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**Characteristics modifying response to biologic treatments for psoriasis: considering subgroups in network meta-analysis**

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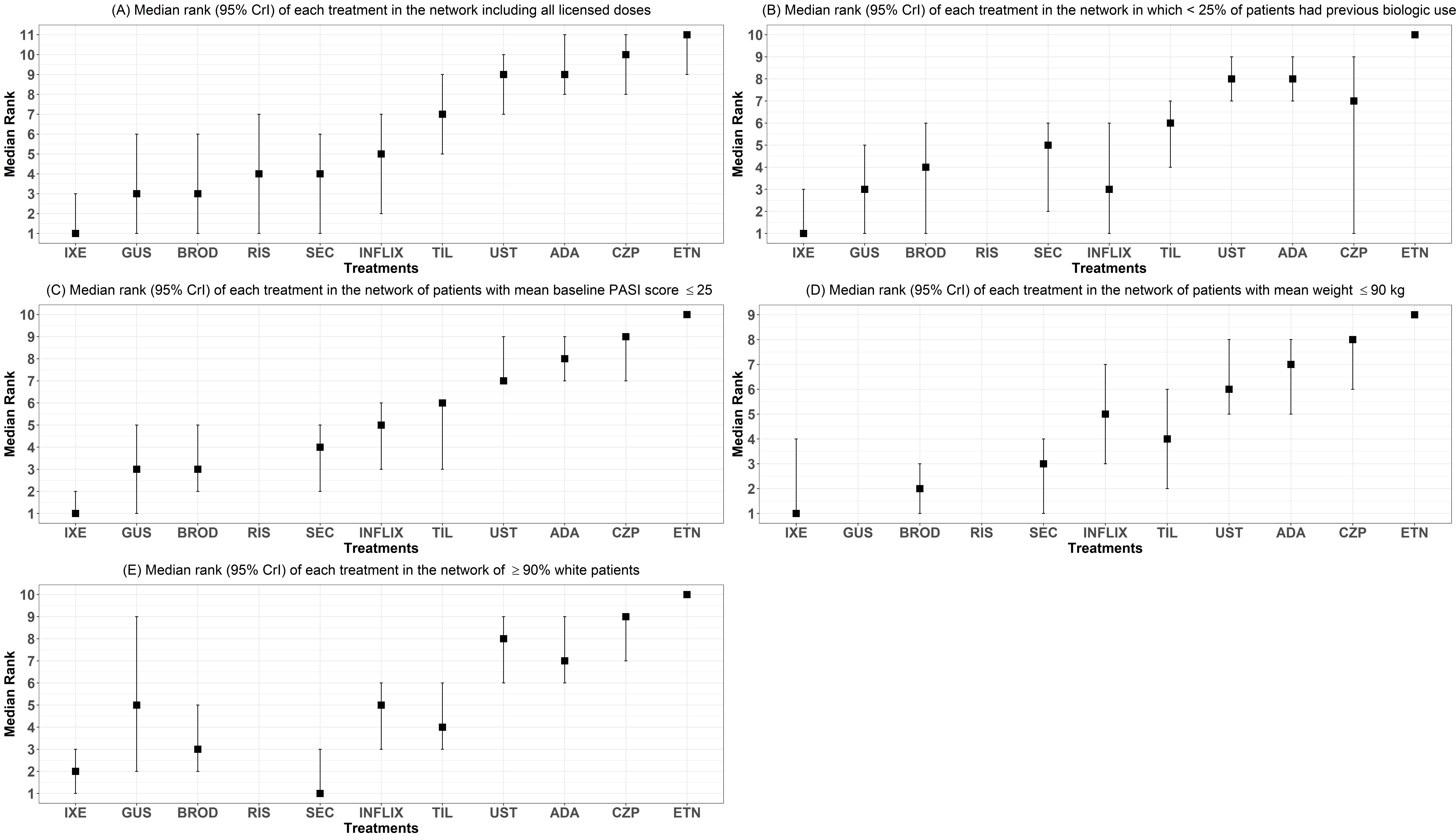
Dear Editor, Network meta-analysis (NMA) is a method used to estimate the relative effectiveness of different interventions in the absence of direct head-to-head trials. However, when there is heterogeneity within the network of evidence this has implications for the reliability of the results. We explored the impact of heterogeneous patient characteristics by undertaking NMA of subgroups to identify characteristics modifying response to biologic treatments for psoriasis.

There have been several National Institute for Health and Care Excellence (NICE) Single Technology Appraisals (STAs) of therapies for moderate to severe plaque psoriasis; many have relied upon the results of NMAs. However, there were considerable differences in the trials included in these NMAs, including differences in treatment dose, outcome assessment and baseline patient characteristics. These differences may affect the reliability of the results of the NMAs and their generalisability to psoriasis patients seen in practice.

We investigated the impact of differences in patient characteristics on relative treatment effectiveness using data from nine NMAs completed as part of NICE STAs of second line therapies for moderate to severe plaque psoriasis. Based on expert clinical advice and previous sensitivity analyses undertaken in the STAs, we selected four patient characteristics to explore: ethnicity, weight, baseline Psoriasis Area Severity Index (PASI) score and previous biologic exposure. Four smaller networks were mapped based on these characteristics, in addition to the original network of all studies using licensed treatment doses. Sixty-nine randomised controlled trials were included in our analyses, including 34,924 patients. An article describing more detailed methods and results has been published in BMC Systematic Reviews.1

The median rank of treatments according to PASI 75 response in each of the five networks is shown in Figure 1. Results for most of the networks were consistent, with ixekizumab ranking best. These results are generally consistent with the results of the NMA undertaken by the guideline development group for the BAD guidelines for biologic therapy for psoriasis.2

**Figure 1: Median rank of treatments according to PASI 75 response in each of the five networks**

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Key: ADA, adalimumab; BROD, brodalumab; CrI, credible interval; CZP, certolizumab pegol (200 mg dose); ETN, etanercept (50 mg once weekly dose); GUS, guselkumab; INFLIX, infliximab; IXE, ixekizumab; RIS, risankizumab; SEC, secukinumab; TIL, tiltrakizumab; UST, ustekinumab (45mg/90mg weight based dose).

Note: Panels B-E have missing treatments because they were not represented in that network.

The four smaller networks unsurprisingly had lower between study heterogeneity than the network of all studies using licensed treatment doses (0.31, 95% CrI 0.17-0.45); the network of studies in which <25% patients had received previous biologic therapy had the lowest heterogeneity (0.14, 95% CrI 0.09-0.23).

The estimated effects did not differ much across the five networks. However, the anti-tumour necrosis factor (TNF) therapies infliximab and certolizumab pegol appeared to have greater efficacy, in terms of their relative ranking, in the network of studies in which <25% patients had received previous biologic therapy. However, the credible intervals were large, particularly for certolizumab pegol (as shown in Figure 1), indicating greater uncertainty. A recent article published in the British Journal of Dermatology evaluated the association between patient characteristics and response to biologic therapies for psoriasis, using a multicentre, observational, prospective pharmacovigilance study (BADBIR).3 This study also found little evidence for predictors of differential treatment response, although only biologic-naïve patients were included.

Different biologic therapies target different parts of the immune pathway; there are four anti- TNF therapies (adalimumab, certolizumab pegol, etanercept and infliximab), three interleukin (IL)-17 inhibitors (brodalumab, ixekizumab, secukinumab), three IL-23 inhibitors (guselkumab, risankizumab and tildrakizumab) and an IL-12/IL-23 inhibitor (ustekinumab). Biologic experienced patients are more likely to have had prior exposure to an anti-TNF therapy (i.e. adalimumab or etanercept), which might explain why subsequent response to certolizumab pegol or infliximab was lower in the networks in which >25% patients had received previous biologic therapy.

There were also some differences in the network in which ≥90% patients were white; secukinumab ranked best and guselkumab ranked lower than in the other networks. However, the credible interval for the rank for guselkumab was very large indicating greater uncertainty. In addition, data on ethnicity was often not reported in the included studies, so some assumptions were made based on the location of the study, adding further uncertainty, making it difficult to know which treatment should be recommended in practice.

Our findings suggest that previous biologic use may be an effect modifier for patients requiring treatment for moderate to severe plaque psoriasis. Future NMAs of psoriasis treatments should consider the subgroup of biologic-naïve patients and the subgroup of biologic-experienced patients.

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