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Network meta-analysis to inform positioning of biologics in patients with Crohn's disease: Promise and perils

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ABSTRACT

With availability of several different classes of biologic agents with variable efficacy and safety profiles for moderate-severe Crohn's disease (CD), positioning of different agents in treatment course is an important question for clinicians. Though in an ideal world, positioning would be personalized and driven by likelihood of response to different agents based on biomarkers in individual patients, that is still far from reality, and decisions are empiric. In the absence of head-to-head trials of different medications, decisions on treatment choice and positioning are primarily based on clinician experience, opinion-based treatment algorithms, patient preference and insurance reimbursement. Understandably, in the absence of guidance, there is considerable practice variability on optimal choice of first- and second-line biologics in the treatment of patients with CD. In the absence of direct evidence from head-to-head trials, network meta-analysis can help assess comparative efficacy of several interventions and synthesize evidence across a network of randomized controlled trials. In this review, we discuss what network meta-analyses, what do they tell us about positioning different agents, and strengths and limitations of such an approach.

Introduction

Anti-tumor necrosis factor-α (TNF) agents have traditionally been considered first-line biologic agents for the management of moderate to severe Crohn's disease (CD) refractory to conventional therapy (mesalamine, steroids, immunosuppressive agents) [1,2]. Approximately one-third of biologic-naïve patients with CD may not respond to induction therapy, and among those who respond, up to 45% will progressively lose response over time [3,4]. Over the last five years, several new therapies including vedolizumab and ustekinumab have been approved for treatment of moderate-severe CD. With availability of several different classes of biologic agents with variable efficacy and safety profiles, positioning of different agents in treatment course, as first-line (in biologic-naïve patients) and second-line (in patients with prior exposure to anti-TNF agents) is an important question for clinicians. However, there is no published head-to-head trial of different medications, and decisions on treatment choice are primarily based on clinician experience, opinion-based treatment algorithms, patient preference and insurance reimbursement. Understandably, in the absence of guidance, there is considerable practice variability on optimal choice of first- and second-line biologics in the treatment of patients with CD. In the absence of direct evidence from head-to-head trials, network meta-analysis can help assess comparative efficacy of several interventions and synthesize evidence across a network of randomized controlled trials (RCTs) [5].

What is network meta-analysis?

There is general paucity of head-to-head trials of active interventions, comparing different pharmacological interventions, which can inform stakeholders regarding the comparative effectiveness of these interventions, an oft-faced clinical dilemma. Traditional, direct pairwise meta-analyses provide only partial information in this case, because they can only answer questions about pairs of treatments and hence, do not optimally inform decision-making. To overcome limitations in this, network meta-analyses, or indirect treatment comparison meta-analyses, have recently gained prominence [5,6]. This method involves the

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simultaneous analysis of direct evidence (from RCTs directly comparing treatments of interest, where treatment A is compared to treatment B) and indirect evidence (from RCTs comparing treatments of interest with a common comparator; for example, if treatments A and B have been compared with a common treatment, C, in two different sets of trials [A versus C and B versus C], then the relative effectiveness between A and B can be estimated indirectly via the common comparator C), to calculate a mixed effect estimate as the weighted average of the two, as shown in Fig. 1 [7]. Such a technique can improve the precision of the estimate (compared with direct evidence alone), and also allows estimation of the comparative efficacy of two active treatments, even if no studies directly compare them. When performing and interpreting a network meta-analysis, it is critical that included trials be conceptually similar in terms of key factors which determine treatment efficacy, including patients (similar disease characteristics and severity, prior failure of therapies), included interventions (standard dose and schedule), co-interventions (which can influence treatment efficacy) and outcome assessment (similar reporting indices, and definitions for outcome, assessed in standard manner). There are two main statistical approaches in performing a network meta-analysis: Bayesian and Frequentist methods [8]. Bayesian models utilize the deviance information criterion to compare models and assess overall goodness of fit whereas non-Bayesian models often use hypothesis tests based on deviance statistics [8]. Regardless of the approach that is selected, it is recommended that the model fits the data well [9]. Such indirect comparisons of competing interventions, adjusted by a common control, such as placebo, can partially take account of prognostic characteristics of patients in different trials, and may inform patients, clinicians, policymakers and other stakeholders regarding the optimal use of these agents in clinical practice.

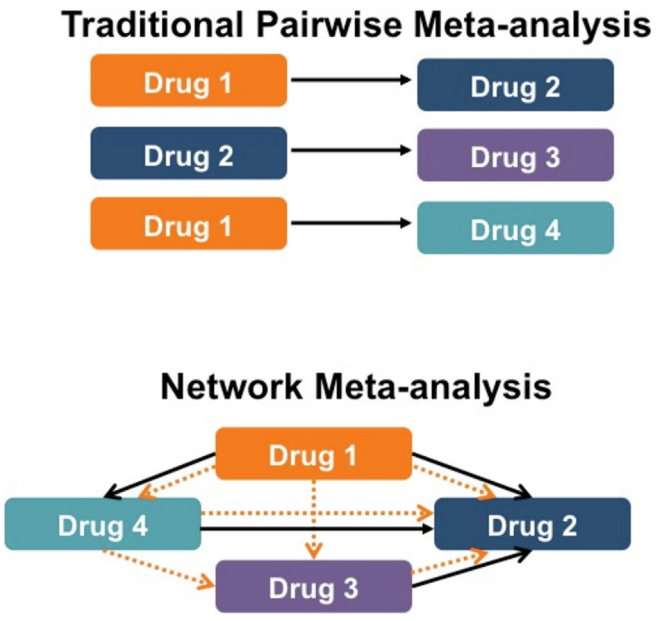

Fig. 1. Differences between traditional meta-analyses and network meta-analyses. In traditional pairwise meta-analysis, only head-to-head direct comparisons can be analyzed. In contrast, network meta-analyses involve the simultaneous analysis of direct evidence (from RCTs directly comparing treatments of interest, indicated by solid arrows) and indirect evidence (from RCTs comparing treatments of interest with a common comparator, indicated by dotted arrows), to calculate a mixed effect estimate as the weighted average of the two.

Comparative efficacy of biologic agents in Crohn's disease based on network meta-analysis

One of the key tenets in indirect treatment comparisons at a study-level is ensuring comparability of participants in trials. In the treatment of luminal CD, one of the strongest and consistent predictor of response to biologic therapy is prior exposure to anti-TNF agents. Most published network meta-analyses in patients with CD have either broadly included all patients in trials regardless of biologic-exposure status, or have focused on comparative efficacy of different agents in a biologic-naïve patient population [10–12]. However, in a recent network meta-analysis, updated with the inclusion of all FDA-approved biologic agents for CD, we separately analyzed the efficacy of first- and second-line biologics for induction of remission, and for all agents for maintenance of remission among patients with clinical response to induction therapy [13].

First-line biologic agents for induction of remission

Eight RCTs including 1458 biologic-naïve patients with moderate-severe CD [14–21], treated with infliximab (2 trials), adalimumab (2 trials), certolizumab pegol (1 trial), vedolizumab (2 trials) and ustekinumab (1 trial) were included. Clinical remission was uniformly assessed based on standard definition of Crohn's Disease Activity Index (CDAI) < 150, between weeks 4 and 12. Endoscopic remission was reported as an outcome in only two trials (Lemann et al., [21] CERTIFI [29]), and that too for a small subset of patients (20/115 patients in Lemann et al.; 31/263 patients in CERTIFI). Patient-reported outcomes were assessed indirectly using quality of life indices (most commonly using inflammatory bowel disease questionnaire), and this outcome was not stratified by prior exposure to biologic agents. No trials evaluating standard FDA-approved induction dosing of infliximab were identified – the study by Targan et al. included a single dose of 5 mg/kg intravenously at week 0 [16], and in the study by Lemann et al. all patients were on concomitant azathioprine [15].

Overall, on network meta-analysis using frequentist approach and GRADE methodology for assessing quality of evidence, as compared to placebo, there was moderate confidence in estimates supporting the use of infliximab, adalimumab, certolizumab pegol, vedolizumab and ustekinumab for induction of clinical remission in biologic-naïve patients. On indirect comparison of active interventions, there was moderate confidence in estimates supporting the use of infliximab over certolizumab pegol (OR, 4.33; 95% CI, 1.83–10.27), and low confidence in estimates supporting its use over vedolizumab (OR, 2.20; 95% CI, 0.79–6.07) and ustekinumab (OR, 2.14; 95% CI, 0.89–5.15); there was moderate confidence in estimates supporting the use of ustekinumab (OR, 2.02; 95% CI, 1.09–3.75) and adalimumab (OR, 2.97; 95% CI, 1.16–6.70) over certolizumab pegol. There was no significant difference in the efficacy of ustekinumab and vedolizumab as a first-line agent. Overall, infliximab (SUCRA, 0.93) and adalimumab (SUCRA, 0.75) were ranked highest, followed by ustekinumab (SUCRA, 0.56), vedolizumab (SUCRA, 0.55) and certolizumab pegol (SUCRA, 0.20) for inducing clinical remission in biologic-naïve patients with moderate-severe CD. With a pooled placebo rate of achieving remission of 20% (range, 10.2–28.0) in included trials, we estimate that 59.6%, 48.7%, 40.7%, 40.2% and 25.4% of infliximab-, adalimumab-, ustekinumab-, vedolizumab- and cerrtolizumab pegol-treated patients, respectively, may be expected to achieve remission with induction therapy (Fig. 2).

Second-line biologic agents for induction of remission (in patients with prior failure of Anti-TNF agents)

Six RCTs including 1606 patients with moderate-severe CD with prior exposure to anti-TNF agents were identified [17–19,21–23].

Agent	Induction of Clinical Remission	Maintenance of Clinical Remission	GRADE Quality of Evidence
Placebo	15.9%	21.6%	-
Infliximab	52.7	45.7	⊕⊕◯◯ [Low]
Adalimumab	41.8	57.4	⊕⊕⊕◯ [Moderate]
Certolizumab pegol	20.5	38.3	⊕⊕◯◯ [Low]
Vedolizumab	33.7	37.7	⊕⊕⊕◯ [Moderate]
Ustekinumab	34.2	35.8	⊕⊕⊕◯ [Moderate]

Fig. 2. Estimated probability of achieving outcome (induction of clinical remission in biologic-naïve patients and maintenance of clinical remission in patients with response to induction therapy) derived from network meta-analysis, assuming pooled placebo rates across clinical trials of biologic agents in patients with moderate-severe Crohn's disease.

These included thee trials conducted exclusively in patients with prior exposure to anti-TNF agents (1 trial of adalimumab [22], 2 of ustekinumab [18,23]), and two subgroup analyses of phase III trials (1 each of adalimumab and vedolizumab) [17,19]; one trial of vedolizumab (GEMINI-III) included 75% patients with prior exposure to anti-TNF agents [21]. There were no trials of infliximab or certolizumab pegol in patients with prior exposure to anti-TNF, that met inclusion criteria. Among patients with prior anti-TNF exposure, the median (range) of patients discontinuing prior anti-TNF therapy due to non-response/inadequate response was 36.5% (28–55%). One trial of adalimumab (GAIN) selectively included only patients with prior response or intolerance to infliximab, and excluded patients with non-response to infliximab [22].

On network meta-analysis, compared to placebo, moderate confidence in estimates supported a moderate effect size of ustekinumab (OR, 2.58; 95% CI, 1.50–4.44) for induction of clinical remission in patients with prior exposure to anti-TNF agents. In contrast, despite a similar summary estimate, only low quality evidence supported the use of adalimumab (OR, 3.57; 95% CI, 1.66–7.65), with evidence being rated down for indirectness due to selective inclusion of patients with prior response or intolerance to anti-TNF agents. There was low confidence in estimates supporting a small effect size of vedolizumab (OR, 1.53; 95% CI, 0.77–3.06) for induction of clinical remission over placebo. On indirect comparison of active interventions, There was very low confidence in all estimates due to differences in patients included in trials of adalimumab and ustekinumab or vedolizumab. No agent was clearly superior to others. Overall, adalimumab (SUCRA, 0.91) and ustekinumab (SUCRA, 0.71) were ranked higher than vedolizumab (SUCRA, 0.35) for inducing clinical remission in patients with moderate-severe CD with prior exposure to anti-TNF agents. With a pooled placebo rate of achieving remission of 8.5% (range, 7.3–9.7) in included trials, we estimated that 19.3%, 24.9% and 12.4% and of ustekinumab-, adalimumab- and vedolizumab-treated patients would achieve induction of remission.

Comparative efficacy of biologic agents for maintenance of remission

Overall, 9 RCTs including 1854 patients with moderate-severe CD [17–19,23–28], treated with infliximab (2 trials), adalimumab (3 trials), certolizumab pegol (1 trial), vedolizumab (1 trial) and ustekinumab (2 trials) were included. All trials re-randomized patients who responded to induction therapy, regardless of prior anti-TNF-exposure status.

On network meta-analysis, compared to placebo, moderate confidence in estimates supported a large effect size for adalimumab, and a moderate effect size of infliximab, certolizumab pegol, ustekinumab and vedolizumab for maintenance of clinical remission in patients who had responded to induction therapy with the same medication. On indirect comparison of active interventions, moderate quality evidence supported moderate benefit of adalimumab over certolizumab pegol (OR, 1.97; 95% CI, 1.04–3.73) and ustekinumab (OR, 2.19; 95% CI, 1.15–4.16) for maintenance of remission. Overall, adalimumab (SUCRA, 0.97) was ranked highest, followed by infliximab (SUCRA, 0.68), vedolizumab (SUCRA, 0.52), certolizumab pegol (SUCRA, 0.48) and ustekinumab (SUCRA, 0.36) for maintaining clinical remission. With a pooled placebo rate of maintaining remission of 24% (range, 14.3–32.8) in included trials, we estimate that 58.3%, 47.5%, 42.3%, 41.5% and 38.9% of adalimumab-, infliximab-, vedolizumab-, certolizumab pegol and ustekinumab-treated patients may be expected to maintain remission over 12 months (Fig. 2).

Comparative safety of biologic agents in Crohn's disease based on network meta-analysis

In contrast to comparative efficacy, comparative safety of agents is more difficult to define based on clinical trials and subsequent network meta-analysis due to rare events, particularly in short-term trials of induction therapy. Moreover, trials do not stratify safety events by prior biologic-exposure status; open-label extension studies have suggested an association between prior anti-TNF exposure and increased risk of serious infections in patients treated with vedolizumab. In a network meta-analysis of 9 RCTs of maintenance therapy with biologic agents, among patients with clinical response to induction therapy with index agent, we did not observe any significant difference in the incidence of serious adverse events between active biologic therapy and placebo. Ustekinumab (SUCRA, 0.72) and adalimumab (SUCRA, 0.68) were ranked highest (had lowest risk), followed certolizumab pegol (SUCRA, 0.53), infliximab (SUCRA, 0.42) and vedolizumab (SUCRA, 0.25), in terms of risk of serious adverse events. In these trials, rate of serious infections was low, and was not deemed amenable to network meta-analysis; hence, risk of overall infections was used a surrogate safety outcome. On network meta-analysis, rate of any infection was higher in adalimumab-treated patients compared to placebo (OR, 1.49; 95% CI, 1.06–2.07) and infliximab (OR, 1.78; 95% CI, 1.04–3.03). Overall, amongst active interventions, infliximab (SUCRA, 0.83) and ustekinumab (SUCRA, 0.71) were rated highest (had lowest risk), followed by vedolizumab (SUCRA, 0.47), adalimumab (SUCRA, 0.22) and certolizumab pegol (SUCRA, 0.12) for risk of any infections.

In another network meta-analysis of 49 RCTs of biologic agents in inflammatory bowel diseases, there was no significant difference between anti-TNF agents and anti-integrin agents (serious infections: OR, 1.04; 95% CI, 0.60–1.78; opportunistic infections: OR, 0.95; 95% CI, 0.28–3.28; TB: OR, 0.80; 95% CI, 0.02–39.1; any infection: OR, 1.06; 95% CI, 0.90–1.26; and malignancies: OR, 0.87; 95% CI, 0.26–2.88) [29].

Limitations of network meta-analysis

Unfortunately, there were no head-to-head trials comparing different biologic agents for the management of CD, and all comparative efficacy and safety analyses were based on indirect comparisons. Although network meta-analyses have the potential to provide more precise results than those only based on direct evidence, the incremental gain may reliably occur only when at least two head-to-head studies are available and treatments are well connected [30].

Most trials in patients with CD do not consistently report endoscopic outcomes. There were subtle differences in timing of outcomes assessment in induction studies, and time-dependent

variability in efficacy could not be analyzed in detail. While corticosteroid-free remission may be a more relevant clinical endpoint, this was inconsistently reported in included trials. Using trials of maintenance therapy to assess safety of therapies may be biased, due to selective inclusion of patients who have demonstrated tolerability in the induction phases. Findings from these indirect comparisons need to be interpreted with caution since these trials did not always mirror clinical practice. For example, current trials did not utilize therapeutic drug monitoring to understand the plausible mechanism of failure of initial biologic intervention. Given potential differences in efficacy of second line interventions depending on underlying reason for discontinuation of prior anti-TNF therapy (primary non-response vs. secondary loss of response vs. intolerance), such information may be useful in making clinical treatment decisions in conjunction with findings from our analyses [31,32]. In these analyses, data on how many prior anti-TNF agents to which a patient had been exposed was not consistently reported. It is conceivable (and likely) that since anti-TNF agents were the first class of medications to be approved, patients treated with adalimumab or certolizumab pegol in clinical trials generally had exposure to only a single anti-TNF agent; in contrast, in subsequent trials of vedolizumab and ustekinumab, a significant proportion of patients may have been exposed to two or more biologic agents prior to clinical trial intervention, and may inherently be difficult to treat.

Implications for clinical practice

Integrating findings from this meta-analysis and other studies, current evidence suggests that infliximab or adalimumab may be preferred first-line agents for moderate-severe CD, from an efficacy perspective. However, ustekinumab and vedolizumab are also effective in this patient population, and may offer a superior safety profile. In patients who fail anti-TNF agents, particularly those with primary non-response, evidence suggests that ustekinumab may be most efficacious; in a subset of patients with secondary loss of response or intolerance to an anti-TNF agent, adalimumab would be a reasonable alternative. However, besides quality of evidence, several other factors including a balance of risk-benefit profile, clinical judgment and experience of the treating physicians, values and preferences of patients as well as costs/resources available are important to facilitate shared decision-making, in developing a personalized treatment strategy for each patient, and shape healthcare policy on positioning different agents. Evidence on comparative efficacy is significantly limited, being based on indirect comparisons alone. Pragmatic head-to-head trials in both biologic-naïve and biologic-exposed patients are warranted to optimally inform relative positioning of newly available agents in clinical practice.

Practice points

- Network meta-analysis which combine direct and indirect treatment comparisons may be useful in informing comparative efficacy and safety of therapies in patients with moderate to severe Crohn's disease
- Based on network meta-analysis, infliximab or adalimumab may be preferred first-line agents for moderate-severe CD, from an efficacy perspective. However, ustekinumab and vedolizumab are also effective in this patient population, and may offer a superior safety profile
- In patients who fail anti-TNF agents, particularly those with primary non-response, evidence suggests that ustekinumab may be most efficacious; in a subset of patients with secondary loss of response or intolerance to an anti-TNF agent, adalimumab would be a reasonable alternative.

Research agenda

- Pragmatic head-to-head trials in both biologic-naïve and biologic-exposed patients are warranted to optimally inform relative positioning of newly available agents in clinical practice.
- Long-term data on comparative safety incorporating patient- and disease-related factors are warranted to inform safety of therapies

Conflicts of interest

Dr. Singh has received research support from Pfizer and AbbVie, consulting fees from Takeda within the last 12 months.

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Author contribution

Siddharth Singh conceived the idea, acquired and assimilated data, wrote and finalized the manuscript.

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