Interventions for maintenance of surgically induced remission in Crohn’s disease: protocol for a network meta-analysis

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Contributorship Statement:

An original draft for this protocol manuscript was made by MG with SL and VS and then finalized by the wider team.

Co-Authors agreed on the review questions, approved the protocol and contributed to the final version of this manuscript.

Background

Crohn’s disease (CD) is a chronic, progressive inflammatory bowel disease that can affect any part of the gastrointestinal tract, with the terminal ileum and colon being the most commonly involved sites. Recently, the prevalence of CD is found increasing, causing a substantial economic burden (1, 2).

Despite advancements in pharmacological management, more than 50% of patients still require surgical intervention (3). While surgery can induce remission, postoperative relapse, identified through clinical symptoms and endoscopic findings, is still common. Data from referral centres indicate that approximately 50% of patients occur clinical postsurgical relapse after 5 years, and 85–100% of patients experienced endoscopic relapse 3 years after the surgery (4).

Several pharmacological interventions are used to maintain surgically induced remission, including 5-aminosalicylates (5-ASA), imidazolic antibiotics (metronidazole or ornidazole), purine analogues (azathioprine or mercaptopurine), and anti-TNF agents. However, recent studies have reported conflicting evidence regarding their effectiveness and safety (5-7).

A comprehensive synthesis of the available evidence is required to determine the comparative effectiveness of these interventions. Network meta-analysis (NMA) allows for the integration of direct and indirect evidence, facilitating a comparative evaluation of all available treatments. Beyond ranking interventions according to their efficacy and safety, NMA enables the integration of interventions from multiple standalone comparisons into a single node, improving the precision of estimates. It also allows for a more accurate evaluation of therapies with borderline effectiveness. Additionally, NMA facilitates subgroup and sensitivity analyses, helping to clarify the confounding factors.

 This protocol outlines the methodology of an NMA for maintaining surgically induced remission in CD.

**Methods**

**Eligibility/Exclusion criteria**

Types of studies: Randomized controlled trials (RCTs) for maintenance of surgically induced remission in CD irrespective of language or year of publication.

Types of participants: Trials enrolling participants of any age with Crohn's disease as determined by conventional clinical, radiological, or endoscopic criteria, will be considered for inclusion.

Types of interventions: Trials using oral or topical corticosteroids, 5-ASA agents, purine analogues, TNF-α antagonists, other classes of biologic agents, probiotics, antibiotics, or any other pharmaceutical intervention will be included. Trials assessing enteral diet, diet manipulation, herbal medicine, or nutritional supplementation will not be considered. All administration routes and dosages will be considered. Studies where participants were given additional treatments that are not typically prescribed for maintaining remission will be included.

**Types of outcome measures**

The primary outcome is clinical relapse, as defined by the studies.

The secondary outcomes include:

1) Endoscopic relapse, as defined by the original studies.

2) Total adverse events

4) Serious adverse events

5) Withdrawal due to adverse events

**Search methods for identification of studies**

The search strategies of this review are designed by a information specialist with Cochrane expertise.

We will search EMBASE, MEDLINE, CENTRAL, PubMed (excluding MEDLINE), ClinicalTrials.gov and WHO ICTPR. We will inspect the references of all identified studies and relevant systematic reviews to identify any additional trials. Additionally, we will manually search abstracts submitted to major gastroenterology conferences.

**Data collection and analysis**

We will carry out data collection and analysis according to the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions (8).

**Selection of studies**

Two reviewers will independently screen the titles and abstracts, with all records screened in duplicate. Any disagreements will be resolved by a third senior author. Full-text reports will be retrieved for studies considered potentially eligible, and the same screening process will be applied. Multiple reports of the same RCT will be consolidated while data will be extracted once.

**Data extraction**

Two reviewers will independently extract information on relevant features and outcome data of included studies. Disagreements will be resolved by discussion with a third senior author. We will attempt to contact authors or sponsors of the studies for unclear or missing data and information.

**Assessment of risk of bias in included studies**

Two authors will independently assess risk of bias in the included studies using the Cochrane Risk of Bias 1 tool, outlined in the Cochrane Handbook for Systematic Reviews of Interventions (8). Disagreements will be resolved by discussion with a third senior author.

**Measures of treatment effect**

Treatment effects will be reported as risk ratios (RR) with corresponding 95% confidence intervals (CI), using the participant as the unit of analysis.

**Dealing with missing data**

We will perform analyses on a modified intention-to-treat basis. For safety outcomes, patients with missing or unclear withdrawal data were considered as withdrawals due to adverse events. In maintenance trials that report remission or response rates instead of relapse or loss of response, we will invert the reported remission and response rates to derive relapse and loss of response data.

**Assessment of transitivity across treatment comparisons**

We will evaluate the assumption of transitivity by examining the distribution of potential effect modifiers across different pairwise comparisons. In this context, we anticipate that transitivity will hold, provided that the common comparator used for indirect comparisons remains consistent across trials and that pairwise comparisons do not significantly differ in terms of effect modifier distribution.

To assess this assumption epidemiologically, we will compare the clinical and methodological characteristics of studies across the various treatment comparisons.

**Assessment of statistical heterogeneity and inconsistency**

In standard pairwise meta-analyses we will estimate heterogeneity variances for each pairwise comparison by calculating the Chi² and I² statistics.

In the network meta-analysis, we will assume a common heterogeneity variance estimate across all comparisons. Statistical heterogeneity across the network will be assessed based on the magnitude of the heterogeneity variance parameter (Tau²) derived from the network meta-analysis models. We will compare the magnitude of the heterogeneity variance with the empirical distribution as derived by Turner 2012 (9). We will also estimate a total I2 statistic value for heterogeneity in the network as described in Higgins 2012 (10).

We will consider downgrading the certainty of the evidence for inconsistency where I2 is greater than 60%.

We will use global and local approaches to evaluate the statistical agreement between the various sources of evidence in a network of interventions (consistency) to complement the evaluation of transitivity. To evaluate the presence of inconsistency locally we will use the loop-specific approach. This method evaluates the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop (inconsistency factor). Then, the magnitude of the inconsistency factors and their 95% CIs can be used to infer the presence of inconsistency in each loop. We will assume a common heterogeneity estimate within each loop. To check the assumption of consistency in the entire network we will use the 'design-by-treatment' model as described by Higgins 2012 (10). This method accounts for different sources of inconsistency that can occur when studies with different designs (two-arm trials versus three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach, we will infer the presence of inconsistency from any source in the entire network based on a Chi2 test.

All analyses will be run with R statistical package (R Development Core Team) and the netmeta library (11).

**Assessment of reporting biases**

Most reporting biases are minimized by using an inclusive search strategy. We plan to investigate publication bias using a funnel plot if there are 10 or more studies. The magnitude of publication bias will be determined by visual inspection of the asymmetry of the funnel plot. In addition, we will test funnel plot asymmetry by performing a linear regression of intervention effect estimate against its standard error, weighted by the inverse of the variance of the intervention effect estimate (12).

**Direct comparisons of treatment effects**

We will combine data from individual trials for meta-analysis when the interventions, patient populations, and outcomes are deemed sufficiently similar, as determined by consensus. A random-effects model will be employed to pool the data (13).

**Indirect and network comparisons**

We will initially generate and assess the network diagrams to determine if a network meta-analysis is feasible. Then we will perform the network meta-analysis on all outcomes within a frequentist framework using multivariate meta-analysis.

**Relative treatment ranking**

We will estimate the cumulative probabilities for each treatment being at each possible rank and obtained a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA); the larger the SUCRA the higher its rank among all available agents (14).

**Subgroup analyses**

* Subgroup analyses will be conducted based on the length of follow-up, categorised as short-term (≤12 months) and long-term (>12 months).

**Sensitivity analyses**

* Removal of studies where outliers in terms of definition of clinical relapse

**Summary of findings and assessment of the certainty of the evidence**

We will evaluate the certainty of the evidence using the GRADE approach, as outlined in the GRADE handbook, to assess the overall certainty of the evidence for each outcome across all comparisons (15). The GRADE working group’s framework will be applied to rate the certainty of effect estimates derived from the network meta-analysis for all comparisons and outcomes (16). The certainty of direct, indirect, and network evidence will be assessed.

First, we will assess the certainty of the direct evidence (where available) for a given outcome and rate the evidence using the standard GRADE approach based on consideration of trial design limitations (risk of bias); inconsistency; imprecision; indirectness and publication bias (16). In this approach, the direct estimates are rated for risk of bias, inconsistency, indirectness and publication bias; followed by the indirect estimates are rated based on the lowest ratings of the direct comparisons forming the most dominant loop and intransitivity; and finally, the network estimates are rated based on imprecision, incoherence, and the rating of the direct or indirect estimate that contributes the most.

At each of these stages, review authors will independently appraise the certainty ratings for the direct, indirect and network evidence. We will resolve disagreements between authors through discussion and consultation. We will rate the certainty of network evidence for each outcome as ‘high’, ‘moderate’, ‘low’ or ‘very low’ in accordance with the GRADE approach.

* High certainty: we are very confident that the true effect lies close to that of the effect.
* Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
* Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
* Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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**Competing interests statement**

None to declare.