Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Discussion

Learning from previous methodological pitfalls to propose well-designed trials on vitamin D in COVID-19

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To the Editor,

Murai and colleagues recently reported the results of an important randomized controlled trial (RCT) testing the effect of 200,000 IU vitamin D3 on the length of hospital stay in 240 middle-aged patients with moderate-to-severe COVID-19 [1]. The authors found that vitamin D supplements, received 10.3 days on average after symptoms onset, did not shorten the hospital stay compared with placebo [1].

In the dual context of COVID-19 pandemic and hysterization around vitamin D, we wish here to dispassionate the debate and anticipate the more or less justified criticisms that will undoubtedly arise against this first large dedicated RCT. Classically, the reasoning for vitamin D supplementation is not the same as with other drugs because supplements are not the only source of vitamin D and there is no dose-dependent relationship between vitamin D intakes and circulating 25-hydroxyvitamin D (25(OH)D) concentrations [2]. Health events (if any) are related to the changes in 25(OH)D concentrations (i.e., correction of vitamin D insufficiency) but not to the dosage of supplements [2]. In this perspective, Murai and colleagues have successfully avoided at least five pitfalls that are classic in RCTs: i) they used a loading dose to fill the storage, ii) no long-term treatment was needed to maintain improved levels as the main outcome was quickly reached, iii) the adherence to single-dose treatment was high, iv) evidence was provided that improved levels were reached after supplementation, v) the control group was unlikely to receive supplements as part of routine care during the trial since they were hospitalized within the same investigating units.

While recognizing these qualities, the study findings should still be interpretated with caution for two main reasons, besides those highlighted in the editorial by Leaf and Ginde [3]. First, the majority of participants (51.7 %) were vitamin D sufficient at the time of randomization although no extra benefits are usually expected from vitamin D supplementation in those with sufficient status.[2] The post-hoc analysis among participants with 25(OH)D<20 ng/mL was sorely underpowered, thus preventing any firm conclusions. Second, using hospital stay shortening as the primary endpoint was also questionable (for instance, toxic drugs may shorten the length of hospital stay by causing early death), and also does not necessarily reflect the disease severity but may depend on social support upon return home. Other primary outcomes could have been preferred, like the number of days alive and out of the hospital at day28 [4], or indisputable criteria including the measured severity of COVID-19 or mortality. Results from upcoming well-designed RCTs will provide new and additional information on vitamin D interest in COVID-19 [5].

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Declaration of Competing Interest

Annweiler is the coordinating investigator of the COVIT-TRIAL study (ClinicalTrials.gov Identifier: NCT04344041).

Annweiler occasionally serves as a consultant (training and expertise) for Mylan (2020).

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