Meta-Analysis

Maintenance of clinical remission with biologics and small molecules in inflammatory bowel disease according to trial design: Meta-analysis

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ABSTRACT

Background and Aims: Design of randomised controlled trials (RCTs) examining maintenance of clinical remission in inflammatory bowel disease (IBD) varies, with some trials re-randomising patients who have responded to active drug during induction to either active drug or placebo and others treating patients through with active drug or placebo from baseline. Whether this influences therapeutic gain of drug over placebo is unknown.
Methods: We searched the literature to January 2023 for maintenance of remission trials of biologics or small molecules versus placebo in IBD. We extracted maintenance of remission rates according to trial design; either trials re-randomising patients or trials treating patients through. We pooled data in a meta-analysis for all patients, and according to type of IBD. 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 trial design.
Results: We identified 37 maintenance of remission trials (12,075 patients). Rates of maintenance of clinical remission were higher (41.9% with active drug, versus 20.3% with placebo), and NNT lowest (5; 95% CI 4–6), in trials re-randomising patients compared with those treating through (maintenance of remission rate 30.9% with active drug versus 14.6% with placebo, NNT = 7; 95% CI 5–9). Results were similar when trials were analysed according to IBD type but were more marked in ulcerative colitis RCTs (maintenance of remission rates in re-randomised trials 39.4% with active drug versus 17.8% with placebo, NNT = 5; 95% CI 3–7; treat-through trials 27.3% with active drug versus 11.9% with placebo, NNT = 7; 95% CI 5–11.5).
Conclusion: Trials re-randomising patients had generally higher maintenance of remission rates, lower NNTs, and greater therapeutic gains over placebo.

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC), which are the two commonest forms of inflammatory bowel disease (IBD), are chronic disorders causing cause inflammation of the gastrointestinal tract. Both are characterised by phases of remission and relapse, impacting on patients' social functioning, psychological health, and quality of life [1–3]. Despite the availability of a range of therapies for IBD, achieving sustained remission for all patients remains elusive, with most existing treatments exhibiting maintenance of remission rates of approximately 30% to 40% at 12 months [4–11]. With the need to develop efficacious drugs and bring them to market, the number of randomised controlled trials (RCTs) in IBD continues to increase annually. Trials enroling patients with CD have more than doubled between 1999 and the present, while the number of RCTs in patients with UC has increased 10-fold during the same period [12]. The increased number of trials of new investigational drugs gives potential hope for favourable therapeutic developments for patients with IBD.

The design of trials has evolved over the years, becoming increasingly complex and sophisticated, involving new endpoints, which include patient-reported outcomes, biomarkers, mucosal and histological healing, central endoscopy reading, and trials that examine both induction and maintenance of remission within the same study. With respect to this latter feature, the design of such RCTs varies. Some trials re-randomise patients who have

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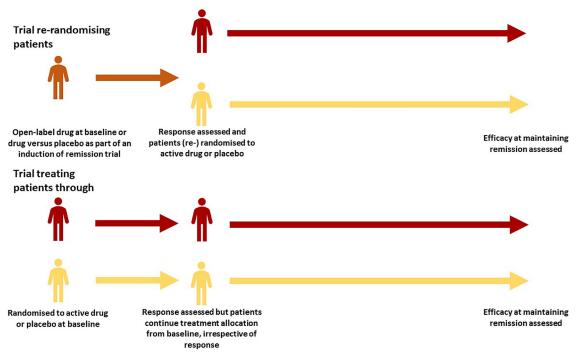[1] Twitter: @alex_ford12399

Fig. 1. Design of *Re*-randomised or Treat-through Trials.

responded to active drug, or placebo, during the induction phase of the trial to maintenance therapy with either active drug or placebo and others treat patients through with active drug or placebo from baseline [13]. The "adaptative" trial design with re-randomisation is pre-planned and involves decision-making based on interim results. Although, theoretically, this improves efficiency and speed within the trial and may better reflect the real-world use of these drugs, logistical and data management requirements for adaptative trials are complex, due to the different phases of the trial and the need for interim decision-making.

However, patients receiving placebo during the maintenance phase of trials that re-randomise are likely to have been exposed to active drug during the induction phase of the trial, whereas those in treat-through studies will have received placebo from baseline and throughout the entire duration of the study. These differences hamper the combination of these RCTs in pairwise and network meta-analyses [14–18], meaning that it is unclear which drug is most likely to maintain remission successfully in IBD. Whether these differences in design influence the therapeutic gain of active drug over placebo during the maintenance phase of a trial is unknown because, to the best of our knowledge, there has been no systematic examination of the effect of these trial design features on efficacy of licensed drugs in patients with IBD. We, therefore, conducted a systematic review and meta-analysis examining these issues.

2. Methods

2.1. Search strategy and selection criteria

We searched MEDLINE (1946 to 18th January 2023), EMBASE and EMBASE Classic (1947 to 18th January 2023), 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 searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, 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-tumour necrosis factor-α antibodies (adalimumab, certolizumab, golimumab, or infliximab), anti-integrin antibodies (etrolizumab or vedolizumab), anti-interleukin-12/23 antibodies (ustekinumab), or anti-interleukin-23 antibodies (mirikizumab or risankizumab)), janus kinase inhibitors (filgotinib, tofacitinib, or upadacitinib), or sphingosine-1-phosphate receptor modulators (ozanimod), for maintenance of clinical remission, at the doses taken through into phase III clinical trials. Trials had to either administer open label drug at baseline, or randomise to active drug or placebo at baseline, with patients assessed for response subsequently and then being re-randomised to maintenance active drug or placebo (re-randomised trials) or be randomised to active drug or placebo at baseline, with treatment through to the final point of follow-up without re-randomisation (treat-through trials) (Fig. 1). Studies needed to recruit ambulatory adults ($\geq$18 years) with UC or luminal CD (Supplementary Table 1) and compare biological therapies or small molecules with placebo. Trials conducted only in patients with perianal CD were excluded. We required a minimum follow-up duration of 26 weeks.

Two investigators (BB and ACF) conducted independent literature searches. We identified studies on IBD with: *inflammatory bowel disease, colitis, ulcerative colitis*, 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, golimumab, simponi, vedolizumab, entyvio, etrolizumab, ustekinumab, stelara, risankizumab, mirikizumab, tofacitinib, xeljanz, filgotinib, upadacitinib*, or *ozanimod*, applying a clinical trials filter. There were no language restrictions. Two investigators (BB and ACF) assessed all identified abstracts, independently. We obtained potentially relevant articles and evaluated them with pre-designed forms, assessing eligibility independently according to our pre-defined criteria. We translated foreign language papers,

if required. We resolved disagreements between investigators by discussion.

2.2. Outcome assessment

We assessed efficacy of biological therapies or small molecules, compared with placebo, in terms of maintenance of clinical remission at last point of follow-up of the trial.

2.3. 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 (maintenance of clinical remission or no maintenance of clinical remission). We assessed efficacy according to the proportion of patients maintaining clinical remission. We also extracted the following data for each trial, where available: country, number of centres, IBD type, dose and dosing schedule of active therapy and placebo, and follow-up duration. We extracted all data as intention-to-treat analyses, with all dropouts to assumed be treatment failures (i.e., no maintenance of clinical remission with biological therapy, small molecule, or placebo), wherever trial reporting allowed. If this was unclear in the original article, we performed an analysis on all evaluable patients. We compared results of the two investigators' data extraction and resolved all discrepancies by discussion.

2.4. Data synthesis and statistical analysis

We used the proportion of patients assigned to drug or placebo maintaining clinical remission in each study to give pooled maintenance of clinical remission rates. We pooled data separately according to the design of the trials (re-randomised or treat-through). 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 [19]. We used StatsDirect version 3.2.7 (StatsDirect Ltd, Sale, Cheshire, England) to generate Forest plots of pooled maintenance of clinical remission rates, with 95% confidence intervals (CIs), and Review Manager version 5.4.1 (The Cochrane Collaboration 2020) to generate forest plots of pooled relative risks (RRs) for all primary and secondary outcomes with 95% CIs. We used a random effects model for all analyses [20]. We assessed therapeutic gain of active drug over placebo according to trial design, and by IBD type separately, 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 – RR)). We performed subgroup analyses according to type of IBD, duration of disease (<8 years or ≥8 years), whether trials only recruited biological naïve patients, duration of treatment (<50 weeks or ≥50 weeks) and whether central reading of endoscopy was performed (for UC trials only).

3. Results

The search generated 9016 citations. In total, 199 appeared relevant and we retrieved these. We excluded 163 studies that did not fulfil eligibility criteria, with reasons provided in Supplementary Fig. 1, leaving 36 eligible articles, reporting 37 separate maintenance of remission trials, containing 12,075 patients [4–6,8–11,21–48]. (NCT01551290) Twenty-one of these RCTs were conducted in UC [4–6,8,21–35], (NCT01551290) 13 re-randomising patients to active drug or placebo [6,8,21–31], and eight treating patients through.4, 5, 32–35 (NCT01551290) The other 16 trials were conducted in patients with CD [9–11,36–48] 14 of which re-randomised

patients [9–11,36–46], and two were treat-through trials [47,48]. Agreement between investigators for study eligibility was excellent (kappa statistic = 0.88). Of eligible RCTs, one was reported online [44], and another was available on clinicaltrials.gov (NCT01551290). Characteristics of individual trials are provided in Supplementary Tables 2 and 3.

3.1. Maintenance of clinical remission according to trial design

When we compared maintenance of clinical remission according to trial design across all trials, irrespective of type of IBD, there were 27 trials re-randomising 9036 patients [6,8–11,21,31,36–46], and 10 trials treating 3039 patients through [4,5,32–35,47,48]. (NCT01551290) Pooled maintenance of remission rates were 41.9% with active drug, versus 20.3% with placebo in trials re-randomising, compared with 30.9% with active drug and 14.6% with placebo in treat-through trials (Fig. 2). There was moderate heterogeneity between trials re-randomising patients (I^2 = 67%) but no heterogeneity between treat-through trials (I^2 = 2%). The therapeutic gain of active drug was greater in trials re-randomising patients (RR of maintenance of remission with active drug = 2.02; 95% CI 1.76 to 2.32, NNT = 5; 95% CI 4 to 6) compared with treat-through trials (RR = 1.95; 95% CI 1.69 to 2.25, NNT = 7; 95% CI 5 to 9) (Fig. 3 and Table 1). However, this difference was not statistically significant (χ^2 for subgroup interactions, p = 0.73). Of the trials re-randomising patients in CD, one re-randomised patients responding to either active drug or placebo at baseline [37], and one re-randomised patients irrespective of response to open-label active drug [36]. Excluding these two RCTs in a sensitivity analysis did not alter the therapeutic gain to any great extent (RR = 1.98; 95% CI 1.72 to 2.28, NNT = 5; 95% CI 4 to 6.5).

Subgroup analysis according to duration of disease, whether trials only recruited biological naïve patients, and duration of treatment revealed similar differences between trials re-randomising and trials treating through, with a lower NNT in the former, but no statistically significant differences (Supplementary Table 4).

3.2. Maintenance of clinical remission according to trial design and IBD type

When we compared maintenance of clinical remission according to trial design across all trials according to type of IBD there were 13 trials re-randomising 4784 patients with UC to active drug or placebo [6,8,21–31], and eight treating 2040 patients with UC through [4,5,32–35]. (NCT01551290) Pooled maintenance of remission rates in UC were 39.4% with active drug, versus 17.8% with placebo in trials re-randomising, compared with 27.3% with active drug and 11.9% with placebo in treat-through trials (Fig. 2). Again, there was moderate heterogeneity between trials re-randomising patients (I^2 = 65%) but no heterogeneity between treat-through trials (I^2 = 0%) and therapeutic gain was greater in trials re-randomising patients (RR = 2.16; 95% CI 1.77 to 2.63, NNT = 5; 95% CI 3 to 7), despite similar efficacy in treat-through trials (RR = 2.19; 95% CI 1.77 to 2.71, NNT = 7; 95% CI 5 to 11.5) (Fig. 4 and Table 1), but with no statistically significant difference between the two (χ^2 for subgroup interactions, p = 0.91). Again, subgroup analysis according to disease duration, whether trials only recruited biological naïve patients, treatment duration, and whether central reading of endoscopy was employed revealed similar differences between the two trial designs, with a lower NNT in the former, but no statistically significant differences (Supplementary Table 4).

There were 14 RCTs in CD that re-randomised 4252 patients [9–11,36–46], and two treating 999 patients through [47,48]. Pooled maintenance of remission rates were 44.6% with active drug, versus 22.9% with placebo in trials re-randomising, compared with
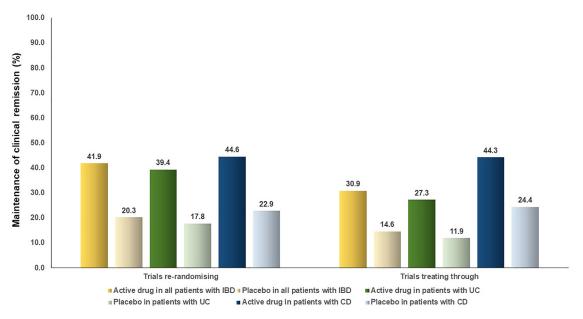
Fig. 2. Rates of Maintenance of Clinical Remission According to Trial Design and Type of IBD.

Study or Subgroup	Active drug Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
7.1.1 Re-randomisation of patients responding to active drug							
Rutgeerts 1999	20	37	7	36	2.3%	2.78 [1.34, 5.76]	1999
Hanauer 2002 ACCENT I	75	225	15	110	3.4%	2.44 [1.47, 4.05]	2002
Colombel 2007 CHARM	127	329	20	170	3.9%	3.28 [2.13, 5.06]	2007
Schreiber 2007 PRECISE 2	103	216	60	212	5.2%	1.68 [1.30, 2.18]	2007
Sandborn 2007 CLASSIC II	30	37	8	18	3.2%	1.82 [1.06, 3.13]	2007
Watanabe 2012	8	21	2	22	0.8%	4.19 [1.00, 17.50]	2012
Rutgeerts 2012 EXTEND	21	64	6	65	1.9%	3.55 [1.54, 8.23]	2012
Feagan 2013 GEMINI 1	107	247	20	126	3.9%	2.73 [1.78, 4.18]	2013
Sandborn 2013 GEMINI 2	116	308	33	153	4.6%	1.75 [1.25, 2.44]	2013
Sandborn 2014 PURSUIT-M	101	308	34	156	4.6%	1.50 [1.07, 2.11]	2014
Feagan 2016 IM-UNITI	131	264	47	133	5.2%	1.40 [1.08, 1.82]	2016
Hibi 2017 PURSUIT-J	16	32	2	31	0.8%	7.75 [1.94, 30.94]	2017
Sandborn 2017 OCTAVE Sustain	148	395	22	198	4.0%	3.37 [2.23, 5.10]	2017
Sandborn 2019 VISIBLE 1	72	160	8	56	2.6%	3.15 [1.62, 6.12]	2019
Motoya 2019	23	41	13	42	3.3%	1.81 [1.07, 3.07]	2019
Sands 2019 UNIFI	143	348	42	175	4.9%	1.71 [1.28, 2.29]	2019
Watanabe 2020	5	12	2	12	0.8%	2.50 [0.60, 10.46]	2020
Vermeire 2021 VISIBLE 2	132	275	46	135	5.1%	1.41 [1.08, 1.84]	2021
Feagan 2021 SELECTION	115	381	23	190	4.0%	2.49 [1.65, 3.77]	2021
Peyrin-Biroulet 2021 HICKORY	27	117	23	115	3.5%	1.15 [0.70, 1.89]	2021
Sandborn 2021 TRUE NORTH	85	230	42	227	4.7%	2.00 [1.45, 2.75]	2021
Vermeire 2021 LAUREL	32	108	21	106	3.6%	1.50 [0.92, 2.42]	2021
Dubinsky 2022 LUCENT-2	182	365	45	179	5.1%	1.98 [1.51, 2.61]	2022
Ferrante 2022 FORTIFY	161	298	67	164	5.5%	1.32 [1.07, 1.63]	2022
Danese 2022 U-ACHIEVE maintenance	143	302	18	149	3.8%	3.92 [2.50, 6.14]	2022
Sandborn 2023 BERGAMOT	76	217	52	217	4.9%	1.46 [1.08, 1.97]	2023
U-ENDURE	143	337	25	165	4.3%	2.80 [1.91, 4.10]	2023
Subtotal (95% CI)		5674		3362	100.0%	2.02 [1.76, 2.32]	
Total events	2342		703				

Heterogeneity: Tau² = 0.08; Chi² = 79.04, df = 26 (P < 0.00001); I² = 67%
Test for overall effect: Z = 10.06 (P < 0.00001)

Study or Subgroup	Active drug Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
7.1.2 Treat through of patients							
NCT01551290	14	50	5	49	2.3%	2.74 [1.07, 7.04]	1290
Rutgeerts 2005 ACT 1	84	243	20	121	10.7%	2.09 [1.35, 3.23]	2005
Rutgeerts 2005 ACT 2	74	241	13	123	6.8%	2.91 [1.68, 5.03]	2005
Sandborn 2007 PRECISE 1	96	331	59	329	24.1%	1.62 [1.21, 2.15]	2007
Colombel 2010 SONIC	102	169	54	170	30.6%	1.90 [1.48, 2.44]	2010
Sandborn 2012 ULTRA 2	43	258	21	260	8.4%	2.06 [1.26, 3.38]	2012
Suzuki 2014	41	177	7	96	3.6%	3.18 [1.48, 6.81]	2014
Jiang 2015	21	41	10	41	5.4%	2.10 [1.13, 3.89]	2015
Sandborn 2016 TOUCHSTONE	14	67	4	65	1.9%	3.40 [1.18, 9.78]	2016
Kobayashi 2016	22	104	17	104	6.3%	1.29 [0.73, 2.29]	2016
Subtotal (95% CI)		1681		1358	100.0%	1.95 [1.69, 2.25]	
Total events	511		210				

Heterogeneity: Tau² = 0.00; Chi² = 9.19, df = 9 (P = 0.42); I² = 2%
Test for overall effect: Z = 9.08 (P < 0.00001)

Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%

Fig. 3. Forest Plot of Maintenance of Remission Trials of Biological Therapies or Small Molecules in IBD.

Table 1
Maintenance of Clinical Remission According to Trial Design and Type of IBD.

	Type of Trial	Number of Trials	Number of Patients	RR of Maintaining Remission (95% CI)	NNT (95% CI)	P value for χ^2 for subgroup interaction
All patients with IBD	Trials re-randomising patients	27	9036	2.02 (1.76 – 2.32)	5 (4 – 6)	
	Treat-through trials	10	3039	1.95 (1.69 – 2.25)	7 (5 – 9)	0.73
Patients with UC only	Trials re-randomising patients	13	4784	2.16 (1.77 – 2.63)	5 (3 – 7)	
	Treat-through trials	8	2040	2.19 (1.77 –2.71)	7 (5 – 12)	0.91
Patients with CD only	Trials re-randomising patients	14	4252	1.88 (1.57 – 2.25)	5 (3 – 7)	
	Treat-through trials	2	999	1.77 (1.47 – 2.14)	6 (4 – 9)	0.65

Fig. 4. Forest Plot of Maintenance of Remission Trials of Biological Therapies or Small Molecules in UC.

44.3% with active drug and 24.4% with placebo in treat-through trials (Fig. 2). There was moderate heterogeneity between trials re-randomising patients ($I^2 = 64\%$). Therapeutic gain was again greater in trials re-randomising patients (RR = 1.88; 95% CI 1.57 to 2.25, NNT = 5; 95% CI 3 to 7), compared with treat-through trials (RR = 1.77; 95% CI 1.47 to 2.14, NNT = 6; 95% CI 4 to 9) (Fig. 5 and Table 1). Again, there was no statistically significant difference between the two (χ^2 for subgroup interactions, $p = 0.65$). Excluding the two trials re-randomising patients that were of slightly different design did not affect the results to any degree (RR = 1.80; 95% CI 1.50 to 2.15, NNT = 5; 95% CI 3.5 to 8) [36,37]. Subgroup analysis according to duration of disease, whether trials only recruited biological naïve patients, and duration of treatment revealed that NNTs were the same for trials re-randomising and treating through for patients with a shorter disease duration, and a lower NNT in treat-through trials for biological naïve patients than in re-randomised trials. Otherwise, differences between the two trial designs were similar, with a lower NNT in re-randomised trials, but no statistically significant differences (Supplementary Table 4).

4. Discussion

The methodology of trials in IBD has evolved over the years with studies increasingly favouring re-randomised designs. This approach may better reflect real-world clinical practice and may also have advantages over treat-through trials in terms of efficiency. However, individuals who receive placebo during the maintenance phase of a re-randomised trial are likely to have been exposed to active drug during the induction phase, whereas in a treat-through trial, participants randomised to the placebo arm receive this treatment throughout the study. The effect of these differing trial designs on drug efficacy in IBD is unclear. The contrasting methodologies also hamper the ability to accurately compare trial outcomes or synthesise the data using network meta-analysis. We conducted a systematic review and meta-analysis examining the impact of clinical trial design on the likelihood of maintaining clinical remission, as well as the therapeutic gain with active drug over placebo, in patients with IBD treated with biologics or small molecules. We found that, irrespective of type of IBD, pooled maintenance of remission rates were over 40% with active drug, versus

Study or Subgroup	Active drug Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year	Risk Ratio M-H, Random, 95% CI
9.1.1 Re-randomisation of patients responding to active drug								
Rutgeerts 1999	20	37	7	36	4.1%	2.78 [1.34, 5.76]	1999	
Hanauer 2002 ACCENT I	75	225	15	110	6.5%	2.44 [1.47, 4.05]	2002	
Colombel 2007 CHARM	127	329	20	170	7.5%	3.28 [2.13, 5.06]	2007	
Schreiber 2007 PRECISE 2	103	216	60	212	10.5%	1.68 [1.30, 2.18]	2007	
Sandborn 2007 CLASSIC II	30	37	8	18	6.0%	1.82 [1.06, 3.13]	2007	
Rutgeerts 2012 EXTEND	21	64	6	65	3.4%	3.55 [1.54, 8.23]	2012	
Watanabe 2012	8	21	2	22	1.4%	4.19 [1.00, 17.50]	2012	
Sandborn 2013 GEMINI 2	116	308	33	153	9.1%	1.75 [1.25, 2.44]	2013	
Feagan 2016 IM-UNITI	131	264	47	133	10.4%	1.40 [1.08, 1.82]	2016	
Watanabe 2020	5	12	2	12	1.4%	2.50 [0.60, 10.46]	2020	
Vermeire 2021 VISIBLE 2	132	275	46	135	10.4%	1.41 [1.08, 1.84]	2021	
Ferrante 2022 FORTIFY	161	298	67	164	11.3%	1.32 [1.07, 1.63]	2022	
Sandborn 2023 BERGAMOT	76	217	52	217	9.8%	1.46 [1.08, 1.97]	2023	
U-ENDURE	143	337	25	165	8.3%	2.80 [1.91, 4.10]	2023	
Subtotal (95% CI)		**2640**		**1612**	**100.0%**	**1.88 [1.57, 2.25]**		
Total events	1148		390					
Heterogeneity: Tau² = 0.06; Chi² = 35.94, df = 13 (P = 0.0006); I² = 64%								
Test for overall effect: Z = 6.95 (P < 0.00001)								
9.1.2 Treat through of patients								
Sandborn 2007 PRECISE 1	96	331	59	329	43.7%	1.62 [1.21, 2.15]	2007	
Colombel 2010 SONIC	102	169	54	170	56.3%	1.90 [1.48, 2.44]	2010	
Subtotal (95% CI)		**500**		**499**	**100.0%**	**1.77 [1.47, 2.14]**		
Total events	198		113					
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 1 (P = 0.40); I² = 0%								
Test for overall effect: Z = 5.92 (P < 0.00001)								

Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.65), I² = 0%

0.01 0.1 1 10 100
Favours placebo Favours active drug

Fig. 5. Forest Plot of Maintenance of Remission Trials of Biological Therapies or Small Molecules in CD.

around 20% with placebo in trials re-randomising patients, compared with just over 30% with active drug and close to 15% with placebo in treat-through trials. The therapeutic gain of active drug was greater in trials re-randomising patients, with an NNT of 5, than those treating through, where the NNT was 7. However, these differences were not statistically significant. Results were similar when trials were analysed by type of IBD, with a lower NNT in trials that re-randomised both patients with UC and CD, although the differences were less marked in trials in patients with CD. However, there were only two treat-through trials in CD.

We used standard methodology to maximise the likelihood of identifying all pertinent literature and minimise potential bias. The literature search, eligibility assessment, and data extraction for this meta-analysis were undertaken independently by two reviewers, with any discrepancies resolved by consensus. In addition, we searched the "grey" literature and clinicaltrials.gov to identify trials that were not published fully. We used an intention-to-treat analysis, reducing the likelihood that the therapeutic gain of active drug over placebo in our analyses has been overestimated. Limitations include the fact that there was moderate heterogeneity between studies in some of our analyses, and the fact that there were a small numbers of trials treating patients with CD through, as well as some differences in the time point at which endpoints were assessed. Despite these limitations, the results of our study may be useful to optimise design of future maintenance of remission trials in patients with IBD to maximise the likelihood of detecting a therapeutic gain of active drug over placebo.

It is well-known that the phases of development of a new drug are long and expensive, requiring several years from their commencement until drug approval [49]. The mean research and development costs for bringing a drug licensed for gastrointestinal diseases to market is estimated at $1430 million [50]. It is, therefore, desirable to optimise resources and to reduce timeframes for trials to be completed. In recent years, complex adaptive trial designs, including those using adaptative randomisation methods, have been conceived to address some of these issues [51]. These may adjust randomisation schedules during trial conduct, thereby

increasing the number of patients randomised to what appears to be the most beneficial treatment, increasing trial efficiency.

In trials utilising a treat-through approach, patients are randomised to receive induction therapy with either active drug or placebo and remain allocated to this treatment for the remainder of the study, irrespective of whether they respond. Typically, these trials include both an induction of remission endpoint at between 4 and 16 weeks and a later maintenance of remission endpoint, typically after 26 to 52 weeks of treatment. However, this approach does not reflect real-world clinical practice because a physician is unlikely to persist with a drug beyond the induction period if the patient is not responding and would instead change their treatment. Consequently, trials that re-randomise induction responders in a double-blind maintenance phase are likely to demonstrate greater efficacy of the active drug, in terms of maintenance of remission rates, compared with trials that continue treatments assigned at baseline in all trial participants. However, those re-randomised to the placebo arm are also likely to have higher maintenance of remission rates, as they will have been exposed to active drug during the induction phase of the trial, which may have a "carry over" effect. This could, theoretically, reduce the therapeutic gain of active drug over placebo in the maintenance of remission phase of the RCT. However, our meta-analysis confirms, for the first time, that this is not the case in either CD or UC, and across a range of biological drugs and small molecules.

In conclusion, our results show that trial design in IBD has a non-significant impact on the therapeutic gain of active drug over placebo. However, although the differences observed were modest, they could represent the difference between wide uptake of a drug and failure of it to be adopted, and also influence the findings of pairwise and network meta-analyses that pool maintenance trials together, irrespective of design. Adaptive trial methodologies, which re-randomise induction responders in the maintenance of remission phase, led to generally higher rates of maintenance of remission, lower NNTs, and greater therapeutic gains over placebo. This remained the case when trials were analysed according to type of IBD. These findings may have implications for future IBD

research, and these trials are probably more representative of clinical practice. Given the substantial costs involved in developing and evaluating new drugs and bringing them to market, choice of clinical trial design may still be an important consideration for maximising the likelihood that a drug can demonstrate superior efficacy over placebo, and at a margin that leads to its uptake in clinical practice, for the maintenance of IBD remission.

Guarantor of the article

ACF is guarantor.

Author contributions

Study concept and design: BB, DJG, CJB and ACF conceived and drafted the study. BB, CJB, and ACF analysed and interpreted the data. BB, CJB, and ACF drafted the manuscript. All authors have approved the final draft of the manuscript.

Ethics committee approval

Not required.

Data availability

The data underlying this study is available within the manuscript and supplementary materials

Conflict of interest

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Supplementary materials

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