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EDITORIAL COMMENTARY

Ivermectin for the Treatment of COVID-19 Disease: Too Good to Pass Up or Too Good to Be True?

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As of early 2021, the search for coronavirus disease 2019 (COVID-19) therapeutics has been characterized by few landmark achievements [1, 2] and multiple disappointments [3, 4]. After many times bitten from optimism about preliminary and observational data, the scientific community has become increasingly shy about promoting therapeutic interventions before the availability of phase III clinical trial data [5, 6, 7]. This philosophy is well reflected in guidance by the US National Institutes of Health and the Infectious Diseases Society of America, which have made commendable efforts to ensure exploratory interventions are rigorously evaluated in clinical trials before widespread use [8, 9].

Nevertheless, with persistent global vaccine distribution inequity [10] and regional surges overwhelming health systems [11], the need to identify low-cost, scalable, and effective therapeutics for prevention and management of severe COVID-19 remains as acute as ever. Consequently, there is an obligation to consider early and incomplete data of emerging therapeutics. Moreover, the threshold to consider drugs for public use must not be set so high that demands for unassailable data result in preventable deaths. Where exactly that threshold should be set is among the most vexing challenges for the scientific community at present.

Into this fray enters ivermectin, which, depending on your perspective, is perhaps the most promising or most fraught new kid on the COVID-19 therapeutic block. Very early enthusiasm for the use of ivermectin for COVID-19, derived from in vitro data [12], was tempered by subsequent pharmacokinetic data suggesting effective doses to achieve IC_{50} against the virus were not readily achievable in humans [13–15]. More recently, some have proposed alternate mechanisms of action for ivermectin in the treatment of COVID-19 [16]. Such hypotheses, along with an impressively large number of clinical trials assessing the efficacy of ivermectin for COVID-19 disease, have brought ivermectin back into the spotlight.

In this issue of *Open Forum Infectious Diseases*, Hill and colleagues attempt to summarize that large and growing body of clinical trial data thorough an elegant and multifaceted meta-analysis. A particular strength of their work is the ambitious method of data aggregation, which includes the published literature, clinical trial registries, and unpublished work garnered through a COVID-19 clinical trials consortium, resulting in 24 total studies and an analytic data set as large as 2127 participants for the mortality outcome. They also adopted strict inclusion criteria, limiting analyses to studies that prospectively randomized participants to an ivermectin vs a comparator arm. Additional strengths include the evaluation of multiple outcomes (time to viral clearance, time to clinical recovery, duration of hospitalization, and survival, among others), assessment of study quality, and use of standardized meta-analytic methods with mixed-effects regression and heterogeneity assessments.

The results are compelling. They identify a clinically significant benefit in pooled estimates for most of their selected outcomes. For example, they estimate a mean reduction in time to viral clearance of 3 days (95% CI, 1–5), a reduction in time to clinical recovery of 1.5 days (95% CI, 0.4–2.8), a reduction in duration of hospitalization of 4.3 days (95% CI, 0.0–8.6), and a 56% reduced risk of mortality (95% CI, 23%–75%). Notably, their estimates remain largely similar after excluding studies at high risk of bias. And, although the included studies do not overlap, their results are largely consistent with many [17–19] (but not all [20]) meta-analytic evaluations of ivermectin conduct by other groups. Even the most ardent skeptic should be given pause by these data.

But as the authors note, despite the large body of analyzed work, the extrapolation of results remains limited by the nature of the studies included. Only 9 of the 24 studies (n = 785) were rated as having a low risk of bias, and fewer than half of the studies (10) were placebo-controlled. Moreover, only 8 studies have been peer reviewed, with another 11 publicly

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available through preprint or clinical trial registry result reporting, and 4 were unpublished at the time of this writing. Many were also not preregistered on clinical trial repositories. Perhaps the most glaring feature of these studies is the heterogeneity between many aspects of the studies themselves, including ivermectin dose (0.1-mg/kg–24-mg fixed dose) and duration (single dose through 1 week), stage of disease for enrolled participants (mild to severe), use of combination therapies in the intervention arm (multiple evaluated combinations of doxycycline with ivermectin), and a remarkably varied set of comparator arms, ranging from placebo alone to use of favipiravir, hydroxychloroquine, and/or azithromycin.

Where does this leave us? There are arguments to be made both in support of and against a potential benefit of ivermectin for COVID-19 treatment. In borrowing from Sir Bradford Hill's causal criteria framework [21], there are clear elements of strength of association (the pooled estimate of reduction in mortality was >50%), there is consistency across studies (and meta-analyses) with relatively little heterogeneity in effect sizes, and there is evidence of temporality, which is provided by the prospective randomized study designs. Counterbalancing these arguments are the general lack of biologic plausibility and coherence for the use of ivermectin in the treatment of a viral infection. As it does not appear to be active in standard doses as a direct-acting antiviral, we are forced to speculate about anti-inflammatory or indirect antiviral effects. Perhaps most puzzling is the degree and extent of benefit identified—across disease stages, dosing regimens, and viral and clinical outcomes—which strains belief, particularly for a disease that has been characterized by narrow therapeutic windows for most other interventions.

On balance, we are left with a compelling meta-analysis (indeed, a handful of them), suggesting a modest to large benefit of a low-cost, widely available, well-tolerated therapy for COVID-19—a dream scenario—but based on studies with small sample sizes, design flaws, incomplete results, or some combination thereof. Ultimately, guideline authors must review these data and ask themselves if this information crosses the threshold for support of ivermectin outside of clinical trials. Although some have argued that the minimal risk afforded by a well-tolerated medicine does just that, there are secondary harms of early support for therapies before a solid evidence base, such as creating drug shortages of essential medicines [22] and the erosion of trust in the scientific community, which has certainly been degraded over the past year [23]. Nonetheless, if larger clinical trials ultimately confirm the efficacy of this low-cost, widely available drug, we must be willing to add ivermectin to the long list of therapeutic agents in medicine for which the best we can do is guess the mechanism of action.

As of this writing, there at least 5 large, placebo-controlled clinical trials on the use of ivermectin for COVID-19 underway that should be powered to allay residual concerns about the available data. Until these data are released, ivermectin might be best considered an extremely promising therapy, but one not quite ready for public use. Otherwise, there is a real risk that the scientific community will once again be bitten by overenthusiasm and forced to answer to a public that will not be shy about holding us to account.

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