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Harms with Placebo in Trials of Biological Therapies and Small Molecules as Induction Therapy in Inflammatory Bowel Disease: Systematic Review and Meta-analysis

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Introduction

Randomised placebo-controlled trials are the gold standard to assess novel drugs in the inflammatory bowel diseases (IBD): ulcerative colitis (UC) and Crohn's disease (CD).

However, there may be risks associated with receiving placebo. We aimed to examine harms associated with receiving placebo in trials of licensed biologics and small molecules for the induction of remission in UC and luminal CD in a meta-analysis.

The study was registered PROSPERO international prospective register of systematic reviews registration number CRD42024527341.

Method

We searched the literature from inception to 30th May 2024 for randomised placebo-controlled trials:

- Ambulatory adult (aged ≥18 years) patients with moderate to severely active luminal CD or UC.
- Compared biological therapies or small molecules in phase III randomised controlled trials with placebo with minimum duration of follow-up of 4 weeks.
- Expressed the impact of receiving active drug on adverse events (AE) as a relative risk (RR) of the AE occurring compared with placebo with 95% confidence intervals (CIs).
- If the RR was less than 1 and the 95% CI did not cross 1, there was a significantly reduced likelihood of the AE with active drug.
- We assessed inter-study heterogeneity, using the I^2 statistic. The I^2 ranges between 0% and 100%, with values of 25% to 49% considered low, 50% to 74% moderate, and ≥75% high heterogeneity between the studies.

Results

- The search identified 10,826 citations, of which 47 trials with 20,987 patients with 14,267 (68.0%) receiving active drug, and 6720 (32.0%) receiving placebo were eligible.
- The **bold RR** denote a reduced risk of the AE with drug compared with placebo.
- Serious AE is defined as any AE that results in death, is life-threatening, requires hospitalisation or prolongation of an existing hospitalisation, or results in persistent or significant incapacity or disability.

Event of Interest	Number of Placebo-controlled Trials	Number of Patients Receiving Active Drug Experiencing the Event (n/N (%))	Number of Patients Receiving Placebo Experiencing the Event (n/N (%))	RR (95% CI)	I^2
Any treatment-emergent adverse event	47	7660/14 267 (53.7)	3758/6720 (55.9)	0.97 (0.94 – 1.00)	36%
Any drug-related adverse event	15	660/2874 (23.0)	357/2042 (17.5)	1.22 (1.02 – 1.46)	48%
Any infection	42	2294/12 840 (17.9)	996/5947 (16.7)	1.05 (0.98 – 1.13)	5%
Any worsening of IBD activity	44	563/13 473 (4.2)	530/6252 (8.5)	**0.48 (0.40 – 0.59)**	54%
Any withdrawal due to adverse event	45	401/13 363 (3.0)	299/6267 (4.8)	**0.62 (0.48 – 0.79)**	46%
Any serious adverse event	47	682/14 267 (4.8)	483/6720 (7.2)	**0.69 (0.59 – 0.80)**	30%
Any serious infection	46	140/14 194 (1.0)	91/6647 (1.4)	**0.67 (0.50 – 0.89)**	0%
Any serious worsening of IBD activity	35	187/11 271 (1.7)	189/5056 (3.7)	**0.45 (0.34 – 0.60)**	27%
Venous Thromboembolism	18	13/7542 (0.2)	12/2981 (0.4)	**0.45 (0.21 – 0.94)**	0%

Conclusion

- Patients with moderately to severely active IBD receiving placebo are more likely to experience significant worsening disease activity and some serious AEs, which may 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 considered.

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