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HOW NETWORK META-ANALYSIS INFORMS SYSTEMIC TREATMENTS FOR ATOPIC DERMATITIS

What is Network Meta-analysis and How does it Work?

Network meta-analysis (NMA) is an increasingly popular statistical technique employed in clinical research. NMA is extremely appealing because it allows clinicians to compare a wide range of treatments used for the same condition in a single analysis. This is helpful in the clinic setting when deciding between treatment options for a patient with moderate-to-severe atopic dermatitis (AD). It allows us to help patients understand the relative efficacy of various medications.

In an ideal world, randomized clinical trials would be conducted comparing all possible relevant treatment options. In reality, that would not be practical or feasible, particularly in a rapidly expanding therapeutic field. While there are only a few systemic treatment options currently available for AD, that number is set to increase steadily over time. We only need to look to psoriasis and the myriad treatments approved over the last two decades to understand that planning head-to-head clinical studies for all comparisons is not realistic. NMA helps us circumvent this problem.

NMA is different than a traditional meta-analysis which can only report how pairs of treatments compare with each other, and can only compare treatments that have been compared together in head-to-head trials. To circumvent the problem of not having head-to-head studies for all of the treatment comparisons in which we're interested, NMA combines direct data (head-to-head trial data) and indirect data (using connections between common comparators), as illustrated in **Figure 1**.[1]

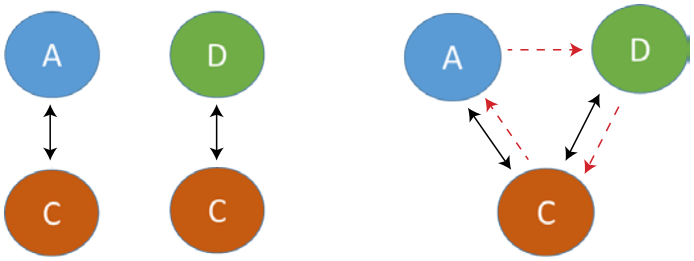

Figure 1. *Direct data vs indirect data; adapted from Watt et al, 2019*

Hypothetical treatments A and D have each been compared in a trial against treatment C (solid arrows) but have never been compared with each other. NMA uses treatment C as a connector (dashed red arrows) to enable comparisons between treatments A and D.

For example, abrocitinib and upadacitinib, two Janus kinase (JAK) inhibitors, have never been compared head-to-head in a trial to treat AD. However, they have each been compared in trials vs placebo and vs dupilumab.[2-5] We can use those connections to estimate how abrocitinib and upadacitinib compare with each other. For AD treatments, we can build a network, taking advantage primarily of common connections with placebo trial arms; this enables us to compare most available systemic immunomodulatory treatments.

How can the Results be Trusted?

Several key assumptions underpin NMA. Unfortunately, each of these is violated to some extent in all NMAs. The key, therefore, is to assess how important and egregious those violations are.

Assumption 1. Transitivity. In my opinion, this is the most important assumption. The transitivity assumption stipulates that for trials to be included in a network with each other, they must be similar. They should be similar in design, including their inclusion criteria, background treatment, timelines, which outcomes are assessed and how they are analyzed and reported. The participants enrolled should be similar in terms of important demographic and clinical features such as age, gender and disease severity. Pose the question: "Could any patient randomized in one study within a network have been randomized to any of the other studies in this same network?"[1] If studies are very dissimilar in terms of their design or population, that is problematic.

Assumption 2. Coherence. NMA lets us make comparisons between treatments that have never been tested head-to-head. However, when a head-to-head trial has been conducted, we need to take it seriously. When assessing coherence, we compare the results generated by the NMA with the results of any existing head-to-head trials. If the results that rely on indirect comparisons are materially different than direct evidence from a well-designed trial, that is problematic. Why would anyone believe the NMA results?

Assumption 3. Network connectivity. This is the most obvious assumption, and I often take it for granted. For a treatment to be included in a network, and therefore compared with other treatments in the network, that treatment must have been tested in at least one trial with another treatment or placebo that is also connected. As much as I would like to include mycophenolate mofetil in an NMA for AD, there aren't any valid connections to make with the other treatments; therefore, it cannot be included in a network.

Living NMA for Atopic Dermatitis

To provide current comparative evidence for systemic immunomodulatory treatments for AD, my colleagues and I established and maintain a living systematic review and NMA.[6-8] We update the systematic review every four months by searching databases such as Medline and clinical trials registries such as ClinicalTrials.gov. We include randomized clinical trials of systemic immunomodulatory treatments for AD with at least eight weeks of active treatment. We extract the outcomes data included in the Harmonizing Outcome Measures for Eczema (HOME) core outcome set: Eczema Area and Severity Index (EASI); Patient Oriented Eczema Measure (POEM); Peak Pruritus Numeric Rating Scale (PP-NRS); and Dermatology Life Quality Index (DLQI).[9] We then perform NMA for each of those outcomes for trials that include adult participants; we intend to conduct analyses for children as more data accumulates.

In our first publication in 2020,[7] we were able to use a statistical measure called standardized mean differences to compare older medications (methotrexate, cyclosporine and azathioprine) with dupilumab, which was the only targeted agent approved at the time. We were able to build a network and conduct a NMA, with the finding that cyclosporine 4-5 mg/kg/day, and dupilumab, may be more efficacious up to 16 weeks of treatment than methotrexate and azathioprine. However, we were unable to draw firm conclusions from this as the trials for the older medications were relatively small.

By the time of our first major update in 2022,[8] numerous additional trials had been published and three new medications had been approved in North America: the JAK inhibitors abrocitinib and upadacitinib, and a biologic, tralokinumab. Each of these newly-approved medications, along with dupilumab, had large Phase 3 clinical trial programs; as a result, there was sufficient data to make robust comparisons between them for adult participants. The trial results revealed that, up to 16 weeks of treatment, higher doses of abrocitinib and upadacitinib were more efficacious than dupilumab and the lower doses of abrocitinib and upadacitinib **(Figure 2)**. We also found that tralokinumab was less efficacious than dupilumab. It should be noted, however, that all of these comparisons were within published minimal clinically important difference (MCID) ranges:[10] the differences between the medications in terms of efficacy were minor.

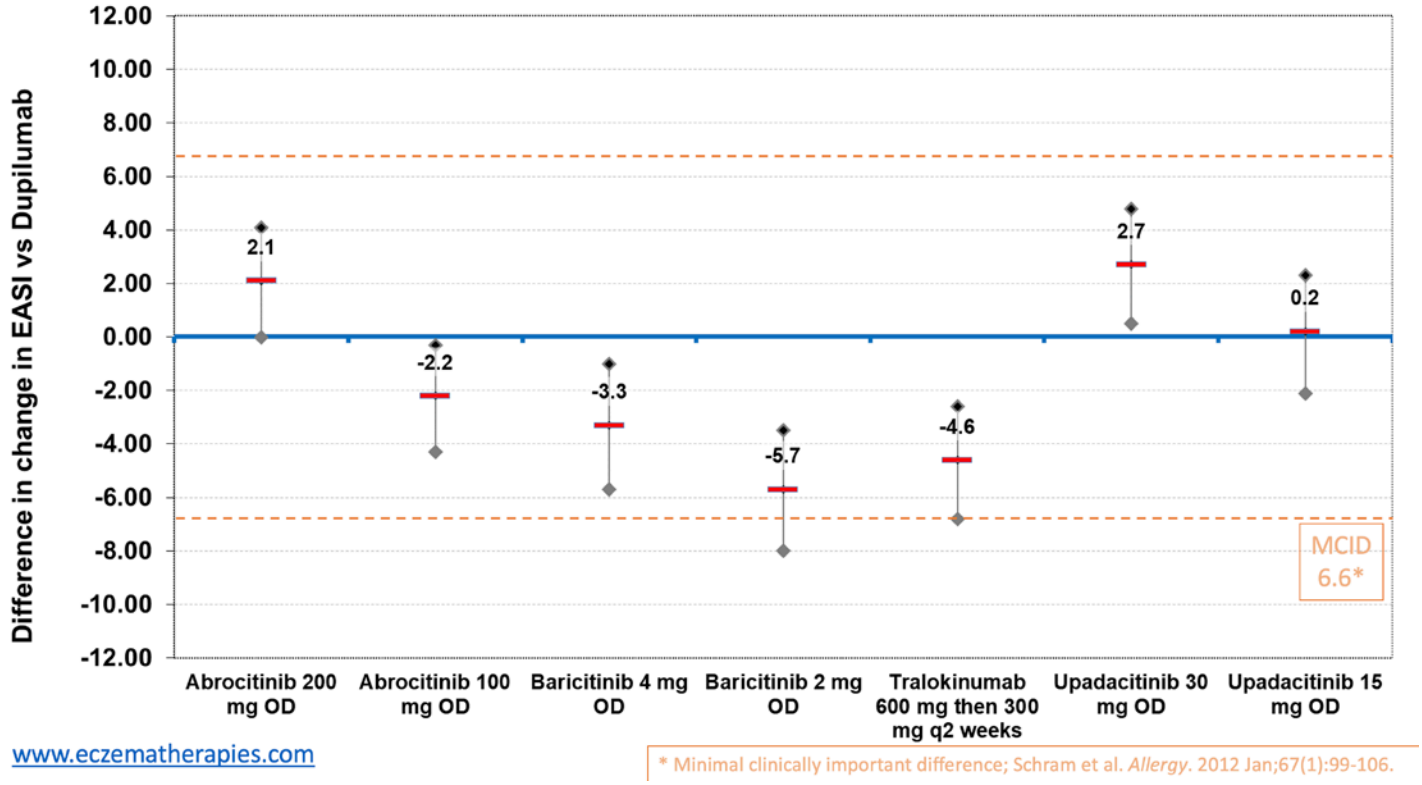

Figure 2. *Comparison of systemic immunomodulatory treatments for AD; adapted from Drucker et al, 2022*
NMA results for approved JAK inhibitors and biologics vs dupilumab up to 16 weeks of treatment among adults. Results are on the EASI scale; the error bars represent credible intervals. Dupilumab is represented by the blue line. Results appearing above the blue line indicates greater treatment efficacy. The dashed orange lines represent the MCID.[10]

Subsequent to the 2022 update, we have continued to maintain an up-to-date analysis, posting results to our website, www.EczemaTherapies.com/research. In addition, EczemaTherapies.com features content to assist patients and clinicians in interpreting the results.[11] It has been reassuring to note that the results of several head-to-head trials have been published[2,4] and that our NMA results are consistent with those of head-to-head trials. We are also reassured that clinical trials for systemic AD treatments are generally conducted with similar methods and participants. One key difference between various trials is that some of these allow participants to use concomitant topical inflammatory agents such as topical steroids, while others do not.[12] We conduct sensitivity analyses separately for those groups of trials and have been reassured that the results are similar.

How can these NMA results be implemented in treatment decision-making?

Treatment decisions for individuals with severe AD should be made using shared decision-making practices between patients and clinicians. The NMA results can be used to inform those discussions by providing both parties an understanding of how the medications rate in terms of their relative efficacy.

However, efficacy is not the sole consideration. My colleagues and I also planned to compare the safety of systemic medications for AD, since that is equally, if not more, important for patients and clinicians. However, because serious adverse events (AEs) and withdrawals due to AEs are uncommon, and AD flares are sometimes listed as AEs, those analyses have not provided meaningful safety information, and we do not consider them useful. Rather, the overall, and particularly long-term, safety profiles of the various medications will be assessed by other means, such as long-term extension studies and clinical trial registries. Clinicians should impart their understanding of the specific serious and nuisance AEs that occur rarely and commonly with each medication, including theoretical risks that may be relevant based on data from similar medications used for other indications. In addition, patient preferences and comorbidities should be taken into account. Nevertheless, my colleagues and I hope that the living NMA of systemic treatments for AD continues to be useful as therapeutic options continue to expand.

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