Article:
Ford, AC, Luthra, P, Hanauer, SB et al. (3 more authors) (2014) Placebo response rate in clinical trials of fistulizing crohn's disease: systematic review and meta-analysis. Clinical Gastroenterology and Hepatology, 12 (12). 1981 - 1990. ISSN 1542-7714

https://doi.org/10.1016/j.cgh.2014.08.038

TITLE PAGE

Title: Placebo Response Rate in Clinical Trials of Fistulizing Crohn's Disease: Systematic Review and Meta-analysis.

Short "running" title: Placebo Response Rate in Fistulizing Crohn's.

Authors: Alexander C. Ford[1,2], Pavit Luthra[1], Stephen B. Hanauer[3], Simon P. Travis[4], M. Scott Harris[5], Walter Reinisch[6].

[1]Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK.

[2]Leeds Institute of Biomedical and Clinical Sciences, University of Leeds, Leeds, UK.

[3]Digestive Health Center, Northwestern University Feinberg School of Medicine, Chicago, USA.

[4]Translational Gastroenterology Unit, Oxford University Hospitals, Oxford, UK.

[5]Georgetown University School of Medicine, Washington, DC, USA

[6]Gastroenterology Division, McMaster University, Health Sciences Center, Hamilton, Ontario, Canada.

Grant support: None.

Abbreviations:

5-ASA	5-aminosalicylate
b.i.d.	twice daily
CD	Crohn's disease
CI	confidence interval

GI	gastrointestinal
o.d.	once daily
RCT	randomized controlled trial
t.i.d.	three times daily

Word count: 3392

Correspondence: Dr. Alex Ford

Leeds Gastroenterology Institute

Room 125

4th Floor

Bexley Wing

St. James's University Hospital

Beckett Street

Leeds

United Kingdom

LS9 7TF

Email: alexf12399@yahoo.com

Telephone: +441132684963

Facsimile: +441132429722

Disclosures: Alexander C Ford: has received speakers' fees from Shire and MSD. Pavit Luthra: none. Stephen B Hanauer has acted as a consultant to AbbVie, Janssen, UCB, Takeda, and Prometheus/Nestle. Simon P Travis has acted as consultant to and received speakers' fees or research support from AbbVie, Ferring Pharmaceuticals,

Genentech-Roche, Johnson & Johnson, MSD, Ocera, Pfizer, Shire, Takeda, TxCell. M. Scott Harris has acted as a consultant to Avaxia Biologics, Drais Pharmaceuticals, Rhythm Pharmaceuticals, Theravance, PATH, CymaBay Pharmaceuticals, ZS Pharmaceuticals, and Biomedical Systems, and owns stock or stock options in Avaxia Biologics and Ocera Therapeutics. Walter Reinisch has served as a speaker, a consultant and/or an advisory board member for Abbott Laboratories, Abbvie, Aesca, Amgen, AM Pharma, Aptalis, Astellas, Astra Zeneca, Avaxia, Bioclinica, Biogen IDEC, Bristol-Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Danone Austria, Elan, Falk Pharma GmbH, Ferring, Galapagos, Genentech, Grünenthal, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Robarts Clinical Trial, Schering-Plough, Setpointmedical, Shire, Takeda, Therakos, Tigenix, UCB, Vifor, Yakult, Zyngenia, and 4SC.

Author contributions: ACF, PL, SBH, SPT, MSH, and WR conceived and drafted the study. ACF and PL collected all data. ACF analyzed and interpreted the data. ACF drafted the manuscript. All authors commented on drafts of the paper. All authors have approved the final draft of the manuscript.

.

ABSTRACT

Background & Aims: It is important to determine the magnitude and identify modifiers of the rate of response to placebo in clinical trials of fistulizing Crohn's disease (CD), to understand disease progression and calculate sample size. We conducted a systematic review and meta-analysis of rates of response to placebo in trials of patients with fistulizing CD.

Methods: We searched MEDLINE, EMBASE, EMBASE CLASSIC, and the Cochrane central register of controlled trials for randomized controlled trials (RCTs) comparing pharmacologic agents with placebo in adults with fistulizing CD. We identified studies that reported complete fistula closure, partial closure or response. Data were extracted as intention-to-treat analyses, and pooled using a random effects model. Proportions of patients who received placebo and had complete or partial fistula(e) closure were calculated, with 95% confidence intervals (CIs). The effects of trial characteristics on the magnitude of response to placebo were examined.

Results: Thirteen RCTs were eligible for our analysis; these included 579 patients assigned to placebo groups. The pooled rate of response to placebo, among all RCTs, for complete fistula closure was 15.6% (95% CI, 10.9%−20.9%), with significant heterogeneity (I^2 = 62.5%; *P*=.001). The pooled rate of response to placebo for partial fistula closure or response in 9 trials, comprising 423 patients, was 18.3% (95% CI, 14.8%–22.1%). Rates of response to placebo were significantly lower in trials with shorter durations of therapy and shorter intervals to assessment of fistula closure. Neither exposure to the pharmacologic agent during the induction phase of the same (or a related) RCT, nor concomitant medications, had any effect.

Conclusions: In a meta-analysis of rate of response to placebo in patients with fistulizing CD, we found that fistulas closed in almost 1/6 patients given placebo in

RCTs of pharmacologic agents. Future research should identify characteristics of patients that predict response to placebo.

KEY WORDS: IBD; fistula; meta-analysis; randomized controlled trials; placebo effect

INTRODUCTION

Perianal fistulizing disease affects up to 40% of patients with Crohn's disease (CD) . [1] It reflects an aggressive disease behavior, leading to irreversible structural damage, and has been shown to be an independent predictor for a disabling course of disease. [2] If perianal fistulizing disease is associated with abscess formation combined surgical and medical management is recommended, but if not then conservative medical approaches only, including treatment with antibiotics, immunosuppressants, and/or tumor necrosis factor α-inhibitors are appropriate. [3]

Evidence from the systematic review literature suggests that a significant proportion of patients assigned to placebo will respond to therapy, even in RCTs of therapies for organic GI conditions such as inflammatory bowel disease or peptic ulcer, where mucosal or ulcer healing are often the outcomes of interest. [4, 5] Placebo response rates in luminal CD have been the subject of prior systematic analysis. [6-9] Endpoints such as the Crohn's disease activity index, [10] are weighted towards patient reported outcome measures, which may drive the high placebo response and remission rates sometimes observed. The adoption of more objective measures of disease activity in trial endpoints in more recent years, including inflammatory biomarkers, radiological imaging, or mucosal healing may minimize this.

Clinical trials in fistulizing CD almost exclusively recruit patients with fistulae draining to the body surface, predominantly the skin. The majority of these fistulae are located in the perianal region. The endpoints in trials of fistulizing CD appear to be more objective and range from partial response, usually defined by a 50% or more reduction in the number of draining fistulae, up to fistula closure referring to complete cessation of drainage. [11] Despite the fact that there have been several published RCTs of pharmacological therapies in fistulizing CD, the magnitude of the placebo response

rate has not been studied. This is important, since high placebo response rates will statistically reduce the possibility of detecting a positive impact of active therapy, and RCTs should be designed to minimize placebo response. We have therefore conducted a systematic review and meta-analysis in order to assess the magnitude of the placebo response rate in treatment trials of fistulizing CD, and have examined trial characteristics and features of design that may influence this.

METHODS

Search Strategy and Trial Selection

A search of the medical literature was conducted using EMBASE CLASSIC and EMBASE (1947 to February 2014), and MEDLINE (1948 to February 2014) and the Cochrane central register of controlled trials (2014). Randomized controlled trials examining the effect of pharmacological therapies in adult patients (over the age of 18 years) with fistulizing CD were eligible for inclusion (Box 1). The first period of cross-over RCTs were also eligible for inclusion. In the case of all RCTs the control arm were required to receive placebo. Time point of fistula assessment had to be at least 4 weeks after therapy commenced, and RCTs had to report complete fistula closure, or partial fistula closure or fistula response.

Placebo-controlled trials in CD were identified with the terms *Crohn disease*, *inflammatory bowel disease*, *colitis*, or *ileitis* (both as medical subject headings and free text terms), and *Crohn$ disease* or *regional enteritis* (as free text terms). These were combined using the set operator AND with studies identified with the free text term *fistul$*. There were no language restrictions and abstracts of the papers identified by the initial search were evaluated by the lead reviewer 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 from the Digestive Diseases Week, European Crohn's and Colitis Organization, and United European Gastroenterology Week between 2001 and 2013 were hand-searched to identify potentially eligible RCTs published only in abstract form. The bibliographies of all identified eligible trials were used to perform a recursive search of the literature. Articles were independently assessed by two

reviewers using pre-designed eligibility forms, according to the prospectively defined eligibility criteria (Box 1). Any disagreement between investigators was resolved by consensus.

Outcome Assessment

The primary outcome assessed was the magnitude of the placebo response rate, in terms of complete fistula closure, or partial fistula closure or fistula response, at study end in all RCTs of pharmacological therapies conducted in fistulizing CD. Secondary outcomes included assessment of placebo response rate according to different trial characteristics.

Data Extraction

All data were extracted independently by two reviewers on to a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (complete fistula closure, or partial fistula closure or fistula response, in the placebo arms of the included RCTs). In addition, the following clinical data were extracted for each trial: geographical location, number of centers, dosing schedule of the placebo, route of administration, duration of therapy, time point at which fistula closure was assessed, whether patients were exposed to open-label active therapy during an earlier induction phase of the same, or a related, RCT, the proportion of trial patients receiving placebo, active pharmacological therapy used, primary outcome measure used to define complete fistula closure, or partial fistula closure or fistula response, and whether it was patient versus physician-reported, location of the fistula(e), and proportion of individuals taking concomitant medications for CD at trial entry. Data were extracted as intention-to-treat analyses,

with all drop-outs assumed to be treatment failures, wherever trial reporting allowed this.

Assessment of Risk of Bias

Risk of bias assessment was performed independently by two investigators, with disagreements resolved by discussion. Risk of bias was assessed as described in the Cochrane handbook, [12] by recording the method used to generate the randomization schedule and conceal allocation, whether blinding was implemented for participants, personnel and outcome assessment, what proportion of subjects completed follow-up, 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 magnitude of the placebo response rate, allowing for any heterogeneity between trials. [13] Outcomes were expressed as the pooled proportion of patients assigned to placebo with complete fistula closure, or partial fistula closure or fistula response, after completion of therapy, with a 95% confidence interval (CI).

The results of individual RCTs 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 50% was chosen to represent low levels of heterogeneity. [14]

Subgroup analyses were conducted for rates of complete fistula closure, according to route of administration of the placebo, duration of therapy, time point at which fistula closure was assessed, whether patients were exposed to active therapy during an earlier induction phase of the same, or a related, RCT, proportion of individuals taking concomitant medications at trial entry including 5-aminosalicylates, glucocorticosteroids, immunosuppressants, or antibiotics, and active pharmacological therapy used. We did not performed meta-regression in this systematic review and meta-analysis, but rather subgroup analyses according to individual trial characteristics, because the former technique evaluates the average of patient characteristics within each trial, and this summary data may misrepresent individual patients within each treatment arm. The technique is therefore vulnerable to giving spurious results due to the ecological fallacy. [15]

StatsDirect version 2.7.2 (StatsDirect Ltd, Sale, Cheshire, England) was used to generate Forest plots of the pooled proportions of patients assigned to placebo with complete fistula closure, or partial fistula closure or fistula response, after completion of therapy, with 95% CIs. Pooled placebo response rates were compared between the pre-defined subgroups using the Cochran Q statistic in order to assess for any heterogeneity between placebo response rates for the different subgroup analyses we conducted and, due to multiple analyses, a P value of < 0.01 was considered statistically significant.

RESULTS

The search strategy generated 9063 citations of which 44 appeared to be relevant to the systematic review and were retrieved for further assessment (Figure 1). Of these 44 RCTs, 31 were excluded for the reasons listed, leaving 13 eligible trials, [16-28] containing 579 individuals with fistulizing CD who were randomized to receive placebo. Agreement between reviewers for assessment of trial eligibility was good (kappa statistic = 0.90). Characteristics of individual RCTs, including the magnitude of the placebo response in each trial, are provided in Table 1. Three trials included only patients with perianal fistulizing disease with fistula closure as the primary endpoint, [17, 18, 28] three trials recruited patients with fistulizing disease exclusively, but at any location, [20, 22, 26] again reporting fistula closure as the primary endpoint, and seven trials reported fistula closure as a secondary endpoint within a mixed population of patients with either luminal or fistulizing CD. [16, 19, 21, 23-25, 27] Six trials were at low risk of bias. [18, 19, 21, 22, 24, 25] Definitions of fistula closure and fistula response used in each trial are provided in Table 2.

Placebo Response Rates for Complete Fistula Closure and Partial Fistula Closure or Response in All Trials

The pooled placebo response rate for complete fistula closure in the 13 RCTs that we identified, and judged by the investigator in all studies, was 15.6% (95% CI 10.9% to 20.9%). There was considerable heterogeneity between trials (I^2 = 62.5%, P = 0.001). The placebo response rate in individual RCTs varied from 5.9% to 43.3% (Figure 2). There were nine trials that reported partial fistula closure or response. [17-22, 24, 26, 28] The pooled placebo response rate in these trials was 18.3% (95% CI 14.8% to 22.1%), with no significant heterogeneity between studies (I^2 = 0.4%, P = 0.43)

(Figure 3). Seven trials used closure of ≥50% of fistulas to define response, [17, 20-22, 24, 26, 28] with the other two trials using improvement or partial closure, [19] or a decrease in the perianal Crohn's disease activity index of ≥5 (Table 2). [18] When only those seven RCTs that used the same definition of partial fistula closure or response were included in the analysis, the pooled placebo response rate was 18.6% (95% CI 14.5% to 23.1%), again with no significant heterogeneity between studies (I^2 = 9.8%, P = 0.35).

Placebo Response Rate for Complete Fistula Closure According to Fistula Location, Route of Administration of Placebo Duration of Therapy, and Time Point at which Fistula Closure was Assessed

Pooled placebo response rates were generally lower among studies that recruited exclusively those with perianal disease compared with those that included patients with fistulae at any location (10.1% vs. 18.1%), with a trend towards this difference being statistically significant (Cochran Q = 4.32, P = 0.04). Pooled placebo response rate for complete fistula closure was lowest in the one trial that used a topical route of administration (7.3%), [18] and highest in the four trials that used subcutaneous administration (23.3%) (Table 3). Heterogeneity between studies was confined to those using a subcutaneous route, with no heterogeneity detected when only the four trials that used the oral route or the four trials that used intravenous administration were included. Differences in pooled placebo response rates did not reach formal statistical significance, although there was a trend towards a lower rate with oral administration compared with either intravenous or subcutaneous (Cochran Q = 4.55, P = 0.03 and Cochran Q = 4.49, P = 0.03 respectively). Duration of therapy varied from 2 to 56 weeks. Pooled placebo response rate in trials using >10 weeks of therapy was 21.2%, which was significantly higher than in RCTs that used ≤10 weeks

of therapy (10.3%, Cochran Q = 7.53, P = 0.006) (Table 3). Time point at which fistula closure was assessed ranged from 4 to 56 weeks, with pooled response rates again significantly higher in trials with >10 weeks of follow-up, compared with those with ≤10 weeks (20.3% vs. 9.9%, Cochran Q = 6.52, P = 0.01) (Table 3).

Placebo Response Rate for Complete Fistula Closure According to Exposure to Active Therapy During Induction, Concomitant Medication at Trial Entry, and Active Therapy

There were four trials in which patients were exposed to active therapy during induction therapy before being re-randomized to placebo. [16, 25-27] Placebo response rates were higher in these four trials, but this difference was not statistically significant (20.6% vs. 13.2%, Cochran Q = 3.16, P = 0.075) (Table 3). There were seven RCTs that reported the proportion of placebo patients receiving concomitant therapy at trial entry with 5-ASAs, glucocorticosteroids, or immunosuppressants, [16-18, 20, 22, 26, 28] and six that reported use of concomitant antibiotics. [17, 18, 20, 22, 26, 28] We used a threshold of ≥30% of the placebo arm using these drugs to distinguish between individual trials for all of these analyses. There were no significant differences observed between placebo response rates according to use of 5-ASAs, glucocorticosteroids, immunosuppressants, or antibiotics, although the placebo response rates in trials where ≥30% of the placebo arm were using glucorticosteroids were generally higher (16.8% vs. 10.0%, Cochran Q = 3.87, P = 0.05) (Table 3).

Biological drugs were the active pharmacological agent used in the greatest number of trials. [16, 20, 21, 23-27] Generally, placebo response rates appeared higher in these trials, but this was not significantly greater than in trials using antibiotics, immunosuppressants, or AST-120 carbon microspheres (Cochran Q = 2.24, P = 0.13,

Cochran Q = 2.35, P = 0.13, and Cochran Q = 4.82, P = 0.03 respectively). Among individual biologics used, pooled placebo response rates were higher in the two trials that used certolizumab (35.8%) compared with trials using other drugs, where placebo response rates varied between 11.1% and 18.1% (Table 3).

DISCUSSION

This systematic review and meta-analysis of placebo-controlled randomized trials conducted in patients with fistulizing CD has demonstrated a pooled placebo response rate of 15.6% for complete fistula closure in 13 studies, and 18.3% for partial fistula closure or fistula response in nine trials. Pooled placebo response rate was significantly higher in trials using >10 weeks of therapy, and trials in which fistula closure was assessed at >10 weeks, compared with those ≤10 weeks. There was also a trend towards a lower placebo response rate in patients with perianal fistula, and with oral, compared with either intravenous or subcutaneous, administration. Active therapy used, whether there was exposure to this during an induction phase of the same, or a related, RCT and concomitant medication use at trial entry did not appear to affect placebo response rates, although rates were generally higher in RCTs where patients were exposed to active therapy during induction, and in trials where ≥30% of those assigned to placebo were using concomitant glucocorticosteroids.

Strengths of the present study include the search strategy, which was exhaustive, in order to maximize the number of identified RCTs providing data for these analyses. We assessed the impact of individual trial characteristics on pooled placebo response rates in subgroup analyses. We also performed an intention-to-treat analysis, where all drop-outs were assumed to be treatment failures, and used a random effects model to provide a more conservative estimate of the pooled placebo response rate, meaning that the magnitude of this effect is unlikely to have been overestimated.

Weaknesses of the study include the fact that there was statistically significant heterogeneity when trial data were pooled in our primary analysis, although this appeared to resolve in some of our subgroup analyses, including route of

administration, duration of therapy, and time point at which fistula closure was assessed. In addition, cessation of drainage from fistulae ('closure') does not equate to healing, since MRI scanning will generally show persistent fistulous tracks even when drainage ceases. [29] It can also be argued that RCTs examine medical therapy to the exclusion of surgical management, although in clinical practice combined medical and surgical management, particularly seton insertion, [30] is the standard of care. [3] Despite the detailed analyses we conducted, it is important to point out that, without access to individual patient level data, it is difficult to draw any firm conclusions about specific patient characteristics that may predict a response to placebo in patients with fistulizing CD. Finally, although we conducted a subgroup including only trials that recruited patients with perianal fistulizing CD exclusively, we were not able to assess the effect of exact fistula location on placebo response rate.

There have been several published systematic reviews and meta-analyses that have examined the placebo response rates in luminal CD. [6-9] In the most definitive of these, which examined placebo response rates in active CD across all therapies, the pooled placebo response rate was 18%, similar to that we observed. The other three meta-analyses restricted themselves to specific therapies, or situations such as post-operative recurrence of CD. However, none have studied this issue specifically in fistulizing CD. The results of this study are therefore novel and important, as they can be used to inform the design of future studies testing novel or existing therapies in fistulizing CD.

Given that most of the outcomes reported in the trials we identified were investigator-reported, and therefore objective rather than subjective, it is unlikely that the magnitude of the placebo response has been exaggerated in this meta-analysis. Possible explanations for the finding that placebo response rates were significantly

higher in RCTs with longer duration of therapy, and a longer time to assessment of fistula closure, are speculative but it may be that, as treatment or follow-up continues in fistulizing CD, there is more likely to be closure with placebo due to regression to the mean, hence the results of our meta-analysis provide an approximation of the spontaneous closure rate of fistulizing CD. This theory is supported by a previous meta-analysis of placebo response rates in luminal CD, where increasing duration of follow-up was significantly associated with higher placebo response rates. [6]

Whether the closure rates of fistulae in these trials is a true effect of placebo, or due to a combination of concomitant medications, other standardized best care, or spontaneous healing is difficult to judge. The concept of placebo as an active treatment with beneficial effects on mind and body has been reported by other investigators in the field of functional GI disorders. [31] With this in mind, it is interesting to note that closure rates with placebo were generally higher in trials that used a non-oral route of administration, which suggests that preconceived conscious or subconscious expectations of the efficacy of the assigned treatment, as judged by the patient, may impact on the likelihood of response to a placebo. [32]

The fact that we did not observe any significant differences in placebo response rates according to whether patients were exposed to active therapy at an earlier stage of the trial, or concomitant medication use, is perhaps surprising, but in the former case there were only four studies of biologic agents where patients received open-label drug therapy prior to re-randomization and pooled rates of fistula closure with placebo were generally higher in these trials, and in the latter instance not all trials reported these data, meaning that our meta-analysis may have been underpowered to detect any difference in closure rates according to these patient characteristics. This underlines the need for access to patient level data when

examining the exact impact of these aspects of trial design or patient characteristics on outcome measures with any great accuracy. This would also allow the impact of baseline disease activity or inflammatory markers on rates of fistula closure or response with placebo to be studied, something we were unable to examine in our meta-analysis. This issue was examined in one of the included RCTs, [28] and it appeared that patients with lower clinical and inflammatory activity were more likely to experience closure of fistulae with placebo.

The number of patients with fistulizing CD experiencing complete fistula closure with placebo in this study appears to be somewhere between one in five and one in 10. When partial fistula closure or response to therapy was assessed, this was between one in five and one in seven. This information is important for the conduct of future RCTs in fistulizing CD, as it may be helpful in informing power calculations on which to base trial recruitment. To date, only one drug that has been studied exclusively in a population of patients with fistulizing CD is licensed for use, [20, 26] underlining the fact that there is still a huge unmet need for the development and testing of novel therapies for this disabling and difficult to treat condition. Our study results should help in designing future trials of drugs with variable mechanisms of action.

This systematic review and meta-analysis has demonstrated a pooled fistula closure rate of 15.6% in all available RCTs of pharmacological therapies, and a partial fistula closure or fistula response rate of 18.3%. This highlights that partial response rates lead to higher estimates of efficacy, and that more stringent endpoints should be preferred in subsequent trials of therapies in fistulizing CD, in order to minimize placebo response rates and maximize the likelihood of detecting a beneficial effect of active therapy over placebo. Future research should concentrate on identifying patient

characteristics that predict such a response to treatment, ideally using trial data at the individual patient level.

REFERENCES

1. Schwartz DA, Loftus EV, Jr., Tremaine WJ, et al. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. Gastroenterology 2002;122:875-80.

2. Beaugerie L, Seksik P, Nion-Larmurier I, et al. Predictors of Crohn's disease. Gastroenterology 2006;130:656.

3. van Assche G, Dignass A, Reinisch W, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: special situations. J Crohns Colitis 2010;4:63-101.

4. de Craen AJ, Moerman DE, Heisterkamp SH, et al. Placebo effect in the treatment of duodenal ulcer. Br J Clin Pharmacol 1999;48:853-60.

5. Ilnyckyj A, Shanahan F, Anton PA, et al. Quantification of the placebo response in ulcerative colitis. Gastroenterology 1997;112:1854-8.

6. Su C, Lichtenstein GR, Krok K, et al. A meta-analysis of the placebo rates of remission and response in clinical trials of active Crohn's disease. Gastroenterology 2004;126:1257-1269.

7. Tine F, Rossi F, Sferrazza A, et al. Meta-analysis: remission and response from control arms of randomized trials of biological therapies for active luminal Crohn's disease. Aliment Pharmacol Ther 2008;27:1210-1223.

8. Pascua M, Su C, Lewis JD, et al. Meta-analysis: factors predicting post-operative recurrence with placebo therapy in patients with Crohn's disease. Aliment Pharmacol Ther 2008;28:545-556.

9. Renna S, Camma C, Modesto I, et al. Meta-analysis of the placebo rates of clinical relapse and severe endoscopic recurrence in postoperative Crohn's disease. Gastroenterology 2008;135:1500-1509.

10. Best WR, Becktel JM, Singleton JW, et al. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976;70:439-444.

11. Sandborn WJ, Feagan BG, Hanauer SB, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. Gastroenterology 2002;122:512-30.

12. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions: Version 5.0.2. www.cochrane-handbook.org 2009.

13. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-188.

14. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. Br Med J 2003;327:557-560.

15. Lau J, Ioannidis JP, Schmid CH. Summing up evidence: one answer is not always enough. Lancet 1998;351:123-7.

16. Colombel JF, Schwartz DA, Sandborn WJ, et al. Adalimumab for the treatment of fistulas in patients with Crohn's disease. Gut 2009;58:940-948.

17. Fukuda Y, Takazoe M, Sugita A, et al. Oral spherical adsorptive carbon for the treatment of intractable anal fistulas in Crohn's disease: a multicenter, randomized, double-blind, placebo-controlled trial. Am J Gastroenterol 2008;103:1721-1729.

18. Maeda Y, Ng SC, Durdey P, et al. Randomized clinical trial of metronidazole ointment versus placebo in perianal Crohn's disease. Br J Surg 2010;97:1340-1347.

19. Present DH, Korelitz BI, Wisch N, et al. Treatment of Crohn's disease with 6-mercaptopurine. A long-term, randomized, double-blind study. N Engl J Med 1980;302:981-987.

20. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340:1398-1405.

21. Sandborn WJ, Feagan BG, Radford-Smith G, 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;53:1485-1493.

22. Sandborn WJ, Present DH, Isaacs KL, et al. Tacrolimus for the treatment of fistulas in patients with Crohn's disease: a randomized, placebo-controlled trial. Gastroenterology 2003;125:380-388.

23. Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med 2007;357:228-238.

24. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Ann Intern Med 2007;146:829-838.

25. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013;369:711-721.

26. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004;350:876-885.

27. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. N Engl J Med 2007;357:239-250.

28. Reinisch W, Travis S, Hanauer S, et al. AST-120 (spherical carbon adsorbent) in the treatment of perianal fistulae in mild-to-moderate Crohn's isease: FHAST-1, a phase 3, multicenter, placebo-controlled study. Inflamm Bowel Dis 2014;20:872-881.

29. Karmiris K, Bielen D, Vanbeckevoort D, et al. Long-term monitoring of infliximab therapy for perianal fistulizing Crohn's disease by using magnetic resonance imaging. Clin Gastroenterol Hepatol 2011;9:130-6.

30. Bouguen G, Siproudhis L, Gizard E, et al. Long-term outcome of perianal fistulizing Crohn's disease treated with infliximab. Clin Gastroenterol Hepatol 2013;11:975-81.

31. Kaptchuk TJ, Friedlander E, Kelley JM, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. PLoS One 2010;5:e15591.

32. Mommaerts JL, Devroey D. The placebo effect: how the subconscious fits in. Perspect Biol Med 2012;55:43-58.

Box 1. Eligibility criteria.

Randomized controlled trials.

Adults (participants aged > 18 years) with active fistulizing Crohn's disease.

Compared pharmacological therapies with placebo.

Contained >15 patients in the placebo arm.

Time point of fistula assessment had to be at least 4 weeks after therapy commenced.

Assessment of complete or partial fistula closure following therapy.

TABLES

Table 1. Characteristics of Included Trials.

Trial	Geographical location	Active treatment*	Duration of therapy	Point at which fistula closure assessed	Sample size (% perianal)	Placebo response rate for complete fistula closure (%)	Placebo response rate for partial fistula closure or response (%)	Fistula endpoint primary or secondary analysis
Present 1980 [19]	USA , one center	Mercaptopurine 1.5m/kg o.d orally	52 weeks	52 weeks	46 (not reported)	1/17 (5.9)	4/17 (23.5)	Secondary
Present 1999 [20]	Multinational, 12 centers	Infliximab 5mg or 10mg/kg at weeks 0, 2, and 6 intravenously	6 weeks	18 weeks	94 (90%)	4/31 (12.9)	8/31 (25.8)	Primary

Sandborn 2003 [22]	USA and Canada, 18 centers	Tacrolimus 0.1mg/kg b.i.d orally	10 weeks	10 weeks	48 (91%)	2/26 (7.7)	2/26 (7.7)	Primary
Sandborn 2004 [21]	Multinational, 68 centers	CDP571 10mg/kg every 8 weeks intravenously	24 weeks	28 weeks	86 (not reported)	5/26 (19.2)	5/26 (19.2)	Secondary
Sands 2004 [26]	Multinational, 45 centers	Infliximab 5mg/kg every 8 weeks intravenously	46 weeks	54 weeks	195 (90%)	19/99 (19.2)	23/99 (23.2)	Primary
Sandborn 2007a [24]	Multinational, 52 centers	Adalimumab 160mg at week 0 and 80mg at week 2 subcutaneously	2 weeks	4 weeks	45 (not reported)	2/25 (8.0)	5/25 (20.0)	Secondary

Sandborn 2007b [23]	Multinational, 171 centers	Certolizumab 400mg at weeks 0, 2, and 4 and then every 4 weeks subcutaneously	24 weeks	26 weeks	107 (not reported)	19/61 (31.1)	Not reported	Secondary
Schreiber 2007 [27]	Multinational, 147 centers	Certolizumab 400mg every 4 weeks subcutaneously	24 weeks	26 weeks	58 (not reported)	13/30 (43.3)	Not reported	Secondary
Fukuda 2008 [17]	Japan, 19 centers	AST-120 2g t.i.d orally	8 weeks	8 weeks	62 (100%)	2/31 (6.5)	3/31 (9.7)	Primary
Colombel 2009 [16]	Multinational, 92 centers	Adalimumab 40mg weekly or every other week subcutaneously	56 weeks	56 weeks	117 (97%)	6/47 (12.8)	Not reported	Secondary

Maeda 2010 [18]	UK and USA, 12 centers	Metronidazole 10% ointment t.i.d topically	4 weeks	4 weeks	74 (100%)	3/41 (7.3)	5/41 (12.2)	Primary
Sandborn 2013 [25]	Multinational, 285 centers	Vedolizumab 300mg at week 0 and 2 then every 4 or 8 weeks intravenously	52 weeks	52 weeks	57 (not reported)	2/18 (11.1)	Not reported	Secondary
Reinisch 2014 [28]	Multinational, 289 centers	AST-120 2g t.i.d orally	8 weeks	8 weeks	249 (100%)	14/127 (11.0)	21/127 (16.5)	Primary

*o.d. once daily, b.i.d. twice daily, t.i.d. three times daily

Table 2. Fistula Location, Definition of Fistula Closure and Fistula Response Used in Each Trial.

Trial	Fistula location	Definition of fistula closure	Definition of partial fistula closure or response
Present 1980 [19]	Any	Complete closure	Improvement or partial healing
Present 1999 [20]	Any	Absence of any draining fistulae at two consecutive visits	Reduction of ≥50% of draining fistulae at two consecutive visits
Sandborn 2003 [22]	Any	Closure of all open, draining fistulae and maintenance of closure for ≥4 weeks	Closure of ≥50% of open, draining fistulae and maintenance of closure for ≥4 weeks
Sandborn 2004 [21]	Any	Closure of 100% of fistulae on two consecutive visits over a 6-week period	Closure of ≥50% of fistulae on two consecutive visits over a 6-week period
Sands 2004 [26]	Any	Absence of draining fistulae	Reduction of ≥50% of draining fistulae at two consecutive visits ≥4 weeks apart
Sandborn 2007a [23]	Any	Closure of all draining fistulae at both of weeks 2 and 4	Reduction of ≥50% of draining fistulae at both of weeks 2 and 4
Sandborn 2007b [24]	Any	Absence of any draining fistulae at two consecutive visits	Not reported

Schreiber 2007 [27]	Any	Absence of any draining fistulae at two consecutive visits ≥3 weeks apart	Not reported
Fukuda 2008 [17]	Perianal only	Closure of all draining fistulae at both of weeks 4 and 8	Closure of ≥50% of fistulae at both of weeks 4 and 8
Colombel 2009 [16]	Any	Absence of any draining fistulae	Not reported
Maeda 2010 [18]	Perianal only	No discharge from fistulae	Decrease in the perianal Crohn's disease activity index of ≥5
Sandborn 2013 [25]	Any	Closure of draining fistulae	Not reported
Reinisch 2014 [28]	Perianal only	Closure of all draining fistulae at both of weeks 4 and 8	50% reduction in the number of draining fistulae at both of weeks 4 and 8

Table 3. Effect of Trial Characteristics on Magnitude of the Placebo Response for Complete Fistula Closure.

	Number of trials	Number of patients receiving placebo	Pooled placebo response rate for complete fistula closure (%)	95% confidence interval	I^2 (%)	P value for I^2
All trials	13	579	15.6	10.9 – 20.9	62.5	0.001
Fistula location						
Perianal only	3	199	10.1	6.3 – 14.6	0	0.75
Any	10	380	18.1	12.2 – 24.8	59.9	0.008
Route of administration of placebo						
Topical	1	41	7.3	1.5 – 19.9	N/A*	N/A*
Oral	4	201	10.1	6.4 – 14.6	0	0.91
Intravenous	4	174	17.8	12.6 – 23.8	0	0.81
Subcutaneous	4	163	23.3	10.6 – 39.2	79.6	0.002
Duration of therapy						
≤10 weeks	6	281	10.3	7.1 – 14.1	0	0.96
> 10 weeks	7	298	21.2	13.8 – 29.8	63.2	0.01

Time point at which fistula closure assessed						
≤10 weeks	5	250	9.9	6.6 – 13.9	0	0.96
> 10 weeks	9	329	20.3	13.7 – 27.9	59.9	0.015
Placebo patients exposed to active therapy during induction						
Yes	4	194	20.6	15.2 – 26.4	70.9	0.02
No	9	385	13.2	8.4 – 18.9	53.4	0.03

Concomitant medication use at trial entry in placebo arm						
<30% 5-ASAs	1	47	12.8	4.8 – 25.7	N/A*	N/A*
≥30% 5-ASAs	6	324	12.7	9.0 – 16.6	14.2	0.32
<30% glucocorticosteroids	4	225	10.0	6.4 – 14.2	0	0.89
≥30% glucocorticosteroids	3	177	16.8	11.7 – 22.6	0	0.58
<30% immunosuppressants	2	62	10.7	4.4 – 19.3	N/A*	N/A*
≥30% immunosuppressants	5	340	13.1	9.3 – 17.4	17.7	0.30
<30% antibiotics	4	298	12.4	7.6 – 18.1	44.7	0.14
≥30% antibiotics	2	57	11.7	4.8 – 21.0	N/A*	N/A*

Active pharmacological therapy						
Antibiotic	1	41	7.3	1.5 – 19.9	N/A*	N/A*
Immunosuppressant	2	43	8.7	2.4 – 18.6	N/A*	N/A*
AST-120	2	158	10.6	6.3 – 15.8	N/A*	N/A*
Biological therapy	8	337	20.3	13.7 – 27.8	60.4%	0.014
CDP571	1	26	19.2	6.6 – 39.4	N/A*	N/A*
Vedolizumab	1	18	11.1	1.4 – 34.7	N/A*	N/A*
Adalimumab	2	91	12.1	5.7 – 20.4	N/A*	N/A*
Certolizumab	2	72	35.8	25.0 – 47.5	N/A*	N/A*
Infliximab	2	130	18.1	12.0 – 25.1	N/A*	N/A*

*N/A: not applicable, too few studies to assess for heterogeneity

FIGURES

Figure 1. Flow Diagram of Assessment of Trials Identified in the Systematic Review.

Figure 2. Forest Plot of Pooled Placebo Response Rates for Complete Fistula Closure.

Figure 3. Forest Plot of Pooled Placebo Response Rates for Partial Fistula Closure or Response.