Colombel 2007](#)

In this multicenter study, 854 patients with active Crohn's disease (CDAI 220 to 450) received open-label induction therapy with adalimumab 80 mg subcutaneously at week 0 followed by 40 mg subcutaneously at week 2. At week 4, patients were stratified by response (CDAI decrease ≥ 70 points from baseline) and randomized to one of three arms: placebo, adalimumab 40 mg every other week, or adalimumab 40 mg weekly through week 56 in double-blinded fashion. The primary study outcomes were the proportion of responders who achieved clinical remission (CDAI < 150) at weeks 26 and 56. Secondary outcomes included the proportion of responders with a clinical response, changes from baseline in IBDQ scores, and proportion of patients in clinical remission and off corticosteroids at weeks 26 and 56. Adverse events were recorded. Patients with sustained nonresponse or experiencing a disease flare at or after week 12 were subsequently switched to open-label adalimumab treatment.

[Sandborn 2007b](#)

In this study, 276 patients with Crohn's disease who were previously enrolled in the Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy for Crohn's Disease (CLASSIC I) trial, a study evaluating adalimumab for induction of remission in Crohn's disease, enrolled in the subsequent maintenance study (CLASSIC 2). All patients were naive to anti-tumor necrosis factor therapy prior to enrolling in CLASSIC I. In the maintenance trial, patients received open-label adalimumab 40 mg at weeks 0 and 2. Patients who were in clinical remission (CDAI < 150) at week 0 and week 4 were then randomized to adalimumab 40 mg every week, adalimumab 40 mg every other week, or placebo to week 56. Patients who were not in remission at week 0 and 4 were enrolled in an open-label arm and received adalimumab 40 mg every other week. The primary outcome was the proportion of patients in remission at week 56 in the randomized cohort of patients. Secondary outcomes included the proportion of patients with a clinical response (CDAI decrease ≥ 70 or ≥ 100) at weeks 24 and 56, changes from baseline in IBDQ scores, and the proportion of patients in remission who discontinued steroids at week 24 and 56. Adverse events were recorded. Patients with a disease flare or continued non-response were switched to open-label adalimumab treatment.

STUDY EVALUATING CERTOLIZUMAB PEGOL

One randomized controlled trial evaluating certolizumab pegol for the maintenance of remission in Crohn's disease was identified ([Schreiber 2007](#)).

[Schreiber 2007](#)

In this multicenter trial, 668 patients with active Crohn's disease (CDAI 220 to 450) underwent open-label induction with certolizumab 400 mg subcutaneously at weeks 0, 2, and 4. Patients that responded to certolizumab induction (428/668 [64%]) were then randomized to either certolizumab 400 mg or placebo subcutaneously every 4 weeks through week 24, with follow up to week 26. The primary outcome was the proportion of patients with a clinical response (CDAI decrease ≥ 100 from baseline) at week 26 in patients with a baseline CRP > 10 mg/L. Secondary outcomes included the proportion of patients with a clinical response and clinical remission (CDAI ≤ 150) at week 26 (irrespective of CRP levels) and changes from baseline in IBDQ scores. Adverse events were recorded. Patients with a disease flare or non-response were not eligible to cross over to open-label certolizumab treatment.

STUDIES EVALUATING CDP571

Three randomized controlled trials evaluating CDP571 for maintenance of remission in Crohn's disease were identified ([Sandborn 2001a](#); [Sandborn 2004](#); [Feagan 2006](#)). All three studies used the CDAI to determine rates of clinical response and remission, and used the IBDQ to evaluate changes in disease-specific quality of life. However, there were differences in medication dosing, primary endpoints, patient demographics, and study duration.

[Sandborn 2001a](#)

This study enrolled 169 patients with moderately to severely active Crohn's disease (CDAI 220 to 450). Patients were randomized to a single intravenous dose of CDP571 10 mg/kg, CDP571 20 mg/kg, or placebo. Patients then continued CDP571 10 mg/kg or placebo every 8 weeks or every 12 weeks until week 24. The primary outcome was clinical response (CDAI decrease ≥ 70 points) at week 2. Secondary outcomes included rate of clinical remission (CDAI < 150) at each study visit and changes in IBDQ scores at each visit. Adverse events were recorded. Corticosteroid-sparing was not assessed. Patients in the placebo arm that experienced a disease flare were ineligible to switch to open-label CDP571.

[Sandborn 2004](#)

This study was a 28 week randomized, double-blind, placebo-controlled trial evaluating CDP571 in patients with moderate to severe Crohn's disease (CDAI 220 to 450). A total of 396 patients were enrolled. Patients received intravenous CDP571 10 mg/kg or placebo every 8 weeks to week 24. The primary outcome was the proportion of patients with a clinical response [CDAI decrease ≥ 100 points from baseline or clinical remission (CDAI ≤ 150)] at week 28. Secondary outcomes included the proportion of patients who showed a clinical response and were in clinical remission at several time points during the study (weeks 2, 4, 8, 12, 16, 24, and 28) and IBDQ scores at weeks 2, 4, 8, 16, 24, and 28. Corticosteroid-sparing was not assessed. Adverse events were recorded. Patients in the placebo arm could not cross over to open-label CDP571.

[Feagan 2006](#)

Feagan et al. performed a multicenter randomized controlled trial

evaluating the steroid-sparing effects of CDP571 in patients with steroid-dependent Crohn's disease. Unlike the previous studies, all patients had a baseline CDAI < 150 at the time of enrollment. A total of 271 patients were randomized to either CDP571 10 mg/kg or placebo every 8 weeks to week 36. A defined steroid-tapering schedule was followed over the course of the study. The primary outcome was the proportion of patients with steroid-sparing [defined as not experiencing a disease flare (CDAI \geq 220) and no longer requiring steroid therapy] at week 36. Secondary outcomes included the percentage of patients with steroid-sparing at week 16, 24 and 32, and differences in IBDQ scores. There was no cross over to open-label CDP571 in this study.

Risk of bias in included studies

Allocation concealment was adequate in all studies. For two studies ([Rutgeerts 1999](#); [Schreiber 2007](#)) allocation concealment was unclear based on published data, but was adequate after further information was obtained from the study authors. All studies were reported as intention to treat (ITT). The methodological quality of each trial was assessed by both investigators independently using the five point Jadad scale ([Jadad 1996](#)). Seven studies scored 5 out of 5 ([Sandborn 2001a](#); [Hanauer 2002](#); [Sandborn 2004](#); [Sands 2004](#); [Feagan 2006](#); [Sandborn 2007b](#); [Schreiber 2007](#)) and two studies scored 4 out of 5 ([Colombel 2007](#); [Rutgeerts 1999](#)).

Effects of interventions

It was decided to not combine the data from trials involving different anti TNF- α agents statistically because of differences in drug administration, patient demographics, definitions of disease activity, and differences in clinical endpoints and study durations. Two studies ([Rutgeerts 1999](#); [Hanauer 2002](#)) evaluating infliximab were grouped together for data analysis for clinical remission due to similarities in definition of remission, duration of therapy, and similar response rates in the 5 mg/kg and 10 mg/kg groups. The study evaluating infliximab in patients with fistulizing disease ([Sands 2004](#)) was evaluated separately. The two studies evaluating adalimumab were evaluated separately due to heterogeneity among the participants in the two trials; namely, that participants in the [Sandborn 2007b](#) trial were TNF- α naive prior to enrolling in CLASSIC I and were in clinical remission at the time of study entry. Two studies evaluating CDP571 were grouped together for data analysis due to similarities in study design and study endpoints ([Sandborn 2001a](#); [Sandborn 2004](#)). One study ([Feagan 2006](#)) was analyzed separately because all study participants were in corticosteroid-induced clinical remission at the time of study enrollment. There were insufficient data to perform subgroup analysis according to disease extent or location. There was not consistent recording of adverse events between studies, so adverse event data was not pooled for analysis. Mean IBDQ scores and standard deviations were not consistently reported, thus this secondary outcome measure was not pooled for analysis.

INFLIXIMAB VERSUS PLACEBO

[Rutgeerts 1999](#)

At week 44, 21/34 (62%) of infliximab-treated patients maintained a clinical response compared with 13/35 (37%) of placebo-treated patients ($P = 0.16$). Clinical remission rates were not reported in the article, and additional information was obtained from the authors. The proportion of patients in clinical remission at week 44 were 18/34 (52.9%) with infliximab and 7/35 (20%) with placebo ($P = 0.013$). Median IBDQ scores were higher in the infliximab group than placebo, but it is not clear if these were statistically significant differences. Twenty-seven percent (10/37) of patients receiving infliximab discontinued treatment, compared to 39% (14/36) of patients receiving placebo. Adverse events were similar in the infliximab and placebo groups (94.6% versus 97.2%). The incidence of serious adverse events were not specifically reported. The most common adverse events included upper respiratory tract infection, headache, abdominal pain, dyspnea, nausea, and fever. One patient who received a single dose of infliximab 10 mg/kg developed a B-cell lymphoma 9 1/2 months after the initial infusion. One case of suspected lupus was reported. No tuberculosis or opportunistic infections were reported. Antibodies to infliximab were detected in 7/47 in whom antibodies could be evaluated.

[Hanauer 2002](#)

There were 335 responders to infliximab that were randomized to one of the three treatment arms. The median time to loss of response was 38 weeks (interquartile range [IQR] 15 to > 54) and > 54 weeks (IQR 21 to > 54) in the infliximab 5 mg/kg and 10 mg/kg arms, respectively. The median time to loss of response was 19 weeks (IQR 10 to 45) in the placebo arm ($P = 0.002$ versus infliximab 5 mg/kg; $P = 0.0002$ versus infliximab 10 mg/kg). The proportion of patients in remission at week 30 was 44/113 (39%) for infliximab 5 mg/kg, 50/112 (45%) for infliximab 10 mg/kg, and 23/110 (21%) for placebo ($P = 0.003$ versus infliximab 5 mg/kg; $P = 0.0002$ versus infliximab 10 mg/kg). Clinical remission rates at week 54 were obtained from the authors. These were significantly higher in the infliximab groups than placebo (32/113 [28.3%; $P = 0.007$] for infliximab 5 mg/kg, 43/112 [38.4%; $P < 0.001$] for infliximab 10 mg/kg, and 15/110 [13.6%] for placebo). Clinical response rates were also significantly higher in patients receiving infliximab than placebo. Patients in the combined infliximab arms were more likely to be in steroid-free remission than patients in the placebo arm at week 54 (32/225 [29%] versus 5/110 [9%]; OR 4.2; 95%CI 1.5 to 11.5). IBDQ scores were significantly higher in patients receiving infliximab than placebo ($P = 0.015$ versus infliximab 5 mg/kg; $P < 0.0001$ versus infliximab 10 mg/kg at week 54). Differences between infliximab 5 mg/kg and 10 mg/kg in rates of clinical response, clinical remission, and IBDQ scores were not statistically significant. Twenty-two percent (124/573) of all patients (including responders and non-responders) discontin-

ued maintenance study treatment by week 54, but data specifically evaluating the week 2 clinical responders were unavailable. Adverse events were similar in the infliximab and placebo groups. Serious adverse events, including serious infections, were not significantly different between the infliximab and placebo groups (infliximab 5 mg/kg 28%, infliximab 10 mg/kg 22%, placebo 29%). Infusion reactions developed in a higher proportion of patients receiving infliximab (infliximab 5 mg/kg 23%, infliximab 10 mg/kg 19%, placebo 9%). One patient who crossed over to episodic infliximab 15 mg/kg developed tuberculosis at week 18. Six cases of malignancy were reported, including a natural-killer-cell lymphoma in a placebo group patient, which developed approximately 13 months after receiving the open-label infliximab infusion. Antibodies to infliximab developed in 14% of study patients: 28% in the placebo group, 9% in the infliximab 5 mg/kg group, and 6% in the infliximab 10 mg/kg group.

Sands 2004

In this study, 195/282 patients (68%) with fistulizing Crohn's disease responded to an infliximab induction regimen (5 mg/kg at week 0, 2, and 6). Patients were then randomly assigned to either infliximab 5 mg/kg or placebo intravenously every 8 weeks. The time to loss of response (defined as recrudescence of draining fistulas or a change in therapy due to persistent or worsening luminal disease) was longer for patients in the infliximab arm compared with patients receiving placebo (more than 40 weeks versus 14 weeks, $P < 0.001$). At week 54, 33/91 (36%) of patients in the infliximab group had complete absence of draining fistulas, compared with 19/98 (19%) patients in the placebo group ($P = 0.009$). There were 64 patients who had a baseline CDAI ≥ 220 at the time of study enrollment. In those patients, clinical response was maintained in 12/33 (36%) of the infliximab group and 2/31 (6%) in the placebo group ($P = 0.004$) at week 54. Clinical remission rates in patients with a baseline CDAI ≥ 220 at study enrollment were not published, but data obtained from the authors found remission rates of 12/33 (36%) in the infliximab group and 5/31 (16%) in the placebo group at week 30 ($P = 0.091$) and 9/33 (27%) in the infliximab group and 1/31 (3%) in the placebo group at week 54 ($P = 0.013$) in subjects who had a baseline CDAI ≥ 220 at study enrollment. Given the differences in this study population and the other two trials, these data were not included in the pooled results. There was a significant increase in IBDQ scores at weeks 30 and 54 in the group receiving infliximab compared with placebo ($P = 0.002$ at week 30; $P = 0.03$ at week 54). Twenty-nine percent (28/96) of patients receiving infliximab and 51% (50/99) of patients receiving placebo crossed over to open-label infliximab prior to week 54. One patient in the infliximab group required surgery and one patient in the placebo group discontinued study drug because of lack of efficacy. Similar rates of adverse events (89% infliximab versus 92% placebo) and serious adverse events (14% infliximab versus 23% placebo) were reported in the infliximab and placebo groups. The incidence of serious infections was also similar between the two groups (3% infliximab versus

6% placebo). Two opportunistic infections, including one case of cytomegalovirus infection and one case of cutaneous nocardia infection, were reported during infliximab induction. No cases of tuberculosis were reported. Multiple sclerosis developed in one patient one month after receiving infliximab, and two cases of rectal carcinoma were reported during long-term follow-up. No cases of lymphoma were reported. Antibodies to infliximab developed in 17% of study patients and antibody status was inconclusive in 52% of patients.

Infliximab: Pooled Results

Infliximab was found to be superior to placebo for the maintenance of remission (RR 2.50; 95% CI 1.64 to 3.80; $P < 0.0001$) and clinical response (RR 2.19; 95% CI 1.27 to 3.75; $P = 0.005$; random effects model) in Crohn's disease. Infliximab was also superior to placebo for corticosteroid-sparing effects (RR 3.13; 95% CI 1.25 to 7.81; $P = 0.01$) and complete healing of perianal and enterocutaneous fistulas (RR 1.87; 95% CI 1.15 to 3.04; $P = 0.01$) to week 54.

ADALIMUMAB VERSUS PLACEBO

Colombel 2007

In this study, 58% (499/854) patients responded to open-label adalimumab induction therapy. In the randomized maintenance phase of the trial the proportion of responders who entered clinical remission with adalimumab 40 mg every other week and 40 mg weekly was significantly higher than placebo at week 26 (40% [68/172] for adalimumab every other week and 47% [73/157] for adalimumab weekly versus 17% [29/170] for placebo; $P < 0.001$) and week 56 (36% [62/172] for adalimumab every other week and 41% [65/157] for adalimumab weekly versus 12% [20/170] for placebo; $P < 0.001$). When both adalimumab groups were combined, adalimumab was found to be superior to placebo for maintenance of clinical remission to week 54 (RR 3.28; 95% CI 2.13 to 5.06). Response rates (CDAI decrease ≥ 70 and ≥ 100) were also higher in the adalimumab groups compared with placebo ($P < 0.001$). IBDQ scores were higher in adalimumab-treated patients compared with placebo, but it is unclear from published reports whether these were significant differences. Adalimumab-treated patients had higher rates of steroid-free remission than placebo-treated patients at week 26 ($P < 0.001$ for both adalimumab groups) and week 56 (6% placebo, versus 29% adalimumab every other week [$P < 0.001$], and 23% adalimumab weekly [$P = 0.008$]). When both adalimumab groups were combined, adalimumab was found to be superior to placebo for maintenance of steroid-free remission to week 54 (RR 4.25; 95% CI 1.57 to 11.47). Fifty-two percent (170/329) of patients receiving adalimumab discontinued therapy before week 56, compared with 81% (138/170) of patients receiving placebo. Adverse events were reported at similar frequencies in the adalimumab and placebo groups (88.8% adalimumab 40 mg every other week, 85.6% adalimumab 40 mg every week, 84.7% placebo). The most commonly reported adverse events included arthralgias, pharyngitis, abdominal pain, and upper respiratory infections. Serious adverse events were higher in

the placebo group (9.2% adalimumab 40 mg every other week, 8.2% adalimumab 40 mg every week, 15.3% placebo; $P < 0.05$). Serious infections were reported at similar frequencies in the adalimumab and placebo groups. Two patients receiving open-label adalimumab developed tuberculosis. No other opportunistic infections were reported. One malignancy (breast cancer) was reported in the placebo group 77 days after starting open-label induction with adalimumab. One case of multiple sclerosis was reported during open-label induction. Neither antibodies to adalimumab nor serum adalimumab concentrations were measured in this study.

Sandborn 2007b

Study patients received open-label adalimumab 40 mg at week 0 and 2 in the maintenance study. A total of 55 patients were in remission at both week 0 and 4, and were then randomized to adalimumab 40 mg every other week, adalimumab 40 mg weekly, or placebo through 56 weeks. An additional 276 patients who were not in remission at both week 0 and 4 received open-label adalimumab maintenance, and were not included in this review. In the randomized group, patients receiving adalimumab were more likely to be in clinical remission at week 56 (adalimumab 40 mg every other week 79% [15/19], adalimumab 40 mg weekly 83% [15/18], placebo 44% [8/18]; $P < 0.05$ for both adalimumab groups). When both adalimumab groups were combined, adalimumab was found to be superior to placebo for maintenance of clinical remission to week 54 (RR 1.82; 95% CI 1.06 to 3.13). Clinical response (CDAI decrease ≥ 100) was higher in the adalimumab group compared with placebo. There was also a trend toward higher response rates when using CDAI decrease ≥ 70 points, but the difference was not clinically significant. The absolute numbers of patients with a clinical response were not reported. Mean IBDQ scores were higher in patients receiving adalimumab compared with placebo, but it is unclear whether these were significant differences. Adalimumab-treated patients had higher rates of steroid-free remission at week 56 (adalimumab 40 mg every other week 67% [4/6], adalimumab 40 mg weekly 88% [7/8], placebo 57% [4/7]; P -value not reported). When both adalimumab groups were combined, there was no statistically significant difference in steroid sparing between adalimumab and placebo to week 54 (RR 1.38; 95% CI 0.68 to 2.76). Thirty percent (11/37) of patients receiving adalimumab discontinued double-blind treatment prior to week 56, compared with 67% (12/18) of patients receiving placebo. A greater proportion of patients in the placebo group experienced adverse events; the most commonly reported events were nasopharyngitis, worsening Crohn's disease, and sinusitis. Serious adverse events were higher in the placebo group (adalimumab 40 mg every other week 5% [1/19], adalimumab 40 mg weekly 0% [0/18], placebo 11% [2/18]). One malignancy (squamous cell carcinoma involving the head) was reported in the placebo group [Abbott Laboratories, personal communication]. A total of 2.6% of patients in both the randomized and open-label groups developed antibodies to adalimumab during the study.

CERTOLIZUMAB PEGOL VERSUS PLACEBO

Schreiber 2007

In this study, 428 patients had a clinical response (CDAI ≥ 100 from baseline) to certolizumab pegol induction and were randomized to certolizumab 400 mg or placebo maintenance every 4 weeks to week 26. At week 26, a significantly higher proportion of patients were in clinical remission with certolizumab than with placebo (certolizumab 103/215 [48%] versus placebo 60/210 [29%]; $P < 0.001$). A significantly higher proportion of patients maintained a clinical response with certolizumab through week 26 (135/215 [63%]) compared with placebo (76/210 [36%]; $P < 0.001$). Similar clinical response rates were found in patients with elevated CRP levels at week 26 (certolizumab 69/112 [62%] versus placebo 34/101 [34%]; $P < 0.001$). Adjusted mean IBDQ scores were significantly higher in the certolizumab group at week 26 (certolizumab 171 versus placebo 163; $P = 0.007$). The proportion of patients in steroid-free remission was not reported. Thirty percent (65/216) of patients receiving certolizumab pegol discontinued treatment prior to week 26, compared to 49% (103/212) of patients receiving placebo. Adverse events were reported in similar frequencies in the certolizumab and placebo maintenance groups (certolizumab 65% versus placebo 67%); the most commonly reported events were headache, nasopharyngitis, cough, Crohn's exacerbation, and pain at injection site. Serious adverse events were reported in 12/216 (6%) of certolizumab patients and 14/212 (7%) of placebo patients. One patient receiving certolizumab developed pulmonary tuberculosis. No malignancies were reported. A total of 9% (58/668) of patients developed detectable antibodies to certolizumab during the study.

Certolizumab pegol: Results

Compared with placebo, certolizumab pegol was found to be effective for maintenance of clinical remission (RR 1.68; 95% CI 1.30 to 2.16; $P < 0.0001$) and clinical response (RR 1.74; 95% CI 1.41 to 2.13; $P < 0.00001$) to week 26.

CDP571 VERSUS PLACEBO

Sandborn 2001a

The rates of clinical remission for CDP571 were not significantly different than placebo at any study visit. The rate of clinical remission at week 24 were 4% for placebo and 11% for CDP571 10 mg/kg every 8 weeks, and 3% for placebo and 11% for CDP571 10 mg/kg every 12 weeks. A significant clinical response to CDP571 (CDAI ≥ 70) was noted at week 2, but not at subsequent study visits. There was no difference in the median IBDQ scores at any study visit. Sixty eight percent (75/111) of patients in the CDP571 group withdrew prior to study completion, compared to 81% (47/58) of patients in the placebo group. The overall incidence of adverse events was higher in the CDP571 group (87% CDP571 versus 69% placebo), but the incidence of serious adverse events was not significantly different. The most common side effects included headache, abdominal pain, and nausea. The incidence of infection was similar in the two groups. No cases of opportunistic

infection or malignancy were reported. Antibodies to CDP571 were found in 7% of patients. Infusion reactions occurred in 12% of patients in the CDP571 group and 7% in the placebo group ($P = .42$).

[Sandborn 2004](#)

In this study, 396 patients were randomized to either CDP571 10 mg/kg ($n = 263$) or placebo ($n = 132$). The proportion of patients with a clinical response (decrease in CDAI score ≥ 100 points or remission) at week 28 was 30.4% (80/263) in the CDP571 group and 23.5% (31/132) in the placebo group ($P = 0.10$). There was no significant difference in clinical remission rates (CDP571 23.6% versus placebo 20.5%). There were no significant differences in mean IBDQ scores. Fewer patients in the CDP571 group withdrew prior to study completion (CDP 571 43% versus placebo 57%). The two treatment groups had similar incidences of total (CDP571 72.2% versus placebo 76%) and serious (CDP571 13.5% versus placebo 10.3%) adverse events. Infusion reactions occurred more frequently in the CDP571 group (20.5% versus 10.5%; P value not reported). No cases of opportunistic infections or malignancy were reported. Antibodies to CDP571 developed in 10.9% of patients receiving CDP571.

[Feagan 2006](#)

A total of 269 patients (181 treatment, 88 placebo) with steroid-dependent Crohn's disease were enrolled and followed until week 36. All patients were in remission (CDAI ≤ 150) at the time of study enrollment. There were no differences in steroid withdrawal between patients treated with CDP571 (53/181, 29.3%) and placebo (33/90, 36.7%; $P = 0.24$). There were no significant differences in steroid-sparing at week 16, 24, and 32, and no differences in IBDQ scores between patients treated with CDP571 and placebo. Rates of study withdrawal were also similar (CDP571 39% versus placebo 42%). There were no significant differences in adverse (CDP571 70.7% versus placebo 70.5%) and serious (CDP571 12.2% versus placebo 6.8%) adverse events in either treatment group. No patients developed tuberculosis or other opportunistic infections and no cases of malignancy were reported. Anti-CDP571 antibodies developed in 6.1% of tested patients. Infusion reactions occurred in 14.8% of patients receiving placebo and 21.5% patients in the CDP571 group.

CDP571: Pooled Results

CDP571 was not found to be effective in the maintenance of response (RR 1.30; 95% CI 0.91 to 1.85; $P = 0.16$) or maintenance of remission (RR 1.28; 95% CI 0.87 to 1.89; $P = 0.21$) in Crohn's disease. CDP571 did not have corticosteroid-sparing effects in Crohn's disease (RR 0.80; 95% CI 0.56 to 1.14; $P = 0.21$).

DISCUSSION

While corticosteroids are effective in the induction of remission in patients with active Crohn's, over 50% of patients become steroid-

dependent or undergo surgical resection within 1 year of commencing therapy ([Faubion 2001](#)). Immunosuppressives can reduce corticosteroid dependency and maintain disease remission, but have not been shown to reduce the need for surgery or the development of other complications of Crohn's disease ([Cosnes 2005](#)). It is important to consider alternative treatment options in this setting. Tumor necrosis factor-alpha (TNF- α) is an important proinflammatory cytokine that plays a pivotal role in the pathogenesis of Crohn's disease ([van Deventer 2001](#)). Biologic agents active against TNF- α have been investigated in clinical trials and have been found to be effective for induction of remission in Crohn's disease ([Akobeng 2003](#)).

Nine randomized controlled trials evaluating the use of anti-TNF- α therapy for maintenance of remission in Crohn's disease were evaluated. Six trials examined anti TNF- α agents in patients with Crohn's disease with a clinical response or remission to induction therapy; 3 evaluating infliximab, 2 evaluating adalimumab, and 1 evaluating certolizumab. Two trials involving CDP571 did not select for patients with a clinical response to induction therapy. One trial evaluated the corticosteroid-sparing effects of CDP571 in patients in clinical remission on corticosteroid therapy. Infliximab was found to be superior to placebo for maintenance of remission (RR 2.50; 95% CI 1.64 to 3.80), clinical response (RR 2.19; 95% CI 1.27 to 3.75), corticosteroid-sparing effects (RR 3.13; 95% CI 1.25 to 7.81), and complete fistula healing (RR 1.87; 95% CI 1.15 to 3.04) to week 54. Adalimumab was found to be superior to placebo for maintenance of clinical remission, and clinical response to week 54. Although no significant corticosteroid sparing effects were found in the [Sandborn 2007b](#) study, the results from the larger [Colombel 2007](#) study suggest that adalimumab is superior to placebo for corticosteroid sparing (RR 4.25; 95% CI 1.57 to 11.47). Certolizumab pegol was found to be superior to placebo for maintenance of remission (RR 1.68; 95% CI 1.30 to 2.16) and clinical response (RR 1.74; 95% CI 1.41 to 2.13) to week 26. CDP571 was not found to be effective for maintenance of remission or corticosteroid sparing in Crohn's disease.

In the studies that assessed variable doses, no significant differences in clinical efficacy were noted when comparing infliximab 5 mg/kg and 10 mg/kg ([Hanauer 2002](#)), or comparing adalimumab 40 mg weekly or every other week ([Colombel 2007](#)). While comparative trials evaluating different anti-TNF- α agents have not been performed, clinical remission rates appear to be similar among infliximab, adalimumab and certolizumab when assessed at similar time points. Taking the largest trials into account, remission rates were 41.8% at week 30 with infliximab ([Hanauer 2002](#)), 42.9% at week 26 with adalimumab ([Colombel 2007](#)), and 48% at week 26 with certolizumab ([Schreiber 2007](#)). There also appears to be similar response rates with respect to fistula closure; rates of complete fistula closure were similar for infliximab (36% [33/91]) ([Sands 2004](#)) and adalimumab (33% [23/70]) ([Colombel 2007](#)) at week 54. Fistula closure with certolizumab pegol at week 26 was

not reported in the paper, but complete fistula closure at any time during the study was 54% (15/28) with certolizumab and 43% (13/30) with placebo (Schreiber 2007). Although differences in trial durations limit direct comparisons of all data, it appears likely that infliximab, adalimumab, and certolizumab pegol have similar clinical efficacy in patients with Crohn's disease.

Adverse events were observed in approximately equal frequencies in the treatment and placebo groups in the included studies. It should be noted that serious adverse events, including tuberculosis and lymphoma, were reported in several trials. The trial durations and size were insufficient to provide an accurate assessment of the risk of serious adverse events associated with long-term anti-TNF- α therapy. In addition, patients in the placebo arms frequently received open-label anti-TNF- α therapy for induction or crossed over to open-label therapy later in the study, making it difficult to accurately compare the risk between the treatment and placebo groups. The overall serious infection rates in the treatment groups were reported to be 2.8% to 4% overall and did not differ significantly from placebo. Further data has been obtained from observational studies, including the Crohn's Therapy, Resource, Evaluation and Assessment Tool (TREAT) registry. While observational data has limitations, it can provide valuable long-term information not obtained from randomized controlled trials. Recent data from the TREAT registry has found no increased risk of serious infections with infliximab after adjusting for disease severity and corticosteroid use (OR 0.99; 95% CI 0.64 to 1.54; Lichtenstein 2006). However, there is less consensus regarding the risk of malignancy with long-term anti-TNF- α therapy in Crohn's disease. A systematic review evaluating the results of placebo-controlled trials of anti-TNF- α agents in patients with rheumatoid arthritis found an increased risk of malignancy with anti-TNF- α therapy (OR 3.3; 95% CI 1.2 to 9.1) (Bongartz 2006). However, this review has been criticized for failing to adjust for differences in duration of follow-up (Okada 2006) and potential bias (Callegari 2006; Shoor 2006; Corona 2007). Data from the TREAT registry has not shown a significant increase of malignancy in patients with inflammatory bowel disease (Lichtenstein 2007). Given available data, a link between anti-TNF- α therapy and malignancy in patients with Crohn's disease remains unclear.

In conclusion, scheduled therapy with the anti-TNF- α agents infliximab, adalimumab, and certolizumab pegol is effective for maintenance of remission in patients with Crohn's disease who have a clinical response to induction therapy. Infliximab and adalimumab have been shown to have corticosteroid-sparing effects. Infliximab has been shown to maintain complete fistula healing. CDP571 is not effective for maintenance of remission in Crohn's disease. The rates of adverse events are similar in the included studies, but the precise risk of serious adverse events associated with anti-TNF- α therapy in Crohn's disease remains to be defined. The efficacy of anti-TNF- α therapy in pediatric patients with Crohn's disease should be investigated in future reviews.

AUTHORS' CONCLUSIONS

Implications for practice

There is evidence from randomized controlled trials that infliximab, adalimumab, and certolizumab pegol are effective for maintenance of remission in patients with Crohn's disease who have a clinical response to induction therapy. Infliximab is effective for maintenance of fistula closure in patients with perianal or enterocutaneous fistulizing disease who have a clinical response to induction therapy. Infliximab and adalimumab are currently approved for use in Crohn's disease in many countries (including the USA, Canada and the European Union), while certolizumab pegol remains under review by regulatory agencies. Adverse events are observed in approximately equal frequencies in the treatment and placebo groups in the included studies, but the follow up duration of these trials is generally too short to allow an adequate assessment of the long-term adverse events associated with anti-TNF- α therapy. There is no evidence to support the use of CDP571 for maintenance of remission in Crohn's disease.

Implications for research

Future trials involving anti-TNF- α therapies should have consistent study endpoints and comprehensive data collection made publicly available to allow more accurate comparisons between trials. Comprehensive data on anti-TNF- α therapy in pediatric and pregnant patients should be obtained. Direct comparative trials assessing different biologic agents should be pursued. Further data on long-term clinical response and remission rates, long-term safety, and data on the impact of anti-TNF- α therapy on hospitalizations and surgeries should be obtained. The impact of concomitant immunosuppressive use on clinical efficacy and safety endpoints should be further defined. The role of anti-TNF- α agents early in the course of Crohn's disease, and whether this strategy may change the natural history of disease, should continue to be evaluated.

ACKNOWLEDGEMENTS

Funding for the IBD/FBD Review Group (October 1, 2005 - September 30, 2010) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch; the Canadian Agency for Drugs and Technologies in Health (CADTH); and the CIHR Institutes of Health Services and Policy Research; Musculoskeletal Health and Arthritis; Gender and Health; Human Development, Child and Youth Health; Nutrition, Metabolism and Diabetes; and Infection and Immunity.

Miss Ila Stewart has provided support for the IBD/FBD Review Group through the Olive Stewart Fund.

REFERENCES

References to studies included in this review

Colombel 2007 *{published data only}*

Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;**132**(1):52–65.

Feagan 2006 *{published data only}*

Feagan BG, Sandborn WJ, Lichtenstein G, Radford-Smith G, Patel J, Innes A. CDP571, a humanized monoclonal antibody to tumour necrosis factor-alpha, for steroid-dependent Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Aliment Pharmacol Ther* 2006;**23**(5):617–28.

Hanauer 2002 *{published and unpublished data}*

Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**(9317):1541–9.

Rutgeerts 1999 *{published and unpublished data}*

Rutgeerts P, D'Haens G, Targan S, Vasilias E, Hanauer SB, Present DH, et al. Efficacy and safety of retreatment with anti-tumour necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* 1999;**117**(4):761–9.

Sandborn 2001a *{published data only}*

Sandborn WJ, Feagan BG, Hanauer SB, Present DH, Sutherland LR, Kamm MA, et al. An engineered human antibody to TNF (CDP571) for active Crohn's disease: a randomized double-blind placebo-controlled trial. *Gastroenterology* 2001;**120**(6):1330–8.

Sandborn 2004 *{published data only}*

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

Sandborn 2007b *{published data only}*

Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, Macintosh DG, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007;**56**(9):1232–9.

Sands 2004 *{published and unpublished data}*

Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;**350**(9):876–85.

Schreiber 2007 *{published data only}*

Schreiber S, Khaliq-Kareemi M, Lawrance IC, Thomsen OO, Hanauer SB, McColm J, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med* 2007;**357**(3):239–50.

References to studies excluded from this review

D'haens 1999 *{published data only}*

D'haens G, Van Deventer S, Van Hogezaand R, Chalmers D, Kothe C, Baert F, et al. Endoscopic and histological healing with infliximab anti-tumour necrosis factor antibodies in Crohn's disease: A European multicenter trial. *Gastroenterology* 1999;**116**(5):1029–34.

Feagan 2003 *{published data only}*

Feagan BG, Yan S, Bala M, Bao W, Lichtenstein GR. The effects of infliximab maintenance therapy on health-related quality of life. *Am J Gastroenterol* 2003;**98**(10):2232–8.

Geboes 2005 *{published data only}*

Geboes K, Rutgeerts P, Opdenakker G, Olson A, Patel K, Wagner CL, et al. Endoscopic and histologic evidence of persistent mucosal healing and correlation with clinical improvement following sustained infliximab treatment for Crohn's disease. *Curr Med Res Opin* 2005;**21**(11):1741–54.

Hanauer 2006 *{published data only}*

Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, et al. Human anti-tumour necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006;**130**(2):323–33.

Hyams 2007 *{published data only}*

Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, Johans J, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology* 2007;**132**(3):863–73.

Lemann 2006 *{published data only}*

Lemann M, Mary JY, Duclos B, Veyrac M, Dupas JL, Delchier JC, et al. Infliximab plus azathioprine for steroid-dependent Crohn's disease patients: a randomized placebo-controlled trial. *Gastroenterology* 2006;**130**(4):1054–61.

Lichtenstein 2005 *{published data only}*

Lichtenstein GR, Yan S, Bala M, Blank M, Sands BE. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. *Gastroenterology* 2005;**128**(4):862–9.

Present 1999 *{published data only}*

Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezaand RA, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;**340**(18):1398–405.

Rutgeerts 2004 *{published data only}*

Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004;**126**(2):402–13.

Rutgeerts 2006a *{published data only}*

Rutgeerts P, Diamond RH, Bala M, Olson A, Lichtenstein GR, Bao W, et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. *Gastrointest Endosc* 2006;**63**(3):433–42.

Rutgeerts 2006b *{published data only}*

Rutgeerts P, Sandborn WJ, Fedorak RN, Rachmilewitz D, Tarabar D, Gibson P, et al. Onercept for moderate-to-severe Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Clin Gastroenterol Hepatol* 2006;**4**(7):888–93.

Sandborn 2001b *{published data only}*

Sandborn WJ, Hanauer SB, Katz S, Safdi M, Wolf DG, Baerg RD, et al. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2001;**121**(5):1088–94.

Sandborn 2007a {published data only}

Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Colombel JF, Panaccione R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007;**146**(12):829–38.

Sandborn 2007c {published data only}

Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, et al. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007;**357**(3):228–38.

Schreiber 2005a {published data only}

Schreiber S, Rutgeerts P, Fedorak RN, Khaliq-Kareemi M, Kamm MA, Boivin M, et al. A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. *Gastroenterology* 2005;**129**(3):807–18.

Stack 1997 {published data only}

Stack WA, Mann SD, Roy AJ, Heath P, Sopwith M, Freeman J, et al. Randomised controlled trial of CDP571 antibody to tumour necrosis factor-alpha in Crohn's disease. *Lancet* 1997;**349**(9051):521–4.

Targan 1997 {published data only}

Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997;**337**(15):1029–35.

Winter 2004 {published data only}

Winter TA, Wright J, Ghosh S, Jahnsen J, Innes A, Round P. Intravenous CDP870, a PEGylated Fab' fragment of a humanized anti-tumour necrosis factor antibody, in patients with moderate-to-severe Crohn's disease: an exploratory study. *Aliment Pharmacol Ther* 2004;**20**(11-12):1337–46.

References to studies awaiting assessment**Sandborn 2007d** {published data only}

Sandborn WJ, Hanauer SB, Rutgeerts PJ, Colombel JF, Schreiber S. Re-induction and maintenance therapy with subcutaneous certolizumab pegol in patients with Crohn's disease following treatment failure: PRECISE 4 results. *Gastroenterology* 2007;**132**(4 Suppl 2):A505.

Schreiber 2007b {published data only}

Schreiber S, Hanauer SB, Feagan BG, Bloomfield R, Rutgeerts P, Sandborn WJ. Long-term treatment with certolizumab pegol for up to 18 months in patients with active Crohn's disease: PRECISE 3 efficacy results. *Gastroenterology* 2007;**132**(4 Suppl 2):A503.

Additional references**Akobeng 2003**

Akobeng AK, Zachos M. Tumor necrosis factor-alpha antibody for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [Art. No.: CD003574. DOI: 10.1002/14651858.CD003574.pub2]

Bongartz 2006

Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and

meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006;**295**(19):2275–85.

Breese 1994

Breese EJ, Michie CA, Nicholls SW, Murch SH, Williams CB, Domizio P, et al. Tumor necrosis factor alpha-producing cells in the intestinal mucosa of children with inflammatory bowel disease. *Gastroenterology* 1994;**106**(6):1455–66.

Callegari 2006

Callegari PE, Schaible TF, Boscia JA. Risk of serious infections and malignancies with anti-TNF antibody therapy in rheumatoid arthritis. *JAMA* 2006;**296**(18):2202.

Corona 2007

Corona R, Bigby M. What are the risks of serious infections and malignancies for patients treated with anti-tumor necrosis factor antibodies?. *Arch Dermatol* 2007;**143**(3):405–6.

Cosnes 2005

Cosnes J, Nion-Larmurier I, Beaugerie L, Afchain P, Tiret E, Gendre JP. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. *Gut* 2005;**54**(2):237–41.

Faubion 2001

Faubion WA Jr, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology* 2001;**121**(2):255–60.

Feagan 2000

Feagan BG, Fedorak RN, Irvine EJ, Wild G, Sutherland L, Steinhart AH, et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. *N Engl J Med* 2000;**342**(22):1627–32.

Higgins 2006

Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.5 [updated May 2005]. In: *The Cochrane Library, Issue 3, 2005*. Chichester, UK: John Wiley & Sons, Ltd., 2005.

Jadad 1996

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gagliardi DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Control Clin Trials* 1996;**17**(1):1–12.

Komatsu 2001

Komatsu M, Kobayashi D, Saito K, Furuya D, Yagihashi A, Araake H, et al. Tumor necrosis factor-alpha in serum of patients with inflammatory bowel disease as measured by a highly sensitive immunoprecipitation. *Clin Chem* 2001;**47**(7):1297–301.

Lichtenstein 2006

Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Chen DM, et al. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol* 2006;**4**(5):621–30.

Lichtenstein 2007

Lichtenstein GR, Cohen RD, Feagan BG, Sandborn WJ, Salzberg BA, Chen DM, et al. Safety of infliximab and other Crohn's disease therapies -- TREAT registry data with nearly 20,000 patient-years of follow up. *Gastroenterology* 2007;**132**(4 Suppl 2):A178.

Okada 2006

Okada SK, Siegel JN. Risk of serious infections and malignancies with anti-TNF antibody therapy in rheumatoid arthritis. *JAMA* 2006;**296**(18):2201–2.

Pearson 1998

Pearson DC, May GR, Fick G, Sutherland LR. Azathioprine for maintenance of remission of Crohn's disease. *Cochrane Database of Systematic Reviews* 1998, Issue 4.

Reimund 1996

Reimund JM, Wittersheim C, Dumont S, Muller CD, Kenney JS, Baumann R, et al. Increased production of tumour necrosis factor-alpha interleukin-1 beta, and interleukin-6 by morphologically normal intestinal biopsies from patients with Crohn's disease. *Gut* 1996;**39**(5):684–9.

Shoor 2006

Shoor S. Review: anti-tumor necrosis factor antibody therapy for rheumatoid arthritis increases risk for serious infection and malignancy. *ACP J Club* 2006;**145**(3):65.

van Deventer 2001

van Deventer SJ. Transmembrane TNF-alpha, induction of apoptosis, and the efficacy of TNF-targeting therapies in Crohn's disease. *Gastroenterology* 2001;**121**(5):1242–6.

van Dullemen 1995

van Dullemen HM, van Deventer SJ, Hommes DW, Bijl HA, Jansen J, Tytgat GN, et al. Treatment of Crohn's disease with anti-tumor necrosis factor chimeric monoclonal antibody (cA2). *Gastroenterology* 1995;**109**(1):129–35.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Colombel 2007

Methods	Randomized, double-blind, placebo-controlled trial involving 92 centers. 60 week maintenance trial.
Participants	854 adults; 326 males, 528 females with active Crohn's disease (baseline CDAI 220-450).
Interventions	Responders to induction (n = 499) randomized to adalimumab 40 mg weekly or every other week (n = 329) or placebo (n = 170)
Outcomes	Coprimary outcome measurements: Responders that achieve clinical remission at weeks 26 and 56. Clinical remission defined as a CDAI <150. Clinical response defined as CDAI reduction of at least 70 or 100.
Notes	

Colombel 2007 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Feagan 2006

Methods	Randomized, double-blind, placebo-controlled trial involving 59 centers. 36 week steroid-withdrawal trial.	
Participants	271 adults with steroid-dependent Crohn's disease currently in clinical remission (CDAI <150).	
Interventions	CDP571 10 mg/kg or placebo q8w; steroid tapering per predefined protocol.	
Outcomes	Primary outcome: Percentage of patients with steroid sparing at week 36. Clinical remission defined as a CDAI <= 150.	
Notes		

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hanauer 2002

Methods	Randomized, double-blind, placebo-controlled trial involving 55 centers. 54 week maintenance trial.	
Participants	573 adults; 239 males, 334 females with active Crohn's disease (baseline CDAI 220-400).	
Interventions	Subjects received one infusion of infliximab 5 mg/kg, then were randomized to placebo or infliximab at weeks 2 and 6 and every 8 weeks thereafter until week 46.	
Outcomes	Coprimary outcome measures: 1) Time to loss of response up to/including week 54. 2) Responders in remission at week 30. Loss of response defined as CDAI of at least 175, CDAI increase of at least 35%, and a CDAI at least 70 points more than the week 2 CDAI for at least 2 consecutive visits. Remission defined as CDAI <150.	
Notes		

Risk of bias

Hanauer 2002 (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Rutgeerts 1999

Methods	Randomized, double-blind, placebo-controlled trial involving 17 centers. 48 week maintenance trial.	
Participants	73 adults; 38 males, 35 females with active Crohn's disease (baseline CDAI 220-400).	
Interventions	Subjects with a clinical response to an initial infusion to infliximab (or placebo) randomized to infliximab 10 mg/kg or placebo.	
Outcomes	Primary outcome: number of subjects maintaining clinical response at each 4 week evaluation. Secondary outcome included clinical remission at each 4 week evaluation. Clinical response defined as CDAI decrease of at least 70. Clinical remission defined as CDAI <150.	
Notes		

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Sandborn 2001a

Methods	Randomized, double-blind, placebo-controlled trial involving 21 centers. 24 week induction and maintenance trial.	
Participants	169 adults; 86 males, 83 females with active Crohn's disease (baseline CDAI 220-450).	
Interventions	Subjects given single dose of CDP571 or placebo, then retreated with CDP571 or placebo every 8 or 12 weeks until week 24.	
Outcomes	Primary outcome measurement: Clinical response at week 2. Secondary outcome measurements included clinical remission at each study visit. Clinical response defined as a CDAI decrease of at least 70 or 100. Clinical remission defined as CDAI <150.	
Notes		

Risk of bias

Item	Authors' judgement	Description
------	--------------------	-------------

Sandborn 2001a (Continued)

Allocation concealment?	Yes	A - Adequate
-------------------------	-----	--------------

Sandborn 2004

Methods	Randomized, double-blind, placebo-controlled trial involving 68 centers. 28 week induction and maintenance trial.
Participants	396 adults; 148 males, 247 females with active Crohn's disease (baseline CDAI 220-450).
Interventions	Subjects received CDP571 10 mg/kg or placebo every 8 weeks to week 24.
Outcomes	Coprimary outcome measurements: Clinical response or remission at week 28. Clinical response defined as CDAI decrease of at least 100. Clinical remission defined as CDAI < 150.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Sandborn 2007b

Methods	Randomized, double-blind, placebo-controlled trial involving 53 centers. 56 week maintenance trial.
Participants	55 adults; 22 males, 33 females in remission (CDAI < 150) at week 0 and 4 after adalimumab induction.
Interventions	Subjects entering clinical remission after adalimumab induction were randomized to adalimumab 40 mg or placebo every week or every other week to week 56.
Outcomes	Primary outcome measurement: Clinical remission at week 56. Clinical remission defined as CDAI < 150.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Sands 2004

Methods	Randomized, double-blind, placebo-controlled trial involving 49 centers. 54 week maintenance trial for fistulizing disease.
Participants	195 adults; 101 males, 94 females. Subjects had one or more abdominal or perianal fistulas with a response to infliximab induction.
Interventions	Subjects with response to induction randomized to infliximab 5 mg/kg or placebo every 8 weeks to week 54.
Outcomes	Primary outcome measurement: Time to loss of response among subjects with a response to a 3 dose induction regimen of infliximab. Secondary outcome measurement included clinical response in those subjects with active Crohn's disease. Clinical response defined as CDAI decrease of at least 70 points and 25 percent.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Schreiber 2007

Methods	Randomized, double-blind, placebo-controlled trial involving 147 centers. 26 week maintenance trial.
Participants	425 adults; 201 males, 224 females with active Crohn's disease (baseline CDAI 220-450) with a response to certolizumab induction.
Interventions	Subjects with a clinical response to certolizumab induction were randomized to certolizumab (400 mg) or placebo every 4 weeks to week 26.
Outcomes	Primary outcome measurement: Clinical response at week 26 in patients with a baseline CRP of at least 10mg/L. Secondary outcome measurements included response and remission at week 26 irrespective of baseline CRP. Clinical response defined as CDAI decrease of at least 100. Clinical remission defined as CDAI < 150.
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

D'haens 1999	Evaluated single infusion of infliximab for induction of remission rather than maintenance
Feagan 2003	Subanalysis of the Hanauer 2002 trial (ACCENT I)
Geboes 2005	Subanalysis of the Hanauer 2002 trial (ACCENT I)
Hanauer 2006	Evaluated adalimumab for induction of remission rather than maintenance
Hyams 2007	Evaluated children only
Lemann 2006	Evaluated infliximab for induction of remission rather than maintenance
Lichtenstein 2005	Subanalysis of the Sands 2004 trial (ACCENT II)
Present 1999	Evaluated infliximab induction for fistula healing
Rutgeerts 2004	Subanalysis of the Hanauer 2002 trial (ACCENT I)
Rutgeerts 2006a	Subanalysis of the Hanauer 2002 trial (ACCENT I)
Rutgeerts 2006b	Evaluated onercept for induction of remission rather than maintenance
Sandborn 2001b	Evaluated etanercept for induction of remission rather than maintenance
Sandborn 2007a	Evaluated adalimumab for induction of remission rather than maintenance
Sandborn 2007c	Evaluated certolizumab for induction and maintenance of remission and used combined induction and maintenance endpoints.
Schreiber 2005a	Evaluated certolizumab for induction of remission rather than maintenance
Stack 1997	Evaluated CDP571 for induction of remission rather than maintenance
Targan 1997	Evaluated infliximab for induction of remission rather than maintenance
Winter 2004	Evaluated certolizumab for induction of remission rather than maintenance

DATA AND ANALYSES

Comparison 1. Infliximab versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Remission	2	404	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [1.64, 3.80]
2 Clinical Response	2	404	Risk Ratio (M-H, Random, 95% CI)	2.19 [1.27, 3.75]
3 Steroid Sparing	1	335	Risk Ratio (M-H, Fixed, 95% CI)	3.13 [1.25, 7.81]
4 Fistula Healing	1	189	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.15, 3.04]

Comparison 2. Adalimumab versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Remission	2	499	Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Clinical Response	1		Risk Ratio (M-H, Fixed, 95% CI)	2.69 [1.88, 3.86]
3 Steroid Sparing	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 3. CDP571 versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Remission	2	562	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.87, 1.89]
2 Clinical Response	1	395	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.91, 1.85]
3 Steroid Sparing	1	271	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.56, 1.14]

Comparison 4. Certolizumab versus placebo

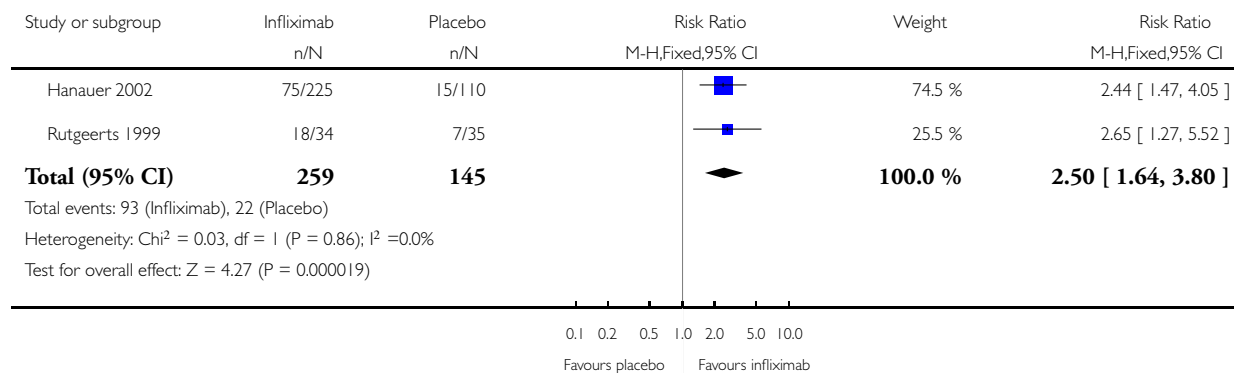
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Remission	1	425	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [1.30, 2.16]
2 Clinical Response	1	425	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [1.41, 2.13]

Analysis 1.1. Comparison 1 Infliximab versus placebo, Outcome 1 Clinical Remission.

Review: Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease

Comparison: 1 Infliximab versus placebo

Outcome: 1 Clinical Remission

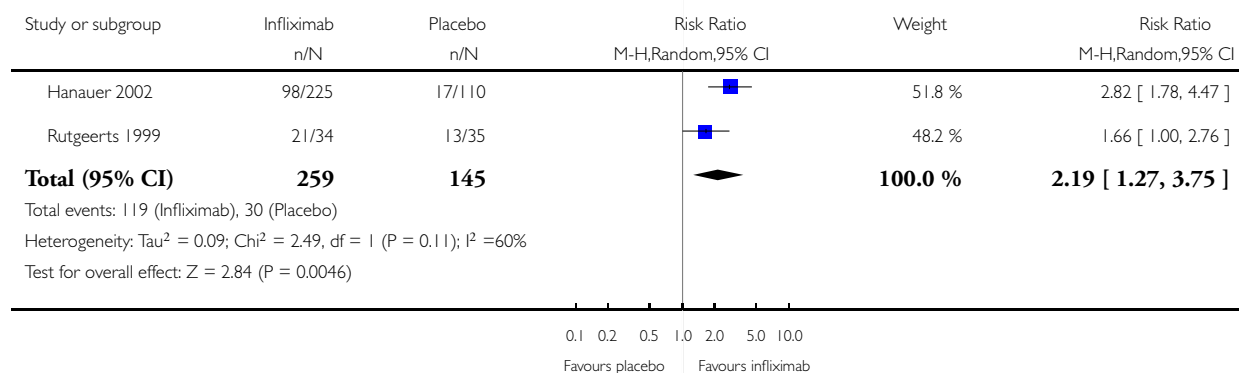


Analysis 1.2. Comparison 1 Infliximab versus placebo, Outcome 2 Clinical Response.

Review: Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease

Comparison: 1 Infliximab versus placebo

Outcome: 2 Clinical Response

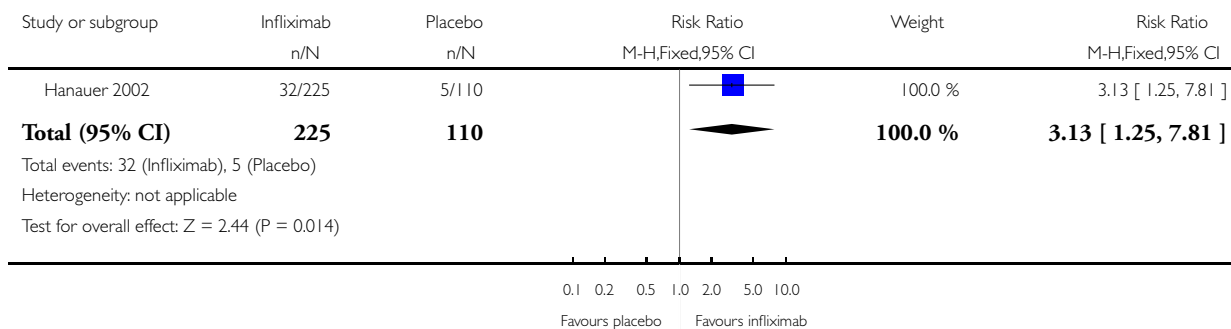


Analysis 1.3. Comparison 1 Infliximab versus placebo, Outcome 3 Steroid Sparing.

Review: Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease

Comparison: 1 Infliximab versus placebo

Outcome: 3 Steroid Sparing

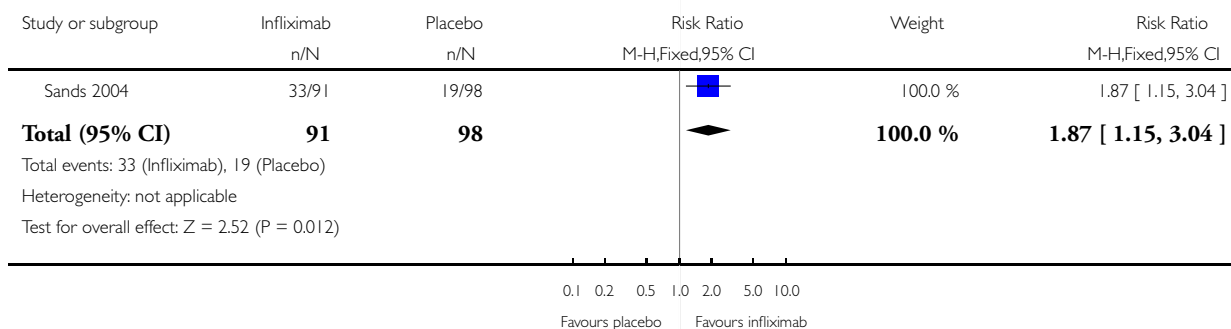


Analysis 1.4. Comparison 1 Infliximab versus placebo, Outcome 4 Fistula Healing.

Review: Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease

Comparison: 1 Infliximab versus placebo

Outcome: 4 Fistula Healing

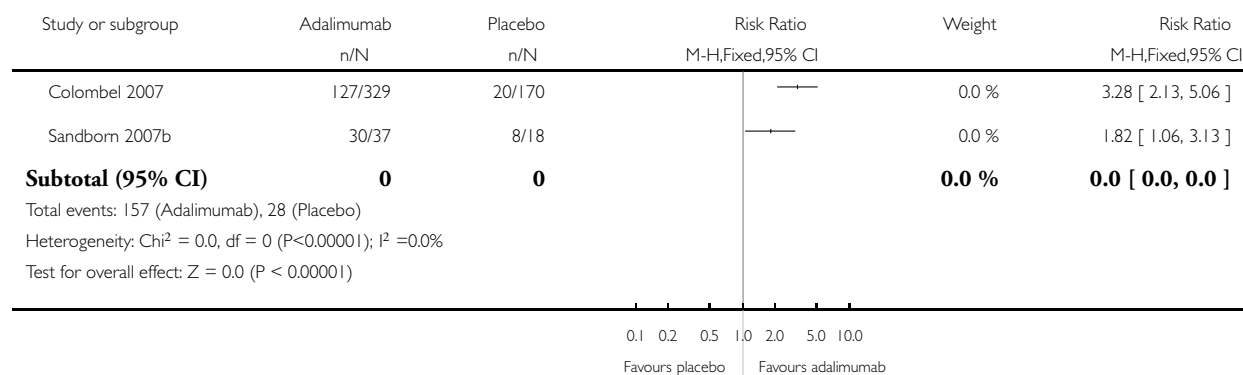


Analysis 2.1. Comparison 2 Adalimumab versus placebo, Outcome 1 Clinical Remission.

Review: Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease

Comparison: 2 Adalimumab versus placebo

Outcome: 1 Clinical Remission

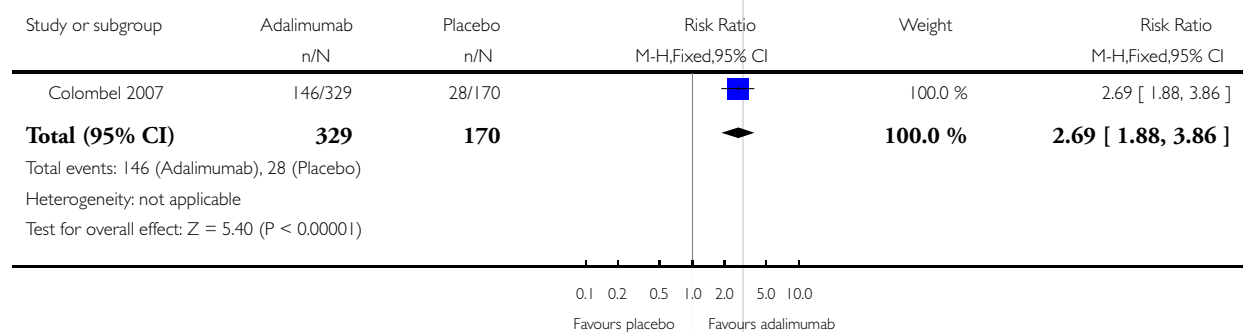


Analysis 2.2. Comparison 2 Adalimumab versus placebo, Outcome 2 Clinical Response.

Review: Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease

Comparison: 2 Adalimumab versus placebo

Outcome: 2 Clinical Response

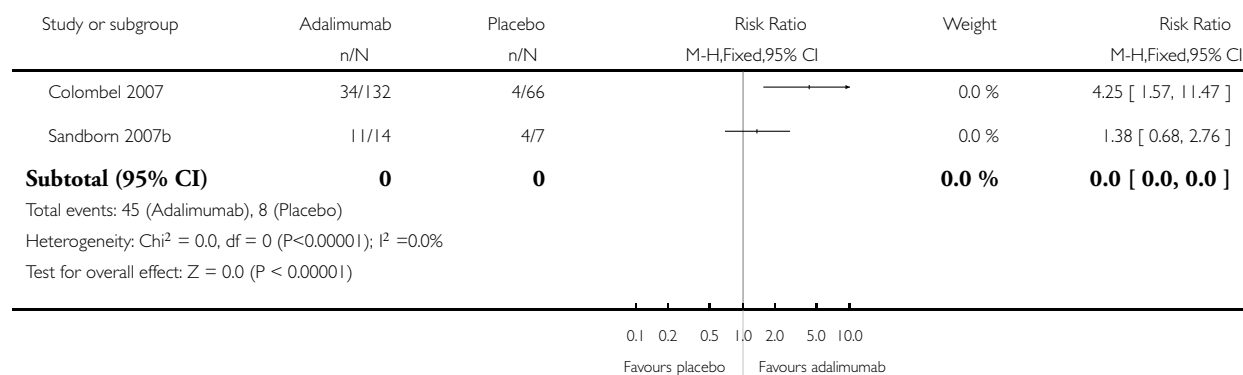


Analysis 2.3. Comparison 2 Adalimumab versus placebo, Outcome 3 Steroid Sparing.

Review: Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease

Comparison: 2 Adalimumab versus placebo

Outcome: 3 Steroid Sparing

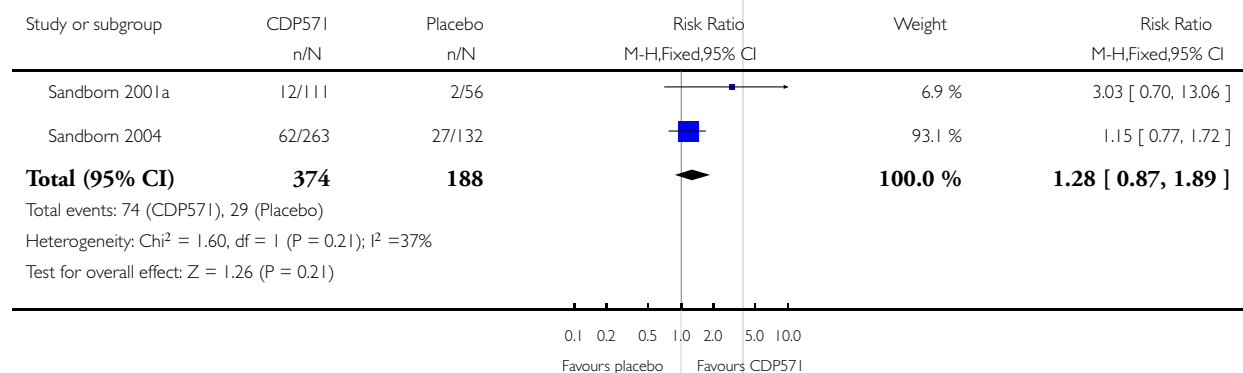


Analysis 3.1. Comparison 3 CDP571 versus placebo, Outcome 1 Clinical Remission.

Review: Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease

Comparison: 3 CDP571 versus placebo

Outcome: 1 Clinical Remission

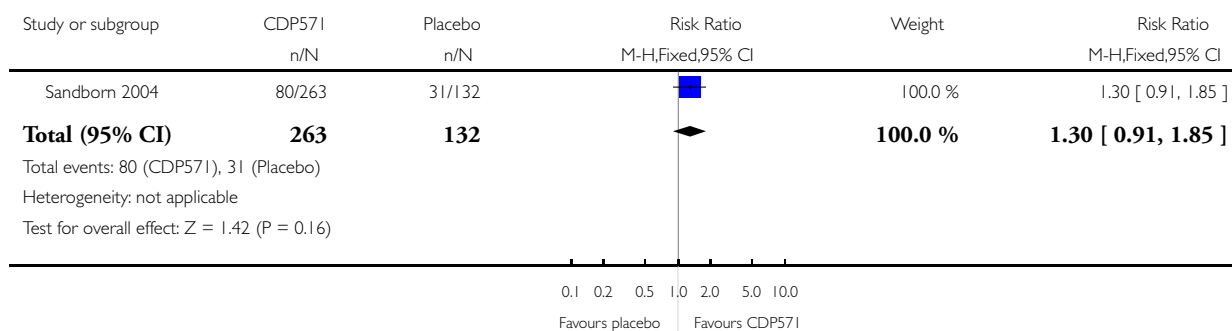


Analysis 3.2. Comparison 3 CDP571 versus placebo, Outcome 2 Clinical Response.

Review: Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease

Comparison: 3 CDP571 versus placebo

Outcome: 2 Clinical Response

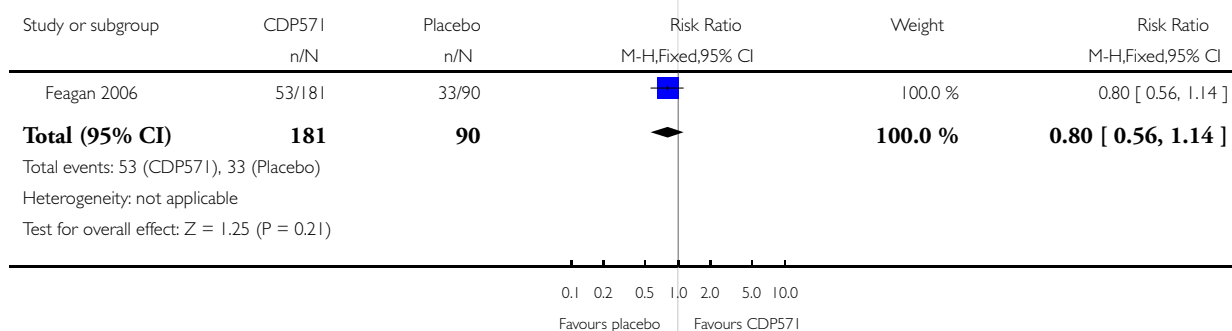


Analysis 3.3. Comparison 3 CDP571 versus placebo, Outcome 3 Steroid Sparing.

Review: Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease

Comparison: 3 CDP571 versus placebo

Outcome: 3 Steroid Sparing

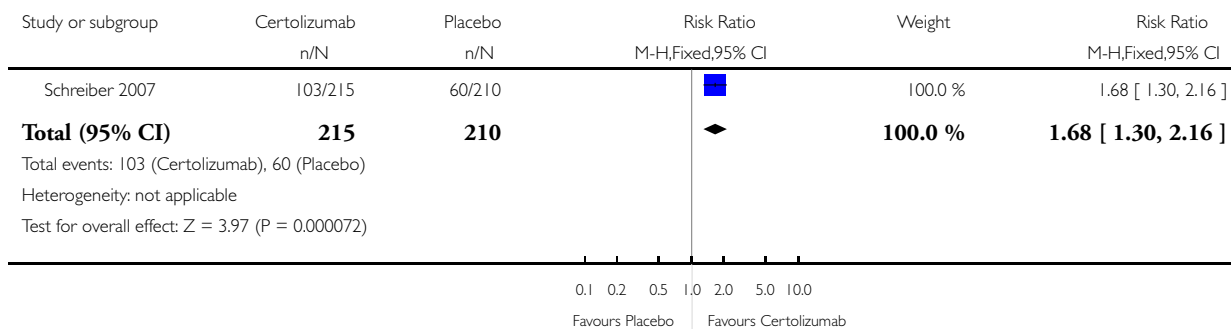


Analysis 4.1. Comparison 4 Certolizumab versus placebo, Outcome 1 Clinical Remission.

Review: Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease

Comparison: 4 Certolizumab versus placebo

Outcome: 1 Clinical Remission

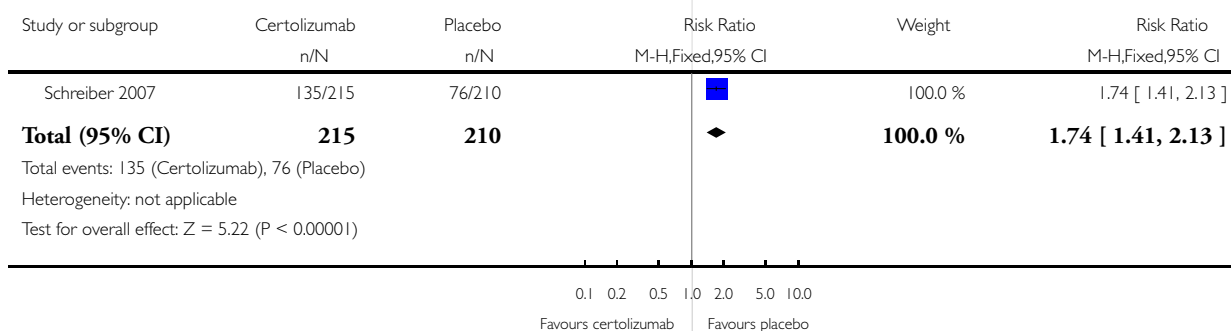


Analysis 4.2. Comparison 4 Certolizumab versus placebo, Outcome 2 Clinical Response.

Review: Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease

Comparison: 4 Certolizumab versus placebo

Outcome: 2 Clinical Response



WHAT'S NEW

Last assessed as up-to-date: 2 October 2007.

1 May 2008	Amended	Non pooled data are presented for adalimumab studies.
1 May 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 1, 2008

3 October 2007	New citation required and conclusions have changed	Substantive amendment
----------------	--	-----------------------

CONTRIBUTIONS OF AUTHORS

Dr. Bickston and Behm contributed equally on conceiving and designing the review, screening search results, appraising quality and extracting data from papers, and writing to authors for additional information.

Dr. Behm was primarily responsible for designing search strategies for the review, undertaking searches, data collection, organizing retrieval of papers, screening retrieved papers against inclusion criteria, obtaining and screening data on unpublished studies, data management, and data analysis.

DECLARATIONS OF INTEREST

Dr Stephen Bickston has been a consultant for Centocor and Abbott and is a PI for ongoing trials for Centocor, Abbott, Elan, and Otsuka. The Centocor trial involves the monitoring of patients who have received TNF-alpha antibody agents or placebo in clinical trials. The Abbott trial will involve the observation of patients receiving TNF-alpha agents as part of their usual clinical care. Dr. Brian Behm has no known potential conflicts of interest.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal [therapeutic use]; Anti-Inflammatory Agents [*therapeutic use]; Crohn Disease [*drug therapy]; Immunoglobulin Fab Fragments [therapeutic use]; Polyethylene Glycols [therapeutic use]; Randomized Controlled Trials as Topic; Remission Induction; Tumor Necrosis Factor-alpha [*antagonists & inhibitors]

MeSH check words

Humans