isolated from fibroblasts (data not shown). We believe that this study demonstrated potential of somatic Muse cells as pluripotent stem cells, which would be a promising source for regenerative medicine in skin.

CONFICT OF INTEREST
The authors state no conflict of interest.

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Takeshi Yamauchi1, Kenshi Yamasaki1, Kenichiro Tsuchiya1, Saaya Koike1 and Setsuya Aiba1

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SUPPLEMENTARY MATERIAL
Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2017.06.021.

SUPPLEMENTARY MATERIAL

TO THE EDITOR
We would like to provide additional context regarding interpretation of the recently published paper by Jabbar-Lopez et al. (2017). This report performed a systematic review of the literature and network meta-analysis (NMA) to compare six biologics licensed for the treatment of psoriasis with each other, methotrexate, or placebo in an attempt to inform patient and clinician decisions as well as to update the British Association of Dermatologists’ guidelines regarding prioritizations of biologic therapies in psoriasis. Of note, in this meta-analysis, the authors combined not only efficacy but also other important markers of clinical decision making such as tolerability and impact on quality of life. From the indirect comparisons, the authors concluded that ixekizumab had the highest efficacy among the biologics but was one of the least well tolerated based on withdrawals due to adverse events (AEs) during the first 12/16 weeks of treatment. We disagree with their conclusions.

Abbreviations: AE, adverse event; NMA, network meta-analysis

Comment on “Quantitative Evaluation of Biologic Therapy Options for Psoriasis: A Systematic Review and Network Meta-Analysis”


Given the lack of feasibility for direct comparisons across all biological therapies, NMA analyses provide a reasonable method for making indirect comparisons between drugs, although NMAs have a number of underlying assumptions that can greatly influence the outcome (Higgins and Thompson, 2002; Salanti et al., 2014; Schacht et al., 2013; Senn, 2000). As Jabbar-Lopez et al. point out, direct comparisons within a clinical trial provide the best evidence for the relative risk/benefit between two drugs. In this regard, we would like to highlight the evidence that has been established for risk and benefit of ixekizumab from direct head-to-head trials with etanercept and ustekinumab. In the two ixekizumab trials that included an
etanercept comparator arm (UNCOVER-2 and UNCOVER-3), absolute discontinuations due to AEs during the first 12 weeks of treatment were quite low, with only 1.6% of patients treated with the approved label dose of ixekizumab, administered every 2 weeks (Q2W), discontinuing the study due to AEs, just slightly higher than the 0.8% of patients treated with placebo and 1.2% of patients treated with etanercept who discontinued due to AEs (Griffiths et al., 2015). Additionally, in the recently published head-to-head trial of ixekizumab and ustekinumab (IXORA-S), there were no significant differences between discontinuations due to AEs out to week 24 in patients treated with recommended doses of ixekizumab (2 patients [1.5%] discontinued because of AEs) and ustekinumab (1 patient [0.6%] discontinued because of AEs), and the differences between ixekizumab and ustekinumab were smaller than those estimated by Jabbar-Lopez et al. Moreover, there were no appreciable differences in rates of serious AEs during the first 24 weeks of treatment; five (3.0%) ustekinumab-treated and three (2.2%) of ixekizumab-treated patients experienced serious AEs. Rates of overall infections were also comparable between the two groups (Reich et al., 2017). At the same time, in pooled UNCOVER-2 and UNCOVER-3 studies, 47.0% more patients receiving ixekizumab Q2W versus etanercept achieved at least a 90% improvement in Psoriasis Area and Severity Index by week 12, and 30.6% and 24.1% more patients receiving label dosing of ixekizumab versus ustekinumab achieved Psoriasis Area and Severity Index 90 at weeks 12 and 24, respectively, in IXORA-S. Although the IXORA-S results were not available for the Jabbar-Lopez NMA, the IXORA-S and UNCOVER results both provide an opportunity to assess the predictive value of this type of analysis against real-world data. In this case, the NMA does not accurately predict the comparable tolerability of ixekizumab to either etanercept or ustekinumab during the first 12 to 24 weeks of treatment.

We recognize that differing study designs, conduct, and methods for collection of safety events make safety comparisons across drugs challenging; however, it is important to note that using discontinuations due to AEs, in the absence of other safety information, could oversimplify results. Evaluating the type and severity of events is critical to understanding true safety concerns. We have recently examined and published the safety profile of ixekizumab from seven clinical trials in adults with chronic plaque psoriasis, with 4,209 patients contributing 6,480 total patient-years of exposure. In this disclosure, we extensively described the types and severity of safety events, and the analyses conducted ultimately found no unexpected safety signals for a drug with the IL-17A antagonist mechanism of action (Strober et al., 2017).

The conclusions drawn by Jabbar-Lopez et al. were based mostly on the surface under the cumulative ranking curve analysis, which provides a rank but offers no information about the actual magnitude of clinical difference between two treatments, presenting a challenge for graphical representation. For example, in Figure 3 of Jabbar-Lopez et al., on the Y axis for tolerability, the proportional difference between ixekizumab and the cluster of adalimumab, ustekinumab, and secukinumab appears to be greater than 60% based on rank; however, graphing according to magnitude of risk differences demonstrates that, in fact, the tolerability for these treatments are quite similar (Table 1 of Jabbar-Lopez et al. and shown here in Figure 1). We note additionally that the surface under the cumulative ranking curve results are based on all doses included in the evaluated trials, rather than restricting on approved label doses. In fact, Jabbar-Lopez et al. point out that the safety ranking of ixekizumab improved when only label doses (Q2W for ixekizumab) were evaluated (Jabbar-Lopez et al., 2017). Both regulatory approval and reimbursement processes regard the approved treatment regimens as the basis for the benefit-risk decision, and thus, we propose that the scientific evidence that is used in this type of analysis that will inform treatment decisions should be based solely on approved and reimbursed dosing regimens for all treatments.

We appreciate the extensive methodology that was undertaken to provide clinicians and patients with information on the relative profile of different biological therapies. Although NMAs can provide some insight, they are limited inferences based on mixed indirect and direct comparisons and tethered by their methodology. In the instance of ixekizumab, which is relatively new to the market, we emphasize the importance of examining the totality of the data, which includes one of the largest pivotal phase 3 clinical trial programs, and propose that clinical decisions regarding optimal therapies rely on the gold standard of well-designed head-to-head trials. Overall, the results of these
trials support that ixekizumab has very high efficacy and is well tolerated.

CONFICT OF INTEREST
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Kristian Reich1*, Craig Leonard2, Kim Papp3, Alice Gottlieb4, Diamant Thaci5, Alexander Schacht6, Susan Ball7, Noah Agada6 and Lotus Mallbris6
1Dermatologikum Hamburg and Georg-August-University, Göttingen, Germany; 2Central Dermatology, St Louis, Missouri, USA; 3K. Papp Clinical Research, Probity Medical Research, Waterloo, Ontario, Canada; 4Department of Dermatology, New York Medical College, Valhalla, New York, USA; 5Comprehensive Center for Inflammation Medicine, University Hospital Schleswig-Holstein, Campus Lübeck, Lübeck, Germany; and 6Eli Lilly and Company, Indianapolis, Indiana, USA
*Corresponding author e-mail: kreich@dermatologikum.de

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TO THE EDITOR
We thank Reich et al. for their correspondence on our paper (Jabbar-Lopez et al., 2017). They helpfully highlight the IXORA-S trial comparing ixekizumab with ustekinumab for moderate-severe plaque psoriasis (Reich et al., 2017). This was published after our search cutoff date and so was not included in our review.

Reich et al. state that direct comparisons within a clinical trial provide the best evidence for evaluation of a drug. We agree that when a large (well-powered), high-quality randomized controlled trial is performed, the inclusion of indirect evidence adds little. However, IXORA-S was a trial of 302 participants and therefore underpowered to detect meaningful

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