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.

Commentary

To the Editor: Akimaya et al[1] conducted a meta-analysis of interleukin-12/-23 (IL-12/23) and IL-23 inhibitors on respiratory tract infections (RTIs), concluding that use of IL-12/23 or IL-23 antagonists for autoimmune diseases increased upper respiratory tract infection (URTI) risk but not viral URTI or lower RTI. In our meta-analyses of pivotal psoriasis trials, we reported odds ratios of RTI associated with biologics that target tumor necrosis factor, IL-17, and IL-23 as 1.08 (95% confidence interval [CI] 0.84-1.38), 1.56 (95% CI 1.04-2.33), and 1.24 (95% CI 0.98-1.56), respectively.[2-4]

We note that the estimates of difference in RTI are the same between the 2 studies. The risk difference (RD) as presented by Akimaya et al[1] was 0.02 (95% CI 0.01-0.03; $P = .007$) whereas ours was 0.02 (95% CI −0.01 to 0.04; $P = .18$). We estimate 1 additional RTI for every 63 patients treated with IL-23, ie, the number needed to harm, over the average trial period (or 25 per year). The main differences between the 2 studies are 1) the inclusion of trials of IL-12/23 inhibitors versus IL-23 inhibitors only, 2) the inclusion of only trials of patients with psoriasis versus patients with other diseases, and 3) the definition of RTI outcomes.

Akiyama et al[1] combined biologics with different mechanisms of action (briakinumab and ustekinumab also block IL-12, which may result in different infection risk) with biologics which are more targeted, only blocking IL-23. Furthermore, including studies of IL-23 inhibitors in nonpsoriasis populations introduces estimates that may be influenced by the coadministration of other immune suppressants or different underlying risk profiles. Therefore, to yield a clinically informative estimate, we believe researchers should only combine biologics with similar mechanism of action (ie, not combining IL-12/23 data with IL-23 data) within a single disease indication (ie, not combining psoriasis with Crohn's disease, ankylosing spondylitis, etc). In addition, nonapproved therapies should be excluded from the primary analysis because their results may be driven by doses that will not be approved.

Finally, the motivating factor behind our 3 meta-analyses is that we recognized that the analysis of safety data on RTI were flawed as >10 adverse event terms are used to identify this outcome in a safety dataset. Analyzing adverse events individually can miss safety signals, making it necessary to pool terms to investigate RTI. However, as we emphasized, evaluating the risk of RTI in clinical trials is difficult because the diagnosis is made clinically without objective testing, and therefore the etiology of these symptoms, be they viral, bacterial, fungal, or allergic, is unknown, and therefore we recommend specific testing for severe acute respiratory syndrome coronavirus 2 in ongoing and future trials (Table I).[2] In addition, meta-analyses of specific AEs depend on reporting consistency, which is difficult because of threshold-dependent reporting criteria for publicly available summaries.

Table I. Recommendations for analysis of respiratory tract infections in clinical trials of psoriasis and related diseases

Recommendation	Rationale
Pool drugs of the same mechanism of action when conducting meta-analyses	Treatments with different biologic targets may have different rates of RTIs
Pool studies within the same disease indication when conducting meta-analyses	Different diseases will have different risk trajectories for RTI and also may vary in use of combination immune modifying treatment vs monotherapy in clinical trials
Use data of approved drugs	The general patient population is not subject to risk profiles of treatments that are not approved, especially as it relates to drug dose
Combine all RTI terms	RTI terms are generally nonspecific and not confirmed using objective testing. Pooling terms increases power for signal detection
Report all adverse events on publicly available domains consistently (for sponsors/investigators)	Threshold-dependent reporting criteria results in variation and missing events that can result in invalid results
Make SARS-CoV-2 testing available to trial subjects (for sponsors/investigators)	COVID-19 is a highly variable illness with nonspecific symptoms. Systematic testing for SARS-CoV-2 in trial subjects presenting with RTI symptoms will allow for robust evaluation of drug safety

COVID-19, Coronavirus disease 2019; *RTI*, respiratory tract infection; *SARS-CoV-2*, severe acute respiratory syndrome coronavirus 2.

Therefore, we believe the impact of biologics targeting IL-12/23 or IL-23 on the risk of viral URTIs is uncertain and cannot be ruled out based on currently available data. These findings emphasize the importance of pooling data in a manner that is biologically and clinically relevant as well as understanding the limitations of trial data.

Daniel B. Shin, PhD,[a] Maha N. Syed, MBBS,[b] and Joel M. Gelfand, MD, MSCE[a,b]

From the Department of Dermatology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania[a]; and Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania.[b]

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Conflicts of interest: Dr Gelfand served as a consultant for Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, Janssen Biologics, Novartis Corp, Regeneron, UCB (Data Safety and Monitoring Board), Sanofi, and Pfizer Inc, receiving honoraria; in addition, he receives research grants (to the Trustees of the University of Pennsylvania) from 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, Dr Gelfand 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.*

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Correspondence to: Joel M. Gelfand, MD, MSCE, Department of Dermatology, 3400 Civic Center Blvd, Perelman Center for Advanced Medicine, South Tower, Office 730, Philadelphia, PA 19104

E-mail: Joel.Gelfand@pennmedicine.upenn.edu

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