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A Review of the Network Meta-Analysis and Psoriasis Management

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Introduction

Clinical trials are the gold standard for evaluating safety and efficacy of new therapeutics and guiding our treatment decisions. However, with the rapid development of new therapeutics in dermatology, we increasingly need additional tools to inform our overall approach to patient care. Previously, meta-analyses were used to evaluate the results of several randomized controlled trials (RCTs). However, they were limited to comparing 2 interventions at a time. Recently, network meta-analysis (NMA) has emerged as a new tool allowing simultaneous comparison of 3 or more interventions by incorporating both direct comparisons from head-to-head trials and indirect evidence drawn from studies that share a common comparator (e.g. placebo or active control).

What is a Network Meta-Analysis?

An NMA is a statistical method that allows the comparison of multiple interventions, even when some of those comparisons have not been directly studied in head-to-head RCTs. In an NMA, each treatment is represented as a node in a network graph, with edges between nodes indicating the presence of direct evidence from clinical studies. When a direct comparison is missing, the common comparator (e.g. placebo) enables an indirect comparison by mathematically combining treatment effects from studies that include that

common treatment **(Figure 1)**. This "indirect evidence" is then combined with any available direct evidence using advanced statistical models, resulting in a network estimate that ideally has improved precision compared to estimates from individual pairwise comparisons.

What are the Assumptions Within a Network Meta-Analysis?

There are 3 main assumptions for the NMA: similarity (homogeneity), transitivity, and consistency (coherence).[1]

Similarity implies that studies comparing the same treatments (e.g. all studies assessing interleukin [IL]-17 versus placebo) should be clinically and methodologically similar. For example, psoriasis clinical trials generally include comparable eligibility criteria (e.g. Psoriasis Area and Severity Index [PASI], Investigator's Global Assessment [IGA]), although the populations included in each individual study may differ in terms of average age, gender, ethnicity, comorbidities, and other factors. When studies are similar, it is more reasonable to assume that any differences in outcomes are due to the treatments themselves rather than variations in study design or patient populations. If there is substantial heterogeneity among these studies, combining them might introduce bias, potentially misleading the overall meta-analytic conclusions.

Transitivity shares the concept of similarity but extends it to indirect comparisons.[2] Using the above example, it can be assumed that: a) if outcomes for an IL-17 agent are similar across studies comparing it with placebo, and b) the same is true for studies comparing an IL-23 agent with placebo, then c) it is valid to indirectly compare outcomes between the IL-17 and IL-23 agents. Consequently, if studies with 1 agent predominately recruit younger patients and those with another agent recruit older patients, then the indirect comparison of the 2 treatments can be confounded by age, leading to inaccurate conclusions.

Finally, consistency requires that direct and indirect evidence are in statistical agreement when both types of evidence are available. If, for example, there are studies that directly compare IL-17 and IL-23 agents, and there is also an indirect comparison derived from studies comparing IL-17 to placebo and IL-23 to placebo, the results from these 2 approaches should be congruent.

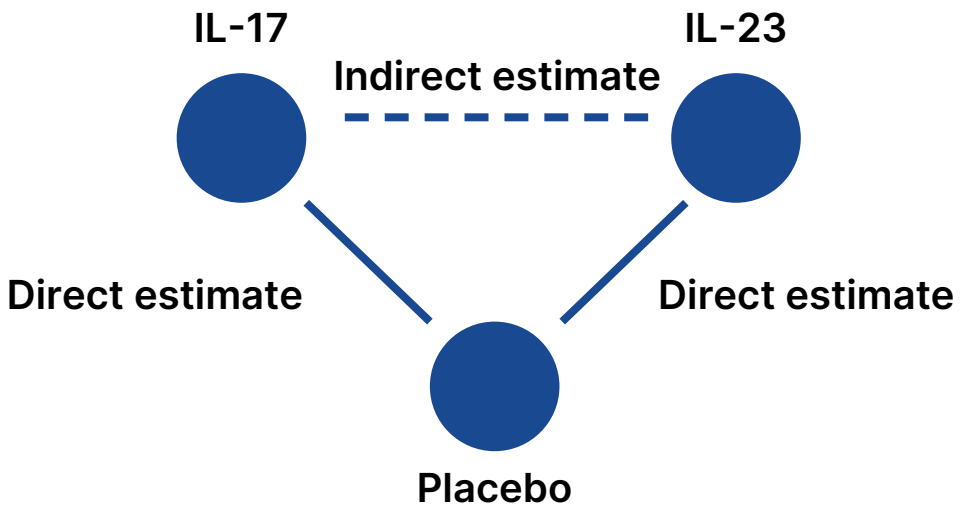

Figure 1. Example: Data on the efficacy of an interleukin (IL)-17 agent versus placebo is available (direct evidence) and data on the efficacy of an IL-23 agent compared to placebo is also available (direct evidence). The NMA can estimate the relative effectiveness of treatment with the IL-17 agent versus the IL-23 agent, even if no head-to-head study has been conducted to compare them directly (indirect estimate); *courtesy of Anastasiya Muntyanu, MD*

Advantages of the Network Meta-Analysis

One of the major strengths of NMA is its ability to provide a comprehensive comparison of the efficacy and safety of all available treatments in one analysis, even when direct head-to-head comparisons are lacking.[3,4] Additionally, NMA can rank the available treatments, making it a valuable clinical decision-making tool, especially in fields with multiple treatment options but limited direct evidence. Lastly, NMAs can also facilitate the evaluation of relative treatment safety, which is useful when weighing the benefits and risks of treatment alternatives.

Disadvantages of the Network Meta-Analysis

One of the primary challenges of NMA is its reliance on several critical assumptions, such as similarity, transitivity, and consistency. If these assumptions are not met, the validity of the NMA results may be compromised. This approach also involves complex statistical modeling, including Bayesian frameworks and sensitivity analyses, to ensure the robustness of the results and the proper integration of direct and indirect evidence.[5]

While NMAs can produce treatment rankings, these should be interpreted with caution.[6] The ranking probabilities, or surface under the cumulative ranking curve (SUCRA) values, are influenced by the quality and quantity of the underlying data, and they may sometimes overstate differences in clinical effectiveness. Small differences in treatment effects might result in large variations in ranking, particularly if the confidence intervals around each estimate are wide. Additionally, NMA does not consider the associated precision or certainty of the studies. Hence, interventions supported by small, low-quality trials that report large differences in treatment effect can rank highly in an NMA.[7] This has the potential to mislead clinicians if the rankings are not considered alongside measures of uncertainty.

Publication bias is another concern for NMAs. Similar to traditional meta-analyses, NMAs are subject to biases arising from the selective publication of studies.[8] However, when multiple interventions and indirect comparisons are involved, the influence of unpublished or selectively reported data may be even more pronounced. In addition, when the evidence network includes a limited number of studies for specific comparisons, the statistical power to detect inconsistency or heterogeneity is reduced, making it difficult to validate the core assumptions of the analysis.

Additionally, NMAs require that all treatments be "jointly randomizable," meaning that the clinical scenario must make it plausible to consider a trial that includes all the interventions under review. In practice, this is not always the case. When treatments are administered in distinct patient populations or under very different conditions, the indirect comparisons may be less meaningful or even invalid. For instance, patients with inflammatory bowel disease are more likely to be treated with an IL-23 or TNF-α inhibitor rather than an IL-17 inhibitor.

Another important limitation of NMAs is that they rely solely on RCT data, which may not fully represent real-world treatment experiences. RCTs are conducted in highly controlled environments that often have strict inclusion and exclusion criteria, leading to study populations that may not reflect the broader, more diverse group of patients seen in routine clinical practice. This limitation can lead to discrepancies when translating NMA findings into real-world clinical decisions.

Finally, there is significant redundancy in the literature on NMAs. Specifically, a 2022 study evaluated 47 redundant NMAs on psoriasis treatment,[9] and found that only 2 (4%) included all available treatments. Both efficacy and safety were considered in 30% of the NMAs, while 11% assessed both short- and long-term outcomes. Confidence in the results was critically low for 83% of the NMAs and only 21.3% registered a protocol. Almost 50% of NMAs did not consider critical limitations such as heterogeneity (considered in only 32%) or consistency (considered in 66%). Hence, numerous NMAs have varying methodologies, inclusion criteria, and confidence in their results, which can confuse interpretation. Clinicians need to interpret NMAs with caution

to identify the most reliable and comprehensive evidence.[9]

Network Meta-Analysis in Psoriasis

In the field of dermatology, particularly for psoriasis treatment, NMAs have gained increasing attention as a means of comparing multiple systemic and topical treatments. Currently, in North America, there are 12 biologic agents as well as 2 targeted oral treatments available, in addition to traditional therapies including methotrexate, acitretin, cyclosporine, among others. Given the abundance of therapeutic choices, clinicians and guideline developers often turn to NMAs to make sense of the complex treatment landscape.

In 2021, a review aimed to summarize the existing NMAs for psoriasis therapeutics, including data on 27 NMAs published up until June 2020.[10] Only 8 of those NMAs (29.6%) were documented in the PROSPERO registry, and only 17 (63%) reported following the PRISMA criteria. The most frequently used outcomes were the PASI 75 (n = 25), PASI 90 (n = 24), and the Dermatology Life Quality Index (n = 10). Most NMAs reported short term data up to weeks 10–16 (n = 25) but long-term follow-up data (weeks 48–56, n = 4) were rarely reported. Despite some variations in the findings based on the included studies and year of publication, there was high concordance in the rankings of psoriasis therapeutics based on the PASI 75. While the similarity of these results is promising, most studies did not provide detailed information on quality criteria and assumptions, and the PROSPERO registry criteria were not followed. Consequently, greater standardization of NMA methodology and reporting is required.

A Cochrane Database of systematic reviews recently published a comprehensive NMA including 179 RCTs with 62,339 randomized participants. The analysis was comprised of 317 direct comparisons among 37 different drug dosages, 20 different drugs, 6 different drug classes, and placebo.[11] Of the patients included, 67.2% were males with a mean age of 44.6 years and a mean baseline PASI score of 20.4

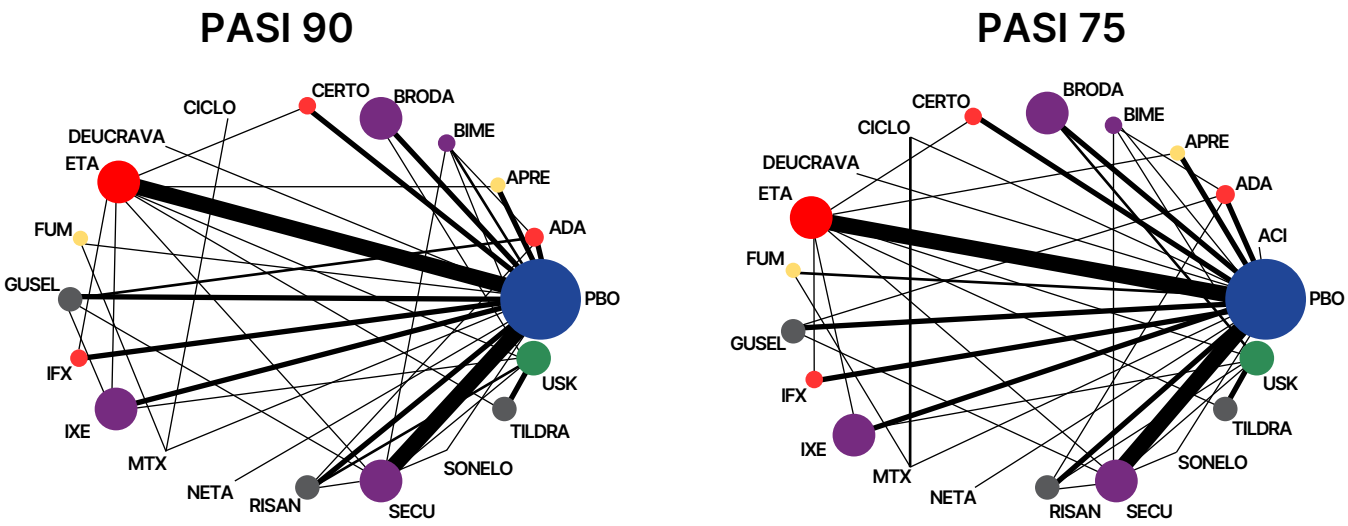

Figure 2. Adapted from Sbidian et al.[11] The size of the nodes is proportional to the total number of participants allocated to each intervention and the thickness of the lines is proportional to the number of studies evaluating each direct comparison.

Abbreviations: ACI: acitretin; **ADA:** adalimumab; **APRE:** apremilast; **BIME:** bimekizumab; **BRODA:** brodalumab; **CERTO:** certolizumab; **CICLO:** ciclosporin; **DEUCRAVA:** deucravacitinib; **ETA:** etanercept; **FUM:** fumaric acid; **IFX:** infliximab; **IXE:** ixekizumab; **GUSEL:** guselkumab; **MTX:** methotrexate; **NETA:** netakimab; **PBO:** placebo; **RISAN:** risankizumab; **SECU:** secukinumab; **SONELO:** sonelokimab; **TILDRA:** tildrakizumab; **USK:** ustekinumab; **AE:** adverse events; **PASI:** Psoriasis Area and Severity Index; **PGA:** Physician Global Assessment; **QoL:** quality of life; **SAE:** serious adverse events

(range: 9.5–39). Seventy-two trials compared the therapeutic in question to a placebo, 34 studies compared therapeutics in head-to-head trials, and 18 included both a placebo and an active comparator. Depending on the RCT, outcomes were assessed over a period of 8–24 weeks. Broadly, at a drug class level, all interventions, including traditional systemic agents, had a higher proportion of patients achieving PASI 90 compared to placebo. In addition, all biologic agents outperformed the traditional systemic treatments. The most effective therapeutics for patients with moderate-to-severe psoriasis, based on PASI 90 scores and compared to placebo, were (in SUCRA rank order, all high-certainty evidence): infliximab (risk ratio [RR] 49.16, 95% confidence interval [CI] [20.49-117.95]), bimekizumab (RR 27.86, 95% CI [23.56-32.94]), ixekizumab (RR 27.35, 95% CI [23.15-32.29]), risankizumab (RR 26.16, 95% CI [22.03-31.07]).

There were no significant differences between any of the interventions and the placebo for the risk of serious adverse events. However, given the short timeline (up to 24 weeks), no long-term data on efficacy and safety were assessed. Additionally, there were a limited number of studies for some of the interventions. Clinical trials often differ from real-world evidence, and in this study the young mean age (44.6 years) and high level of disease severity (PASI 20.4 at baseline) may not reflect the patients seen in daily clinical practice.

In a study by Armstrong et al., 86 RCTs with 34,476 patients were included.[12] The base case model demonstrated the following IL-17 and IL-23 agents as the most effective treatments across all PASI levels: bimekizumab 320 mg, risankizumab 150 mg, ixekizumab 80 mg, brodalumab 210 mg, guselkumab 100 mg, and secukinumab 300 mg. At 10–16 weeks, bimekizumab had the highest probability of achieving PASI 75 (92.3%), PASI 90 (84.0%) and PASI 100 (57.8%). For PASI 90, risankizumab ranked second and brodalumab third. Bimekizumab was also found to have the lower number needed to treat to achieve all PASI levels compared with placebo, followed by risankizumab 150 mg, ixekizumab 80 mg and brodalumab 210 mg.

Few NMAs assessed long-term efficacy and safety data.[13] In 2021 Armstrong et al. conducted an NMA that considered 14 RCTs and the PASI responses at all levels up to weeks 48–56. The highest-ranking therapies in terms of efficacy were risankizumab (SUCRA: 98.5%) and bimekizumab (83.8% for dosing every 4 weeks, 72.7% for dosing every 4 weeks then every 8 weeks). The PASI response rates were comparable between risankizumab and the 2 bimekizumab regimens. In the safety NMAs, which included 8 RCTs, risankizumab had a significantly lower rate of any adverse events compared to bimekizumab, ustekinumab, and secukinumab. Bimekizumab was found to have a higher rate of candidal infections compared to other agents.

Discussion

NMA represents a significant advancement in evidence synthesis methodology. Its ability to integrate multiple sources of evidence and provide treatment rankings based on PASI scores is especially appealing in complex therapeutic areas such as psoriasis. These findings can help guide decision-making and inform treatment guidelines, ensuring that patients receive therapies that have been demonstrated to be both effective and safe.

Nevertheless, the disadvantages of NMA cannot be overlooked. The accuracy of an NMA depends critically on the assumptions of similarity, transitivity, and consistency. If these are not met, indirect comparisons may be unreliable. In the context of psoriasis, variations in study design—such as differences in baseline disease severity or prior treatment exposure—can pose significant challenges to maintaining these assumptions. Clinicians should interpret rankings with caution and consider the absolute differences in efficacy and the precision of the estimates.

Conclusion

By integrating both direct and indirect evidence, NMA provides a comprehensive picture of treatment effectiveness and safety, thereby supporting more informed clinical decision-making. In dermatology, particularly in managing psoriasis, NMAs have played a crucial role in comparing a wide range of systemic therapies and informing treatment guidelines. Future advances in statistical methods will likely address some of the current limitations of NMAs. As these methods become more accessible and widely adopted, NMAs will likely play an even greater role in shaping clinical practice across multiple disciplines.

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