Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Reply to: Do interleukin 17 inhibitors increase risk of respiratory tract infections?

To the Editor: In a recent meta-estimate, Wan et al[1] conclude that patients with psoriasis on interleukin (IL) 17 blockers are possibly at increased risk of respiratory tract infections (RTIs). We agree with the need and wisdom to better understand the infectious risk that these medications pose; however, we take issue with the manner in which the data were derived and how the discussion was framed, especially during the coronavirus disease 2019 (COVID-19) pandemic.

Their meta-analysis grouped patients with psoriasis receiving 3 medications: secukinumab, ixekizumab, or brodalumab. The first 2 drugs block IL-17A, whereas brodalumab blocks IL-17 receptor A, a subunit of the IL-17 receptor (blocking signaling by IL-17A, IL-17C, IL-17-E, and IL-17F).[2] Because brodalumab has a broader mechanism of action than secukinumab and ixekizumab, its use in patients with psoriasis may lead to differential infectious consequences. When running the meta-estimates in 2 treatment groups (patients on secukinumab/ixekizumab vs those on brodalumab), were there significantly more RTIs in either group compared with patients on placebo?

Second, it is well-established that IL-17 inhibition predisposes to mucocutaneous candidiasis.[3] Some of the adverse event terms used to collect "RTI" cases by Wan et al[1] (eg, oropharyngeal pain), may in fact be manifestations of thrush and have no relationship to viral infections such as COVID-19. Importantly, the authors acknowledge this limitation of their article by saying "Sensitivity analyses varying the terms analyzed yielded similar findings but with loss of statistical significance." This critical sentence seems to be lost in the overall message that points to a "potential signal" between IL-17 inhibitors and risk of RTIs. We believe the data suggest that IL-17 inhibitors are unlikely to be associated with increased risk of RTIs.

Third, it is assumed that the reporting of adverse events, including RTIs, in placebo-controlled psoriasis trials is equal in study participants on placebo vs those on active drug. Because the treatment effects with IL-17 inhibitors are so large and occur so early, with investigators and patients often correctly guessing what treatment arm they have been placed on, there may be both patient and investigator bias to report more adverse events when patients are on the active drug.[4] Possible reporting bias may skew results toward a positive safety signal that may not otherwise be detected.

Fourth, the authors start their discussion by speaking of biologics as a class of drugs, which they are not, lumping them together as "immunosuppressives." A "biologic" is simply a drug that is manufactured through biologic means rather than through chemical processes. Each biologic class has distinct mechanisms of action and unique safety profiles. Correct use of terms surrounding biologics discourages misplaced "fear of biologics," which is widely prevalent among misinformed patients with psoriasis and practitioners.[5] Data analyses related to COVID-19 need not unnecessarily be couched in overall ominous terms.

Lastly, one should consider whether the results from this meta-estimate "fit" with real-world use of IL-17 inhibitors. It has been our collective ≥10-year experience of treating hundreds of patients with psoriasis with IL-17 inhibitors, in clinical trials and in clinical practice, that they are not at increased risk for RTIs. More meticulous evaluation is needed on this topic.

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REFERENCES

1. 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.
2. Martin DA, Towne JE, Kricorian G, et al. The emerging role of IL-17 in the pathogenesis of psoriasis: preclinical and clinical findings. *J Invest Dermatol*. 2013;133:17-26.
3. Blauvelt A, Lebwohl M, Bissonnette R. Interleukin-23/interleukin-17A dysfunction phenotypes inform possible clinical effects from anti-interleukin-17A therapies. *J Invest Dermatol*. 2015;135:1946-1953.
4. van der Steen JT, Ter Riet G, van den Bogert CA, Bouter LM. Causes of reporting bias: a theoretical framework. *F1000Res*. 2019;8:280-299.
5. Blauvelt A, Armstrong AW, Krueger GG. Essential truths for the care and management of moderate-to-severe psoriasis. *J Drugs Dermatol*. 2015;14:805-812.

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