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Reply to Banno et al and Padhi et al

To the Editor—We thank Banno et al for their comments [1] on our systematic review on the effects of ivermectin for the treatment of coronavirus disease 2019 (COVID-19) [2]. Our conclusion that ivermectin is not a viable option to treat patients with COVID-19 did not diverge from our results. We relied on 2 different components to reach our conclusion. First, the effects for all outcomes were not statistically significant; we could not exclude the possibility that effects were due to chance. Second, the literature base for all outcomes was comprised of low to very low quality of evidence per Grading of Recommendations Assessment, Development, and Evaluation (GRADE); we could not exclude the possibility that the effects were not due to biases of included randomized controlled trials (RCTs). We do agree with Banno et al [1] that more RCTs are needed in the future as we acknowledged in our conclusions section, in particular RCTs with better methodological quality and reporting. Our study has different inclusion and exclusion criteria than the study by Bryant et al [3] and a different set of included RCTs. In particular, we (*i*) focused on treatment of COVID-19 and excluded prophylaxis RCTs, (*ii*) included RCTs with standard of care or placebo as control arms and excluded RCTs with ivermectin or other active drugs (eg, hydroxychloroquine) in control arms, and (*iii*) included published and preprint RCTs as most patient, trial, and outcome data are missing from trial registries of potential COVID-19 drugs [4]; risk of bias assessment is difficult with incomplete registry reporting. Finally, we did not register our study protocol, as registration was not compulsory per the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5] at the beginning of our project.

We also thank Padhi et al [6] for their comments on the use of sequential methods in meta-analyses. We, however, disagree with several of their statements. First, RCTs in our systematic review only included patients with mild to moderate COVID-19, not severe disease. Second, our objective was not to investigate whether an adequate number of RCTs of ivermectin have been conducted, as information on ivermectin benefits and harms is needed now. Third, trial sequential analysis (TSA) is intended for prospective cumulative meta-analyses and updated meta-analyses, not for retrospective meta-analyses. The meta-analyst is, therefore, unable to control for the trials that have already been performed which are eligible for the meta-analysis [7]. TSA is not recommended by the Cochrane Collaboration for updating meta-analyses [8]. Fourth, TSA outcome is not more reliable than usual meta-analysis; TSA is a type of secondary analysis and should not be used for main analyses or to draw main conclusions [8]. Fifth, TSA cannot accommodate multiple different thresholds for different outcomes, as they are often based on a particular outcome that may not be of interest to all stakeholders [7]. Finally, not only more RCTs are needed, but RCTs that are better designed and of higher quality. Large, well-designed ivermectin RCTs are underway for early treatment in nonhospitalized COVID-19 patients, such as Platform Randomised Trials of Treatment in the Community for Epidemic and Pandemic Illnesses (PRINCIPLE, https://www.principletrial.org/) and Outpatient Treatment for SARS-CoV-2 Infection, a Factorial Randomized Trial (COVID-OUT, https://covidout.umn.edu/). Currently, ivermectin should only be used in well-designed randomized trials.

Notes

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Differential Anti-S Antibody Titers in Vaccinated Residents During an Outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Variant B.1.351 (β) in an Elderly Nursing Home

To the Editor—We previously reported an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant B.1.351 (β) in a nursing home where 83.9% of residents had been fully vaccinated by means of the BNT162b2 messenger RNA (mRNA) vaccine [1]. We read with interest the letter from Vanker and colleagues, who reported a similar outbreak of the same SARS-CoV-2 variant in a Canadian nursing home, despite a high vaccination rate among residents and staff members [2]. Both studies suggested that BNT162b2 mRNA vaccination does not fully protect from outbreaks of SARS-CoV-2 variant B.1.351 (β) in elderly nursing homes.

We further investigated the anti-SARS-CoV-2 immune response in our vaccinated cohort, comparing anti-SARS CoV-2 antibody levels in noninfected versus infected residents. Anti-SARS-CoV-2 immunoglobulin G (IgG) antibodies targeting the spike receptor-binding domain (RBD) antigen were sought by means of the Abbott IgG anti-S kit (Abbott Diagnostics, Lake Forest, Illinois, USA). All vaccinated residents were tested for anti-S antibodies within 1 to 2 months and a half after the second dose of vaccine. Those who were infected were tested within 9 days after the outbreak started (ie, within 4 days after symptom onset in symptomatic residents). Overall, the levels of anti-S antibodies did not differ between those who were infected (n = 13) and those who were not (n = 13): median 1069 AU/mL (range < 6.8–8188 AU/mL) vs median 1481 AU/mL (range 448–2928 AU/mL), respectively (P = .76: Figure 1). The anti-S antibody levels did not significantly differ between vaccinated patients with a severe vs nonsevere infection. However, the 2 infected vaccinated residents who died from the infection had relatively low antibody levels 1 month after the second vaccine dose (139 and 643 AU/mL, respectively).

A high level of anti-S antibodies (>1000 AU/mL) has been associated with in vitro viral neutralization of all major circulating variants of concern, including variant B.1.1.7 (α) [3]. In the majority of elderly patients, antibody responses elicited by 2 doses of the BNT162b2 mRNA vaccine are sufficient to protect against infection or, if infected, severe disease related to the initial SARS-CoV-2 strains or variant B.1.1.7 (α). However, these responses may be insufficient to induce high-level protection against severe disease in some individuals infected with variant B.1.351 (β), a variant carrying several mutations suggested to reduce susceptibility to antibody neutralization (eg, S-Del242-244, S-K417N, S-E484K). Recently, Kamar et al showed that a third dose of the BNT162b2 mRNA vaccine significantly improved the immunogenicity of vaccination in solid organ transplant recipients [4]. The effectiveness of a third vaccine dose, as reflected by anti-S antibody levels, should be explored in elderly individuals, as it may enhance their immune response and ensure protection against emerging variants with reduced susceptibility to neutralizing antibodies. Larger observational studies are needed to confirm this hypothesis.

Note

Potential conflict of interest. S. F. has served as a paid speaker for Abbvie and Abbott diagnostics and has served on an advisory board/Data and Safety Monitoring Board (DSMB) for Merck (MSD), outside the submitted work. C. R. has served as an advisor, and/or speaker for Illumina, and Vela Diagnostics. J.-M. P. has served as a paid advisor, and/or speaker for Abbvie, Gilead, GlaxoSmithKline, Merck, Regulus, and Siemens Healthcare. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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