Reply to: "Do IL-17 inhibitors increase risk of respiratory tract infections?"

To the Editor: We thank Drs Blauvelt and Ehst[1] for their comments about the meta-estimate we reported, in which there was a higher risk of developing respiratory tract infections in patients with psoriasis treated with interleukin (IL) 17–targeting biologics compared with placebo.[2] Respiratory tract infections, which are usually innocuous, have become of special interest since the pandemic caused by severe acute respiratory syndrome coronavirus 2. Therefore, we conducted a meta-estimate to rigorously determine whether there is a safety signal for respiratory tract infection with biologics that target IL-17.

First, Blauvelt and Ehst[1] suggest that grouping secukinumab and ixekizumab (which block IL-17A) with brodalumab (which blocks IL-17RA) may be inappropriate because brodalumab has a broader mechanism of action, which could lead to differential infectious consequences. Brodalumab (odds ratio [OR] 2.14; 95% confidence interval [CI] 1.17-3.89) had the highest respiratory tract infection risk. Inconsistent with this hypothesis, however, is that rates of respiratory tract infection in secukinumab (OR 1.84; 95% CI 1.33-2.5) appeared more similar to those of brodalumab, with ixekizumab (OR 1.11; 95% CI 0.85-1.45) being the outlier. We agree further study is warranted.

Second, Blauvelt and Ehst[1] suggest that mucocutaneous candidiasis infections could explain the results and that loss of statistical significance in sensitivity analyses that eliminate terms that could be related to monilial infections (eg, oropharyngeal pain) suggests that IL-17 inhibitors are unlikely to be associated with increased respiratory tract infections. When oropharyngeal pain is excluded, the measure of association remains identical (OR 1.56), but the *P* value increases from 0.03 to 0.06. We emphasize that it is widely accepted scientifically that the focus is on the point estimate with 95% CIs, not arbitrary thresholds of statistical significance. Therefore, readers should not be reassured by a loss of statistical significance because, in fact, the results are essentially the same.[3]

Third, Blauvelt and Ehst[1] speculate that investigators and patients are unblinded, given that the treatment effects of IL-17 inhibitors are large and occur early. They then hypothesize that there may be both patient and investigator bias to report more adverse events on active drug. Alternatively, one might hypothesize the opposite, that patients responding well to treatment might not want to divulge symptoms that may result in drug discontinuation.

Fourth, Blauvelt and Ehst[1] raise concerns about labeling biologics used for psoriasis as "immunosuppressives" and state this terminology can lead to misplaced "fear of biologics." Although we appreciate the authors' concern, we are merely using the terminology applied by the Food and Drug Administration.[4]

Fifth, we appreciate that Blauvelt and Ehst[1] share their opinion that IL-17 inhibitors do not increase the risk of developing respiratory tract infections, according to their clinical experience. We, too, have treated hundreds of patients with IL-17 inhibitors. We are humbled to know that clinical experience alone is insufficient to determine these risks,[5] and therefore our laboratory is committed to providing our colleagues and patients with the best, most rigorous assessments of available data combined with a measured interpretation of the results. We certainly agree with Blauvelt and Ehst[1] that more meticulous evaluation of the risk of respiratory tract infections associated with various classes of biologics used to treat psoriasis is needed.

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Abbvie, Janssen, Novartis Corp, Sanofi, Celgene, Ortho Dermatologics, and Pfizer Inc, and he has received payment for CME work related to psoriasis that was supported indirectly by Eli Lilly and Company and Ortho Dermatologics. In addition, he is a copatent holder of resiquimod for treatment of cutaneous T-cell lymphoma, and he is a deputy editor for the Journal of Investigative Dermatology, *receiving honoraria from the Society for Investigative Dermatology. Dr Shin has no conflicts of interest to declare.*

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REFERENCES

1. Blauvelt AE, Ehst BD. Do IL-17 inhibitors increase risk of respiratory tract infections? *J Am Acad Dermatol*. 2020;83(4):e303-e304.
2. Wan MT, Shin DB, Winthrop KL, Gelfand JM. The risk of respiratory tract infections and symptoms in psoriasis patients treated with interleukin 17 pathway inhibiting biologics: a meta-estimate of pivotal trials relevant to decision making during the COVID-19 pandemic. *J Am Acad Dermatol*. 2020;83(2):677-679.
3. Ogdie A, Troxel AB, Mehta NN, Gelfand JM. Psoriasis and cardiovascular risk: strength in numbers part 3. *J Invest Dermatol*. 2015;135(9):2148-2150.
4. Center for Drug Evaluation and Research. Application number: 125521Orig1s000. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/125521Orig1s000OtherRedt.pdf. Accessed May 5, 2020.
5. Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ*. 1996;312(7023):71-72.

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