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Using Plasma Vitamin D Concentration as a Surrogate Marker to Predict Drug Response: A New Chapter in the Management of Inflammatory Bowel Disease and Beyond?

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Paradigms for the management of inflammatory bowel disease (IBD) have continued to evolve, yet the treatment response, especially for patients with moderate to severe disease, remains difficult to predict. Although the introduction of biologic agents, such as tumor necrosis factor alpha (TNFα) antagonists (eg, adalimumab, certolizumab, infliximab) and α4-integrin inhibitors (natalizumab and vedolizumab), has improved overall treatment outcome, clinical remission rate remains highly variable, ranging from 40% to 80%.[1-6] In this issue of *JPEN*, the results from the cohort study by Zator and his colleagues showed that the pretreatment plasma vitamin D concentration may be an important marker in predicting the treatment outcomes of anti-TNFα therapy in patients with IBD.[7] Specifically, using a baseline vitamin D concentration of 30 ng/mL as the cutoff, the investigators found that patients who were vitamin D deficient before treatment were more likely to experience early discontinuation of anti-TNFα therapy (hazard ratio [HR], 2.13; 95% confidence interval [CI], 1.03–4.39; $P = .04$). The results remained consistent after exclusion of patients who received concurrent systemic corticosteroid such as prednisone (HR, 2.80; 95% CI, 1.02–7.71). More important, the primary reason (72% of the cases) for early discontinuation of therapy was lack of efficacy, suggesting that pretreatment vitamin D deficiency is associated with suboptimal response to drug therapy.

It has long been suspected that vitamin D status may play a role in the pathogenesis and progression of IBD. Experimental models with the deletion of vitamin D receptor (VDR) were found to be more susceptible to develop colitis, to be less likely to recover from intestinal mucosal injury, and to experience worse prognosis compared with models that express VDR.[8,9] In addition, a number of studies link vitamin D status and various aspects of IBD, ranging from the severity of illness to the development of long-term complications in patients.[10-13] Vitamin D also appears to work in synergy with corticosteroids, a relationship best demonstrated in childhood asthma.[14] Steroid requirements and in vitro steroid responsiveness are significantly inversely associated with vitamin D status.[15] Vitamin D enhances steroid-induced interleukin-10 secretion and MAPK phosphatase 1 expression to produce increased anti-inflammatory effects. Vitamin D also suppresses inflammation by enhancing both corticosteroid inhibition of proinflammatory chemokines such as RANTES (regulated upon activation normal T-cell expressed and secreted) and corticosteroid induction of a tolerogenic dendritic cell phenotype.[16] But the current study by Zator et al is the first to specifically show the link between vitamin D status and anti-TNFα therapy. The finding of this study are supported by previously published papers demonstrating that vitamin D modulates the TNF-mediated proinflammatory pathway.[17-20] What remains unclear is whether vitamin D independently decreases inflammatory response by suppressing TNF expression or works synergistically with anti-TNF agents through other mechanisms.

This study also may have opened a new chapter in the understanding of drug-nutrient interaction. Our existing knowledge leads us to think that the primary reason for us to monitor nutrient status with certain drug therapy is to prevent adverse events. For instance, we supplement a patient with pyridoxine during the course of therapy for tuberculosis with isoniazid to prevent neuropathy; we monitor plasma vitamin D concentrations in patients receiving enzyme-inducing antiepileptic agents such as phenytoin and carbamazepine because of the pharmacokinetic interactions through enzyme induction. But we have not seen any previous example where the treatment efficacy of a drug can be substantially augmented by targeting the plasma concentration of a micronutrient to a specific threshold. If the results are confirmed in future studies, this would likely be the most notable example of a drug-nutrient interaction showing that a micronutrient status can be used as a surrogate marker to predict the outcomes of pharmacotherapy.

Clearly, despite the potential of these results, they are of a pilot nature and must be validated and replicated with

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larger scale trials. A few important aspects that were not the aims of Zator's study should be addressed in future investigations. First, it is unclear whether the predictive value of treatment response of vitamin D concentration can be applied to other biologic agents such as natalizumab, which acts by inhibiting adhesion of leukocytes via integrin function instead of TNFα. Second, the investigators used 30 ng/mL as the single cutoff for vitamin D status. The logical next question is to ask whether a dose-response relationship exists: That is, is a higher plasma vitamin D concentration before treatment associated with better clinical response? Does a ceiling effect exist for vitamin D status where no further treatment benefit can be observed? Third, in patients with severe disease who did not reach remission with prior anti-TNFα therapy, is there a clinical benefit in titrating the plasma vitamin D concentration to 50 ng/mL or even higher before therapy? Fourth, among patients whose vitamin D status could not be effectively optimized before the initiation of anti-TNFα agents, would achieving the threshold plasma vitamin D concentration during drug therapy lead to a comparable treatment success rate? The results from the authors' subgroup analysis suggest that it may be an option. Among patients with hypovitaminosis D, those who received concurrent vitamin D supplementation with anti-TNFα treatment were less likely to experience early discontinuation of drug therapy compared with those who did not receive vitamin D. But how much vitamin D should be given, and to what concentration should it be targeted? Fifth, would the optimal plasma vitamin D concentration vary for an individual anti-TNFα agent in order to achieve the best clinical response? We are constantly being reminded by newer research data that not all drugs in the same class are created equal. And we have evidence to indicate that this applies to anti-TNFα agents as well. Sixth, is the predictiveness of treatment response with vitamin D concentrations altered by the patient's other concurrent medications for IBD? The authors have shown that it may be the case for systemic corticosteroid. What about other agents such as antimetabolites (eg, azathioprine, methotrexate) or other immunosuppressive agents (eg, cyclosporine) or monoclonal antibodies with targets other than TNFα (eg, ustekinumab, vedolizumab)? Seventh, what about using a threshold plasma vitamin D concentration of 20 ng/mL instead of 30 ng/mL? This question will once again invoke heated debate regarding the optimal vitamin D plasma concentration. But it is a fundamentally important question that may affect not only patient management but also policy and reimbursement.

In summary, unlike many other association studies between vitamin D and a disease state, the study by Zator and his colleagues is of significant potential because it may open a new chapter in targeted drug therapy for IBD and possibly other illnesses such as rheumatoid arthritis and multiple sclerosis. Nevertheless, it also raises many important questions that must be answered adequately before this approach becomes a real game changer.

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