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

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Summary

Background Randomised placebo-controlled trials are the gold standard to assess novel drugs in ulcerative colitis and Crohn's disease. However, there might be risks associated with receiving placebo. We aimed to examine the harms associated with receiving placebo in trials of licensed biologics and small molecules for the induction of remission in ulcerative colitis and luminal Crohn's disease in a meta-analysis.

Methods We performed a systematic review and meta-analysis. We searched MEDLINE, Embase, Embase Classic, and the Cochrane Central Register of Controlled Trials from database inception to May 30, 2024, for randomised placebo-controlled trials of licensed biologics and small molecules for induction of remission in adults (≥18 years) with moderately to severely active ulcerative colitis or luminal Crohn's disease reporting data on adverse events over a minimum treatment period of 4 weeks. There were no prespecified study exclusion criteria. We extracted summary data and pooled data using a random-effects model for any treatment-emergent adverse event, any drug-related adverse event, infection, worsening of inflammatory bowel disease (IBD) activity, withdrawal due to adverse events, serious adverse events, serious infection, serious worsening of IBD activity, or venous thromboembolic events (VTEs), reporting relative risks (RRs) with 95% CIs. The protocol for this meta-analysis was registered with PROSPERO (CRD42024527341).

Findings The search identified 10 826 citations, of which 47 trials including 20 987 patients (14 267 [68·0%] receiving active drug and 6720 [32·0%] receiving placebo) were eligible. The risk of any treatment-emergent adverse event was no different with active drug than with placebo (7660/14 267 [53·7%] patients on active drug *vs* 3758/6720 [55·9%] on placebo; RR 0·97, 95% CI 0·94–1·00; I^2=36%). However, the risks of worsening of IBD activity (563/13 473 [4·2%] *vs* 530/6252 [8·5%]; 0·48, 0·40–0·59; I^2=54%), withdrawal due to adverse event (401/13 363 [3·0%] *vs* 299/6267 [4·8%]; 0·62, 0·48–0·79; I^2=46%), serious adverse event (682/14 267 [4·8%] *vs* 483/6720 [7·2%]; 0·69, 0·59–0·80; I^2=30%), serious infection (140/14 194 [1·0%] *vs* 91/6647 [1·4%]; 0·67, 0·50–0·89; I^2=0%), serious worsening of IBD activity (187/11 271 [1·7%] *vs* 189/5056 [3·7%]; 0·45, 0·34–0·60; I^2=27%), or VTEs (13/7542 [0·2%] *vs* 12/2981 [0·4%]; 0·45, 0·21–0·94; I^2=0%) were all significantly lower with active drug than placebo. Numbers needed to treat with active drug to avoid these potentially serious adverse events ranged from 23 for worsening of IBD activity to 452 for VTEs. 27 randomised controlled trials were judged as low risk of bias across all domains.

Interpretation Patients with moderately to severely active IBD receiving placebo are more likely to experience significant worsening of IBD activity and some serious adverse events, which might relate to a reduction in risk of these events with active drug. Patients should be counselled about these potential harms, and alternative trial designs to mitigate these harms should be considered.

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Introduction

Crohn's disease and ulcerative colitis are chronic inflammatory diseases of the bowel, causing chronic gastrointestinal symptoms, significant morbidity, and impaired quality of life. The natural history of inflammatory bowel disease (IBD) results in progressive bowel damage leading to a risk of malnutrition, hospitalisation, surgery, and colorectal cancer.[1,2] Minimising acute disease flares and achieving long-term remission have been associated with improved quality of life, fewer hospitalisations, and reduced need for surgery.[3,4]

Several licensed biological therapies and small molecules are available to induce and maintain remission of IBD, although these are limited by suboptimal response and poor treatment persistence in some patients.[5] Fortunately, the therapeutic armamentarium continues to expand[6] and several novel targeted drugs are anticipated in the future. The randomised placebo-controlled trial is considered the most rigorous method for demonstrating proof of efficacy of a new treatment, with the majority in IBD supported by industry.[7] Placebo-controlled trials are especially important during the early

Research in context

Evidence before this study

Since the development of the first advanced molecule, infliximab, over 20 years ago, the treatment for inflammatory bowel disease (IBD) has been revolutionised, offering more therapeutic options than before. Despite the availability of therapies proven to be efficacious in randomised controlled trials (RCTs), many induction of remission trials in IBD still use placebo as a comparator. This practice might have been justified in the past when no other therapeutic alternatives existed. However, in the current era, randomising patients to receive a placebo has become debatable among some physicians and patients. Given that patients recruited to such RCTs have moderate to severe disease activity at enrolment, they might be unwell. A previous meta-analysis, which included both induction and maintenance trials, suggested there might be harms associated with use of placebo in RCTs in IBD. In the intervening 5 years, multiple new biologics and small molecules have been shown to be efficacious for inducing remission in IBD. We performed 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 30, 2024. We also searched ClinicalTrials.gov. The 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 study. We aimed to assess the harms associated with placebo in induction of remission trials in adults with IBD over a minimum treatment period of 4 weeks and investigate whether these harms varied by type of IBD (ulcerative colitis or Crohn's disease).

Added value of this study

We did a contemporaneous systematic review of RCTs of licensed biologics or small molecules as induction therapy in adults with IBD to assess harms associated with receiving placebo in these trials. The relative risk of any 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 worsening of IBD activity, withdrawal due to adverse events, serious adverse event, serious infection, serious worsening of IBD activity, or venous thromboembolic event were all significantly lower than those in the placebo group. Subgroup analyses according to type of IBD were consistent with the main findings for several of these adverse events.

Implications of all the available evidence

The increased risk of adverse events with placebo seen in this meta-analysis are likely to be related to a reduction in risk of their occurrence in those receiving active drug, rather than a true increase in risk associated with receiving placebo. Placebo-controlled clinical trials have yielded valuable insights into drug efficacy and safety and facilitated the approval of numerous drugs for treating active IBD. However, this design option was primarily attributed to the scarcity of therapeutic alternatives until 20 years ago. The results of this meta-analysis should prompt reflection on the current clinical trial model in IBD, encouraging critical thinking about possible strategies to minimise placebo exposure. Alternative trial designs should be considered for future novel drugs for IBD. These trial designs would include head-to-head trials of novel drugs against existing drugs with proven efficacy, platform studies, or Bayesian analysis of existing data on expected placebo response rates. Any move away from placebo-controlled trials would need collaboration between clinicians in the field, regulators, and industry and, most importantly, should consider the patient's perspective.

phases of drug development, as use of placebo aids early detection of efficacy or futility.[8] The potential gains to participating in randomised controlled trials (RCTs) include closer monitoring of the enrolled patient, potential exit mechanisms for a patient not thriving in a trial, the opportunity to receive active drug beyond the trial, and the altruism involved in accepting potential harm to oneself to benefit other patients in the long term.[9]

From a regulatory and legal perspective, the European Medicines Agency Committee for Medical Products for Human Use states that, if it is feasible and ethical, a placebo group should be included in pivotal trials to support the marketing of an active drug product.[10,11] As an example, to achieve adequate power to detect significant differences between treatments, placebo-controlled trials could allow for a more feasible recruitment target compared with head-to-head studies of one active drug versus another with the aim to show either superiority or non-inferiority.[12] Additionally, in patients with IBD who have exhausted established medical therapies, comparing a new active drug head-to-head against an existing gold standard drug that has already been used without success is unlikely to be ethical. Similarly, the US Food and Drug Administration permits placebo-controlled trials in three circumstances: if there are no established treatments available; if their use would be of negligible harm to the patient; and if there are compelling reasons for their use.[13] The Declaration of Helsinki also suggests that placebo can be used, if methodologically indicated, as long as the patient is not exposed to any long-term harmful consequences.[14] However, in trials in paediatric IBD, recommendations have been made that a placebo should only be used if there is genuine equipoise between active drug and placebo, if it is used in addition to an effective therapy, or if it is used to facilitate assessment of exit strategies from a long period of maintenance therapy with an active drug.[15] A commentary by Turner and colleagues[16] discussing the design of paediatric IBD trials asserted that no child with IBD should be treated as part of a clinical trial using a treatment known to be inferior to that which is routinely available.[16]

As effective treatments exist for moderately to severely active IBD, establishing the potential harm from a placebo is warranted in adults so that participants can be counselled fully before enrolling in RCTs. A previous meta-analysis examined this issue in 195 RCTs in ulcerative colitis and Crohn's disease,[17] and reported no clinically relevant differences in adverse events between placebo and active drug. However, this meta-analysis included all conventional treatments, as well as maintenance of remission trials, and in the intervening 5 years multiple new drugs have been licensed for IBD. We hypothesised there would be significant harms associated with receiving placebo in induction trials in patients with moderately to severely active IBD. Therefore, we examined this issue in all placebo-controlled trials of licensed biologics and small molecules for the induction of remission in adults with ulcerative colitis and luminal Crohn's disease in a meta-analysis. An accompanying Article analyses the harms associated with placebo in maintenance of remission trials in IBD.[18]

For the **PROSPERO registration** see https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024527341

Methods

Search strategy and selection criteria

We searched MEDLINE, Embase and Embase Classic, and the Cochrane Central Register of Controlled Trials from database inception to May 30, 2024. In addition, we searched ClinicalTrials.gov to identify unpublished completed trials or supplementary data for potentially eligible RCTs. We also searched conference proceedings (Digestive Disease Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2001 and 2024 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, such as anti-TNF antibodies (ie, infliximab, adalimumab, certolizumab, or golimumab), anti-integrin antibodies (ie, natalizumab, vedolizumab, or etrolizumab), anti-interleukin-12 and anti-interleukin-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 induction of remission of moderate to severe IBD at the doses taken through into phase 3 clinical trials and to report detailed adverse events in all patients. Studies recruited adults (≥18 years) with luminal Crohn's disease or ulcerative colitis (appendix p 1) and compared biological therapies or small molecules with placebo. Trials conducted only in patients with perianal Crohn's disease were ineligible. 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 the following terms: "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 identified. We obtained potentially relevant papers and evaluated them in more detail, using predesigned forms to assess eligibility independently according to our predefined criteria. We translated foreign language papers, if required. We resolved disagreements between investigators by discussion. We sought summary data estimates from published reports. The study protocol is registered with PROSPERO (CRD42024527341).

Data analysis

Our 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 events (VTEs). CJB and ACF extracted summary data from published reports from all eligible studies independently onto a Microsoft Excel spreadsheet as dichotomous outcomes (adverse event occurring or not occurring). We also extracted the following data for each trial, if available: country of origin, number of centres, disease type, location, or extent, and dose and dosing schedule of active therapy and placebo, and proportion of patients receiving concomitant immunosuppressants. There was no duplication of data, all trials were unique. 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 in the analysis, wherever possible. Active treatment groups were combined in trials that used more than one dose of active drug, or more than one active drug. All discrepancies in data extraction were resolved by discussion.

We assessed risk of bias at the study level using the Cochrane risk of bias tool.[19] This assessment was performed independently by CJB and ACF, with disagreements resolved by discussion. We recorded 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.

We pooled data using a random-effects model,[20] to provide a more conservative estimate of the likelihood of

having the adverse events of interest with placebo versus active drug in IBD, if there was heterogeneity between studies. We expressed the impact of receiving active drug on each of these events as a relative risk (RR) of the adverse event occurring compared with placebo with 95% CIs. If the RR was less than 1 and the 95% CI did not cross 1, there was a significantly reduced likelihood of the adverse event with active drug. We performed subgroup analyses according to IBD type (ulcerative colitis or Crohn's disease).

We assessed heterogeneity, which occurs due to variation between individual study results arising as a result of either differences in their participants or methods, using both the χ^2 test, with a p value of less than 0·10 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.[21]

We used Review Manager 5.4 (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. We assessed the funnel plots for evidence of asymmetry, and therefore possible publication bias or other small study effects, using the Egger test,[22] if there were sufficient (≥10) eligible studies included in the meta-analysis, in line with recommendations.[23] We calculated the number needed to treat (NNT) with active drug to avoid one of the adverse events of interest, with a 95% CI, using the formula NNT=1/(assumed control risk × [1−pooled RR]), with the 95% CIs for the NNT 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 205 articles for further assessment. We excluded 166 that were not eligible for inclusion, leaving 39 separate articles, reporting on 47 RCTs, two of which are currently unpublished (NCT00291668 and NCT03234907, with data only available on ClinicalTrials.gov; figure).[24–62] Eight articles reported on two trials each within the same publications.[32,33,36,38,51,56–58] The agreement between investigators for trial eligibility was excellent (κ=0·88). The 47 RCTs included 20 987 participants, with 14 267 (68·0%) participants randomly assigned to active drug and 6720 (32·0%) participants randomly assigned to placebo. 23 trials were conducted in patients with ulcerative colitis, reported in 19 articles,[24–42] and 24 trials were conducted in in Crohn's disease, reported in 18 articles and two reports on ClinicalTrials.gov.[43–62] The appendix provides characteristics of individual studies (pp 2–6) and risk of bias of all trials (pp 7–8). 27 RCTs were low risk of bias across all domains.

All 47 trials provided data for any treatment-emergent adverse event.[24–62] In total, 7660 (53·7%) of 14 267 patients receiving active drug had any treatment-emergent adverse event, compared with 3758 (55·9%) of 6720 receiving placebo (RR 0·97, 95% CI 0·94–1·00; I^2=36%; table and appendix p 9), with no evidence of publication bias (Egger test p=0·81). Results were similar for RCTs in ulcerative colitis and Crohn's disease.

Only 15 trials provided data for any drug-related adverse event.[26,28,38,40,44–48,50,54,58,59] 660 (23·0%) of 2874 patients receiving active drug had any drug-related adverse event, compared with 357 (17·5%) of 2042 receiving placebo (RR 1·22, 95% CI 1·02–1·46; I^2=48%; table and appendix p 10), with no evidence of publication bias (Egger test p=0·53). There was no significant increase in drug-related adverse event with active drug when trials in ulcerative colitis and Crohn's disease were considered separately.

In total, 42 trials provided data for any infection.[24–29,31–37,39,40,42–45,47–62] 2294 (17·9%) of 12 840 patients receiving active drug had any infection, compared with 996 (16·7%) of 5947 receiving placebo (RR 1·05, 95% CI 0·98–1·13; I^2=5%; table and appendix p 11), and there was no evidence of publication bias (Egger test p=0·47). Results were similar for RCTs in ulcerative colitis and Crohn's disease.

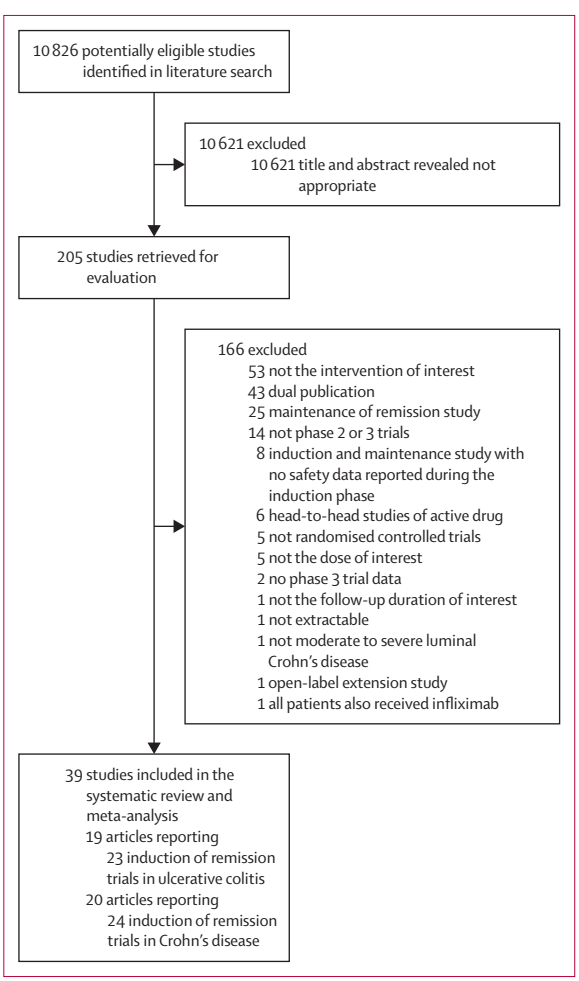

Figure: **Study selection**

	Number of placebo-controlled trials	Number of patients receiving active drug who experienced the event	Number of patients receiving placebo who experienced the event	Relative risk (95% CI)	I^2	χ^2 p value
Any treatment-emergent adverse event	47	7660/14 267 (53·7%)	3758/6720 (55·9%)	0·97 (0·94–1·00)	36%	0·0088
Ulcerative colitis	23	3934/8319 (47·3%)	1733/3510 (49·4%)	0·97 (0·92–1·02)	38%	0·037
Crohn's disease	24	3726/5948 (62·6%)	2025/3210 (63·1%)	0·97 (0·93–1·02)	35%	0·047
Any drug-related adverse event	15	660/2874 (23·0%)	357/2042 (17·5%)	1·22 (1·02–1·46)	48%	0·019
Ulcerative colitis	5	216/1054 (20·5%)	73/564 (12·9%)	1·44 (0·83–2·48)	73%	0·0054
Crohn's disease	10	444/1820 (24·4%)	284/1478 (19·2%)	1·18 (1·00–1·39)	23%	0·24
Any infection	42	2294/12 840 (17·9%)	996/5947 (16·7%)	1·05 (0·98–1·13)	5%	0·38
Ulcerative colitis	19	1107/6965 (15·9%)	419/2810 (14·9%)	1·05 (0·94–1·16)	0%	0·83
Crohn's disease	23	1187/5875 (20·2%)	577/3137 (18·4%)	1·04 (0·92–1·17)	28%	0·10
Any worsening of IBD activity	44	563/13 473 (4·2%)	530/6252 (8·5%)	0·48 (0·40–0·59)	54%	<0·0001
Ulcerative colitis	22	298/7669 (3·9%)	223/3185 (7·0%)	0·55 (0·43–0·72)	44%	0·014
Crohn's disease	22	265/5804 (4·6%)	307/3067 (10·0%)	0·42 (0·31–0·56)	58%	0·0005
Any withdrawal due to adverse event	45	401/13 363 (3·0%)	299/6267 (4·8%)	0·62 (0·48–0·79)	46%	0·0005
Ulcerative colitis	23	208/8319 (2·5%)	134/3510 (3·8%)	0·67 (0·44–1·01)	58%	0·0004
Crohn's disease	22	193/5044 (3·8%)	165/2757 (6·0%)	0·60 (0·45–0·81)	31%	0·087
Any serious adverse event	47	682/14 267 (4·8%)	483/6720 (7·2%)	0·69 (0·59–0·80)	30%	0·029
Ulcerative colitis	23	303/8319 (3·6%)	223/3510 (6·4%)	0·60 (0·49–0·74)	23%	0·16
Crohn's disease	24	379/5948 (6·4%)	260/3210 (8·1%)	0·76 (0·62–0·94)	32%	0·065
Any serious infection	46	140/14 194 (1·0%)	91/6647 (1·4%)	0·67 (0·50–0·89)	0%	0·68
Ulcerative colitis	23	65/8319 (0·8%)	38/3510 (1·1%)	0·65 (0·42–1·00)	0%	0·80
Crohn's disease	23	75/5875 (1·3%)	53/3137 (1·7%)	0·69 (0·46–1·03)	8%	0·36
Any serious worsening of IBD activity	35	187/11 271 (1·7%)	189/5056 (3·7%)	0·45 (0·34–0·60)	27%	0·073
Ulcerative colitis	17	98/6803 (1·4%)	76/2638 (2·9%)	0·50 (0·36–0·68)	0%	0·76
Crohn's disease	18	89/4468 (2·0%)	113/2418 (4·7%)	0·39 (0·24–0·64)	51%	0·0075
Venous thromboembolic event	18	13/7542 (0·2%)	12/2981 (0·4%)	0·45 (0·21–0·94)	0%	0·71
Ulcerative colitis	12	9/5478 (0·2%)	9/2113 (0·4%)	0·40 (0·16–1·01)	0%	0·60
Crohn's disease	6	4/2064 (0·2%)	3/868 (0·3%)	0·55 (0·15–1·99)	0%	0·81

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

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

44 trials provided data for any worsening of disease activity.[24–40,42–45,47,48,50–62] Overall, 563 (4·2%) of 13 473 patients receiving active drug had any worsening of IBD activity, compared with 530 (8·5%) of 6252 receiving placebo (RR 0·48, 95% CI 0·40–0·59; I^2=54%; table and appendix p 12), with no evidence of publication bias (Egger test p=0·67). Reduced likelihood of any worsening of IBD activity with active drug was seen in trials in ulcerative colitis and Crohn's disease. The NNT with active drug to prevent a worsening of IBD activity was 23 (95% CI 20–29).

Overall, 45 trials reported withdrawal due to adverse events.[24–55,57–62] 401 (3·0%) of 13 363 patients receiving active drug withdrew due to an adverse event, compared with 299 (4·8%) of 6267 receiving placebo (RR 0·62, 95% CI 0·48–0·79; I^2=46%; table and appendix p 13), with no evidence of publication bias (Egger test p=0·92). A significantly reduced rate of withdrawals due to adverse events with active drug was only seen in trials in Crohn's disease. The NNT with active drug to prevent a withdrawal due to an adverse event was 55 (95% CI 40–100).

All 47 trials provided data for any serious adverse event.[24–62] In total, 682 (4·8%) of 14 267 patients receiving active drug had any serious adverse event, compared with 483 (7·2%) of 6720 receiving placebo (RR 0·69, 95% CI 0·59–0·80; I^2=30%; table and appendix p 14), with no evidence of publication bias (Egger test p=0·20). Results were similar for RCTs in ulcerative colitis and Crohn's disease. The NNT with active drug to prevent a serious adverse event was 45 (95% CI 34–70).

In total, 46 trials provided data for any serious infection.[24–45,47–62] 140 (1·0%) of 14 194 patients receiving active drug had any serious infection, compared with 91 (1·4%) of 6647 receiving placebo (RR 0·67, 95% CI 0·50–0·89; I^2=0%; table and appendix p 15) and there was no evidence of possible publication bias or other small study effects (Egger test p=0·068). There was no significant reduction in serious infection with active drug when trials in ulcerative colitis and Crohn's disease were considered separately. The NNT with active drug to prevent a serious infection was 221 (95% CI 146–664).

35 trials provided data for any serious worsening of disease activity.[25,28,29,31–40,42,44,45,47,48,50,51,53–58,61,62] Overall, 187 (1·7%) of 11271 patients receiving active drug had any serious worsening of IBD activity, compared with 189 (3·7%) of 5056 receiving placebo (RR 0·45, 95% CI 0·34–0·60, I^2=27%; table and appendix p 16), with no evidence of publication bias (Egger test p=0·47). Reduced likelihood of any serious worsening of IBD activity with active drug was seen in both trials in ulcerative colitis and Crohn's disease. The NNT with active drug to prevent a serious worsening of IBD activity was 49 (95% CI 41–67).

Finally, 18 trials reported VTEs.[25,28,29,32,33,36–38,40,42,50,51,53,56,57] 13 (0·2%) of 7542 patients receiving active drug had a VTE, compared with 12 (0·4%) of 2981 receiving placebo (RR 0·45, 95% CI 0·21–0·94; I^2=0%; table and appendix p 17), with no evidence of publication bias (Egger test p=0·32). There was no significant reduction in VTE with active drug when trials in ulcerative colitis and Crohn's disease were considered separately. The NNT with active drug to prevent a VTE was 452 (95% CI 314–4140). VTEs with placebo occurred in trials of adalimumab,[25] vedolizumab,[28] ustekinumab,[37] filgotinib,[33] etrolizumab or adalimumab,[36] mirikizumab,[42] and etrasimod in ulcerative colitis,[40] and RCTs studying ustekinumab and risankizumab in Crohn's disease.[51,56] VTEs with active drug occurred in trials studying adalimumab,[25] golimumab,[29] tofacitinib,[32] etrolizumab or adalimumab,[36] upadacitinib,[38] and mirikizumab in ulcerative colitis,[42] and RCTs of ustekinumab,[53] risankizumab,[50] and etrolizumab in Crohn's disease.[57]

Discussion

This systematic review and meta-analysis examined the harms associated with receiving placebo in RCTs of advanced therapies in IBD. It included data from almost 21000 patients with IBD recruited to 47 RCTs. The RR of any treatment-emergent adverse event occurring in patients in the placebo groups was similar to that in patients receiving active drug, whereas the RR of drug-related adverse events was higher with active drug. When looking specifically at worsening of IBD activity, withdrawals due to adverse events, serious adverse events, serious infection, serious worsening of IBD activity, or VTEs, active drug was associated with a decrease in the RR of these events versus placebo, although some of these events were rare. In some cases, there was a 40% to 50% decrease in RR with active drug. The NNT to prevent one event with active drug was 23 for worsening of IBD activity and 45 for a serious adverse event. These findings clearly show that in moderately to severely active ulcerative colitis and Crohn's disease, even over the relatively short duration of an induction of remission RCT, there were small but statistically significant harms associated with not receiving an active drug and being assigned to placebo.

The adverse events that patients receiving placebo have in trials are likely to differ depending on the disease under study. For example, patients with irritable bowel syndrome, distinct from patients with IBD, are unlikely to experience serious adverse events with placebo during the course of an RCT as a potential consequence of their disease. In trials in irritable bowel syndrome, adverse event reporting with placebo arising to some degree from a nocebo response is more likely,[63] related to knowledge of potential side-effects of the active drug under study or even contributing factors from the health-care providers.[64] Meta-research suggests that almost half of the treatment effect seen in RCTs is attributable to factors other than the specific effects of the treatments under study.[65] Therefore, the findings of our study do not necessarily imply that receiving placebo is harmful. An active drug could provide beneficial effects in a specific group of patients. For example, the drug could be more likely to prevent a patient who is at high risk of VTE from having a VTE, rather than receiving placebo causing VTEs directly.

However, there are several other potential reasons for the results we observed. Patients recruited with IBD in induction of remission trials are unwell, with at least moderate disease activity. Those who receive placebo will not be receiving any new active treatment and, therefore, these patients are more likely to have continuing IBD activity during the RCT than those receiving the active drug, for which efficacy is at least hypothesised. IBD is reported to be associated with a three-fold risk of VTE relative to the general population, and during a flare of IBD, this increase in risk is even greater.[66] The inclusion criteria for induction of remission RCTs select for a population with active IBD, often patients who have had no benefit from multiple standard treatments and have a high disease burden, carrying significant morbidity into the trial, and are at substantial risk of VTE without treatment. In addition, they might require glucocorticosteroids, which are associated with an increased risk of VTE.[67,68] Although the absolute numbers of VTEs in these trials were small, there was a significant decrease in RR with active drug, even in spite of the inclusion of JAK inhibitors. There can be long-term sequelae of VTEs, such as pulmonary hypertension,[69] meaning their impact should not be underestimated. The explanation for the decreased RR of serious infection with active drug is less clear, but might be associated with uncontrolled inflammation in patients receiving placebo.[70,71] Patients in placebo groups in induction of remission trials are also more likely to have worsening IBD activity, as shown in this meta-analysis and, therefore, be given glucocorticosteroids, which are also associated with serious infection.[72]

Some patients with IBD can still experience benefits from receiving a placebo as part of a trial. For example, both clinical and endoscopic remission rates with placebo in induction RCTs in IBD have been estimated at between 10% and 20%.[73,74] Another meta-analysis has shown that disease-specific and generic health-related quality of life in IBD can also improve significantly with placebo.[75] In addition, placebo-controlled trials can still

be useful to assess novel therapies, whose mechanisms of action might be only partly understood, as a means of detecting harms of the drug, if they exist. However, when adverse events are rare, even placebo-controlled trials are unlikely to detect some of these potential risks. Rarer events might only become obvious during post-marketing surveillance.

Our findings highlight the potential harms associated with receiving placebo in placebo-controlled induction of remission IBD trials, which might relate to a reduction in risk of these events with active drug and the need to counsel patients carefully about the possible consequences of enrolling in such studies. Data on patients' perspectives are sparse, although one study has suggested that patients would value the opportunity to understand clinical trials in the context of their own disease.[9] Another study of 949 adults with IBD suggested that minimising placebo groups would encourage trial participation.[76] Therefore, considering whether future novel drugs for IBD should be tested with alternative trial designs, such as head-to-head trials against existing drugs with proven efficacy, is important. However, these alternatives also come with challenges. These challenges include the selection of a suitable comparator in medically refractory patients and the larger sample size required to generate statistical power to show superiority of one drug over another, which could be a barrier to trial completion, although use of objective endpoints (eg, mucosal healing) has reduced placebo response rates, meaning the sample size might be less of an issue. Other options include prospective randomised open blinded endpoint trials or platform studies.[77] Prospective randomised open blinded endpoint trials rely on objective endpoints that are assessed centrally by blinded assessors, negating the need for masking treatment allocation in head-to-head trials using a double-dummy design, and platform studies allow patients to access several active treatment options, and can even allow sequencing of therapies.

Conducting RCTs without a placebo group by using defined thresholds for an expected placebo response rate in an induction of remission trial might be possible. In the EXPLORER study, the authors estimated a benchmark placebo endoscopic remission rate of 14% from 13 previous trials and used Bayesian analysis to compare this remission rate with the observed endoscopic remission rates obtained with active treatment, consisting of triple therapy with vedolizumab, adalimumab, and methotrexate.[78] Although there are numerous placebo-controlled trials in IBD, and establishing an accepted placebo response rate in such RCTs might be expected, a previous meta-analysis of placebo response rates found significant heterogeneity between studies.[79] This heterogeneity might have been related to the different implementation of the intervention (ie, tablet *vs* injection), different patient populations, and the varying definitions of clinical and endoscopic response and remission used. However, in the intervening period since this meta-analysis, placebo response rates have possibly stabilised due to more standardised outcome definitions, which warrants further evaluation.

We acknowledge the limitations of this study, including the possibility that not all adverse events associated with placebo will be captured over the course of a trial, particularly if rare, and these might not have been assessed fully in this study. However, we accessed ClinicalTrials.gov wherever possible to obtain full safety data for each of the included trials. As only RCTs of drugs with now proven efficacy in IBD were included in our analysis, we might have overestimated the potential harms of being allocated to placebo in a trial. Other limitations are those associated with any meta-analysis. There was heterogeneity in some of our analyses and possible publication bias or small study effects in one analysis. Only 27 (57%) of 47 trials were at low risk of bias across all domains, although as drug safety was not the primary endpoint of any of these trials this risk is unlikely to have had an impact on our findings. There were also minor differences in the duration of treatment between some of these trials, as well as the time points at which safety was assessed. A further limitation is 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,[80] but these are often incorporated incorrectly into the total number of adverse events in RCTs. This possibility that disease-related adverse events and drug-related adverse events were combined is supported by the fact that we observed no significant difference in the overall likelihood of any treatment-emergent adverse event occurring between active drug and placebo but, if individual trials reported these data, a higher RR of drug-related adverse events and a lower RR of disease-related adverse events with active drug than placebo.

In conclusion, although placebo-controlled clinical trials have yielded valuable insights into drug efficacy and safety and facilitated the approval of numerous drugs for treating active IBD, this design option was primarily attributed to the scarcity of therapeutic alternatives until the turn of the 21st century. We are in an unprecedented era of IBD management with a plethora of treatment options available. This meta-analysis has highlighted inherent potential harms associated with randomisation to a placebo group. As discussed, potential reasons for these harms, rather than them relating directly to placebo, include ongoing moderate to severe disease activity or deleterious effects of other treatments, such as glucocorticosteroids. These findings could serve as an impetus to move away from placebo-controlled induction of remission trials in adults with IBD. This approach would be similar to the recommendations for avoiding trials of this design in children, unless there is a strong rationale for such an approach. Any such move

would need collaboration between clinicians in the field, regulators, and industry and, most importantly, will need to consider the patient's perspective.

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. ACF 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; is a consultant to AbbVie; speaker fees from Janssen, Takeda, and Ferring; and meeting and travel grants from Janssen, Takeda, Lilly, and Dr Falk. JB has received a grant from Crohn's and Colitis UK, speaker fees from Thermo Fisher Scientific and Takeda, and support for attending meetings from Janssen. JS has received speaker fees for Takeda, Sandoz, Pfizer, and Bristol Myers Squibb; support for attending meetings from Takeda, Pfizer, Janssen, and Bristol Myers Squibb; and an unrestricted research grant from Tillotts. BG is a consultant to Galapagos, Pfizer, and AbbVie, speaker for AbbVie, Jansen, Takeda, Pfizer, and Galapagos, and has received support for attending meetings from 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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