Harms with placebo in trials of biological therapies and small molecules as maintenance therapy in inflammatory bowel disease: a systematic review and meta-analysis

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Lancet Gastroenterol Hepatol 2024; 9: 1030–40

Published Online September 19, 2024 https://doi.org/10.1016/S2468-1253(24)00233-4

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Summary

Background Randomised placebo-controlled trials for the induction of inflammatory bowel disease (IBD) remission involve potential harms to those receiving placebo. Whether these harms are also apparent with placebo during maintenance of remission trials in IBD is unclear. We aimed to examine the potential harms associated with receiving placebo in trials of licensed biologics and small molecules for maintenance of remission of ulcerative colitis and luminal Crohn's disease in a meta-analysis.

Methods We performed a systematic review and meta-analysis. We searched several medical literature databases including MEDLINE (from Jan 1, 1946, to May 31, 2024), Embase and Embase Classic (Jan 1, 1947, to May 31, 2024), and the Cochrane Central Register of Controlled Trials from database inception to May 31, 2024, for randomised placebo-controlled trials of licensed biologics and small molecules for maintenance of remission in adults with IBD reporting data on adverse events over a period of 20 weeks or more. There were no language restrictions or prespecified exclusion criteria. We extracted summary data and pooled data using a random-effects model for any treatment-emergent adverse event, drug-related adverse event, infection, worsening of IBD activity, withdrawal due to adverse events, serious adverse events, serious infection, serious worsening of IBD activity, or venous thromboembolic events, reporting relative risks (RRs) for placebo versus active drug with 95% CIs for each outcomes. The protocol for this meta-analysis was registered with PROSPERO (CRD42024542624).

Findings Our search identified 10 826 citations, of which 45 trials including 16 562 patients (10 319 [62·3%] receiving active drug and 6243 [37·7%] placebo) were eligible. The risks of any treatment-emergent adverse event (7297/9546 [76·4%] patients on active drug *vs* 4415/5850 [75·5%] on placebo; RR 1·01, 95% CI 0·99–1·04; I^2=47%), serious infection (260/10 242 [2·5%] *vs* 155/6149 [2·5%]; 0·97, 0·79–1·19; I^2=0%), or venous thromboembolic event (12/4729 [0·3%] *vs* 9/2691 [0·3%]; 0·72, 0·31–1·66; I^2=0%) were not significantly lower with active drug than placebo. The risks of any infection (3208/8038 [39·9%] *vs* 1713/4809 [35·6%]; 1·14, 1·05–1·23; I^2=60%) or any drug-related adverse event (1094/2997 [36·5%] *vs* 609/1950 [31·2%]; 1·24, 1·02–1·50; I^2=75%) were higher with active drug than placebo. However, the risks of any worsening of IBD activity (1038/8090 [12·8%] *vs* 1181/5191 [22·8%]; 0·58, 0·52–0·64; I^2=40%), any withdrawal due to adverse events (610/10 282 [5·9%] *vs* 561/6207 [9·0%]; 0·71, 0·60–0·84; I^2=43%), any serious adverse events (1066/10 292 [10·4%] *vs* 742/6198 [12·0%]; 0·85, 0·77–0·94; I^2=17%), or any serious worsening of IBD activity (101/5707 [1·8%] *vs* 143/3640 [3·9%]; 0·55, 0·42–0·71; I^2=0%) were lower with active drug than placebo. 21 randomised controlled trials were judged as low risk of bias across all domains.

Interpretation In maintenance of remission trials in IBD, placebo was associated with some clinically significant potential harms. Patients should be counselled about these before participating in clinical trials and consideration given to alternative designs to test novel drugs in IBD.

Funding None.

Introduction

Ulcerative colitis and Crohn's disease are chronic gastrointestinal conditions characterised by acute flares of disease activity interspersed by periods of remission.[1,2] Medical management of active disease aims to induce remission with efficacious drugs. By contrast, maintenance therapy with drugs aims to sustain remission and minimise the risk of future flares.[3,4] In the late 1990s, the introduction of infliximab marked a significant advance in therapeutic options for inflammatory bowel disease (IBD), improving patient outcomes and quality of life.[5] In the intervening years, multiple drugs with different mechanisms of action have been approved for both induction and maintenance of remission in ulcerative colitis and Crohn's disease. Currently, several drugs are being assessed in phase 2 and 3 randomised controlled trials (RCTs), many of which use placebo as the control intervention.[6]

Research in context

Evidence before this study

Randomised controlled trials (RCTs) are the gold standard for assessing the efficacy of novel drugs in inflammatory bowel disease (IBD). Many maintenance of remission trials in IBD use placebo as the control intervention. Patients could be unwell at the point of entry into such trials, and a previous meta-analysis suggested there could be harms associated with use of placebo in IBD RCTs. However, this meta-analysis included induction of remission trials, and in the intervening 5 years multiple new biologics and small molecules have become available for the maintenance of IBD remission. We conducted a comprehensive search of the medical literature, with no language restrictions, using MEDLINE, EMBASE, EMBASE Classic, and the Cochrane central register of controlled trials from database inception to May 31, 2024, as well as searching ClinicalTrials.gov. This search identified multiple RCTs of biologics and small molecules in IBD published since the conduct of the previous meta-analysis, thus providing a rationale for this systematic review and meta-analysis. We aimed to assess the harms associated with placebo in maintenance of remission trials in adults with IBD over a period of more than 20 weeks, and investigated whether these harms varied by type of IBD (ulcerative colitis or Crohn's disease) or trial design (treat-through or re-randomised).

Added value of this study

We did a contemporaneous systematic review of RCTs of licensed biologics or small molecules as maintenance therapy in adults with IBD to assess harms associated with receiving placebo in these trials. The relative risk of any infection or drug-related adverse event was significantly higher in patients receiving active drug than patients receiving placebo. However, among patients receiving active drug, the relative risk of any worsening of IBD activity, withdrawal due to adverse events, serious adverse events, or serious worsening of IBD activity were all significantly lower than those in the placebo group. Subgroup analyses according to type of IBD and trial design were consistent with the main findings for several of these adverse events.

Implications of all the available evidence

Placebo-controlled trials have been instrumental in establishing the efficacy, safety, and optimal use of available drugs for IBD. They are acceptable if there are no established treatments available and the use of placebo would be of negligible harm to the patient, or if there are other compelling reasons for using placebo. However, effective treatments exist for maintaining remission in IBD. Although many stakeholders are likely to be aware of the potential harms associated with placebo, the default position has remained a placebo-controlled trial. Our results reinforce that the harms associated with placebo should be considered in the design of future RCTs. They also suggest that other approaches, which are available and include alternative trial designs or stringent exit strategies for patients not responding to placebo, should be used to minimise exposure to placebo, and the potential associated harms, in IBD trials.

Placebo-controlled induction of remission trials in IBD have been shown to involve an increased risk of potential harms to patients receiving placebo.[7,8] This increased risk was driven by significantly higher rates of worsening of disease activity, including serious worsening of IBD activity, serious infections, venous thromboembolic events, and trial withdrawals due to adverse events compared with patients allocated to active drug. These differences might be due, in part, to the increased inflammation present in patients enrolled into induction of remission trials. Maintenance trials use different designs, such as treat-through (in which patients continue their assigned treatment, either active drug or placebo, from the induction phase of the trial, irrespective of whether they responded during the induction period) or re-randomised (in which patients usually receive open-label active drug to induce either response or remission and are then randomised to receive either active drug or placebo as maintenance therapy). Therefore, depending on their design, a proportion of patients could enter a maintenance trial having responded to induction therapy with an active drug, which could affect the occurrence of subsequent adverse events. These different designs have been shown to be associated with differences in trial outcomes, with higher rates of maintenance of clinical remission in trials re-randomising patients compared with those treating through.[9] However, whether there is any effect of trial design on adverse event rates is unclear.

According to the Declaration of Helsinki, placebo can be used in clinical trials provided the patient is not at risk of long-term harmful consequences.[10] The European Medicines Agency Committee for Medical Products for Human Use states that a placebo group should be included in pivotal trials to support the marketing of an active drug, if feasible and ethical.[11,12] Similarly, the US Food and Drug Administration allows placebo-controlled trials if there are no established treatments available, if the use of placebo would be of negligible harm to the patient, or if there are other compelling reasons for use of placebo.[13] However, in paediatric IBD trials, guidelines state that placebo should only be used if there is equipoise between active drug and placebo, if placebo is used in addition to an effective therapy, or if placebo is used to facilitate assessment of exit strategies from a period of maintenance therapy with an active drug.[14] A commentary in 2020 proposed no child with IBD should participate in a clinical trial that uses a treatment known to be inferior to those available routinely.[15]

As effective treatments exist for maintaining remission in IBD, establishing the potential harm with placebo is warranted so that adult participants can be informed fully before participating in RCTs. A previous meta-analysis examined this issue in 195 ulcerative colitis or Crohn's disease RCTs,[8] but this included induction of remission trials, and in the intervening 5 years, new drugs have become available. We hypothesised there would be significant harms associated with receiving placebo in maintenance of remission trials. Therefore, we conducted a systematic review and meta-analysis of maintenance of remission trials of licensed biological therapies and small molecules to examine this issue, and to assess the effects of trial design and IBD subtype.

Methods

Search strategy and selection criteria

For the **PROSPERO registration** see https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024542624

In this systematic review and meta-analysis, we conducted a comprehensive search of multiple databases, including MEDLINE, Embase and Embase Classic, and the Cochrane Central Register of Controlled Trials from database inception to May 31, 2024. Additionally, we used ClinicalTrials.gov to identify unpublished trials and supplementary data for potentially eligible RCTs. Conference proceedings (Digestive Disease Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2001 and 2024 were also examined to identify trials published only as abstracts. A recursive search of eligible articles' bibliographies was conducted.

Eligible RCTs had to assess efficacy of biological therapies, such as anti-TNF antibodies (ie, infliximab, adalimumab, golimumab, or certolizumab), anti-integrin antibodies (ie, natalizumab, vedolizumab, or etrolizumab), anti-interleukin 12 and 23 antibodies (ie, ustekinumab), and anti-interleukin-23 antibodies (ie, risankizumab or mirikizumab), or small molecules, such as JAK inhibitors (ie, tofacitinib, filgotinib, or upadacitinib) and S1PR modulators (ie, ozanimod or etrasimod) for maintenance of IBD remission at the doses taken through into phase 3 clinical trials and to report detailed adverse events in all patients. Trials had to administer open-label drug at baseline or randomly assign participants to active drug or placebo at baseline, with patients subsequently assessed for response and then being re-randomly assigned to maintenance active drug or placebo (re-randomised trials), or had to randomly assign patients to active drug or placebo at baseline, with treatment through to the final point of follow-up without re-randomisation (treat-through trials). Trials needed to recruit ambulatory adults (16 years and older) with ulcerative colitis or luminal Crohn's disease (appendix p 1) and compare biological therapies or small molecules with placebo over a period of 20 weeks or more. There were no prespecified exclusion criteria. Ethical approval was not required.

See Online for appendix

We identified studies on IBD with the search terms: "inflammatory bowel disease", or "Crohn's disease", or "colitis", or "ulcerative colitis" (both as medical subject headings and free text terms). We used the set operator AND to combine these with studies identified with: "infliximab", "remicade", "adalimumab", "humira", "certolizumab", "cimzia", "golimumab", "simponi", "natalizumab", "tysabri", "vedolizumab", "entyvio", "etrolizumab", "ustekinumab", "stelara", "risankizumab", "mirikizumab", "tofacitinib", "xeljanz", "filgotinib", "upadacitinib", "ozanimod", or "etrasimod", applying a clinical trials filter. There were no language restrictions. CJB and ACF independently evaluated all abstracts and assessed potentially relevant papers according to pre-defined criteria. Foreign language papers were translated, if required. We resolved disagreements between investigators by discussion. We sought summary data estimates from published reports. The study protocol was registered with PROSPERO (CRD42024542624).

Data analysis

Outcomes of interest were any treatment-emergent adverse event, any drug-related adverse event, any infection, any worsening of IBD activity, any withdrawal due to adverse events, any serious adverse event (usually defined as any adverse event that results in death, is life-threatening, requires hospitalisation or prolongation of an existing hospitalisation, or results in persistent or significant incapacity or disability), any serious infection, any serious worsening of IBD activity, or any venous thromboembolic event. CJB and ACF extracted summary data from published reports from all eligible studies independently onto a Microsoft Excel spreadsheet with dichotomous outcomes recorded (eg, adverse event occurring or not occurring). Trial characteristics were also extracted if available, including country of origin, number of centres, disease type, location, or extent, dose and dosing schedule of active therapy and placebo, whether trials defined exit strategies to allow patients not responding to placebo to access open-label drug, and duration of follow-up. No duplicate data were included, all trials were unique and we pooled all active drug groups and all placebo groups. As we were pooling data in a safety analysis, we used the number of patients receiving at least one dose of the study drug as the denominator wherever possible. Active treatment groups were combined in trials that used more than one dose of active drug, or more than one active drug. Discrepancies were resolved by discussion.

Risk of bias was assessed independently by CJB and ACF at the study level using the Cochrane risk of bias tool. Disagreements were resolved by discussion. The method used to generate the randomisation schedule and conceal treatment allocation, 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 were recorded.

We pooled data using a random-effects model,[16] to provide a more conservative estimate of the likelihood of having the adverse events of interest in IBD. The impact of receiving active drug on each of these events was expressed as a relative risk (RR) of the adverse event occurring with active therapy compared with placebo with 95% CIs; if the RR was less than 1 and the 95% CI did not cross 1, the likelihood of the adverse event with active drug was significantly reduced. We performed subgroup analyses according to IBD type (ulcerative colitis or Crohn's disease) and trial design (treat-through or randomised).

Heterogeneity, which occurs due to variation between individual study results arising because of differences in participants or methods, was assessed using both the χ^2 test, with a $p<0{\cdot}10$ used to define a significant degree of heterogeneity, and the I^2 statistic. I^2 ranges between 0% and 100%, with values of 25% to 49% considered low, 50% to 74% moderate, and more than 75% high heterogeneity.[17]

We used Review Manager 5.4 (The Cochrane Collaboration 2020) to generate forest plots of pooled RRs for each of the adverse events of interest with 95% CIs. We used StatsDirect version 3.3.6 to generate funnel plots. The Egger test was used to assess for evidence of asymmetry, relected in the funnel plots, and therefore possible publication bias or other small study effects,[18] if there were sufficient (≥10) eligible studies included in the meta-analysis, in line with recommendations.[19] We calculated the number needed to treat (NNT) or the number needed to harm (NNH) with active drug to avoid or have one of the adverse events of interest using the formula NNT or NNH=1/(assumed control risk×[1−pooled RR]), with the 95% CIs for the NNT or NNH derived from the 95% CIs of the RR.

Role of the funding source

There was no funding source for this study.

Results

The search strategy generated 10 826 citations. In total, we retrieved 208 articles for further assessment. We excluded 165 that were not eligible for inclusion, leaving 43 separate articles reporting on 45 RCTs (figure),[20–62] two of which are currently unpublished with data only available on ClinicalTrials.gov.[41,42] The agreement between investigators for trial eligibility was excellent ($\kappa=0{\cdot}86$). These 45 RCTs had a total of 16 562 participants, with 10 319 (62·3%) participants randomly assigned to active drugs and 6243 (37·7%) randomly assigned to placebo. The appendix contains the characteristics of individual studies (pp 2–5) and risk of bias (pp 6–7). 23 RCTs had defined exit strategies for patients not responding to placebo during the maintenance period, allowing access to open-label active drug. 21 RCTs had low risk of bias across all domains. Two of the re-randomised trials in luminal Crohn's disease reported safety data for all patients randomly assigned to active drug or placebo, irrespective of whether they had responded to induction therapy at baseline.[45,46] We included these trials in the main analyses but excluded them in a sensitivity analysis.

43 trials provided data for any treatment-emergent adverse event.[20–39,41–44,46–62] In total, 7297 (76·4%) of 9546 patients receiving active drug had any treatment-emergent adverse event, compared with 4415 (75·5%) of 5850 patients receiving placebo (RR 1·01, 95% CI 0·99–1·04; I^2=47%; table and appendix p 8). There was no evidence of publication bias (Egger test p=0·21). Results were similar for RCTs in ulcerative colitis and Crohn's disease and according to trial design. Excluding the single trial that reported safety data for all patients randomly assigned to active drug or placebo irrespective of their response to induction therapy at baseline did not alter the summary result (RR 1·01, 95% CI 0·99–1·04).[46]

Only 15 trials provided data for any drug-related adverse event.[23,25,26,32,33,40,41,43,47,50,53,57,59,62] 1094 (36·5%) of 2997 patients receiving active drug had any drug-related adverse event, compared with 609 (31·2%) of 1950 patients receiving placebo (RR 1·24, 95% CI 1·02–1·50; I^2=75%; table and appendix p 9), with no evidence of publication bias (Egger test p=0·16). The NNH with active drug to cause one drug-related adverse event was 13 patients (95% CI 6–160). There was no

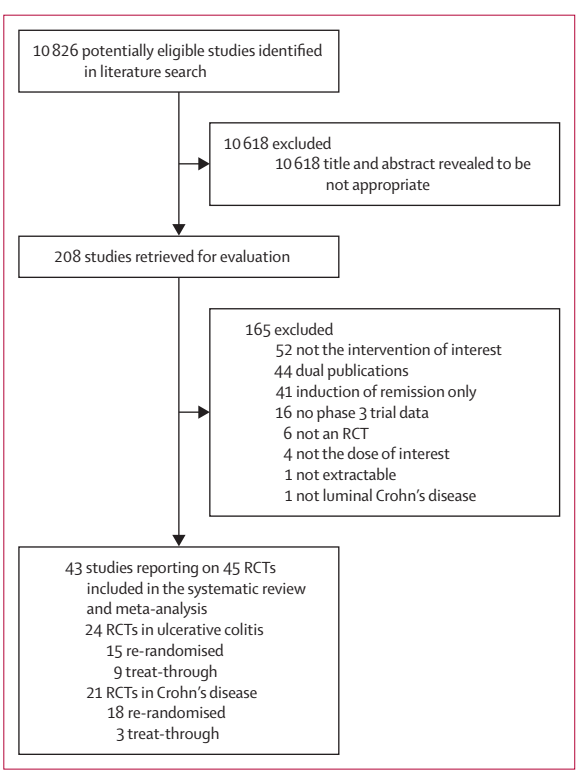

Figure: **Study selection**
RCT=randomised controlled trial.

significant increase in drug-related adverse event with active drug when trials in ulcerative colitis and Crohn's disease were considered separately. Neither of the two trials that reported safety data for all patients randomly assigned to active drug or placebo reported data for drug-related adverse events.[45,46]

In total, 38 trials provided data for any infection.[20–37,39,41–43,45,46,48–51,53–56,58,60–62] 3208 (39·9%) of 8038 patients receiving active drug had any infection, compared with 1713 (35·6%) of 4809 patients receiving placebo (RR 1·14, 95% CI 1·05–1·23; I^2=60%; table and appendix p 10), and there was no evidence of publication

	Number of placebo-controlled trials	Number of patients receiving active drug experiencing the event	Number of patients receiving placebo experiencing the event	Relative risk (95% CI)	I^2	χ^2 p value
Any treatment-emergent adverse event	43	7297/9546 (76·4%)	4415/5850 (75·5%)	1·01 (0·99–1·04)	47%	0·0006
Ulcerative colitis	23	3661/5016 (73·0%)	2104/2997 (70·2%)	1·03 (0·99–1·07)	51%	0·0028
Treat-through	9	1138/1469 (77·5%)	728/1003 (72·6%)	1·05 (1·00–1·11)	31%	0·17
Re-randomised	14	2523/3547 (71·1%)	1376/1994 (69·0%)	1·02 (0·97–1·08)	60%	0·0021
Crohn's disease	20	3636/4530 (80·3%)	2311/2853 (81·0%)	1·00 (0·97–1·02)	34%	0·073
Treat-through	3	925/1140 (81·1%)	558/701 (79·6%)	1·03 (0·99–1·08)	0%	0·48
Re-randomised	17	2711/3390 (80·0%)	1753/2152 (81·5%)	0·99 (0·96–1·02)	33%	0·092
Any drug-related adverse event	15	1094/2997 (36·5%)	609/1950 (31·2%)	1·24 (1·02–1·50)	75%	<0·0001
Ulcerative colitis	8	519/1411 (36·8%)	239/870 (27·5%)	1·41 (1·00–1·98)	79%	<0·0001
Treat-through	3	264/484 (54·5%)	125/405 (30·9%)	1·68 (0·92–3·07)	88%	0·0003
Re-randomised	5	255/927 (27·5%)	114/465 (24·5%)	1·18 (0·82–1·68)	47%	0·11
Crohn's disease	7	575/1586 (36·3%)	370/1080 (34·3%)	1·05 (0·89–1·24)	42%	0·11
Treat-through	1	108/331 (32·6%)	120/329 (36·5%)	0·89 (0·71–1·10)	..	..
Re-randomised	6	467/1255 (37·2%)	250/751 (33·3%)	1·12 (0·91–1·39)	45%	0·11
Any infection	38	3208/8038 (39·9%)	1713/4809 (35·6%)	1·14 (1·05–1·23)	60%	<0·0001
Ulcerative colitis	22	1692/4515 (37·5%)	881/2752 (32·0%)	1·17 (1·08–1·27)	36%	0·046
Treat-through	9	585/1469 (39·8%)	346/1003 (34·5%)	1·12 (1·02–1·23)	0%	0·91
Re-randomised	13	1107/3046 (36·3%)	535/1749 (30·6%)	1·21 (1·06–1·38)	60%	0·0031
Crohn's disease	16	1516/3523 (43·0%)	832/2057 (40·4%)	1·08 (0·94–1·24)	75%	<0·0001
Treat-through	2	336/809 (41·5%)	146/372 (39·2%)	1·06 (0·82–1·37)	61%	0·11
Re-randomised	14	1180/2714 (43·5%)	686/1685 (40·7%)	1·08 (0·92–1·28)	77%	<0·0001
Any worsening of IBD activity	38	1038/8090 (12·8%)	1181/5191 (22·8%)	0·58 (0·52–0·64)	40%	0·0069
Ulcerative colitis	20	501/4227 (11·9%)	562/2585 (21·7%)	0·55 (0·47–0·64)	45%	0·016
Treat-through	8	195/1428 (13·7%)	201/962 (20·9%)	0·69 (0·58–0·82)	0%	0·70
Re-randomised	12	306/2799 (10·9%)	361/1623 (22·2%)	0·48 (0·39–0·59)	48%	0·031
Crohn's disease	18	537/3863 (13·9%)	619/2606 (23·8%)	0·60 (0·52–0·69)	34%	0·076
Treat-through	2	49/510 (9·6%)	556/2116 (26·3%)	0·73 (0·46–1·15)	37%	0·21
Re-randomised	16	488/3353 (14·6%)	63/490 (12·9%)	0·59 (0·51–0·68)	34%	0·087
Any withdrawal due to adverse event	44	610/10 282 (5·9%)	561/6207 (9·0%)	0·71 (0·60–0·84)	43%	0·0016
Ulcerative colitis	24	262/5414 (4·8%)	237/3193 (7·4%)	0·67 (0·53–0·85)	35%	0·047
Treat-through	9	98/1469 (6·7%)	86/1003 (8·6%)	0·80 (0·54–1·19)	33%	0·16
Re-randomised	15	164/3945 (4·2%)	151/2190 (6·9%)	0·60 (0·45–0·81)	34%	0·094
Crohn's disease	20	348/4868 (7·1%)	324/3014 (10·7%)	0·75 (0·59–0·96)	52%	0·0035
Treat-through	3	96/1130 (8·5%)	97/710 (13·7%)	0·74 (0·55–0·99)	16%	0·31
Re-randomised	17	252/3738 (6·7%)	227/2304 (9·9%)	0·76 (0·56–1·04)	57%	0·0018
Any serious adverse event	44	1066/10 292 (10·4%)	742/6198 (12·0%)	0·85 (0·77–0·94)	17%	0·017
Ulcerative colitis	24	474/5414 (8·8%)	325/3193 (10·2%)	0·87 (0·74–1·01)	20%	0·19
Treat-through	9	194/1469 (13·2%)	143/1003 (14·3%)	0·89 (0·72–1·10)	6%	0·39
Re-randomised	15	280/3945 (7·1%)	182/2190 (8·3%)	0·85 (0·68–1·07)	30%	0·13
Crohn's disease	20	592/4878 (12·1%)	417/3005 (13·9%)	0·84 (0·73–0·96)	17%	0·24
Treat-through	3	124/1140 (10·9%)	98/701 (14·0%)	0·79 (0·45–1·37)	79%	0·0093
Re-randomised	17	468/3738 (12·5%)	319/2304 (13·8%)	0·86 (0·76–0·99)	0%	0·71

(Table continues on next page)

	Number of placebo-controlled trials	Number of patients receiving active drug experiencing the event	Number of patients receiving placebo experiencing the event	Relative risk (95% CI)	I^2	χ^2 p value
(Continued from previous page)						
Any serious infection	43	260/10 242 (2·5%)	155/6149 (2·5%)	0·97 (0·79–1·19)	0%	0·98
Ulcerative colitis	23	106/5364 (2·0%)	61/3144 (1·9%)	0·95 (0·68–1·31)	0%	0·93
Treat-through	8	33/1419 (2·3%)	20/954 (2·1%)	0·96 (0·54–1·72)	0%	0·49
Re-randomised	15	73/3945 (1·9%)	41/2190 (1·9%)	0·94 (0·63–1·39)	0%	0·94
Crohn's disease	20	154/4878 (3·2%)	94/3005 (3·1%)	0·98 (0·76–1·27)	0%	0·84
Treat-through	3	28/1140 (2·5%)	17/701 (2·4%)	0·98 (0·53–1·80)	0%	0·37
Re-randomised	17	126/3738 (3·4%)	77/2304 (3·3%)	0·98 (0·74–1·31)	0%	0·81
Any serious worsening of IBD activity	29	101/5707 (1·8%)	143/3640 (3·9%)	0·55 (0·42–0·71)	0%	0·58
Ulcerative colitis	19	66/4123 (1·6%)	82/2481 (3·3%)	0·58 (0·39–0·85)	13%	0·29
Treat-through	7	38/1324 (2·9%)	34/858 (4·0%)	0·87 (0·55–1·36)	0%	0·99
Re-randomised	12	28/2799 (1·0%)	48/1623 (3·0%)	0·38 (0·21–0·68)	18%	0·27
Crohn's disease	10	35/1584 (2·2%)	61/1159 (5·3%)	0·47 (0·30–0·72)	0%	0·88
Treat-through	1	6/179 (3·4%)	12/161 (7·5%)	0·45 (0·17–1·17)	..	..
Re-randomised	9	29/1405 (2·1%)	49/998 (4·9%)	0·47 (0·29–0·76)	0%	0·82
Venous thromboembolic event	17	12/4729 (0·3%)	9/2691 (0·3%)	0·72 (0·31–1·66)	0%	0·79
Ulcerative colitis	12	9/3489 (0·3%)	9/1940 (0·5%)	0·56 (0·22–1·43)	0%	0·68
Treat-through	3	4/723 (0·6%)	5/500 (1·0%)	0·59 (0·17–2·07)	0%	0·64
Re-randomised	9	5/2766 (0·2%)	4/1440 (0·3%)	0·54 (0·13–2·15)	0%	0·41
Crohn's disease (all re-randomised)	5	3/1240 (0·2%)	0	1·90 (0·30–11·99)	0%	0·94

Data are n/N (%), unless otherwise specified. IBD=inflammatory bowel disease.

Table: **Adverse events with active drug versus placebo in placebo-controlled remission maintenance trials of biological therapies or small molecules in ulcerative colitis or luminal Crohn's disease**

bias (Egger test p=0·16). The NNH with active drug to cause one infection was 20 patients (95% CI 12–56). The RR of infection was significantly higher with active drug in trials of both designs in ulcerative colitis, but not in Crohn's disease. Excluding the two trials that reported safety data for all patients randomly assigned to active drug or placebo did not alter the summary result (RR 1·12, 95% CI 1·05–1·20).[45,46]

There were 38 trials providing data for any worsening of disease activity.[21–33,35–37,39,41–43,46–59,61,62] Overall, 1038 (12·8%) of 8090 patients receiving active drug had any worsening of IBD activity, compared with 1181 (22·8%) of 5191 patients receiving placebo (RR 0·58, 95% CI 0·52–0·64; I^2=40%; table and appendix p 11), with no evidence of publication bias (Egger test p=0·21). The NNT with active drug to prevent any worsening of IBD activity was 10 patients (95% CI 9–12). A reduced RR of any worsening of IBD activity with active drug was seen in trials of both designs in ulcerative colitis, but only in re-randomised trials in Crohn's disease, although there were only two RCTs using a treat-through design. Excluding the single trial that reported safety data for all patients randomly assigned to active drug or placebo did not alter the summary result (RR 0·59, 95% CI 0·53–0·65).[46]

Overall, 44 trials reported withdrawal due to adverse events.[20–43,45–62] 610 (5·9%) of 10 282 patients receiving active drug withdrew due to an adverse event, compared with 561 (9·0%) of 6207 patients receiving placebo (RR 0·71, 95% CI 0·60–0·84, I^2=43%; table and appendix p 12), with no evidence of publication bias (Egger test p=0·81). The NNT with active drug to prevent a withdrawal due to an adverse event was 38 patients (95% CI 28–69). A lower RR of withdrawal due to adverse events with active drug was only seen in re-randomised trials in ulcerative colitis and treat-through trials in Crohn's disease. Excluding the two trials that reported safety data for all patients randomly assigned to active drug or placebo did not alter the summary result (RR 0·71, 95% CI 0·61–0·83).[45,46]

There were 44 trials providing data for any serious adverse event.[20–43,45–62] In total, 1066 (10·4%) of 10 292 patients receiving active drug had any serious adverse event, compared with 742 (12·0%) of 6198 patients receiving placebo (RR of any serious adverse event 0·85, 95% CI 0·77–0·94, I^2=17%; table and appendix p 13), with no evidence of publication bias (Egger test p=0·99). The NNT with active drug to prevent a serious adverse event was 56 patients (95% CI 36–139). The RR of serious adverse events was only lower with active drug in re-randomised trials in Crohn's disease. Excluding the

two trials that reported safety data for all patients randomly assigned to active drug or placebo did not alter the summary result (RR 0·87, 95% CI 0·77–0·97).[45,46]

In total, 43 trials provided data for any serious infection.[20–40,42,43,45–62] 260 (2·5%) of 10 242 patients receiving active drug had any serious infection, compared with 155 (2·5%) of 6149 patients receiving placebo (RR 0·97, 95% CI 0·79–1·19, I^2=0%; table and appendix p 14), and there was no evidence of possible publication bias (Egger test p=0·35). There was no significant increase in serious infection when trials in ulcerative colitis and Crohn's disease were considered separately or according to trial design. Excluding the two trials that reported safety data for all patients randomly assigned to active drug or placebo did not alter the summary result (RR 0·99, 95% CI 0·80–1·23).[45,46]

There were 29 trials providing data for any serious worsening of disease activity.[21–33,36,37,39,41,42,47,49–51,53,55,56,58,62] Overall, 101 (1·8%) of 5707 patients receiving active drug had any serious worsening of IBD activity, compared with 143 (3·9%) of 3640 receiving placebo (RR 0·55, 95% CI 0·42–0·71, I^2=0%; table and appendix p 15), with no evidence of publication bias (Egger test p=0·17). The NNT with active drug to prevent a serious worsening of IBD activity was 57 patients (95% CI 44–88). Increased likelihood of serious worsening of IBD activity with placebo was seen for both ulcerative colitis and Crohn's disease, although only in trials with a re-randomised design. Neither of the two trials that reported safety data for all patients randomly assigned to active drug or placebo reported data for any serious worsening of disease activity.[45,46]

Finally, 17 trials reported venous thromboembolic events.[21,22,26–28,30,32,33,37–39,51,55,58,59,62] 12 (0·25%) of 4729 patients receiving active drug had a venous thromboembolic event, compared with nine (0·33%) of 2691 patients receiving placebo (RR 0·72, 95% CI 0·31–1·66, I^2=0%; table and appendix p 16), and there was no evidence of publication bias (Egger test p=0·74). Neither of the two trials that reported safety data for all patients randomly assigned to active drug or placebo reported data for venous thromboembolic events.[45,46]

Discussion

This systematic review and meta-analysis assessed the harms associated with receiving placebo in maintenance of remission trials in IBD. Although some of the adverse events studied are to be expected in a placebo-controlled trial, the magnitude of these adverse events has not been assessed fully in trials of biologic therapies and small molecules. In addition, to date, some adverse events have not been assessed systematically, such as serious adverse events, which are an important issue, as is the separation of treatment-emergent adverse events from drug-related adverse events. There were no significant differences in the total number of treatment-emergent adverse events between patients randomly assigned to either active drug or placebo in maintenance RCTs. RR of any infection and any drug-related adverse event were significantly higher with active drug than placebo. However, those randomly assigned to active drugs were significantly less likely to have any worsening of their IBD activity, withdrawal due to an adverse event, serious adverse events, and serious worsening of their IBD activity than those randomly assigned to placebo. NNTs with active drug to avoid these adverse events ranged from ten patients for worsening of IBD activity to 57 patients for serious worsening of IBD activity. We have examined the harms associated with placebo in induction trials in IBD in another article,[7] showing an NNT with active drug to prevent a worsening of IBD activity of 23 patients, higher than the NNT of ten patients in this meta-analysis of maintenance trials. This finding might seem counter-intuitive, as patients enrolled into induction trials have more active disease and one might assume that placebo in that context poses a greater risk. One explanation for our findings could be the substantially longer timelines in maintenance of remission trials than induction of remission trials, meaning individuals in the placebo groups received no additional efficacious therapy for up to a year.

In subgroup analyses according to trial design, the RRs of adverse events were generally more pronounced in re-randomised trials than treat-through trials. These re-randomised trials accounted for the majority of the studies included in this meta-analysis and are designed to eliminate selection bias by bringing all patients to the same baseline.[63] Use of re-randomised trials means that all patients have responded to induction therapy on entry into the maintenance phase, before being randomly assigned to either continuing active drug or switching to placebo. They allow a better assessment of the efficacy of maintenance therapy than treat-through trials by accounting for any disease variability at baseline and enables any differences between a response to induction therapy and the maintenance of remission to be differentiated. Randomisation to placebo in such trials is, in essence, the withdrawal of an effective therapy and studies that have examined therapy withdrawal in IBD have shown it results in higher rates of relapse than those who continued an effective therapy, in line with the natural history of untreated IBD.[64] Therefore, even if the re-randomisation design is susceptible to carry-over effects and there is likely to be some persistence of response to induction therapy with active drug, the risk of flare in the placebo group could be considerable. This consequence is especially important as patients who enter placebo-controlled studies might have limited alternatives remaining and, hence, there are ethical concerns regarding the withdrawal of an active drug that appears to be working.

Furthermore, adverse events (eg, development of immunogenicity and hypersensitivity), especially with anti-TNF drugs, are more likely to occur when drug concentrations are low or if the active drug is interrupted,

which are additional harms that patients receiving placebo after re-randomisation might encounter if they are exposed to anti-TNF drug in the future.[65,66] However, we acknowledge that several of these trials were done more than 20 years ago. At that time, many questions regarding the optimal use of these drugs, the risk of immunogenicity, and the required dose and length of therapy, were unanswered. These trials have, therefore, contributed to an improved understanding of how to use biologics and small molecules and have shaped clinical practice.

In terms of contextualising our other findings, we found that the RR of infection was higher with active drug than placebo, which considering the mechanism of action of the drugs of interest is, perhaps, not surprising.[67,68] There are several possible explanations for finding no difference in treatment-emergent adverse events between active drug and placebo. First, those not responding to placebo might have withdrawn from the study early and hence adverse events were not captured. Second, especially in the context of a re-randomised design, in the induction phase of the trial, disease activity was possibly downgraded by the initial active drug and, hence, patients were carrying less morbidity into the maintenance stage, creating similar baseline characteristics of patients entering each group. Third, some drugs used in the induction phase might have a long half-life, meaning that despite receiving placebo, there was some carry-over effect.[69] Fourth, finding no difference in treatment-emergent adverse events between active drug and placebo might relate to how disease-related adverse events and drug-related adverse events are reported in RCTs. Good clinical practice mandates that disease-related adverse events, such as a worsening of the disease, are reported separately from drug-related adverse events,[70] but these are often incorporated incorrectly into the total number of adverse events in RCTs. Of note, drug-related adverse events were higher with active drug than placebo in this meta-analysis. Finally, patients entering RCTs are allowed, in most cases, to continue 5-aminosalicylates, thiopurines, or methotrexate, which are also efficacious in maintaining remission in some patients,[71–73] and there might be differences regarding corticosteroid tapering in maintenance trial protocols, which could influence safety outcomes.[74]

One role of placebo-controlled maintenance trials is to assess the safety of an active drug. Nevertheless, we argue careful consideration should be given to whether there is a genuine need to reassess the safety of a drug compared with placebo if its safety has already been established in other conditions. For example, in the U-ACHIEVE maintenance study, 681 patients with ulcerative colitis with a response to induction therapy received either upadacitinib or placebo for 1 year.[38] However, by the time the results of this trial were published there were already safety data for upadacitinib over a period 15 000 patient-years across rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and atopic dermatitis.[75]

Although regulatory agencies are likely to be aware of the potential harms associated with placebo, no systematic change has been implemented in the design of IBD trials to date, and the default position remains a placebo-controlled trial. Nevertheless, several approaches have been proposed and implemented over the years to minimise exposure to placebo in IBD trials. These include using open-label active drug groups from study entry or for patients who do not show a response to therapy with prompt evaluation, some of which occur as early as the second week. This use of open-label active drugs was stated to be the case in 50% of the RCTs in this meta-analysis. Adaptive trial designs, which have been used in other fields,[76] have also been proposed in IBD.[77] These designs include dose-finding studies, which are used in the early phases of drug development; adaptive hypothesis designs, with pre-planned modification of the study hypothesis; adaptive group sequential design; sample size re-estimation design; adaptive treatment-switching design; pick-the-winner or drop-the-loser design; biomarker adaptive design; seamless phase 2–3 design; adaptive platform trials; or a combination of more than one of these elements in what is termed a multiple adaptive design. These designs have the advantage of being shorter and more flexible than traditional designs. However, they also have drawbacks, including the need for sophisticated statistical models and difficulties in interpretation, as well as a long planning phase. Nevertheless, these might be better accepted by sponsors and patients than traditional trials because of the added flexibility,[78] and a review from 2024 highlighted the need for more patient-centric trials in IBD.[79] The information obtained from the patients assigned to placebo in existing trials to date could also be used to infer placebo response rates in future maintenance of remission trials. This approach has already been used by others, via Bayesian analysis, in one induction of remission trial.[80]

Our study has some limitations. There is a possibility that rare adverse events associated with placebo might not have been fully captured throughout the maintenance trial duration. However, we made diligent efforts to mitigate this limitation by sourcing comprehensive safety data from ClinicalTrials.gov for each trial, wherever feasible. Moreover, acknowledging the inherent constraints of meta-analyses, such as the heterogeneity observed in some of our analyses, is important. In fact, due to the low number of event rates for some of the rarer adverse events of interest, heterogeneity between studies could have been underestimated.[81] Zero events in one or both treatment groups, if events are rare, can also be an issue in meta-analysis. Although the Review Manager software corrects for this issue automatically,[82] this fixed correction can bias study estimates towards no difference and over-estimate variances of study

estimates.[83] If events are rare, meta-analyses are also vulnerable to sparse data bias, which can lead to inflation of summary estimates.[84] In addition, RCTs often vary in their assessment time points for both efficacy and safety, with safety considerations often treated as secondary outcomes and collected in a non-standardised way. Another limitation is the reporting of drug-related adverse events versus disease-related adverse events, as discussed previously. Finally, reporting of adverse events has become more detailed in trials conducted more recently, meaning that the harms associated with placebo might have been underestimated in this meta-analysis, although more than half of the trials we identified had been published in the past 10 years.

In conclusion, placebo-controlled trials have been instrumental in establishing the efficacy, safety, and optimal use of available drugs for IBD, and maintenance trials have enriched our understanding of immunogenicity, carry-over effects, and disease behaviour. However, acknowledging that this design has persisted, until recent years, primarily due to the historical scarcity of therapeutic alternatives is crucial. The current treatment landscape is markedly different, with multiple available treatment options. Given the potential harms associated with placebo highlighted in this meta-analysis of maintenance trials in IBD, considering the risks and benefits associated with this approach in the design of future studies is imperative. We advocate for robust conversations between regulatory organisations, industry, health-care providers and, more importantly, with patients to mitigate these harms, ensuring that future research endeavours in IBD prioritise patient safety while continuing to advance our understanding and treatment options in these complex diseases. Finally, if a placebo-controlled trial is still deemed the most appropriate design, stringent exit strategies, such as the opportunity to switch to open-label active treatment, could help mitigate against some of the associated harms highlighted in our study.

Contributors

BG, JB, JS, CJB, SD, and ACF conceived and drafted the study. ACF and CJB collected all data. ACF and CJB analysed and interpreted the data. BG, JB, JS, SD, and ACF drafted the manuscript. All authors have approved the final draft of the manuscript. SD is guarantor. All authors had full access to all data and accept responsibility to submit for publication.

Declaration of interests

SD declares grants from The Helmsley Charitable Trust, Edinburgh, Lothians Health Foundation, Pathological Society of Great Britain and Northern Ireland, and Lord Leonard and Lady Estelle Wolfson Foundation; consulting fees from AbbVie; personal speaker fees from Janssen, Ferring, and Takeda; and meeting and travel grants from Janssen, Takeda, Lilly, and Dr Falk. JB received a grant from Crohn's and Colitis UK and speaker fees from Thermo Fisher Scientific and Takeda. JS has received speaker fees for Takeda, Sandoz, Pfizer, and Bristol Myers Squibb; conference sponsorship from Takeda, Pfizer, Bristol Myers Squibb, and Jassen; and an unrestricted research grant from Tillots. BG has served as consultant to Galapagos, Pfizer, and AbbVie and as speaker for AbbVie, Janssen, Takeda, Pfizer, and Galapagos, and has received support for attending meetings by Dr Falk, Galapagos, Takeda, and Janssen. All other authors declare no competing interests.

Data sharing

Trial level data are already in the public domain, but we would consider reasonable requests to share the trial data we extracted with others. No other data are available.

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