

Correspondence

Reply

To the Editor:

We thank Apte and Salvi¹ for their commentary on our recent article.² They are right that some studies show that vitamin D might either cause or exacerbate allergies, although most studies show the opposite.³ Because our study was a proof-of-principle study, we were keen to give a high dose of vitamin D and to exclude nonadherence with treatment. This was the rationale for choosing a single long-acting dose of 400,000 IU vitamin D. It was not our intention to investigate whether this regime would be suitable for routine clinical practice.

Apte and Salvi also question the influence of baseline eosinophil levels on the outcome of our study. Despite stratification for baseline sputum eosinophil levels, our patients showed 3.2% and 6.7% sputum eosinophils in the intervention arm and the placebo arm, respectively. Although this was not statistically different, we found it relevant enough to analyze the influence of baseline eosinophil values on the effect of vitamin D in asthma. This analysis showed a highly significant interaction between the 2 parameters (interaction $P = .015$), indicating stronger effects of vitamin D₃ in patients with higher baseline sputum eosinophil levels. We confirmed this effect by analyzing the patients with the highest levels of baseline sputum eosinophils separately. Although we were well aware of the small number of patients, we could not deny this strong interaction.

Whether the changes in eosinophils we observed in our patients are clinically relevant is difficult to judge and depends on whether they are accompanied by any clinical improvement. Although we observed a trend toward better asthma control in patients receiving vitamin D, the study design and the choice of patients in our study were probably not suitable to observe the full effect on asthma control.

Finally, we fully agree with Apte and Salvi that patients with severe asthma are the ones with the highest unmet needs for new treatment options, including vitamin D.⁴ Our proof-of-principle

study was performed in patients with mild to moderate asthma to exclude confounding factors, such as comorbidities. Because there exists a strong association between asthma severity and sputum eosinophilia,⁵ we speculate that vitamin D might be particularly beneficial for patients with severe asthma and active eosinophilic inflammation. However, this has to be confirmed in large clinical trials in patients with this severe asthma phenotype.

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REFERENCES

1. Apte K, Salvi SS. Vitamin D reduces eosinophilic airway inflammation in nonatopic asthma: are we sure? *J Allergy Clin Immunol* 2015;136: XXX-XXX.
2. de Groot JC, van Roon EN, Storm H, Veeger NJ, Zwinderman AH, Hiemstra PS, et al. Vitamin D reduces eosinophilic airway inflammation in nonatopic asthma. *J Allergy Clin Immunol* 2015;135:670-5.e3.
3. Cassim R, Russell MA, Lodge CJ, Lowe AJ, Koplin JJ, Dharmage SC. The role of circulating 25 hydroxyvitamin D in asthma: a systematic review. *Allergy* 2015;70: 339-54.
4. Poon AH, Mahboub B, Hamid Q. Vitamin D deficiency and severe asthma. *Pharmacol Ther* 2013;140:148-55.
5. Amelink M, de Groot JC, de Nijs SB, Lutter R, Zwinderman AH, Sterk PJ, et al. Severe adult-onset asthma: a distinct phenotype. *J Allergy Clin Immunol* 2013;132: 336-41.

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