Reply to: "Comment on 'Incidence of pneumocystosis among patients exposed to immunosuppression'"

To the Editor: On the basis of their meta-analysis in which 3.1% of patients with hematologic and solid malignancies and transplants receiving trimethoprim-sulfamethoxazole (TSX) developed hematologic aberrations requiring discontinuation, Green et al proposed that prophylaxis is warranted when expected pneumocystis Jirovecchi pneumonia (PJP) risk is ≥3.5%.[1] Number needed to treat (NNT) to prevent 1 PJP case in this meta-analysis is equal to the number needed to harm (NNH) with regard to serious adverse events (SAEs) when baseline PJP risk is 3.5%.[1] Using results from Green's meta-analysis, Kowalski et al[2] calculate that prophylaxis would result in 16 patients harmed for every prevented PJP case among those exposed to both immunosuppressants and glucocorticoids, the population at highest risk in our analysis. Their figure is calculated by dividing the NNT of 502 (1/0.00199) to prevent 1 PJP case with our data, by the NNH of 32 (1/0.031) based on the meta-analysis. This calculation forms the basis of their contention against prophylaxis.

We caution against this comparison of NNT and NNH; it is misleading to directly compare NNTs (or NNH) across disease conditions, particularly when outcomes of interest differ in severity.[3] PJP carries significant mortality risk, estimated to range 30%-60% in patients without HIV infection. In arguing that NNH must approach 502 to justify prophylaxis, Kowalski et al[2] placed the same value on prevention of hematologic conditions as prevention of PJP, despite marked differences in related severity and mortality. All 9 of the 288 patients who experienced a SAE in the Green meta-analysis had resolution of laboratory test abnormalities with discontinuation, and there were no mortalities.[1] Moreover, it is necessary to note that there were no significant differences in total AE rates, AEs requiring discontinuation, or SAEs between TSX and placebo groups in Green's meta-analysis.[1] Nonsignificant differences in AEs between these 2 groups were also observed in a more recent Cochrane meta-analysis, again suggesting that underlying conditions (ie, hematologic malignancy) might be more related to hematologic aberrations than TSX.[4]

Data on TSX-related SAEs having high associated mortality is extremely limited given the event rarity. Kowalski et al[2] reference a study in patients with rheumatic diseases who received prophylaxis with TSX, in which severity of SAEs (pancytopenia or Stevens-Johnson syndrome) was indeed closer to that of PJP. However, the estimated NNH (131) was based only on 2 cases with SAEs among 262 patients and the confidence interval was 55−∞, making it impossible to draw concrete conclusions from this data.[5] In another analysis of patients exposed to TSX, incidence of cutaneous drug reaction severe enough to result in hospitalization was 0.0026% (2/76,655),[6] which is substantially lower than the incidence of PJP among patients treated with combination therapy in our analysis.

For these reasons, we disagree with the conclusions of Kowalski et al.[2] We maintain that after careful deliberation of individual risks and benefits, prophylaxis for patients receiving combination immunosuppressant and glucocorticoid therapy should be considered. Our population-based evidence inform this decision.

Sergey Rekhtman, MD, PharmD, MPH, Andrew Strunk, MA, and Amit Garg, MD

From the Department of Dermatology, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, New Hyde Park, New York

Funding sources: None.

Conflicts of interest: Dr Garg has served as an advisor for AbbVie, Pfizer, Janssen, and Asana Biosciences and has received honoraria. Dr Rekhtman and Mr Strunk have no conflicts of interest to disclose.

A preliminary analysis was previously presented at the Medical Dermatological Society annual meeting in San Diego, California, on February 15, 2018.

Correspondence to: Amit Garg, MD, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, 1991 Marcus Ave, Ste 300, New Hyde Park, NY 11042

E-mail: amgarg@northwell.edu

REFERENCES

1. Green H, Paul M, Vidal L, Leibovici L. Prophylaxis of pneumocystis pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. *Mayo Clin Proc*. 2007;82:1052-1059.
2. Kowalski EH, Kneiber D, Kridin K, Amber KT. Comment on "incidence of pneumocystosis among patients exposed to immunosuppression". *J Am Acad Dermatol*. 2019;80(6).
3. McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. *Ann Intern Med*. 1997;126:712-720.
4. Stern A, Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. *Cochrane Database Syst Rev*. 2014;(10):CD005590.
5. Park JW, Curtis JR, Moon J, Song YW, Kim S, Lee EB. Prophylactic effect of trimethoprimsulfamethoxazole for pneumocystis pneumonia in patients with rheumatic diseases exposed to

prolonged high-dose glucocorticoids. *Ann Rheum Dis*. 2018;77:644-649.

6. Chan HL, Stern RS, Arndt KA, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol*. 1990;126(1):43-47.

https://doi.org/10.1016/j.jaad.2019.03.072