6. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, Okafor EC, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. N Engl J Med 2020;383: 517–25.
7. Mitjà O, Corbacho-Monné M, Ubals M, Alemany A, Suñer C, Tebé C, et al. A cluster-randomized trial of hydroxychloroquine for prevention of Covid-19. N Engl J Med 2021;384:417–27.
8. Salvarani C, Mancuso P, Gradellini F, Viani N, Pandolfi P, Reta M, et al. Susceptibility to COVID-19 in patients treated with antimalarials: a population based study in Emilia-Romagna, Northern Italy. Arthritis Rheumatol 2021;73:48–52.
9. Dhibar DP, Arora N, Kakkar A, Singla N, Mohindra R, Suri V, et al. Post-exposure prophylaxis with hydroxychloroquine for the prevention of COVID-19, a myth or a reality? The PEP-CQ Study. Int J Antimicrob Agents 2020;56:106224.
10. Tan DH, Agrawal R, Barnabas RV, Giles JT, Dull P. Moving fast but going slow: coordination challenges for trials of COVID-19 post-exposure prophylaxis. Trials 2020;21:815.
11. Adrian Hernandez, sponsor. Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine (HERO-HCQ). ClinicalTrials.gov identifier: NCT04334148; 2020.

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Reply

To the Editor:

We thank Dr. Tang and colleagues for their interest in our study and for their correspondence on an important clinical question. In May of 2020, when our literature search was last updated, we did not identify any case series, cohort studies, or randomized controlled trials (RCTs) that evaluated the role of HCQ as prophylaxis for COVID-19. Consequently, our analysis was unable to address this issue. The authors should be commended for their efforts to conduct an RCT during the early phases of the pandemic when there was widespread misinformation about antimalarials. We empathize with the difficulties they encountered, which highlight broader issues impacting the COVID-19 research agenda.

As noted in our analysis, early observational studies frequently had a high risk of bias, which could be attributed to small sample sizes, inappropriate or inadequate comparator groups, and issues related to confounding by indication. Overinterpretation of the preliminary evidence led to off-label HCQ use months before the first randomized trial was finished. An "infodemic" began, fueled by anecdotal reports of encouraging benefits and concerning harms (1). A seemingly contradictory situation arose, in which enrollment slowed because of overconfidence in HCQ's purported benefit, and trials were paused or terminated in response to potential safety signals. The typical regulatory and logistic hurdles to initiating RCTs compounded delays, resulting in many RCTs beginning after COVID-19 peaks had passed. Perhaps most importantly, aside from notable exceptions like the RECOVERY trials, few large-scale coordinated RCTs of HCQ were performed (2).

The importance of conducting large-scale, adequately powered RCTs and the consequences of relying on suboptimal evidence when they are absent will be one of the enduring legacies of the COVID-19 pandemic (3,4). Performing such trials will require greater collaboration between centers and a regulatory environment that encourages their execution. It will also require investigators like Dr. Tang and colleagues, who were willing to expend time and effort in this worthy endeavor.

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1. The Lancet Infectious Diseases. The COVID-19 infodemic [editorial]. Lancet Infect Dis 2020;20:875.
2. Anon. Effect of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020;383:2030–40.

3. Berwanger O. Azithromycin, RECOVERY, and the power of large, simple trials. Lancet 2021;397:559–60.
4. Collins R, Bowman L, Landray M, Peto R. The magic of randomization versus the myth of real-world evidence. N Engl J Med 2020;382:674–8.

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Use of tofacitinib in the context of COVID-19 vaccination: comment on the American College of Rheumatology clinical guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases

To the Editor:

We read with great interest the American College of Rheumatology (ACR) clinical guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases (1). We commend the Task Force's emphasis on the importance of immunization in this population and for providing guidance to the rheumatology community. Regarding their recommendation to withhold JAK inhibitors for 1 week after each COVID-19 vaccine dose (1), we propose the following available tofacitinib data for consideration in this context.

Tofacitinib is a reversible JAK inhibitor characterized by rapid absorption and elimination and a short half-life (2). The impact of tofacitinib on lymphocyte subsets consists of small and variable changes in T cell counts, increases in B cell counts, and decreases in natural killer (NK) cell counts. After drug discontinuation, B and NK cell counts can take from 2 to 6 weeks to return to baseline levels (2), which suggests that the impact of a 1-week hold of tofacitinib on immune cell counts would likely be small.

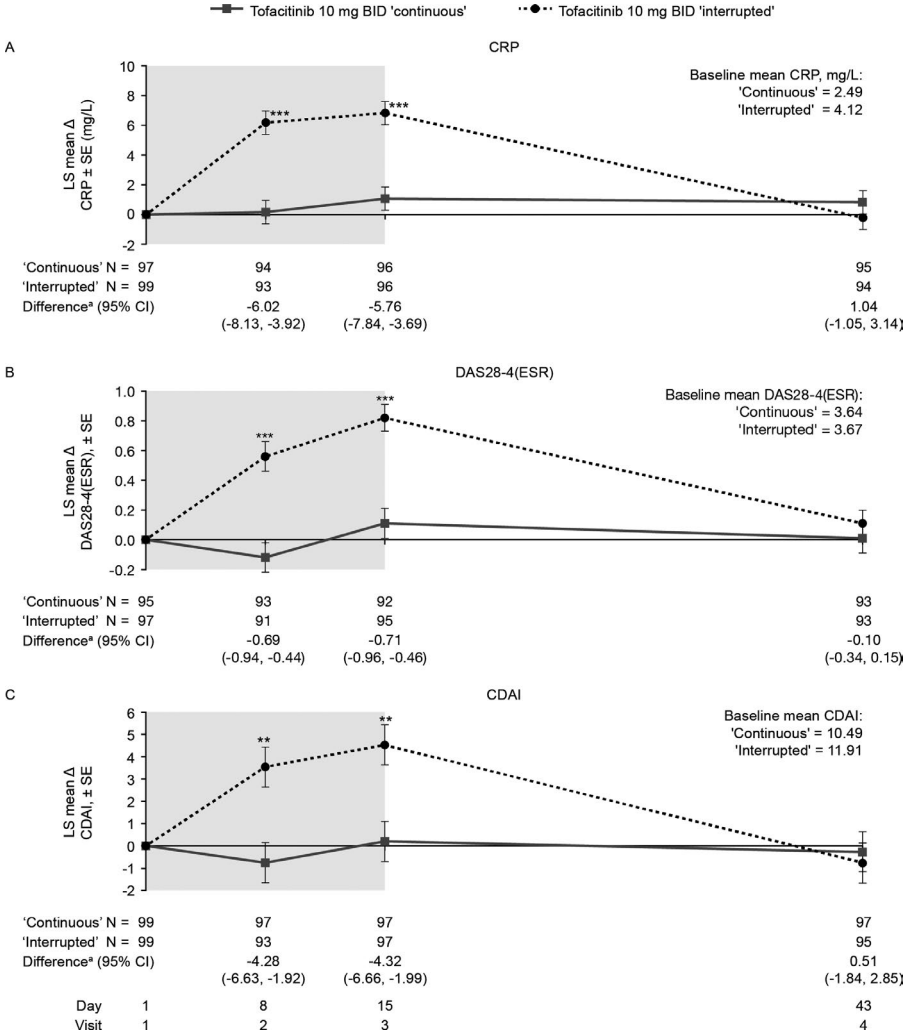

Figure 1. Least squares (LS) mean changes from baseline in C-reactive protein (CRP) levels (**A**), Disease Activity Score in 28 joints (4-variable) using the erythrocyte sedimentation rate (DAS28-4[ESR]) (**B**), and Clinical Disease Activity Index (CDAI) (**C**) over time during the sub-study of the long-term extension study, ORAL Sequel. Shaded areas indicate the dose-interruption period. Baseline was defined as visit 1 of the sub-study. [a]LS mean change (Δ) in continuous treatment group minus LS mean change in interrupted treatment group. bid = twice a day; 95% CI = 95% confidence interval. ** = $P < 0.001$; *** = $P < 0.0001$ for interrupted versus continuous treatment. Adapted from Figure 3 in Kaine et al (5) (available at https://link.springer.com/article/10.1007%2Fs10067-020-04956-1) by removing the original panel B from the figure; used under Creative Commons attribution 4.0 International (CC BY 4.0) at https://creativecommons.org/licenses/by/4.0/.