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Vitamin D_3 to Treat COVID-19:

Different Disease, Same Answer

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Biological activity of vitamin D and its metabolites include, among other properties, potent antimicrobial and anti-inflammatory effects in vitro.[1] In animal models, administration of vitamin D metabolites attenuates a variety of acute organ dysfunction, including acute lung injury.[2] Observational data from patient cohorts support the potential therapeutic application of these findings.[3] Specifically, lower circulating levels of vitamin D metabolites are independently associated with worse outcomes in patients with acute illness, including patients with coronavirus disease 2019 (COVID-19).[4]

These multiple lines of evidence in support of a potential therapeutic role for vitamin D generated enthusiasm over the past decade for testing whether administration of large doses of vitamin D might improve outcomes in various groups of patients, including those with critical illness. The Correction of Vitamin D Deficiency in Critically Ill Patients (VITdAL-ICU) study was a multicenter randomized clinical trial that tested the effect of vitamin D_3 administration (540 000 IU) vs placebo in 475 critically ill patients with vitamin D deficiency, defined as 25-hydroxyvitamin D (25[OH]D) less than or equal to 20 ng/mL. The primary end point, hospital length of stay, was similar between the groups, although hospital mortality (a secondary end point) was lower in patients who received vitamin D_3 vs placebo among those with severe vitamin D deficiency (defined as 25[OH]D ≤12 ng/mL).[5] The Vitamin D to Improve Outcomes by Leveraging Early Treatment (VIOLET) trial sought to examine the effect of the same dose of vitamin D_3 (540 000 IU) vs placebo on 90-day mortality in 3000 critically ill patients with vitamin D deficiency, but was stopped early for futility after enrollment of 1360 patients demonstrated very low likelihood for benefit.[6] Randomized clinical trials testing vitamin D_3 administration as a therapeutic strategy for disease prevention in other settings have yielded similarly null results.[7–9]

The COVID-19 pandemic has spurred renewed interest in vitamin D to address viral replication and hyperinflammation that have a major role in the pathogenesis of severe COVID-19. In addition to known antimicrobial and anti-inflammatory effects, vitamin D metabolites also have direct action on angiotensin-converting enzyme 2 (ACE2), which serves as the cell surface entry receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Vitamin D metabolites upregulate ACE2 expression in pulmonary microvascular endothelial cells in animal models of acute lung injury.[10] Although enhanced

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expression of ACE2 could theoretically increase viral entry into cells, it may paradoxically have beneficial effects in patients who are already infected because SARS-CoV-2–mediated downregulation of ACE2 may perpetuate lung injury.[11]

In this issue of *JAMA*, Murai et al[12] examine the therapeutic efficacy of vitamin D_3 administration in patients with COVID-19. The authors enrolled 240 hospitalized patients with moderate to severe COVID-19 admitted to 2 hospitals in Brazil and randomly assigned them to receive a single dose of vitamin D_3 (200 000 IU) or placebo. Approximately 90% of the patients in both groups required supplemental oxygen or noninvasive mechanical ventilation at enrollment, but patients who required invasive mechanical ventilation were excluded, as were patients admitted to the intensive care unit (as shown in Figure 1 in the article,[12] although this exclusion criterion does not appear on ClinicalTrials.gov [NCT04449718]). The mean time from hospitalization to randomization was 1.4 days, which is consistent with other inpatient COVID-19 trials that tested early administration of therapies. The mean 25 (OH)D level at randomization was approximately 21 ng/mL in both groups, which is considerably higher than the mean 25 (OH)D levels in previous vitamin D_3 trials.[5,6] After treatment with vitamin D_3, the mean 25(OH)D level increased to approximately 44 ng/mL, an appropriate dose response.

The primary end point, hospital length of stay, was not significantly different between the vitamin D_3 group and the placebo group (median [interquartile range] of 7.0 [4.0–10.0] days vs 7.0 [5.0–13.0] days; log-rank $P = .59$; unadjusted hazard ratio for hospital discharge, 1.07 [95% CI, 0.82–1.39]; $P = .62$). There were no significant differences in the secondary outcomes between the vitamin D_3 group and the placebo group, including in-hospital mortality (7.6% vs 5.1%; difference, 2.5% [95% CI, −4.1% to 9.2%]; $P = .43$), admission to the intensive care unit, or need for mechanical ventilation. Administration of a high dose of vitamin D_3 also did not appear to improve outcomes in the subgroup of 115 patients with vitamin D deficiency (25[OH]D <20 ng/mL) at randomization.

Although this is an important contribution as the largest published randomized, double-blind, placebo-controlled trial of vitamin D_3 administration among hospitalized patients with COVID-19 to date, several limitations should be considered. First, the study was underpowered. The authors state that the number of participants was chosen on the basis of feasibility, and that with 208 participants they would have 80% power to detect a 50% difference in hospital length of stay, which is a highly improbable result. Second, the authors excluded patients who required invasive mechanical ventilation and those admitted to the intensive care unit, and less than 15% of patients required noninvasive ventilation. Accordingly, most of the patient population would be considered moderately ill and the results cannot be generalized to critically ill patients, who were excluded. This is important because the benefit of other anti-inflammatory therapies among patients with COVID-19 (eg, dexamethasone, tocilizumab) is highly dependent on severity of illness, with moderately ill patients receiving little or no benefit and severely ill patients receiving a substantial benefit.[13–15] Third, only 115 study participants (48.3%) had vitamin D deficiency (25[OH]D <20 ng/mL), and only about one-fourth of the patients had severe vitamin D deficiency (25[OH]D <12 ng/mL) (based on Figure 3 in the article[12]). Fourth, although the authors demonstrated that circulating levels of 25(OH)D increased in the patients who received

vitamin D_3, they did not measure circulating levels of 1,25-dihydroxyvitamin D, the active form of vitamin D. Accordingly, it is unclear whether patients were able to efficiently convert 25(OH)D to 1,25-dihydroxyvitamin D, because this conversion is inhibited by the osteocyte-derived hormone fibroblast growth factor 23, which is elevated in acutely ill patients.[16]

When this clinical trial is taken is isolation, the findings may appear ambiguous; that is, the findings do not exclude clinically important benefit (or harm) from high-dose vitamin D_3 administration in hospitalized patients with moderate to severe COVID-19. In addition, this study did not address the use of vitamin D for patients with mild (outpatient) COVID-19 who are early in their symptom course or for use as prophylaxis against COVID-19. Therapeutic agents, such as monoclonal antibodies, also have demonstrated divergent results across settings.[17,18] Clinicaltrials.gov lists at least 30 studies of vitamin D interventions in COVID-19, globally and across the spectrum of disease. Based on experience in the pandemic, it seems likely that many of these studies will be underpowered or will not achieve target enrollment.

Given the lack of highly effective therapies against COVID-19, except perhaps for corticosteroids, it is important to remain open-minded to emerging results from rigorously conducted studies of vitamin D (despite smaller sample sizes and important limitations of some studies). However, taken together with existing randomized clinical trials of vitamin D administration in hospitalized patients with respiratory infection and critical illness, the results reported by Murai et al[12] do not support routine administration of vitamin D in hospitalized patients with moderate to severe COVID-19.

Conflict of Interest Disclosures:

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