Clinical Infectious Diseases

EDITORIAL COMMENTARY

A Potential Role for Zinc to Enhance Treatment for Coronavirus Disease 2019 (COVID-19)?

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(See the Major Article by Ben Abdallah et al. "Twice-Daily Oral Zinc in the Treatment of Patients With Coronavirus Disease 2019: A Randomized Double-Blind Controlled Trial", https://doi.org/10.1093/cid/ciac807.)

Attempts to find effective treatments for coronavirus disease 2019 (COVID-19) have dominated human medicine in the last 3 years. The pandemic has swept across the entire world and pharmacological tools to both prevent and treat its health consequences were swiftly seen to be limited. In parallel, the spread of the pandemic and the unavoidable, high degree of public concern have generated several expectations in the lay public, in many cases without reliable support in an otherwise huge and probably excessive literature on COVID-19 [1, 2]. Among these is the potential role of micronutrients in disease therapy (and prevention), particularly zinc and selenium, and vitamins D and C [2, 3]. For these micronutrients, and in particular zinc, it was hypothesized that either a nutritional deficiency of the mineral favored the risk of infection and of developing a serious form of the disease or that "pharmacological" high doses of the element would counteract disease progression. These hypotheses are derived from observational human studies [3–5] and animal and laboratory data suggesting a role for these elements in counteracting COVID-19 [3, 6, 7].

Unfortunately, neither of these lines of evidence can be claimed as sufficient to justify the use of a micronutrient in clinical practice, since direct experimental data in humans are an essential requisite. In particular, the substantial limitations of observational human studies, such as exposure and outcome misclassification, particularly unmeasured confounding, may outweigh any interesting suggestions from these studies and lead to unsubstantiated expectations. For instance, it is conceivable that individuals with poor nutritional status may undergo a higher risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and of severe COVID-19 complications, but the actual nutrient (or combination of nutrients) responsible for increased susceptibility to more adverse disease endpoints is difficult to determine from the many potential candidates. In addition, the relevance of laboratory and animal models is unclear for humans, often being based on short-term experiments using high levels of micronutrients such as zinc when measuring immune response or virulence of a pathogen [3, 6].

Given these uncertainties, there is a strong argument for studies that can provide convincing evidence on the efficacy (and safety) of any COVID-19 treatment with micronutrients (ie, well-designed randomized controlled trials [RCTs]). Unfortunately, specifically for zinc, such studies have generally been lacking so far, and in addition, almost all the 77 trials registered in ClinicalTrials.gov (as of 14 October 2022) for COVID-19 encompassing as active intervention the administration of high doses of intravenous or oral zinc in different chemical forms (zinc chloride, gluconate, and sulfate) have a number of limitations [3, 4]. They generally include nonrandom allocation to study arms and interventions, nonblinded design by both participants and investigators, selective or partial reporting of the endpoints, and the addition of other potentially active drugs and substances, thus precluding an independent assessment of zinc efficacy and safety. Finally, most of these trials have still not been completed or provided final results.

For these reasons, the well-designed and executed study published in this issue of *Clinical Infectious Diseases* by Abdallah et al [8] represents an important methodological advancement. This carefully designed trial with recruitment of a much larger population compared with the few previous trials was therefore

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able to achieve a considerably higher statistical precision of the effect estimates, in addition to performing a careful randomization of the participants and blinding of both study subjects and investigators. The authors enrolled a final population of 470 newly diagnosed patients and tested the effects of a large dose of zinc (50 mg/day, given in 2 doses) on 2 major COVID-19 endpoints, intensive care unit (ICU) admission and death, alongside additional clinical endpoints. The results indicated a benefit comparable to a risk ratio of 0.43 for ICU admissions and 0.68 for short-term mortality in the zinc-supplemented group, with additional benefits on hospital stay length and, in outpatients, symptom duration. Although these estimates were statistically rather imprecise, they indicated a beneficial effect of the intervention with dietary zinc on COVID-19 clinical course in patients meeting the inclusion criteria for this trial—that is, those not admitted to the ICU and having had a symptom onset of 7 days or less. Such beneficial effects were higher in patients with a very short disease duration, in men, in patients with comorbidity or needing oxygen support, and particularly in older subjects and inpatients. A possible role of the vaccination status and of baseline zinc status as effect modifiers of the intervention was not tested in the trial.

The observation of such beneficial effects of the intervention on key COVID-19 endpoints is also of importance since it indicates the feasibility of the oral route for zinc administration in disease therapy, a finding that is advantageous in term of efficacy when compared with the alternative, more cumbersome intravenous route [6], and which has major implications in making this treatment suitable for use in outpatients, not only in the hospital setting.

Another important and reassuring finding of the trial was the absence of severe adverse effects, a common concern in intervention studies with high doses of a nutrient, given the capacity of trace elements of nutritional importance, including zinc, to exert toxic effects at very high levels of exposure, even in the short term, and depending on their bioavailability [9]. The authors, in fact, used a dose of the trace element that is above the upper level for chronic intake set by the European Food Safety Authority of 25 mg/day. However, such a choice appears to be acceptable given the pharmacological nature of the intervention, its short duration, the severity of the disease, and taking into account the lack of identified adverse effects at dietary zinc exposure of up to 50 mg/day (ie, the no-observed-adverse-effect-level identified by the European Food Safety Authority [10]. Although further investigations of subtle adverse effects in additional trials and in clinical settings are warranted, as well as confirmation of the study findings in other populations with different nutritional and lifestyle characteristics, the safety findings allow full consideration of zinc administration in the therapy of early-diagnosed COVID-19. Clearly, the results of this trial by no means offset the utility of standard therapy, nor do they provide absolute certainty about their beneficial effect on disease course, given the individual variability highlighted by the study results.

As acknowledged by the authors, some caveats must be carefully considered when assessing the results of this RCT and before considering a policy of widespread zinc supplementation in COVID-19 treatment. Importantly, the enrollment criteria and the final results make the results valid only for the patients investigated in the study and particularly for those mainly benefitting from the treatment—that is, those with a short time from symptom onset, having no need for ICU admission for respiratory or cardiovascular organ support, with comorbidity, and aged 65 years or more. This means that, unless justified by future RCTs, the use of oral zinc for COVID-19 treatment must be considered only for such patients. Overall, although these positive results from the Abdallah et al study need to be corroborated by additional trials, they provide sufficient initial evidence to consider high-dose zinc supplementation in the therapy of COVID-19 in patients with early disease, in addition to the standard therapy.

Note

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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