Vitamin D and tuberculosis

Coussens et al. reported an analysis of markers of immune and inflammatory response in a subset of participants from a randomized clinical trial of vitamin D₃ supplementation in culture-positive pulmonary tuberculosis (1). In that trial, the vitamin D intervention did not alter the primary endpoint, time to sputum culture conversion (2), a result that is congruent with that from another randomized controlled trial, in which a clinical severity score was not improved by vitamin D supplementation (3). In the present work Coussens et al. perform a per-protocol analysis of participants who met narrow inclusion criteria (receipt of at least three of four doses of study medication, compliance with anti-tuberculous therapy, completion of all study visits, no requirement for second-line therapy or corticosteroids, infection with a rifampicin-sensitive isolate of *Mycobacterium tuberculosis*, and HIV seronegative). This analysis did not change the result for the primary trial endpoint but generated a marginally significant effect of the active therapy on time to sputum smear conversion, a secondary endpoint the authors had previously indicated has little clinical utility (2).

The per-protocol analysis reported by Coussens et al. is simply a subgroup analysis in which the subgroups are defined principally by compliance to treatment and at least one other variable that could only be determined after randomization. Such analyses should not be endorsed because they violate the trial randomization: participants who comply differ from those who do not in ways other than medication taking, such that the findings might not be attributable to the intervention being studied but to the favorable prognostic characteristics within the compliant subgroup. It is therefore unsurprising that such analyses generate more optimistic, and often incorrect, estimates of treatment effect (4). Further, Coussens et al. do not follow the recommended approach to subgroup analysis, which is to report the interaction test between subgroups (i.e., per-protocol and non–per-protocol groups) and only consider individual subgroup results if the interaction test is statistically significant (5). Finally, claiming treatment efficacy from analyses of secondary endpoints when there was no effect on the primary trial endpoint is statistically unwise (5). Therefore, we contend that the claim that vitamin D supplementation enhances sputum smear conversion made by Coussens et al. in their abstract and the first paragraph of their Discussion is invalid. The appropriate conclusion from the available clinical trial data is that supplementation with vitamin D₃ may modulate biomarkers of inflammation and immune function in patients with tuberculosis but has no beneficial effect on treatment outcome.

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