CME

REVIEW

Efficacy of Biological Therapies in Inflammatory Bowel Disease: Systematic Review and Meta-Analysis

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OBJECTIVES: **Crohn's disease (CD) and ulcerative colitis (UC) are inflammatory disorders of the gastrointestinal tract of unknown etiology. Evidence for treatment of the condition with biological therapies exists, but no systematic review and meta-analysis has examined this issue in its entirety.**

METHODS: **MEDLINE, EMBASE, and the Cochrane central register of controlled trials were searched (through to December 2010). Trials recruiting adults with active or quiescent CD or UC and comparing biological therapies (anti-tumor necrosis factor-α (TNFα) antibodies or natalizumab) with placebo were eligible. Dichotomous symptom data were pooled to obtain relative risk (RR) of failure to achieve remission in active disease and RR of relapse of activity in quiescent disease once remission had occurred, with a 95% confidence interval (CI).**

RESULTS: **The search strategy identified 3,061 citations, 27 of which were eligible. Anti-TNFα antibodies and natalizumab were both superior to placebo in inducing remission of luminal CD (RR of no remission = 0.87; 95% CI 0.80–0.94 and RR = 0.88; 95% CI 0.83–0.94, respectively). Anti-TNFα antibodies were also superior to placebo in preventing relapse of luminal CD (RR of relapse = 0.71; 95% CI 0.65–0.76). Infliximab was superior to placebo in inducing remission of moderate to severely active UC (RR = 0.72; 95% CI 0.57–0.91).**

CONCLUSIONS: **Biological therapies were superior to placebo in inducing remission of active CD and UC, and in preventing relapse of quiescent CD.**

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INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory disorders of the gastrointestinal tract of unknown etiology. The incidence of CD in the United States has been estimated at between 6 and 8 per 100,000 (1,2), with a prevalence of between 130 and 200 per 100,000 (1–3). Both the incidence and prevalence of UC are slightly higher at between 7 and 9 (1,4) and 210 and 240 per 100,000, respectively (1,3,4). Extrapolating these data to the population of the United States suggests that there are in excess of 1 million people living with inflammatory bowel disease (IBD).

Patients with CD and UC often experience flares of disease activity, despite maintenance therapy with 5-aminosalicylic acid compounds. These flares are usually treated with corticosteroids (5–7), but these have potentially serious adverse effects. In addition, between 20 and 40% of IBD patients become either dependent on them to maintain remission of disease activity (8–10), despite immunosuppressant drugs used in an attempt to reduce corticosteroid requirements, or become resistant to their beneficial effects. Such patients often require surgery, such as limited intestinal resection in CD or panproctocolectomy and ileal pouch formation in UC. Patients with UC may also present acutely with fulminant colitis, which does not respond to intravenous corticosteroids in a timely manner, and until recently, treatment options in this situation were limited, consisting of either cyclosporine or emergency colectomy (11).

Proposed mediators of inflammation in IBD include the pro-inflammatory cytokine tumor necrosis factor-α (TNFα) and α_4 integrins, which are cell-surface glycoproteins. Concentrations of TNFα are elevated in the stool (12), mucosa (13,14), and blood of patients with IBD (15). The α_4 integrins are thought to have a role in

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Box 1. Eligibility criteria

Randomized controlled trials.
Adults (>90% of patients aged >16 years) with inflammatory bowel disease.
Compared biological therapies* with placebo.
Minimum duration of therapy of 14 days in trials reporting induction of remission in active disease.
Minimum duration of therapy of 6 months in trials reporting prevention of relapse of disease activity in quiescent disease.
Assessment of failure of remission in active disease or relapse of disease activity in quiescent disease.†

*Anti-TNFα antibodies (infliximab, adalimumab, and certolizumab) or anti-α_4-integrin antibodies (natalizumab).
†Preferably using the Crohn's disease activity index in active or quiescent Crohn's disease (CD), fistula healing or recrudescence in fistulizing CD, and endoscopic mucosal healing or endoscopic relapse in ulcerative colitis; however, if these outcome measures were not reported then other measures were permissible according to a pre-defined hierarchy (**Box 2**).

Box 2. Data extraction methodology

Outcome of interest: failure of remission in active luminal Crohn's disease (CD) or active ulcerative colitis (UC), failure of fistula healing in active fistulizing CD, relapse of disease activity in quiescent luminal CD or quiescent UC, recrudescence of fistula in quiescent fistulizing CD.
Hierarchy of reporting of outcomes used:
Luminal CD remission: Crohn's disease activity index (CDAI) < 150 (or other validated index), endoscopic evidence of complete remission (most stringent definition available, for example, complete mucosal healing), clinical assessment of complete remission, or other author-defined criteria for remission.
Luminal CD relapse: CDAI≥150, endoscopic/radiological evidence of relapse (most stringent definition available), other CDAI cutoff, clinical assessment as relapsed, or other author-defined criteria for relapse.
Fistulizing CD remission: healing of fistula.
Fistulizing CD relapse: recrudescence of fistula.
UC remission: endoscopic evidence of complete remission (most stringent definition available, for example, complete mucosal healing), clinical assessment as complete remission, recognized scoring system of complete remission (for example, Truelove and Witt (6)), other author-defined criteria for remission.
UC relapse: endoscopic evidence of any degree of relapse, clinical assessment as relapsed, recognized scoring system as relapsed (for example, Truelove and Witt (6)), or other author-defined criteria for relapse.
Time of outcome assessment: up to 4 months for induction of remission trials, and ≥6 months for prevention of relapse trials. Last point of trial follow-up used to extract outcomes data wherever trial reporting allowed this, and it was within the limit of the time of outcome assessment (for example, if outcome data were reported at 6, 12, and 24 weeks for an induction of remission trial, the outcome at 12 weeks was extracted preferentially).
Denominator used: true intention-to-treat analysis, if not available then all evaluable patients.

the migration of leukocytes across the vascular endothelium, facilitating their homing to areas of inflammation in the gut, where they initiate and maintain this inflammation (16,17). Monoclonal antibodies to both TNFα and α_4 integrin were developed in the 1990s, and preclinical studies demonstrated that they could treat the spontaneous colitis observed in the cotton-top tamarin effectively (18,19).

Monoclonal antibodies, or antigen-binding fragments of antibodies attached to polyethylene glycol, targeting TNFα, and monoclonal antibodies targeting α_4 integrin, have been used to treat patients with IBD who have failed conventional therapies. Chimeric, partly humanized, or fully humanized monoclonal antibodies, or antibody fragments, have been compared with placebo in randomized controlled trials (RCTs) for the induction of remission of active CD, prevention of relapse of quiescent CD, healing and prevention of recrudescence of fistulizing CD, and monoclonal antibodies targeting TNFα in moderate-to-severe, or fulminant, UC. Previous meta-analyses have examined the benefit of these biological therapies in various situations (20–28), but none have studied all current available evidence for their role in IBD, and some have important limitations. We have therefore conducted a systematic review and meta-analysis of RCTs to estimate the efficacy and safety of these drugs in IBD.

METHODS

Search strategy and study selection

A search of the medical literature was conducted using MEDLINE (1966 to December 2010), EMBASE (1984 to December 2010), the Cochrane central register of controlled trials (Issue 4, October 2010), and the Cochrane IBD Group Specialized Trials Register. RCTs examining the effect of biological therapies, restricted to those approved for use by the US Food and Drug Administration (FDA), in adult patients (> 90% of participants over the age of 16 years) with active or quiescent IBD were eligible for inclusion (**Box 1**). The first period of crossover RCTs were also eligible for inclusion. The control arms were required to receive placebo. Duration of therapy had to be at least 14 days for induction of remission trials in active IBD and at least 6 months in maintenance of remission trials in quiescent IBD. Trials using any dose and regimen of biological therapy were considered eligible. Studies had to report either an assessment of failure of remission in active IBD or relapse of disease activity in quiescent IBD, preferably using the Crohn's disease activity index in luminal CD, fistula healing or recrudescence in fistulizing CD, or endoscopic mucosal healing or endoscopic relapse in UC; however, if these outcome measures were not reported then other measures were

permissible according to a pre-defined hierarchy (**Box 2**). First and senior authors of studies were contacted to provide additional information on trials where required.

The literature search was performed as part of a broader exercise to inform the update of the American College of Gastroenterology's monograph for the management of IBD. Specifically, studies on IBD were identified with the terms *Crohn disease*, *inflammatory bowel disease*, *colitis*, *ileitis*, or *ulcerative colitis* (both as medical subject headings and free text terms) or *Crohn's disease* and *regional enteritis* (as free text terms). These were combined using the set operator and with studies identified with the terms *tumor necrosis factor-alpha or tumour necrosis factor antibody* (both as medical subject headings terms and free text terms) or the following free text terms *infliximab*, *monoclonal antibody cA2*, *remicade*, *adalimumab*, *humira*, *certolizumab*, *CDP-870*, *CDP870*, *natalizumab*, *antegren*, *tysabri*, *tumor necrosis factor antibody*, *anti tumour necrosis factor*, *anti tumor necrosis factor*, *anti tumour necrosis factor alpha*, *anti tumor necrosis factor alpha*, *anti TNF*, or *TNF alpha antibody*.

There were no language restrictions and abstracts of the papers identified by the initial search were evaluated by the lead investigator for appropriateness to the study question, and all potentially relevant papers were obtained and evaluated in detail. Foreign language papers were translated where necessary. Abstract books of conference proceedings between 2002 and 2009 were hand searched to identify potentially eligible studies published only in abstract form. The bibliographies of all identified relevant studies were used to perform a recursive search of the literature. Experts in the field were contacted to try to identify other unpublished studies. Articles were assessed independently by two investigators using pre-designed eligibility forms, according to the pre-defined eligibility criteria. Any disagreement between investigators was resolved by discussion with a third investigator.

Outcome assessment

The primary outcome assessed was the efficacy of biological therapies compared with placebo in terms of failure to achieve remission in active IBD and relapse of disease activity in quiescent IBD. Secondary outcomes included assessing incidence of adverse events occurring as a result of therapy (overall numbers, as well as serious adverse events, infections, and individual adverse events, including abdominal pain, nausea or vomiting, rash, myalgia or arthralgia, fever, headache, or fatigue).

Data extraction

All data were extracted independently by two investigators on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, WA, USA) as dichotomous outcomes (remission or failure of remission in active IBD, and relapse or no relapse of disease activity in quiescent IBD; **Box 2**). In addition, the following clinical data were extracted for each trial, where available: demographic data of trial participants (age, gender, and ethnicity), IBD characteristics (duration of IBD, proportion with new-onset IBD, distribution of IBD, and severity of IBD), number of centers, country of origin, geographical region, dosage and schedule of biological therapy, duration of therapy, compliance with therapy, number of individuals incurring each (or any) of the adverse events of interest, primary outcome measure used to define remission or relapse following therapy, duration of follow-up, and proportion of patients with a previous history of intestinal resection (CD patients only). Data were extracted as intention-to-treat analyses, in which all dropouts are assumed to be treatment failures (that is, failed to achieve remission in active IBD trials, and disease activity relapsed in quiescent IBD trials), wherever trial reporting allowed this.

Assessment of risk of bias

This was performed independently by two investigators, with disagreements resolved by discussion with a third investigator. Risk of bias was assessed as described in the Cochrane handbook (29), by recording the method used to generate the randomization schedule, the method used to conceal allocation, whether blinding was implemented, what proportion of patients completed follow-up, whether an intention-to-treat analysis was extractable, and whether there was evidence of selective reporting of outcomes.

Data synthesis and statistical analysis

Data were pooled using a random effects model, to give a more conservative estimate of the effect of individual therapies, allowing for any heterogeneity between studies (30). The impacts of different interventions were expressed as a relative risk (RR) of failure to achieve remission with 95% confidence intervals (CIs) in trials of therapy for active IBD or RR of relapse of disease activity in trials of therapy for quiescent IBD, with intervention compared with control. The number needed to treat (NNT) and 95% CIs were calculated from the reciprocal of the risk difference from the meta-analysis. Adverse events were summarized with RRs and a number needed to harm was calculated from the reciprocal of the risk difference.

The results of individual studies can be diverse, and this inconsistency within a single meta-analysis can be quantified with a statistical test of heterogeneity, to assess whether the variation across trials is due to true heterogeneity, or chance. This quantity is termed I^2, and its value ranges from 0 to 100%, with 0% representing no observed heterogeneity and larger values indicating increasing heterogeneity. A value below 25% was arbitrarily chosen to represent low levels of heterogeneity (31). Where the degree of statistical heterogeneity was greater than these between-trial results in this meta-analysis, possible explanations were investigated using sensitivity analyses according to dosage and duration of therapy, compliance with therapy, duration of disease, proportion with new-onset disease, and high-risk of bias and unclear risk of bias vs. low-risk of bias trials, wherever trial reporting allowed this. These were exploratory analyses only, and may explain some of the observed variability, but the results should be interpreted with caution.

Review Manager version 5.0.23 (RevMan for Windows 2008, the Nordic Cochrane Centre, Copenhagen, Denmark) and StatsDirect version 2.7.7 (StatsDirect, Cheshire, England) were used to generate Forest plots of pooled RRs and risk differences for primary and secondary outcomes with 95% CIs, as well as funnel plots. The

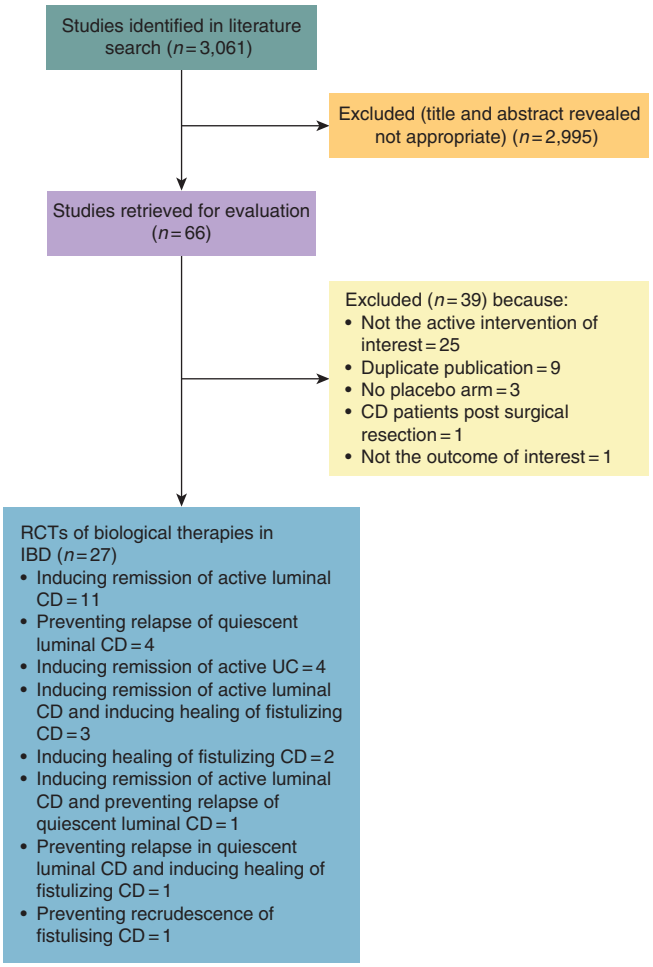

Figure 1. Flow diagram of assessment of studies identified in the systematic review. CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

latter were assessed for evidence of asymmetry, and therefore possible publication bias or other small study effects, using the Egger test (32).

RESULTS

The broad search strategy used to inform the American College of Gastroenterology monograph identified 3,061 citations, 2,995 of which were excluded after examining the title and abstract. A total of 66 RCTs of biological therapy were retrieved and evaluated in more detail. Of these, 39 were excluded for various reasons (**Figure 1**), leaving 27 articles eligible for inclusion. Of these, 23 articles reported the efficacy of biological therapies vs. placebo in CD (33–55), 10 in inducing remission in active luminal CD (33–36,39,41,43–45,54), 4 in preventing relapse of luminal CD once remission had been achieved (46–49), 2 in inducing healing of fistulizing CD (51,52), 3 in inducing both remission in active luminal CD and healing of fistulizing CD (37,38,40), 1 in both inducing remission in active luminal CD and preventing relapse of luminal CD once remission had been achieved (42), 1 in both preventing relapse of luminal CD once remission had been achieved and healing of fistulizing CD (50), and 1 in preventing relapse of fistulizing CD once healing had been achieved (53). A further RCT, the SONIC trial, evaluated the efficacy of infliximab and azathioprine vs. azathioprine alone in inducing remission in biological therapy- and immunosuppressant-naïve patients with active luminal CD (55). Owing to the slight difference in the design of this study, we included it in our primary analysis, but excluded it in a sensitivity analysis. One article reported results from two separate RCTs (42), and different aspects of another RCT were reported in two separate articles (48,52). There were a further four articles that reported the efficacy of infliximab in inducing remission in active UC in five separate RCTs (56–59).

Efficacy and safety of biological therapies vs. placebo in inducing remission in active luminal CD

There were 15 RCTs (33–45,54,55), including a total of 4,527 patients with active luminal CD, reporting remission rates at 2 to 12 weeks. A total of 11 trials included patients with moderately to severely active CD (33–35,37,38,40–44,54), two included mild to moderately active (45,55), one included corticosteroid-dependent patients (39), and the final trial included patients already receiving infliximab infusions who were not in remission, with a Crohn's disease activity index > 150 (36). For detailed characteristics of individual trials see **Table 1**. Only three trials were at low risk of bias (38,39,54).

Efficacy of anti-TNFα antibodies vs. placebo in inducing remission in active luminal CD

In total, 10 trials used anti-TNFα antibodies in 2,756 patients (33,34,37–41,43,54,55). Remission of CD was not achieved in 1,142 (71.5%) of 1,598 patients randomized to receive anti-TNFα antibodies at 4 to 12 weeks, compared with 935 (80.7%) of 1,158 patients allocated to placebo. The RR of failure to achieve remission with anti-TNFα antibodies compared with placebo in active CD was 0.87 (95% CI 0.80–0.94, $I^2 = 68\%$, $P = 0.001$; **Figure 2**), and there was no statistically significant funnel plot asymmetry (Egger test, $P = 0.23$), suggesting no evidence of publication bias or other small study effects. The NNT with anti-TNFα antibodies to achieve remission in one patient with active CD was 8 (95% CI 6–17). Exclusion of the SONIC study from the analysis had little impact on the RR of failure to achieve remission (0.89; 95% CI 0.83–0.96) (55).

There was heterogeneity between the three different types of TNFα antibodies studied (Cochran $Q = 9.89$, $P = 0.007$). This appeared to be driven by the more positive results reported with infliximab and adalimumab, compared with trials of certolizumab. There were three trials of infliximab, with follow-up at between 10 and 12 weeks (34,39,55). Overall, remission was not achieved in 169 (54.7%) of 309 patients receiving infliximab, compared with 189 (74.7%) of 253 patients randomized to placebo (RR = 0.68; 95% CI 0.52–0.90, $I^2 = 78\%$, $P = 0.01$; **Figure 2**). The NNT was 4 (95% CI 3–7). Exclusion of the SONIC trial from the analysis led to there being no statistically significant difference in terms of failure to achieve remission detected between infliximab and

Table 1. Characteristics of randomized controlled trials of biological therapies vs. placebo in inducing remission in active luminal CD

Study	Country and number of centers	Disease distribution	Criteria used to define remission and point at which extracted	Number of patients	Dosage and schedule of biological therapy used	Concomitant medications allowed	Methodology
Targan *et al.* (34)	North America and Europe, 18 sites	16% Ileal, 54% ileocolonic, 30% colonic	CDAI < 150, 12 weeks	108	Infliximab 5 mg/kg, 10 mg/kg, or 20 mg/kg at week 0	Stable doses of corticosteroids (≤ 40 mg), 5-ASAs, azathioprine, or mercaptopurine	Randomization unclear, concealment stated, double-blind
Lemann *et al.* (39)	France, 22 sites	20% Ileal, 50% ileocolonic, 30% colonic	CDAI < 150 and off corticosteroids, 12 weeks	113[a]	Infliximab 5 mg/kg at weeks 0, 2, and 6	Corticosteroids, azathioprine, or mercaptopurine	Randomization and concealment stated, double-blind
Colombel *et al.* (55)	Multinational, 92 sites	36% Ileal, 42% ileocolonic, 21.5% colonic	CDAI < 150 and off corticosteroids, 10 weeks	339[b]	Infliximab 5 mg/kg at weeks 0, 2, and 6	Stable doses of corticosteroids (prednisone ≤40 mg or budesonide ≤9 mg) or 5-ASAs	Randomization unclear, concealment stated, double-blind
Hanauer *et al.* (40) CLASSIC-I	Multinational, 55 sites	62% Ileal, 9% ileocolonic, 25% colonic	CDAI < 150, 4 weeks	299	Adalimumab 40/20 mg, 80/40 mg, or 160/80 mg at weeks 0 and 2	Stable doses of corticosteroids (≤20 mg prednisone, ≤9 mg budesonide), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization unclear, concealment stated, double-blind
Sandborn *et al.* (38) GAIN	North America and Europe, 52 sites	Not extractable	CDAI < 150, 4 weeks	325[c]	Adalimumab 160/80 mg at weeks 0 and 2	Stable doses of corticosteroids (≤40 mg prednisone, ≤9 mg budesonide), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization and concealment stated, double-blind
Hibi *et al.* (33)	Japan, multiple sites	Not reported	CDAI < 150, 4 weeks	90	Adalimumab 80/40 mg or 160/80 mg at weeks 0 and 2	Corticosteroids, 5-ASAs, and immunosuppressants allowed	Randomization and concealment unclear, double-blind
Winter *et al.* (43)	Multinational, 24 sites	Not reported	CDAI ≤ 150, 12 weeks	90	Certolizumab 5 mg/kg, 10 mg/kg, or 20 mg/kg at week 0	Stable doses of corticosteroids, 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization and concealment unclear, double-blind
Schreiber *et al.* (41)	Multinational, 58 sites	Not extractable	CDAI ≤ 150, 12 weeks	292	Certolizumab 100 mg, 200 mg, or 400 mg at weeks 0, 4, and 8	Stable doses of corticosteroids (≤30 mg prednisolone, ≤9 mg budesonide), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization unclear, concealment stated, double-blind
Sandborn *et al.* (37) PRECISE 1	Multinational, 171 sites	28% Ileal, 48% ileocolonic, 24% colonic	CDAI ≤ 150, 6 weeks	660	Certolizumab 400 mg at weeks 0, 2, and 4	Stable doses of corticosteroids (≤30 mg prednisolone), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization unclear, concealment stated, double-blind
Sandborn *et al.* (54)	Multinational, 120 sites	27% Ileal, 41% ileocolonic, 29% colonic	CDAI ≤ 150, 6 weeks	439	Certolizumab 400 mg at weeks 0, 2, and 4	Stable doses of corticosteroids, 5-ASAs, azathioprine, mercaptopurine, methotrexate, antibiotics, probiotics, or anti-diarrheals	Randomization and concealment stated, double-blind

(continued)

Table 1. continued

Study	Country and number of centers	Disease distribution	Criteria used to define remission and point at which extracted	Number of patients	Dosage and schedule of biological therapy used	Concomitant medications allowed	Methodology
Gordon *et al.* (45)	UK, 2 sites	40% Ileal or ileocecal, 30% ileocolonic, 27% colonic	CDAI < 150, 2 weeks	30	Natalizumab 3 mg/kg at week 0	Stable doses of corticosteroids (≤40 mg prednisolone, ≤9 mg budesonide), 5-ASAs, azathioprine, or mercaptopurine	Randomization unclear, concealment stated, double-blind
Ghosh *et al.* (44)	Multinational, 35 sites	21% Ileal, 55% ileocolonic, 24% colonic	CDAI < 150, 12 weeks	248	Natalizumab 3 mg/kg at week 0, 3 mg/kg at weeks 0 and 4, or 6 mg/kg at weeks 0 and 4	Stable doses of corticosteroids (≤25 mg prednisolone), 5-ASAs, azathioprine, or mercaptopurine	Randomization stated, concealment unclear, double-blind
Sandborn *et al.* (42) ENACT-1	Multinational, 142 sites	27% Ileal, 50% ileocolonic, 23% colonic	CDAI < 150, 10 weeks	905	Natalizumab 300 mg at weeks 0, 4, and 8	Stable doses of corticosteroids (≤25 mg prednisolone, ≤6 mg budesonide), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization unclear, concealment stated, double-blind
Sands *et al.* (36)	USA, 17 sites	19% Ileal, 54% ileocolonic, 27% colonic	CDAI < 150, 10 weeks	79[d]	Natalizumab 300 mg at weeks 0, 4, and 8	Stable doses of corticosteroids (≤25 mg prednisolone), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization and concealment unclear, double-blind
Targan *et al.* (35) ENCORE	Multinational, 114 sites	24% Ileal, 50% ileocolonic, 26% colonic	CDAI < 150, 12 weeks	509	Natalizumab 300 mg at weeks, 0, 4, and 8	Stable doses of corticosteroids (≤20 mg prednisone, ≤6 mg budesonide), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization unclear, concealment stated, double-blind

5-ASA; 5-aminosalicylic acids; CD, Crohn's disease; CDAI; Crohn's disease activity index.
[a]All patients were corticosteroid-dependent and were either already taking azathioprine or mercaptopurine, or if not one of these was started.
[b]All patients were biological therapy- and immunosuppressant naïve and were commenced on azathioprine.
[c]All patients were secondary non-responders to therapy with infliximab or were intolerant.
[d]All patients were receiving infliximab, but had active disease with a CDAI ≥ 150.

placebo (RR = 0.61; 95% CI 0.26–1.45). Three trials used adalimumab, reporting remission rates at 4 weeks (33,38,40). There were 342 (75.8%) of 451 patients receiving adalimumab who failed to achieve remission, compared with 239 (90.9%) of 263 assigned to placebo (RR = 0.85; 95% CI 0.79–0.91, $I^2 = 0\%$, $P = 0.99$; **Figure 2**). The NNT with adalimumab was 7 (95% CI 5–12.5). Four trials evaluated certolizumab at 6 to 12 weeks, with remission not being achieved in 631 (75.3%) of 838 assigned to active therapy, compared with 507 (79.0%) of 642 with placebo (37,41,43,54). No statistically significant difference was detected between certolizumab and placebo in inducing remission of active luminal CD (RR = 0.95; 95% CI 0.90–1.01, $I^2 = 0\%$, $P = 0.62$; **Figure 2**).

When subgroup analyses were conducted according to dosing schedule of anti-TNFα used, there were sufficient data to pool for infliximab 5 mg/kg, adalimumab 80/40 mg at 0 and 2 weeks, adalimumab 160/80 mg at 0 and 2 weeks, and certolizumab 400 mg. Infliximab 5 mg/kg was superior to placebo (RR = 0.66; 95% CI 0.52–0.84). Both adalimumab 80/40 mg (RR = 0.84; 95% CI 0.74–0.96, NNT = 7; 95% CI 4–29) and 160/80 mg (RR = 0.84; 95% CI 0.74–0.94, NNT = 7; 95% CI 4–14) were of similar efficacy compared with placebo, but the difference between certolizumab 400 mg and placebo was of borderline statistical significance (RR = 0.94; 95% CI 0.89–1.00, $P = 0.05$).

Efficacy of anti-α_4-integrin antibodies vs. placebo in inducing remission in active luminal CD

A further five trials used anti-α_4-integrin antibodies, in the form of natalizumab, in 1,771 patients (35,36,42,44,45). Failure to achieve remission occurred in 810 (65.4%) of 1,238 patients receiving natalizumab at 2 to 12 weeks, compared with 412 (77.3%) of 533 randomized to placebo. The RR of not achieving remission was reduced with natalizumab (0.88; 95% CI 0.83–0.94,

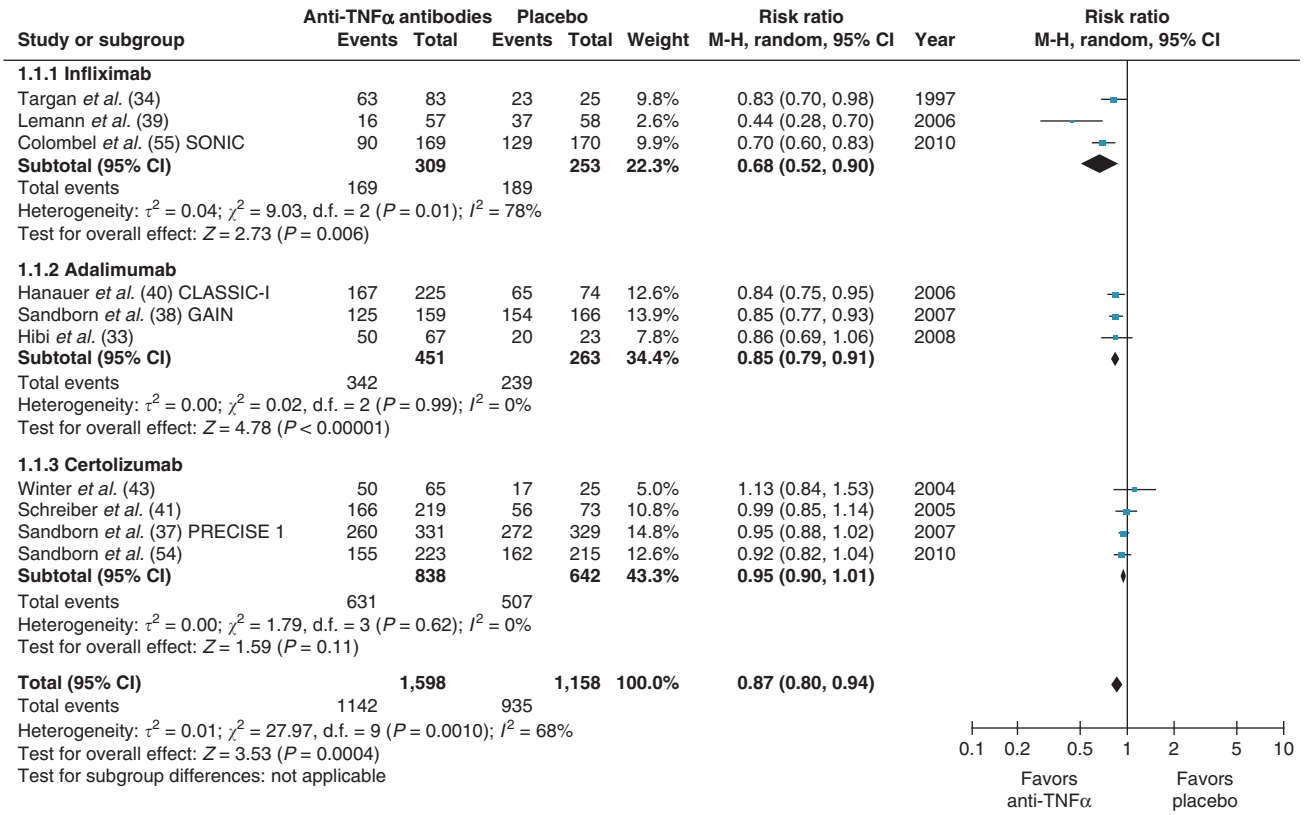

Figure 2. Forest plot of randomized controlled trials of anti-TNFα antibodies versus placebo in inducing remission in active luminal CD. Anti-TNFα, anti-tumor necrosis factor-α; CD, Crohn's disease; CI, confidence interval.

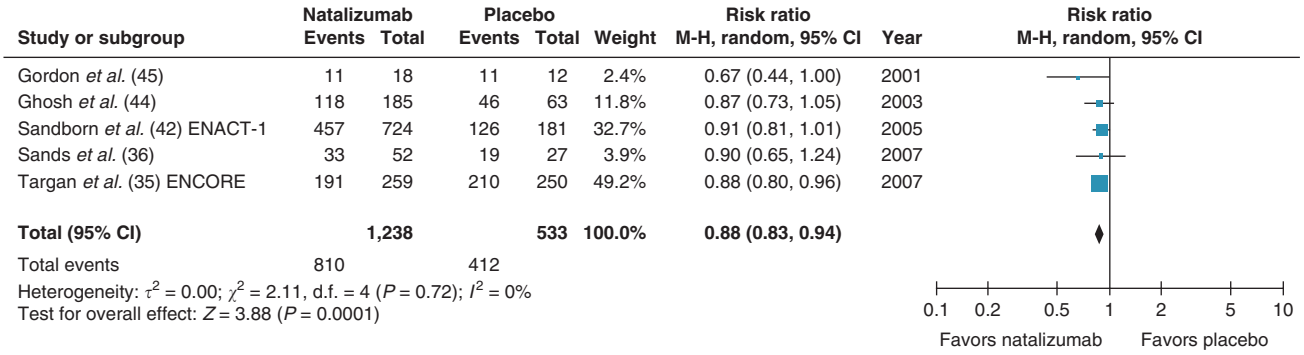

Figure 3. Forest plot of randomized controlled trials of natalizumab vs. placebo in inducing remission in active luminal CD. CD, Crohn's disease; CI, confidence interval.

$I^2 = 0\%$, $P = 0.72$; **Figure 3**), with no statistically significant funnel plot asymmetry (Egger test, $P = 0.29$). The NNT with natalizumab was 11 (95% CI 7–20).

Adverse events with biological therapies vs. placebo in inducing remission in active luminal CD

There were eight trials of anti-TNFα antibodies that provided adverse events data for extraction (33,37–41,43,54). No statistically significant difference in the incidence of adverse events was detected with anti-TNFα antibodies compared with placebo (RR of experiencing any adverse event = 0.99; 95% CI 0.90–1.08). The RR for each individual adverse event is provided in **Table 2**. There was no statistically significant difference detected in the frequency of any of these, including infusion or injection site reactions.

All five trials of natalizumab provided adverse events data (35,36,42,44,45). There were significantly more patients allocated to natalizumab reporting headache, compared with placebo (RR = 1.23; 95% CI 1.03 to 1.47, $I^2 = 0\%$) (**Table 3**), and trends towards a greater number of infusion reactions (RR = 1.41; 95% CI 0.94 to 2.10, $I^2 = 0\%$), and infections with natalizumab (RR = 1.12; 95% CI 0.97 to 1.30, $I^2 = 0\%$). The number needed to harm with natalizumab to cause one headache was 17 (95% CI 9–71).

Table 2. Adverse events with anti-TNFα antibodies vs. placebo in inducing remission in active luminal CD

Adverse event	Number of trials	Total number of anti-TNFα antibody patients	Number of anti-TNFα antibody patients experiencing event (%)	Total number of placebo patients	Number of placebo patients experiencing event (%)	Relative risk	95% Confidence interval
Any	7	1,279	863 (67.5)	940	630 (67.0)	0.99	0.90–1.08
Serious	8	1,346	90 (6.7)	963	61 (6.3)	0.97	0.64–1.49
Infection	7	1,279	195 (15.2)	940	115 (12.2)	1.08	0.86–1.37
Infusion or injection site reactions	7	1,279	105 (8.2)	940	69 (7.3)	1.33	0.42–4.15
Headache	6	1,214	129 (10.6)	915	96 (10.5)	1.03	0.80–1.32
Abdominal pain	6	1,214	83 (6.8)	915	67 (7.3)	1.06	0.77–1.45
Nausea or vomiting	5	1,055	103 (9.8)	749	56 (7.5)	1.50	0.91–2.49
Arthralgia or myalgia	5	989	61 (6.2)	841	40 (4.8)	1.32	0.80–2.17
Fever	4	830	40 (4.8)	675	39 (5.8)	0.86	0.55–1.34

Anti-TNFα, anti-tumor necrosis factor-α; CD, Crohn's disease.

Table 3. Adverse events with natalizumab vs. placebo in inducing remission in active luminal CD

Adverse event	Number of trials	Total number of natalizumab patients	Number of natalizumab patients experiencing event (%)	Total number of placebo patients	Number of placebo patients experiencing event (%)	Relative risk	95% Confidence interval
Any	4	1,220	1,043 (85.5)	521	437 (83.9)	1.0	0.95–1.05
Serious	4	1,220	85 (7.0)	521	44 (8.4)	0.80	0.54–1.17
Headache	5	1,238	367 (29.6)	533	125 (23.5)	1.23	1.03–1.47
Abdominal pain	5	1,238	141 (11.4)	533	59 (11.1)	0.99	0.74–1.32
Nausea or vomiting	4	1,220	246 (20.2)	521	93 (17.9)	0.96	0.75–1.22
Infusion reactions	4	1,220	108 (8.9)	521	31 (6.0)	1.41	0.94–2.10
Fatigue	3	1,035	101 (9.8)	458	34 (7.4)	1.31	0.89–1.93
Infection	3	1,168	461 (39.5)	494	161 (32.6)	1.12	0.97–1.30

CD, Crohn's disease.

Efficacy and safety of biological therapies vs. placebo in preventing relapse of disease activity in quiescent luminal CD

There were six RCTs of biological therapies vs. placebo that reported relapse rates at 26 to 60 weeks, in 1,640 patients with luminal CD (42,46–50). These trials differed subtly in their methodology. Three randomized those individuals who had exhibited either response to, or achieved remission following, initial open-label treatment with the intervention under study (47,48,50); one took individuals involved in the CLASSIC-I trial who had received two subsequent open-label treatments with adalimumab and were in remission and re-randomized them to adalimumab or placebo (49); one re-randomized individuals who were in remission after natalizumab was given as part of the ENACT-1 RCT and re-randomized them to natalizumab or placebo (42); and the final RCT re-randomized individuals who had responded to an initial randomized infusion of either infliximab or placebo (46). For detailed characteristics of individual trials see **Table 4**. None of the trials were at low risk of bias.

Efficacy of anti-TNFα antibodies vs. placebo in preventing relapse of disease activity in quiescent luminal CD

There were five trials of anti-TNFα antibodies in 1,390 CD patients (46–50). There were 472 (55.9%) of 844 patients assigned to anti-TNFα whose disease relapsed at 26 to 56 weeks, compared with 428 (78.4%) of 546 randomized to placebo. The RR of relapse with anti-TNFα compared with placebo was 0.71 (95% CI 0.65–0.76, $I^2 = 5\%$, $P = 0.38$; **Figure 4**), with no statistically significant funnel plot asymmetry (Egger test, $P = 0.15$). The NNT with anti-TNFα antibodies to prevent one CD patient from relapsing once remission of active disease was achieved was 4 (95% CI 3–5). Infliximab and certolizumab were both superior to placebo in preventing relapse; however, there was no statistically significant difference detected between adalimumab and placebo (**Figure 4**). When only the three studies that randomized those who responded to, or achieved remission following, open-label treatment with anti-TNFα were considered in the analysis,

Table 4. Characteristics of randomized controlled trials of biological therapies vs. placebo in preventing relapse in quiescent luminal CD

Study	Country, and number of centers	Disease distribution	Criteria used to define relapse, and point at which extracted	Number of patients	Dosage and schedule of biological therapy used	Concomitant medications allowed	Methodology
Rutgeerts *et al.* (46)	North America and Europe, 17 sites	14% Ileal, 55% ileocolonic, 31% colonic	CDAI ≥ 150, or need for surgery, or escalation of medical therapy, 44 weeks	73	Initial response to placebo or infliximab, then infliximab 10 mg/kg at week 12, then 10 mg/kg at 8-weekly intervals thereafter	Stable doses of corticosteroids (≤40 mg), 5-ASAs, azathioprine, or mercaptopurine	Randomization unclear, concealment stated, double-blind
Hanauer *et al.* (47) ACCENT I	Multinational, 55 sites	22% Ileal, 55% ileocolonic, 22% colonic	CDAI ≥ 150, or need for surgery, or escalation of medical therapy, 30 weeks	335	Initial response to open-label infliximab, then infliximab 5 mg/kg at week 2 and 6, then 5 mg/kg or 10 mg/kg at 8-weekly intervals thereafter	Stable doses of corticosteroids (≤40 mg prednisone), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization unclear, concealment stated, double-blind
Colombel *et al.* (48) CHARM	Multinational, 92 sites	Not extractable	CDAI ≥ 150, 56 weeks	499	Initial response to open-label adalimumab, then adalimumab 40 mg weekly or 40 mg every other week thereafter	Stable doses of corticosteroids (≤30 mg prednisone, ≤9 mg budesonide), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization unclear, concealment stated, double-blind
Sandborn *et al.* (49) CLASSIC II	North America and Europe, 53 sites	Not reported	CDAI ≥ 150, 56 weeks	55	Initial adalimumab or placebo as part of CLASSIC-I, then remission after open-label adalimumab, then adalimumab 40 mg weekly or 40 mg every other week thereafter	Stable doses of corticosteroids (≤20 mg prednisone, ≤9 mg budesonide), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization unclear, concealment stated, double-blind
Schreiber *et al.* (50) PRECISE 2	Multinational, 147 sites	24% Ileal, 48% ileocolonic, 28% colonic	CDAI > 150, 26 weeks	428	Initial response to open-label certolizumab, then certolizumab 400 mg at week 8, then 400 mg at 4-weekly intervals thereafter	Stable doses of corticosteroids (≤30 mg prednisolone), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization unclear, concealment stated, double-blind
Sandborn *et al.* (42) ENACT-2	Multinational, 142 sites	Not extractable	CDAI ≥ 150 or need for intervention, 60 weeks	250	Initial remission after natalizumab as part of ENACT-1, then natalizumab 300 mg at week 12, then 300 mg at 4-weekly intervals thereafter	Stable doses of corticosteroids (≤25 mg prednisolone, ≤6 mg budesonide), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization unclear, concealment stated, double-blind

5-ASA; 5-aminosalicylic acids; CD, Crohn's disease; CDAI; Crohn's disease activity index.

the efficacy remained almost identical (RR of relapse = 0.71; 95% CI 0.66–0.77).

Subgroup analysis by dosing schedule was possible for infliximab and adalimumab. Infliximab (10 mg/kg) at 8-weekly intervals was superior to placebo in preventing relapse of quiescent luminal CD (RR = 0.69, 95% CI 0.58–0.81; NNT = 4, 95% CI 3–7). There was no statistically significant difference between adalimumab 40 mg every other week (RR of relapse = 0.62; 95% CI 0.36–1.08) or 40 mg

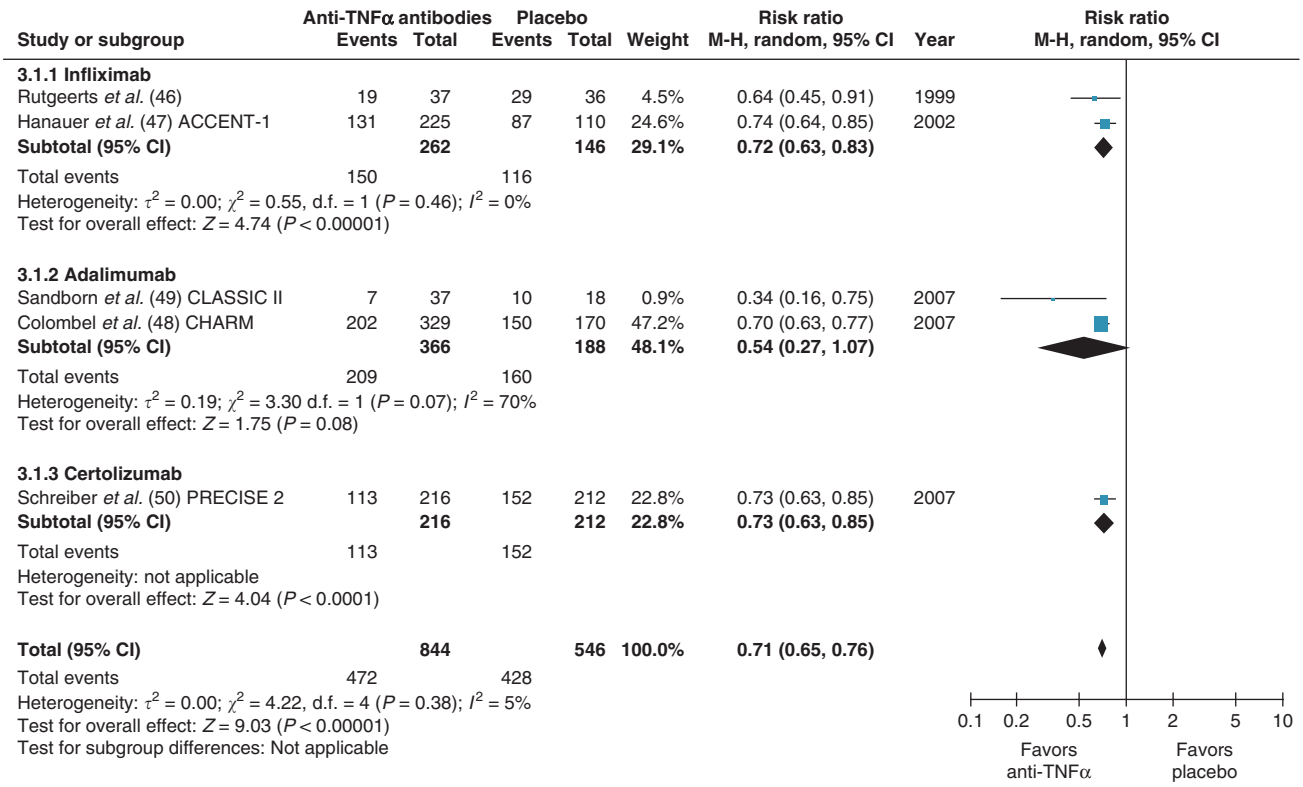

Figure 4. Forest plot of randomized controlled trials of anti-TNFα antibodies vs. placebo in preventing relapse in quiescent CD. Anti-TNFα, anti-tumor necrosis factor-α; CD, Crohn's disease; CI, confidence interval.

weekly (RR of relapse = 0.54; 95% CI 0.27–1.09) and placebo. Only two RCTs reported the number of patients who had required corticosteroids before induction therapy and who remained in remission with all corticosteroids discontinued (47,48). There was a significant benefit in favor of anti-TNFα in this subgroup analysis (RR of relapse or requirement for corticosteroids = 0.79, 95% CI 0.72–0.86; NNT = 5, 95% CI 4–8).

Efficacy of anti-α_4-integrin antibodies vs. placebo in preventing relapse of disease activity in quiescent luminal CD

There was only one trial that used natalizumab in the maintenance of remission of CD in 250 patients (42). Natalizumab was effective in preventing relapse of quiescent CD at 60 weeks, with 79 (60.8%) of 130 patients allocated to intervention relapsing compared with 102 (85.0%) of 120 receiving placebo (RR = 0.71; 95% CI 0.61–0.84).

Adverse events with biological therapies vs. placebo in preventing relapse of disease activity in quiescent luminal CD

Only three trials provided extractable adverse events in 556 patients (46,49,50). There were 204 (70.3%) of 290 patients allocated to active therapy reporting any adverse event, compared with 196 (73.7%) of 266 receiving placebo (RR = 0.93; 95% CI 0.84–1.03). Infusion or injection site reactions were fewer in those assigned to active therapy (4.5 vs. 12.4%), although this difference was not statistically significant (RR = 0.64; 95% CI 0.06–6.66). There were too few data to allow any other meaningful analyses.

Efficacy and safety of biological therapies vs. placebo in healing of fistulizing CD

Six trials used anti-TNFα antibodies in 453 patients with active fistulizing CD (37,38,40,50–52), although only one of the trials was designed specifically to address this issue, with fistula healing as the primary end point (51). Only one of the RCTs was at low risk of bias (38). For detailed characteristics of individual trials see **Table 5**. Overall, healing of fistulas did not occur in 170 (67.2%) of 253 patients randomized to anti-TNFα at 4 to 26 weeks, compared with 155 (77.5%) of 200 assigned to placebo. There was no statistically significant difference detected in the RR of fistulas remaining unhealed with anti-TNFα vs. placebo (0.88; 95% CI 0.73–1.05; **Figure 5**), with considerable heterogeneity between studies ($I^2 = 67\%$, $P = 0.01$), but no statistically significant funnel plot asymmetry (Egger test, $P = 0.65$). The trial designed with healing of fistulas as the primary outcome of interest demonstrated a clear benefit of infliximab over placebo (RR of fistulas remaining unhealed = 0.62; 95% CI 0.48–0.81) (51). Two of the RCTs that reported fistula healing only treated patients up to 4 weeks (38,40). When these studies were excluded from the analysis, the effect of anti-TNFα on fistula healing became statistically significant (RR of fistulas remaining unhealed = 0.80; 95% CI 0.65–0.98), although significant heterogeneity between studies remained ($I^2 = 56\%$, $P = 0.08$).

Only two trials reported adverse events data in patients with fistulizing CD (51,52), meaning that there were too few data to pool. There were higher numbers of patients reporting any adverse event

Table 5. Characteristics of randomized controlled trials of biological therapies vs. placebo in healing of fistulizing CD

Study	Country, and number of centers	Criteria used to define fistula healing, and point at which extracted	Number of patients	Dosage and schedule of biological therapy used	Concomitant medications allowed	Methodology
Present *et al.* (51)	USA and Europe, 12 sites	Absence of any draining fistulas at two consecutive visits, 18 weeks	94	Infliximab 5 mg/kg or 10 mg/kg at weeks 0, 2, and 6	Stable doses of corticosteroids (≤40 mg), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization unclear, concealment stated, double-blind
Hanauer *et al.* (40) CLASSIC-I	Multinational, 55 sites	Closure of all draining fistulas for at least two consecutive visits, 4 weeks	32	Adalimumab 40/20 mg, 80/40 mg, or 160/80 mg at weeks 0 and 2	Stable doses of corticosteroids (≤20 mg prednisone, ≤9 mg budesonide), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization unclear, concealment stated, double-blind
Sandborn *et al.* (38) GAIN	North America and Europe, 52 sites	Closure of all fistulas at weeks 2 and 4 that were draining at baseline or screening visits, 4 weeks	45	Adalimumab 160/80 mg at weeks 0 and 2	Stable doses of corticosteroids (≤40 mg prednisone, ≤9 mg budesonide), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization and concealment stated, double-blind
Colombel *et al.* (52) CHARM	Multinational, 92 sites	Absence of draining fistulas for the last two post-baseline visits, 26 weeks	117	Initial response to open-label adalimumab, then adalimumab 40 mg weekly or 40 mg every other week thereafter	Stable doses of corticosteroids (≤30 mg prednisone, ≤9 mg budesonide), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization unclear, concealment stated, double-blind
Sandborn *et al.* (37) PRECISE 1	Multinational, 171 sites	Absence of any draining fistulas at two consecutive visits, 26 weeks	107	Certolizumab 400 mg at weeks 0, 2, and 4, then 400 mg at 4-weekly intervals thereafter	Stable doses of corticosteroids (≤30 mg prednisolone), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization unclear, concealment stated, double-blind
Schreiber *et al.* (50) PRECISE 2	Multinational, 147 sites	Absence of any draining fistulas on gentle compression at any two consecutive visits post-baseline, 26 weeks	58	Initial response to open-label certolizumab, then certolizumab 400 mg at week 8, then 400 mg at 4-weekly intervals thereafter	Stable doses of corticosteroids (≤30 mg prednisolone), 5-ASAs, azathioprine, mercaptopurine, methotrexate, or antibiotics	Randomization unclear, concealment stated, double-blind

5-ASA; 5-aminosalicylic acids; CD, Crohn's disease.

with anti-TNFα compared with placebo (79.7 vs. 74.4%), serious adverse events (10.5 vs. 6.4%), infusion or injection site reactions (5.3 vs. 2.6%), and abscesses (11.3 vs. 7.7%).

Efficacy and safety of biological therapies vs. placebo in preventing relapse of disease activity in healed fistulizing CD

There was only one RCT identified that reported relapse rates with biological therapy vs. placebo in individuals with fistulizing CD once healing had occurred (53). ACCENT II was a double-blind trial conducted in 45 sites worldwide, with patients with fistulizing CD receiving open-label infliximab (5 mg/kg) at weeks 0, 2, and 6. Those classed as responders at weeks 10 and 14 were then randomized to receive either further infliximab or placebo at 8-weekly intervals and were followed up until week 54. Method of generation of the randomization schedule was reported, but concealment of allocation was unclear. Loss of response was defined as fistula recrudescence, need for a change in medical therapy, or need for surgery. At 54 weeks, 63 (65.6%) of 96 patients who had responded and were randomized to infliximab had loss of response or relapse, compared with 80 (80.8%) of 99 assigned to placebo (RR of loss of response or relapse = 0.81, 95% CI 0.68–0.96). Adverse events data were not extractable from this trial.

Efficacy and safety of biological therapies vs. placebo in inducing remission in active UC

There were five RCTs, reported in four separate articles (56–59), that reported efficacy of biological therapies in inducing remission in 827 patients with moderately to severely active UC who had failed, or were receiving, therapy with corticosteroids. All trials used infliximab, and none were at low risk of bias. Three RCTs recruited hospitalized inpatients (56–58) and two recruited ambulatory outpatients (59). For detailed characteristics of

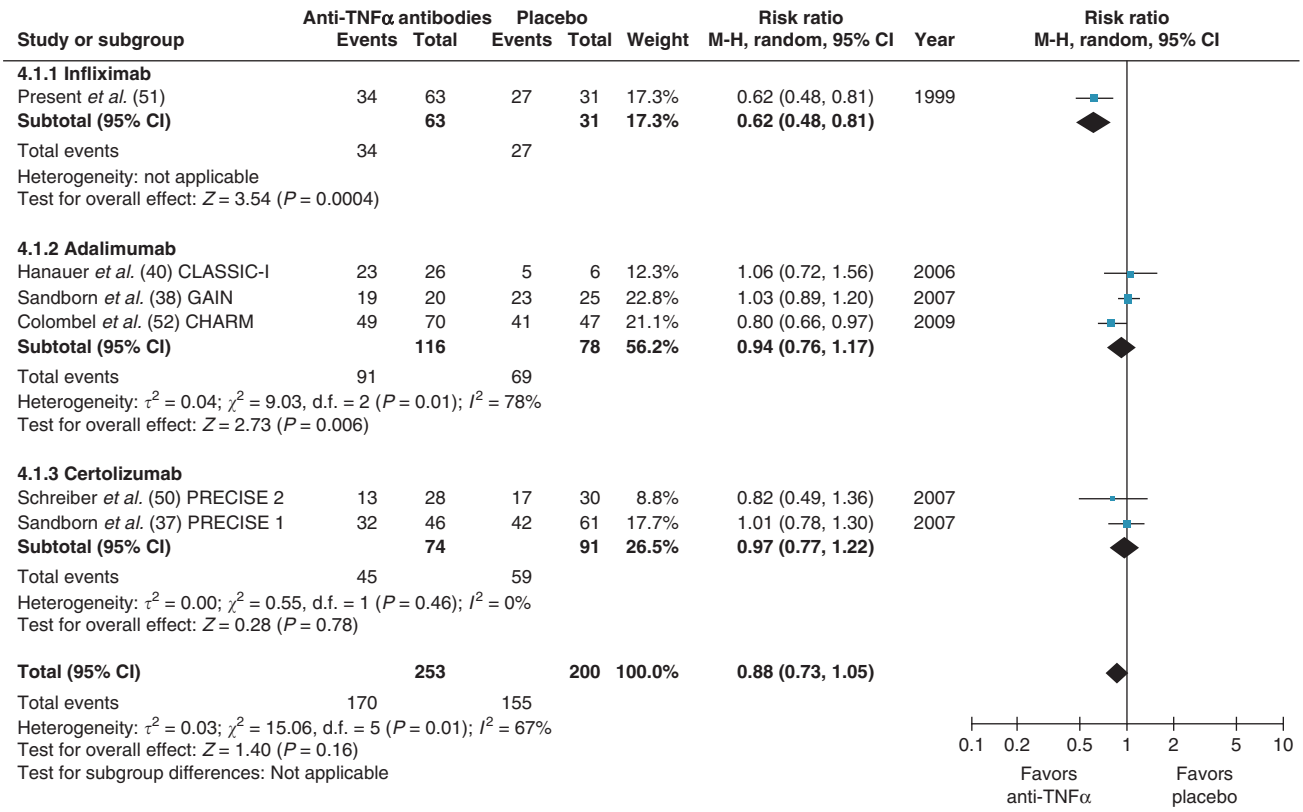

Figure 5. Forest plot of randomized controlled trials of anti-TNFα antibodies vs. placebo in healing of fistulizing CD. Anti-TNFα, anti-tumor necrosis factor-α; CD, Crohn's disease; CI, confidence interval.

individual trials see **Table 6**. Remission was not achieved in 231 (42.9%) of 539 patients randomized to infliximab at 6 weeks to 3 months, compared with 201 (69.8%) of 288 assigned to placebo. There was a statistically significant benefit of infliximab over placebo, with a RR of remission not being achieved of 0.72 (95% CI 0.57–0.91; **Figure 6**), with considerable heterogeneity between studies ($I^2 = 70\%$, $P = 0.009$), but no statistically significant funnel plot asymmetry (Egger test, $P = 0.12$). The NNT with infliximab to achieve remission in one patient with moderately or severely active UC was 4 (95% CI 3–8).

Adverse events data were reported by all five trials (**Table 7**). The RR of any adverse event was no higher with infliximab, and serious adverse events were lower (RR = 0.64; 95% CI 0.41–1.00, $P = 0.05$) with a NNT with infliximab to prevent one serious adverse event of 13 (95% CI 8–50). No statistically significant differences were detected in numbers of patients experiencing infusion reactions, headache, rash, or arthralgia with infliximab compared with placebo.

Efficacy and safety of biological therapies vs. placebo in preventing relapse of disease activity in quiescent UC

There were no RCTs examining this issue. Both the ACT 1 and ACT 2 trials reported relapse rates during extended follow-up (59), but as neither trial re-randomized those in remission at 8 weeks to infliximab or placebo, it is impossible to ascertain whether any effect of infliximab in reducing relapse rates in quiescent UC simply occurred because of a significantly higher proportion of individuals with active disease entering remission with infliximab vs. placebo at 8 weeks.

DISCUSSION

This systematic review and meta-analysis is the first to assimilate all the available evidence for the treatment of IBD with biological therapies that are approved for use in clinical practice in the United States. It has demonstrated that these drugs are more efficacious than placebo in inducing remission in moderate to severely active luminal CD, preventing relapse of quiescent luminal CD once remission has been achieved and, in the case of infliximab, in inducing remission in moderate to severely active UC. There was no overall benefit for anti-TNFα antibodies in promoting the healing of fistulizing CD compared with placebo, but a statistically significant difference was detected when only studies that reported these data in the longer term were included in the analysis. There was also a significant reduction in fistula recrudescence in CD, although only one RCT examined this issue (53). We did not identify any RCTs adequately designed to answer the question as to whether or not biological therapies are effective in preventing relapse of UC once remission has been achieved.

In terms of the individual drugs studied, there were sufficient data to examine the efficacy of anti-TNFα antibodies in remission and relapse of luminal CD, as well as in healing of fistulizing CD.

Table 6. Characteristics of randomized controlled trials of infliximab vs. placebo in inducing remission in active UC

Study	Country, and number of centers	Disease distribution	Criteria used to define remission, and point at which extracted	Number of patients	Dosage and schedule of infliximab used	Concomitant medications allowed	Methodology
Sands *et al.* (56)	USA and Belgium, 6 sites	Not reported	Modified Truelove and Witts score of ≤4 and endoscopic remission, 12 weeks	11[a]	Infliximab 5 mg/kg, 10 mg/kg, or 20 mg/kg at week 0	Stable doses of 5-ASAs, azathioprine, mercaptopurine, antibiotics, or antidiarrheals	Randomization and concealment unclear, double-blind
Probert *et al.* (57)	UK and Germany, 4 sites	63% Extensive colitis, 18.5% left sided, 18.5% distal	Endoscopic remission (Baron score of 0 at endoscopy), 6 weeks	43[a]	Infliximab 5 mg/kg at weeks 0 and 2	Stable doses of corticosteroids, 5-ASAs, azathioprine, or mercaptopurine	Randomization unclear, concealment stated, double-blind
Jarnerot *et al.* (58)	Denmark and Sweden, 10 sites	42% Pancolitis, 38% extensive, 20% distal	Clinical (Seo index) and endoscopic remission, 3 months	45[a]	Infliximab 5 mg/kg at week 0	All patients were receiving betamethasone 4 mg intravenously b.i.d, 5-ASAs added or continued, azathioprine could be added at the discretion of the investigator	Randomization and concealment unclear, double-blind
Rutgeerts *et al.* (59) ACT 1	Multinational, 62 sites	46% Extensive colitis, 54% left sided	Endoscopic remission (Mayo subscore of ≤1 at endoscopy), 8 weeks	364[a]	Infliximab 5 mg/kg or 10 mg/kg at week 0, 2, and 6	Stable doses of corticosteroids, azathioprine, or mercaptopurine	Randomization unclear, concealment stated, double-blind
Rutgeerts *et al.* (59) ACT 2	Multinational, 55 sites	60% Extensive colitis, 40% left sided	Endoscopic remission (Mayo subscore of ≤1 at endoscopy), 8 weeks	364[a]	Infliximab 5 mg/kg or 10 mg/kg at week 0, 2, and 6	Stable doses of corticosteroids, 5-ASAs, azathioprine, or mercaptopurine	Randomization unclear, concealment stated, double-blind

5-ASA; 5-aminosalicylic acids; b.i.d; twice daily; UC, ulcerative colitis.
[a]All patients had failed therapy with corticosteroids.

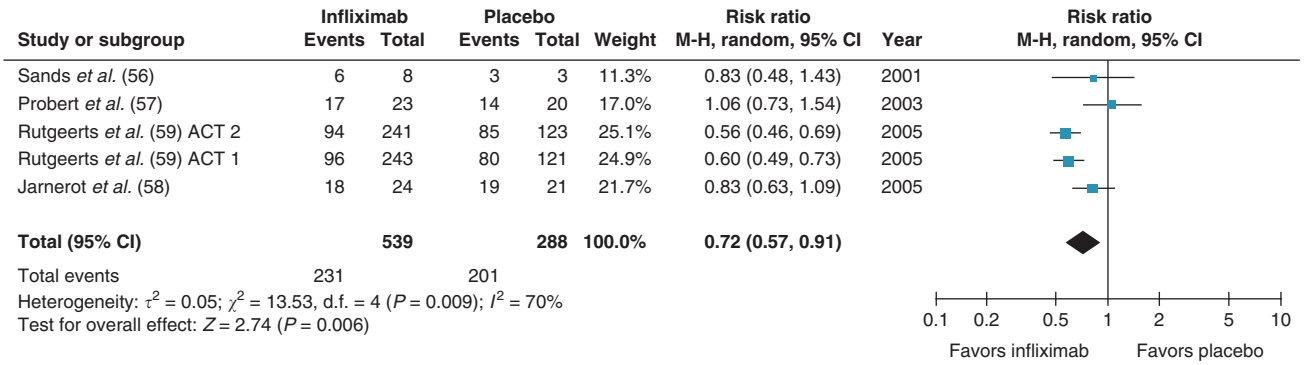

Figure 6. Forest plot of randomized controlled trials of infliximab vs. placebo in inducing remission in active UC. CI, confidence interval; UC, ulcerative colitis.

Infliximab and adalimumab were superior to placebo in inducing remission of active luminal CD, while there was no statistically significant difference detected between certolizumab and placebo. However, when the SONIC study was excluded from the analysis, there was no statistically significant difference detected between infliximab and placebo (55). In preventing relapse of quiescent luminal CD, once remission or response to therapy had been achieved, both infliximab and certolizumab appeared more effective than placebo, although the latter was studied in only one trial (50). For healing of fistulizing CD, there was evidence of benefit with infliximab over placebo in one RCT (51), but not for adalimumab or certolizumab. Serious safety concerns with these drugs include opportunistic infection, reactivation of latent tuberculosis, development of hematological malignancies (including hepatosplenic T-cell lymphoma), and, in the case of natalizumab, progressive multifocal leukoencephalopathy. In these RCTs, numbers of individuals experiencing serious adverse events were no commoner with biological therapies compared with placebo.

Table 7. Adverse events with infliximab vs. placebo in inducing remission in active UC

Adverse event	Number of trials	Total number of infliximab patients	Number of infliximab patients experiencing event (%)	Total number of placebo patients	Number of placebo patients experiencing event (%)	Relative risk	95% Confidence interval
Any	3	492	420 (85.4)	247	196 (79.4)	1.07	0.99–1.15
Serious	4	515	81 (15.7)	267	59 (22.1)	0.64	0.41–1.00
Infusion reactions	5	539	56 (10.4)	288	24 (8.3)	1.19	0.75–1.87
Headache	4	516	87 (16.9)	268	46 (17.2)	0.94	0.64–1.40
Rash	3	508	27 (5.3)	265	20 (7.5)	0.69	0.40–1.19
Arthralgia	3	508	70 (13.8)	265	24 (9.1)	1.45	0.89–2.38

UC, ulcerative colitis.

The number of patients experiencing any adverse event was not greater with biological therapies in active or quiescent CD, and in patients with moderate to severely active UC randomized to infliximab; there was a significant reduction in the number of serious adverse events with active treatment. The fact that the eligible RCTs included a relatively small number of subjects, with a relatively short duration of exposure, means that the safety data may not be particularly robust. Prospective, observational studies with longer follow-up, such as the TREAT registry (60), will continue to provide more useful information on this issue, and clinicians need to remain aware of the potential for serious adverse events during longer-term exposure beyond the confines of clinical trials.

Strengths of this systematic review and meta-analysis are that we have used rigorous and conservative methodologies. These include the reporting of our search strategy, inclusion criteria, and data extraction processes. In addition, independent data extraction was undertaken by two reviewers, and discrepancies were checked and resolved. We used an intention-to-treat analysis and pooled data with a random effects model, in order to reduce the likelihood that treatment effect of biological therapies in IBD has been overestimated. The pooling of data from trials of different biological therapies, different doses, and different durations of therapy could be criticized by some because of potential differences in the action of individual agents, or efficacy of various doses and durations of therapy. However, we performed subgroup analyses for each individual biological therapy, and according to dose wherever possible, to assess which of these, if any, were effective in each setting. In terms of outcomes reporting, we were able to extract the most rigorous definition of remission or relapse, using the Crohn's disease activity index in CD and endoscopic activity in UC, in the majority of the trials that we included. Finally, we extracted and pooled adverse events data, in order to provide further useful information for both the physician and the patient.

There are limitations of this systematic review and meta-analysis, which arise because of characteristics of the published literature available for synthesis. Although eligible RCTs of biological therapies were published in highly regarded medical journals, the overall risk of bias, in terms of the method used to generate the randomization schedule and conceal allocation in individual trials, was low in only three instances (38,39,54). There was evidence of heterogeneity between studies when data were pooled for efficacy of anti-TNFα antibodies in inducing remission in active luminal CD, inducing healing of fistulizing CD, and in inducing remission of moderate to severely active UC. We were only able to conduct limited subgroup analyses in most instances to explore reasons for this because of the small number of published trials available. It is, therefore, difficult to know whether when the observed heterogeneity disappeared this was truly as a result of differences between trials resolved by these subgroup analyses, or whether it was because of a low power to detect heterogeneity when fewer trials were included in them. One issue with the RCTs of biological therapies in preventing relapse of quiescent CD is the fact that only three reported the number of patients in corticosteroid-free remission (42,47,48). As this may be one of the reasons for stepping-up to biological therapy, particularly in CD, these data would be of interest. Finally, for the induction of remission trials in active luminal CD, the fact that all doses of anti-TNFα antibodies, regardless of efficacy, were pooled at time points that are not necessarily those which are optimal for the demonstration of induction effects, together with the fact that one of the trials of adalimumab was conducted in infliximab non-responders, may have led to an underestimation of the true efficacy of anti-TNFα antibodies in this setting.

There have been four previous systematic reviews and meta-analyses conducted that have examined the efficacy of anti-TNFα antibodies in inducing remission of active luminal CD (20,23,24,28). The results of these are conflicting and differ from those of the present meta-analysis in some instances, because of a less contemporaneous search date (20), the inclusion of non-FDA-approved therapies in the analysis (23), and different time points for data extraction, which were not the primary end points of the included trials (24). A Cochrane review has studied the efficacy of natalizumab in inducing remission of active luminal CD (22). This showed some benefit of natalizumab over placebo, but this effect was not consistent, because trials were pooled according to dose of natalizumab used and duration of follow-up, which may have reduced the power of the meta-analysis to detect any statistically significant difference between active therapy and placebo. Two meta-analyses have examined the efficacy of anti-TNFα antibodies in preventing relapse of quiescent luminal CD (21,28), the results

of which are similar to the results of our analysis. One of these reviews also studied the effect of biological therapies on fistula healing, and reported that, in the short-term, there was no benefit of anti-TNFα antibodies over placebo (28). In terms of the efficacy of infliximab in inducing remission of moderate to severely active UC, previous systematic reviews and meta-analyses all agree that the drug is superior to placebo, with numbers needed to treat varying between four and five, although not all trials were pooled in these studies, because of perceived differences in underlying methodology (25–27).

The evidence from this systematic review and meta-analysis, for the most part, supports the use of FDA-approved biological therapies in patients with luminal CD who have failed treatment with first and second-line agents or who are corticosteroid dependent. For induction of remission of active luminal CD, infliximab, natalizumab, and adalimumab appear to have the most evidence for their use, although the latter two therapies performed only modestly in this setting. The most marked effect of biological therapies was in preventing relapse of luminal CD once remission had been achieved, with a NNT of only 4. This benefit was observed for both infliximab and certolizumab, but not for adalimumab. In terms of fistulizing CD, there is less evidence for the use of biological therapies, though there was a clear beneficial effect when only infliximab was studied, although in one trial, and when only RCTs with follow-up in excess of 4 weeks were considered in the analysis. There was also a benefit in favor of biological therapies over placebo when only studies that reported fistula healing in the longer term were included in the analysis. In preventing recrudescence of fistula, there was only one RCT reporting on this end point, which demonstrated that infliximab was superior to placebo. Although concerns about adverse events arising from the long-term use of these drugs is understandable, the data from the RCTs included in this meta-analysis did not demonstrate any increase in overall adverse events, or serious adverse events, with use for up to 1 year. Infliximab was highly effective in inducing remission in patients with moderate to severely active UC who had failed therapy with first and second-line agents, and who had also failed to respond to a course of high-dose corticosteroids, with a NNT of only 4.

Despite these positive findings, the numbers of RCTs contributing data to these analyses were small in most cases. Other trials studying the efficacy of infliximab in inducing remission in active luminal CD have been conducted, including the COMMIT study and the step-up vs. top-down trial (61,62), but these were ineligible for inclusion in the meta-analysis because of the lack of a placebo arm. Our methodologies were the most conservative, to date, to minimize potential biases and we dichotomized, rather than quantified, outcomes. There remains potential heterogeneity in outcome measures, as trials were not individualized according to the "hierarchy" of outcomes (clinical definitions of remission, with or without endoscopic criteria). Further trials are required to assess alternative end points or outcomes, such as mucosal healing in CD, reductions in surgery and hospitalization, and other measures of relevant comparative effectiveness between agents, as well as to more accurately estimate the efficacy of these drugs in certain situations, including inducing fistula healing, preventing fistula recrudescence, and preventing relapse of disease activity in UC patients who have failed other therapies, once remission has been achieved.

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CONFLICT OF INTEREST

Guarantor of the article: Alexander C. Ford, MBChB, MD, MRCP.
Specific author contributions: Alexander C. Ford, William J. Sandborn, Khurram J. Khan, Stephen B. Hanauer, Nicholas J. Talley, and Paul Moayyedi conceived and drafted the study; Alexander C. Ford, Khurram J. Khan, and Paul Moayyedi collected all data; Alexander C. Ford and Paul Moayyedi analyzed and interpreted the data; Paul Moayyedi provided statistical advice and support; Alexander C. Ford drafted the manuscript. All authors commented on drafts of the paper and all authors have approved the final draft of the manuscript.
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Potential competing interests: William J. Sandborn has served as a consultant to, and received research support from, Centocor, Merck (previously Schering-Plough), Abbott Laboratories, and UCB Pharma. Stephen B. Hanauer has served as a consultant to Centocor, Abbott, UCB Pharma, Elan, and Biogen, and has received research support from Centocor, Abbott, and UCB Pharma. Paul Moayyedi is the chairperson at McMaster University, is partly funded by an unrestricted donation by AstraZeneca, and has received consultant's and speaker's bureau fees from AstraZeneca, AxCan Pharma, Nycomed, and Johnson and Johnson. The remaining authors declare no conflict of interest.

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