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TITLE PAGE

Title: Impact of Baseline Disease Activity and Trial Duration on Efficacy of Biologics in Active Crohn's Disease: Meta-analysis.

Short title: Influence of Disease Activity and Trial Duration on Efficacy in CD.

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Abbreviations:

CD	Crohn's disease
CDAI	Crohn's disease activity index
CI	confidence interval
CRP	C-reactive protein
FC	fecal calprotectin
NNT	number needed to treat
RCT	randomized controlled trial
RR	relative risk

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ABSTRACT

Objective: Timings of assessment of efficacy and criteria used to define Crohn's disease (CD) activity at baseline may affect therapeutic gain of active drug over placebo in induction of remission trials in CD, but these issues have not been assessed systematically. We examined these issues in a meta-analysis.

Design: We searched the literature to June 2022 for randomized controlled trials of biologics versus placebo in active CD. We extracted clinical remission and response rates according to criteria used to define CD activity and timepoint of assessment, pooling them in a meta-analysis for all patients, and according to previous biologic exposure. We calculated the number needed to treat (NNT), with a 95% confidence interval (CI), to assess therapeutic gain of active drug over placebo according to these characteristics of trial design.

Results: We identified 20 induction of remission trials (6754 patients). Rates of clinical remission were highest (42.6% with active drug, versus 21.0% with placebo), and NNT lowest (5; 95% CI 3-7.5), in trials using clinical and endoscopic activity to define active CD, and rates of remission lower (26.5% with active drug, versus 18.6% with placebo), and NNT highest (12; 95% CI 6-61), in trials using clinical activity alone. Results were similar according to previous biologic exposure. Timepoint of assessment seemed to have less of an effect, although the NNT was lowest in trials assessing remission rates at 9 to 12 weeks (NNT = 5.5; 95% CI 4-8). Again, results were similar according to previous biologic exposure.

Conclusion: Both criteria used to define CD activity at study entry, and timepoint used to confirm efficacy, may be important in maximizing therapeutic gain of active drug over placebo.

Key words: Crohn's disease**;** endoscopic activity; calprotectin; efficacy**;** drugs.

What is already know

- Current therapies focus on reducing inflammatory burden in patients with active Crohn's disease (CD) and maintaining remission in those with inactive disease.
- Timings of assessment of efficacy and criteria used to define CD activity at baseline may affect therapeutic gain of active drug over placebo in induction of remission trials in CD, but these issues have not been assessed systematically.

What is new here

- In this systematic review and meta-analysis of RCTs of biologics versus placebo in active CD, highest pooled clinical remission rates were in trials using clinical and endoscopic activity to define baseline CD activity.
- The greatest therapeutic gain over placebo was in RCTs using clinical and endoscopic activity (number needed to treat (NNT) 5), while the lowest therapeutic gain was in trials using only clinical indices to define CD activity (NNT of 12).
- When we evaluated achievement of clinical remission according to timepoint of assessment, the highest pooled remission rates and the largest therapeutic gain over placebo were in studies assessing remission at 9 to 12 weeks (NNT of 5.5).
- When we restricted the analysis to biologic-naïve or exposed patients, similar trends were observed.

How can this study help patient care

- Both criteria used to define CD activity at study entry, and timepoint used to confirm efficacy, may be important in maximizing therapeutic gain of active drug over placebo.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal tract with a remitting and relapsing course,[1] and substantial implications for the lives of patients,[2-4] as well as a considerable economic impact on society.[5] Current management strategies and therapies focus on reducing inflammatory burden in patients with active disease and maintaining remission in those with inactive disease. Over the last 20 years the efficacy of multiple novel drugs in inducing remission of active CD has been evaluated, mostly in randomized controlled trials (RCTs) versus a placebo. Many of these have been brought to market successfully, changing the lives of millions of patients.

However, the timepoint at which endpoints of efficacy are judged in these induction of remission trials varies. In addition, there may be important differences between the patient populations studied. Some trials recruit patients with only evidence of clinical activity at baseline, measured using symptom-based disease activity indices, whereas others combine these activity indices with more objective assessment of disease activity, such as biochemical markers or endoscopic evidence of active CD. These difference in trial design may be important. Assessing efficacy of a drug too early may lead to an underestimation of its ability to induce remission, versus a placebo, particularly for drugs with a slower onset of action. In addition, when symptom-reporting alone is used to define active disease, there may be a cohort of patients recruited who do not have ongoing disease activity, but whose gastrointestinal symptoms instead arise via other mechanisms, including visceral hypersensitivity,[6] altered mucosal permeability,[7] or co-existent functional bowel disease.[8, 9] Recruitment of such patients may affect efficacy of a drug targeting inflammation. As an example, a prior trial of infliximab in combination with azathioprine, versus infliximab or azathioprine alone, demonstrated lower rates of clinical remission in patients with clinical

activity but with a normal C-reactive protein (CRP), compared with those with clinical activity and an elevated CRP.[10]

The process of developing novel drugs and bringing them to market is expensive. A prior study estimated mean research and development costs of $1430 million for drugs licensed for gastrointestinal diseases.[11] Therefore, timepoint of assessment of endpoints and methods used to confirm disease activity in patients with CD recruited into induction of remission trials may have important implications, in terms of whether a drug succeeds or fails. However, to the best of our knowledge, there has been no systematic examination of the effect of these issues on the efficacy of licensed drugs in patients with active CD. We, therefore, conducted a systematic review and meta-analysis examining the impact of these features of clinical trial design on the likelihood of achieving clinical remission or clinical response, as well as therapeutic gain over placebo. We hypothesized that some induction of remission trials may have assessed drug efficacy at too short an interval to detect a meaningful rate of clinical remission, and that trials that recruited patients who did not have objective evidence of CD activity confirmed, and whose symptoms may, therefore, arise via other mechanisms, would demonstrate a lower therapeutic gain of active drug over placebo.

METHODS

Search Strategy and Selection Criteria

We searched MEDLINE (1946 to 3rd June 2022), EMBASE and EMBASE Classic (1947 to 3rd June 2022), and the Cochrane central register of controlled trials. We also searched clinicaltrials.gov for recently completed trials or supplementary data for potentially eligible RCTs. In addition, we hand-searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, the European Crohn's and Colitis Organization, and the Asian Pacific Digestive Week) between 2001 and 2022 to identify trials published only in abstract form. Finally, we performed a recursive search of the bibliographies of all eligible articles.

To be eligible, RCTs had to examine efficacy of biological therapies (anti-tumor necrosis factor-α antibodies (infliximab, adalimumab, or certolizumab), anti-integrin antibodies (vedolizumab or etrolizumab), anti-interleukin-12/23 antibodies (ustekinumab), or anti-interleukin-23 antibodies (risankizumab)) for induction of remission, at the doses taken through into phase III clinical trials. Studies needed to recruit ambulatory adults (≥18 years) with moderate to severely active CD (Supplementary Table 1) and compare biological therapies with placebo. We required a minimum follow-up duration of 4 weeks.

Two investigators (BB and ACF) conducted independent literature searches. We identified studies on CD with the terms: *inflammatory bowel disease* or *Crohn's disease* (both as medical subject headings and free text terms). We used the set operator AND to combine these with studies identified with the following terms: *infliximab*, *remicade*, *adalimumab*, *humira*, *certolizumab*, *cimzia*, *vedolizumab*, *entyvio*, *etrolizumab*, *ustekinumab*, *stelara*, or *risankizumab*, applying a clinical trials filter. There were no language restrictions. Two investigators (BB and ACF) evaluated all abstracts identified, independently. We

obtained potentially relevant papers and evaluated them using pre-designed forms, assessing eligibility independently according to the pre-defined criteria. We translated foreign language papers, where required. We resolved disagreements between investigators by discussion.

Outcome Assessment

We assessed efficacy of biological therapies, compared with placebo, in terms of achievement of clinical remission (Crohn's disease activity index (CDAI) <150) or clinical response (a fall in CDAI of ≥70), at last point of follow-up of the induction of remission phase of the trial.

Data Extraction

Two investigators (BB and ACF) extracted data from all eligible studies independently onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (clinical remission or no clinical remission; clinical response or no clinical response). We assessed efficacy according to the proportion of patients achieving clinical remission or clinical response. We also extracted the following data for each trial, where available: country, number of centers, disease distribution, proportion of patients naïve to biologics, dose and dosing schedule of active therapy and placebo, and follow-up duration. We extracted all data as intention-to-treat analyses, assuming all dropouts to be treatment failures (i.e., no remission or response to biological therapy or placebo), wherever trial reporting allowed. If this was not clear from the original article, we performed an analysis on all evaluable patients. We compared results of the two investigators' data extraction with all discrepancies resolved by discussion.

Assessment of Risk of Bias

We used the Cochrane risk of bias tool to assess this at the study level.[12] Two investigators (BB and ACF) performed this independently. We resolved disagreements by discussion. We recorded the method used to generate the randomization schedule and conceal treatment allocation, as well as whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes.

Data Synthesis and Statistical Analysis

We used the proportion of patients assigned to drug or placebo achieving each of the endpoints in each study to give pooled remission and response rates. We pooled data separately according to the criteria used to define CD activity at baseline and the time point at which the endpoints of interest were assessed. CD activity at baseline was subgrouped according to four categories: a) clinical activity only, using a Crohn's disease activity index CDAI of ≥220 and ≤450; b) clinical and biochemical activity, using a combination of a CDAI of ≥220 and ≤450 and an elevated CRP and/or fecal calprotectin (FC); c) clinical, biochemical, and/or endoscopic activity, using a combination of a CDAI of ≥220 and ≤450, and one or more of an elevated CRP and/or FC or evidence of endoscopic disease activity; or d) clinical and endoscopic activity, using a combination of a CDAI of ≥220 and ≤450 and evidence of endoscopic disease activity. For trials that recruited patients with only clinical activity at baseline but reported data according to an abnormal CRP threshold at baseline, we extracted data separately according to this CRP threshold and these trials, therefore, contributed patients to both the clinical activity only and clinical and biochemical activity analyses. We subgrouped time point of assessment according to three categories: a) 4 weeks; b) 5 to 8 weeks; or c) 9-12 weeks. For each of these analyses we performed an analysis

according to all patients randomised, as well as according to whether patients had prior biologic exposure.

We assessed heterogeneity between studies using the I^2 statistic, which ranges between 0% and 100%. Values of 25% to 49%, 50% to 74%, and ≥75% are considered low, moderate, and high levels of heterogeneity, respectively.[13] We used StatsDirect version 3.2.7 (StatsDirect Ltd, Sale, Cheshire, England) to generate Forest plots of pooled remission and response rates, with 95% confidence intervals (CIs), using a random effects model. We assessed therapeutic gain of active drug over placebo according to each endpoint of interest using the number needed to treat (NNT). We calculated the NNT, with a 95% CI, using the formula NNT = 1 / (assumed control risk x (1 – relative risk (RR)).

RESULTS

The search generated 3786 citations. In total, 98 appeared relevant and we retrieved these. We excluded 80 studies that did not fulfil eligibility criteria, with reasons provided in Figure 1, leaving 18 eligible articles, reporting 20 separate induction of remission trials.[10, 14-29] (NCT00291668) Agreement between investigators for study eligibility was excellent (kappa statistic = 0.85). Of eligible RCTs, one was available on clinicaltrials.gov (NCT00291668). Characteristics of individual studies are provided in Supplementary Table 2 and risk of bias of all trials in Supplementary Table 3. Thirteen trials, reported in 12 articles,[10, 15-18, 20, 21, 23, 25-27, 29] were low risk of bias across all domains. Criteria used to define disease activity at baseline are provided in Supplementary Table 5. Clinical response data are provided in the Supplementary Materials.

Achievement of Clinical Remission According to Criteria Used to Define CD Activity at Baseline

We first compared achievement of clinical remission according to criteria used to define CD activity at baseline in all 20 trials,[10, 14-29] (NCT00291668) reporting on 6754 patients, 4066 of whom received active drug. Five of these provided data according to an abnormal CRP threshold and, therefore, provided data for both clinical activity only and clinical and biochemical activity analyses.[15, 16, 18-20] Pooled remission rates were 26.5% in patients receiving active drug compared with 18.6% in patients in the placebo arms in nine trials,[10, 14-16, 18-20, 26, 28] containing 1770 patients, that used clinical activity only (Figure 2), with borderline moderate heterogeneity between studies (I^2 = 48%). There were seven RCTs,[15-20] (NCT00291668) containing 1051 patients, using clinical and biochemical activity, with pooled remission rates of 30.8% with active drug vs. 12.7% with placebo, with moderate heterogeneity between studies (I^2 = 59%). Pooled remission rates were 20.7% with active

drug vs. 11.1% with placebo in five trials,[21, 25, 27, 29] containing 2310 patients, using clinical, biochemical, and/or endoscopic activity. Finally, in four RCTS using clinical and endoscopic activity,[22-24] which recruited 1623 patients, pooled remission rates were 42.6% with active drug vs. 21.0% with placebo. There was no heterogeneity between studies in the latter two analyses (I^2 = 0%). The greatest therapeutic gain over placebo was in trials using clinical and endoscopic activity (RR of achieving remission with active drug = 1.99; 95% CI 1.64 to 2.41, NNT = 5; 95% CI 3 to 7.5) (Table 1), but a similar treatment effect in terms of NNT was seen in trials using clinical and biochemical activity (5; 95% CI 2.5 to 13).

When we restricted the analysis to 11 trials,[10, 14, 15, 17, 20-22, 24, 25, 27, 28] reporting on 2055 biologic-naïve patients with CD, pooled remission rates with active drug were 34.9% compared with 23.6% with placebo in five studies using clinical activity only (I^2 = 38%),[10, 14, 15, 20, 28] 35.5% vs. 11.7% in three studies using clinical and biochemical activity (I^2 = 75%),[15, 17, 20] 30.5% vs. 11.1% in three studies using clinical, biochemical, and/or endoscopic activity (I^2 = 0%),[21, 25, 27] and 48.5% vs. 23.4% in two studies using clinical and endoscopic activity (I^2 = 0%) (Figure 2, Table 1).[22, 24] The greatest therapeutic gain over placebo was seen in one trial using clinical and endoscopic activity to define CD activity at baseline (RR = 2.15; 95% CI 1.49 to 3.11, NNT = 4; 95% CI 2 to 9), but the effect was similar in studies using clinical and biochemical activity (NNT = 4; 95% CI 1 to 28).

Finally, when we only included the 11 trials,[16, 21-29] which reported data on 3201 biologic-exposed patients with CD, pooled remission rates with active drug were 18.6% compared with 9.5% with placebo in three studies using clinical activity only (I^2 = 0%),[16, 26, 28] 24.7% vs. 7.4% in one study using clinical and biochemical activity,[16] 14.1% vs. 8.7% in four studies using clinical, biochemical, and/or endoscopic activity (I^2 = 36%),[21, 25, 27, 29] and 40.4% vs. 19.9% in four studies using clinical and endoscopic activity (I^2 = 14%) (Figure 2, Table 1).[22-24] The largest therapeutic gain over placebo was seen in studies using clinical and

endoscopic activity at baseline to define active CD (RR = 1.94; 95% CI 1.50 to 2.51, NNT = 5; 95% CI 3 to 10).

Achievement of Clinical Remission According to Timepoint of Assessment

We compared achievement of clinical remission according to timepoint of assessment in all 20 trials.[10, 14-29] (NCT00291668) Pooled remission rates were 28.4% with active drug compared with 8.8% with placebo at 4 weeks in four studies containing 845 patients (I^2 = 10%),[15-17, 28] 22.9% vs. 14.0% at 5 to 8 weeks in eight studies containing 3579 patients (I^2 = 25%),[19-21, 25, 26, 29] (NCT00291668) and 35.6% vs. 19.4% at 9 to 12 weeks in eight studies containing 2345 patients (I^2 = 0%) (Figure 3, Table 1).[10, 14, 18, 22-24, 27] The largest therapeutic gain over placebo was seen in studies assessing remission at 9 to 12 weeks (RR = 1.89; 95% CI 1.63 to 2.21, NNT = 5.5; 95% CI 4 to 8).

Restricting the analysis to the 11 trials reporting data in biologic-naïve patients,[10, 14, 15, 17, 20-22, 24, 25, 27, 28] pooled remission rates were 33.2% with active drug vs. 10.4% with placebo at 4 weeks in three studies (I^2 = 40%),[15, 17, 28] 26.5% vs. 15.6% at 5 to 8 weeks in three studies (I^2 = 43%),[20, 21, 25] and 43.3% vs. 21.8% at 9 to 12 weeks in five studies (I^2 = 0%) (Figure 3, Table 1).[10, 14, 22, 24, 27] The greatest therapeutic gain with active drug over placebo in biologic-naïve patients was seen at 9 to 12 weeks (RR = 2.08; 95% CI 1.65 to 2.62, NNT = 4; 95% CI 3 to 7).

Finally, in 11 trials in biologic-exposed patients with CD,[16, 21-29] pooled remission rates with active drug were 21.0% compared with 7.7% with placebo at 4 weeks in two trials (I^2 = 0%),[16, 28] 16.1% vs. 9.0% at 5 to 8 weeks in four studies (I^2 = 3%),[21, 25, 26, 29] and 32.9% vs. 17.5% at 9 to 12 weeks in five RCTs (I^2 = 26%) (Figure 3, Table 1).[22-24, 27] Again, the largest therapeutic gain over placebo was seen at 9 to 12 weeks (RR = 1.87; 95% CI 1.40 to 2.51, NNT = 6; 95% CI 4 to 13).

DISCUSSION

We conducted a systematic review and meta-analysis to assess efficacy and therapeutic gain of biologics, compared with placebo, in moderate to severely active CD in terms of achieving clinical remission or clinical response according to the criteria used to define CD activity at study entry, as well as the time point at which endpoints were assessed. We included data from 20 separate induction of remission trials, recruiting almost 7000 patients. Our analysis suggested that the highest pooled clinical remission rates were in trials using clinical and endoscopic activity to define baseline CD activity. Consequently, the greatest therapeutic gain over placebo was in these RCTs, with a NNT of 5. The lowest therapeutic gain was in trials using only clinical indices to define CD activity, with a NNT of 12. When we restricted the analysis to biologic-naïve or exposed patients, results were similar. When we evaluated achievement of clinical remission according to timepoint of assessment, the highest pooled remission rates and the largest therapeutic gain over placebo were in studies assessing remission at 9 to 12 weeks, with a NNT of 5.5. Again, similar trends were observed when these analyses were performed according to prior biologic exposure. Finally, when assessing achievement of clinical response according to criteria used to define CD activity, the highest pooled response rates were in studies using clinical and endoscopic activity and in studies assessing response at 9 to 12 weeks, although the differences in therapeutic gain between the various definitions of CD activity and timepoints of assessment were less marked than for clinical remission.

Limitations include the fact that only 13 of 20 trials were low risk of bias across all domains. We identified no phase III trials of etrolizumab in CD. Other weaknesses include the fact that there was significant heterogeneity between studies in some analyses, and small numbers of trials contributed data to some subgroup analyses. It is also possible that data on biochemical or endoscopic disease activity were collected in subsets of patients in some of

these trials but, as we did not have access to individual patient data, we had to categorize patients according to the overall criteria used to define CD activity in each trial. Finally, we were able to examine the influence of prior biologic exposure on endpoints of interest because these endpoints were reported *a priori* in the original articles. However, other patient level factors, such as sex, disease distribution or location, or glucorticosteroid exposure, which may also influence remission and response rates, again cannot be studied without access to individual patient data. Despite these limitations, the results of our study may be useful to optimize design of future clinical trials in moderate to severely active CD to minimize likelihood of underestimating therapeutic gain of active drug over placebo.

Our data show that how CD activity is defined should be considered carefully in future clinical trial design. For decades, the CDAI has been used in RCTs.[30] However, some studies show a poor correlation between symptom-based measures, like the CDAI, and endoscopic indices of disease activity.[31] Physical symptoms, such as abdominal pain and diarrhea, could result from post-inflammatory processes, including the effects of surgery on bowel motility and bile acid homeostasis, fibrosis, adhesions, or stricture formation. Moreover, the transmural nature of CD may result in inflammation of enteric neurons in the absence of significant mucosal inflammation. General well-being, which is also incorporated in the CDAI, can be influenced by other factors, such as anxiety or depression, which are commoner in patients with CD than healthy individuals.[2] For all these reasons, use of clinical indices alone could overestimate disease activity in some patients with CD.

Using biochemical markers without confirmation of endoscopic activity may also be problematic. Although CRP is regarded as a serologic marker of disease activity, elevated CRP is less common in ileal, compared with colonic or ileocolonic, CD.[32] Moreover, as CRP is not specific to intestinal inflammation, it may be elevated due to concomitant conditions, such as extraintestinal manifestations of CD (e.g., arthritis), again leading to potential

overestimation of disease activity. FC correlates more closely with endoscopic indices of activity than CRP, total white cell count, or CDAI.[33] However, its utility as a marker of active small bowel inflammation in CD is less certain.[34] Nevertheless, in our analyses the NNT for remission in trials using a combination of clinical and biochemical activity was lower than in trials using only clinical activity.

Given that pooled remission rates based on studies using only clinical activity are lower than in those using clinical and biochemical activity or clinical and endoscopic activity, and this affects therapeutic gain over placebo, this may influence both the pursuit of licensing for, and recommendations regarding access to, novel drugs by pharmaceutical companies and regulatory agencies if the NNT is only modest. Our overall findings are reinforced by data from the SONIC trial,[10] where remission rates at 26 weeks with infliximab or infliximab and azathioprine were 40.3% and 50.7%, respectively, in patients with a CRP <0.8mg/dL, compared with 47.5% and 63.5% in patients with a CRP ≥0.8mg/dL. Taken together, this suggests that patients with clinical activity alone, who may have other aforementioned reasons for high symptom burden, are less likely to respond to therapies targeting specific immunological pathways in CD, which dilutes the therapeutic effect of active therapy. These individuals may be better managed using alternative strategies, as recommended elsewhere.[35]

In order to assess this issue formally in the current study, we would have needed all trials to report efficacy according to the various criteria used to define disease activity at baseline. Unfortunately, few RCTs did this. However, in the two trials of adalimumab that reported efficacy in all patients with clinically active disease and in a subset with both clinical and biochemical activity,[15, 16] the NNT fell from 10 (95% CI 4 to 61) to 5 (95% CI 2 to 18). Similarly, in three trials of certolizumab,[18-20] the NNT in patients with clinically active disease was not estimable, as the drug was not superior to placebo, but in patients with

clinical and biochemical activity the NNT was 9.5 (95% CI 4 to 64). Confidence intervals are wide in all these analyses due to the relatively small numbers of trials and included patients.

Our meta-analysis also highlights that different induction of remission trials of biologics in active CD assess efficacy at varying timepoints. The reasons for choosing to assess efficacy of drugs like adalimumab at 4 weeks in the original RCTs, versus ustekinumab or risankizumab, where efficacy was assessed at 12 weeks, are uncertain. This makes it problematic to compare relative efficacy of different drugs in other evidence synthesis exercises, such as network meta-analysis, and therefore inform choices as to which drug to prescribe in clinical practice. In addition, as our results show, it may affect likelihood of achieving remission with active drug versus placebo, and therefore therapeutic gain. Remission rates with active drug were generally higher at 9 to 12 weeks in all analyses, irrespective of prior exposure to biologics. This may reflect either a slower onset of action of some drugs or the fact that, in some trials using later timepoints of assessment, patients were exposed to higher numbers of infusions or injections of active drug before assessment of efficacy.

Although mucosal healing is an important recommended therapeutic target in CD,[36] and endoscopic evaluation is used to inform management decisions in clinical practice, in many RCTs in CD rates of endoscopic improvement or healing are not reported. In a recent network meta-analysis evaluating the efficacy of biologics and small molecules in CD,[37] only 11 of 25 eligible induction of remission trials assessed these endpoints. Analysis was further hampered by incomplete data for patients in some studies, inconsistent definitions of endoscopic response or remission, and different time points of assessment of between 6 and 52 weeks. Taken together with the results of the current meta-analysis, which suggest higher remission and response rates with active drug when disease activity is confirmed using a combination of clinical and endoscopic data, future trials should confirm endoscopic

evidence of CD activity prior to inclusion and assess its response during treatment. Finally, given the costs involved in developing and evaluating new drugs and bringing them to market, both the criteria used to define CD activity at study entry, as well as the timepoint used to confirm efficacy, may be important in maximizing the likelihood that a drug of potential benefit demonstrates superior efficacy to placebo.

FIGURE AND TABLE LEGENDS

Table 1. Achievement of Clinical Remission According to Criteria Used to Define CD Activity at Baseline and Timepoint

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

Figure 2. Clinical Remission Rates According to Criteria Used to Define CD Activity at Baseline.

Figure 3. Clinical Remission Rates According to Timepoint of Assessment.

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Table 1. Achievement of Clinical Remission According to Criteria Used to Define CD Activity at Baseline and Timepoint of Assessment.

	Trial/Patient Group	Number of Trials	Number of Patients	Drugs Studied	RR of Remission (95% CI)	Number Needed to Treat (95% CI)
Criteria used to define active CD at baseline	**All patients**					
	Clinical activity	9	1770	ADA, CER, IFX, UST	1.42 (1.08 – 1.86)	12 (6 – 61)
	Clinical and biochemical activity	7	1051	ADA, CER	3.45 (1.27 – 9.37)	5 (2.5 – 13)
	Clinical and biochemical/endoscopic activity	5	2310	UST, VED	1.88 (1.53 – 2.30)	10 (7 – 16.5)
	Clinical and endoscopic activity	4	1623	RIS, UST	1.99 (1.64 – 2.41)	5 (3 – 7.5)
	Biologic-naïve patients					
	Clinical activity	5	829	ADA, CER, IFX	1.50 (1.09 – 2.07)	7 (3 – 39)
	Clinical and biochemical activity	3	482	ADA, CER	3.28 (1.29 – 8.33)	4 (1 – 28)
	Clinical and biochemical/endoscopic activity	3	328	VED	2.49 (1.46 – 4.28)	6 (3 – 21)
	Clinical and endoscopic activity	2	416	RIS, UST	2.15 (1.49 – 3.11)	4 (2 – 9)

	Biologic-exposed patients					
	Clinical activity	3	495	ADA, UST	2.00 (1.23 – 3.23)	11 (5 – 48)
	Clinical and biochemical activity	1	145	ADA	3.36 (1.32 – 8.50)	6 (2 – 42.5)
	Clinical and biochemical/endoscopic activity	4	1354	UST, VED	1.65 (1.04 – 2.64)	18 (7 – 291)
	Clinical and endoscopic activity	4	1207	RIS, UST	1.94 (1.50 – 2.51)	5 (3 – 10)
Timepoint of assessment	**All patients**					
	4 weeks	4	845	ADA	3.09 (2.09 – 4.57)	6 (3 – 11)
	5 – 8 weeks	8	3579	CER, UST, VED	1.59 (1.33 – 1.90)	12 (8 – 21)
	9 – 12 weeks	8	2345	CER, IFX, RIS, UST, VED	1.89 (1.63 – 2.21)	5.5 (4 – 8)
	Biologic-naïve patients					
	4 weeks	3	468	ADA	3.15 (1.67 – 5.95)	5 (2 – 15.5)
	5 – 8 weeks	3	733	CER, VED	1.63 (1.02 – 2.62)	8 (3 – 261)
	9 – 12 weeks	5	869	IFX, RIS, UST, VED	2.08 (1.65 – 2.62)	4 (3 – 7)
	Biologic-exposed patients					
	4 weeks	2	377	ADA	2.90 (1.60 – 5.24)	7 (3 – 21)
	5 – 8 weeks	4	1494	UST, VED	1.81 (1.33 – 2.47)	14 (8 – 34)
	9 – 12 weeks	5	1330	RIS, UST, VED	1.87 (1.40 – 2.51)	6 (4 – 13)

ADA, adalimumab; CER, certolizumab; IFX, infliximab; RIS, risankizumab; UST, ustekinumab; VED, vedolizumab.