Effect of Vitamin D₃ on Asthma Treatment Failures in Adults With Symptomatic Asthma and Lower Vitamin D Levels
The VIDA Randomized Clinical Trial

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IMPORTANCE In asthma and other diseases, vitamin D insufficiency is associated with adverse outcomes. It is not known if supplementing inhaled corticosteroids with oral vitamin D₃ improves outcomes in patients with asthma and vitamin D insufficiency.

OBJECTIVE To evaluate if vitamin D supplementation would improve the clinical efficacy of inhaled corticosteroids in patients with symptomatic asthma and lower vitamin D levels.

DESIGN, SETTING, AND PARTICIPANTS The VIDA (Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma) randomized, double-blind, parallel, placebo-controlled trial studying adult patients with symptomatic asthma and a serum 25-hydroxyvitamin D level of less than 30 ng/mL was conducted across 9 academic US medical centers in the National Heart, Lung, and Blood Institute’s AsthmaNet network, with enrollment starting in April 2011 and follow-up complete by January 2014. After a run-in period that included treatment with an inhaled corticosteroid, 408 patients were randomized.

INTERVENTIONS Oral vitamin D₃ (100 000 IU once, then 4000 IU/d for 28 weeks; n = 201) or placebo (n = 207) was added to inhaled ciclesonide (320 μg/d). If asthma control was achieved after 12 weeks, ciclesonide was tapered to 160 μg/d for 8 weeks, then to 80 μg/d for 8 weeks if asthma control was maintained.

MAIN OUTCOMES AND MEASURES The primary outcome was time to first asthma treatment failure (a composite outcome of decline in lung function and increases in use of β-agonists, systemic corticosteroids, and health care).

RESULTS Treatment with vitamin D₃ did not alter the rate of first treatment failure during 28 weeks (28% [95% CI, 21%-34%] with vitamin D₃ vs 29% [95% CI, 23%-35%] with placebo; adjusted hazard ratio, 0.9 [95% CI, 0.6-1.3]). Of 14 prespecified secondary outcomes, 9 were analyzed, including asthma exacerbation; for those 9, the only statistically significant outcome was a small difference in the overall dose of ciclesonide required to maintain asthma control (111.3 μg/d [95% CI, 102.2-120.4 μg/d] in the vitamin D₃ group vs 126.2 μg/d [95% CI, 117.2-135.3 μg/d] in the placebo group; difference of 14.9 μg/d [95% CI, 2.1-27.7 μg/d]).

CONCLUSIONS AND RELEVANCE Vitamin D₃ did not reduce the rate of first treatment failure or exacerbation in adults with persistent asthma and vitamin D insufficiency. These findings do not support a strategy of therapeutic vitamin D₃ supplementation in patients with symptomatic asthma.

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n children and adults with asthma, serum 25-hydroxyvitamin D levels of less than 30 ng/mL have been linked to airway hyperresponsiveness, impaired lung function, increased exacerbation frequency, and reduced corticosteroid responsiveness.\(^5\)\(^6\) Although the underlying mechanisms are not yet known, it has been suggested that vitamin D enhances anti-inflammatory functions of corticosteroids in asthma, either by enhancing the ability of T cells to produce IL-10\(^1\) or through inhibition of TNFα cytokine production.\(^5\)\(^6\) Low vitamin D levels also create an inflammatory state, and vitamin D signaling pathways and receptor polymorphisms\(^7\)\(^8\) can influence the balance between Th1 and Th2, smooth muscle contraction, and airway remodeling.\(^1\)\(^2\) All of which have been implicated in asthma pathogenesis and severity. These data suggesting that vitamin D supplementation could modify steroid response and reduce airway inflammation have led to open questions about whether treatment with vitamin D might improve outcomes in patients with asthma.\(^1\)\(^4\)\(^5\)

National and international guidelines recommend inhaled corticosteroids as the primary anti-inflammatory controller therapy for persistent asthma; however, there is significant variability in the responses of patients to inhaled corticosteroids, with clinical studies demonstrating that up to 45% of patients do not have a clinical or physiological response to these agents.\(^3\)\(^4\) An element of this variability may be explained by vitamin D status, with studies suggesting that vitamin D may augment the effects of corticosteroids.\(^4\) We hypothesized that vitamin D supplementation would improve the clinical efficacy of inhaled corticosteroids in patients with asthma as measured by exacerbations, lung function, and the dose of inhaled corticosteroids required to maintain asthma control.

Methods

Participants

Eligible participants were aged 18 years or older with asthma and a serum 25-hydroxyvitamin D level of less than 30 ng/mL. Asthma entry criteria included (1) physician-diagnosed disease and (2) evidence of either bronchodilator reversibility (forced expiratory volume in the first second of expiration [FEV\(_1\)] ≥12% following 180 μg [4 puffs] of levalbuterol) or airway hyperresponsiveness (proconvulsive concentration of methacholine at which FEV\(_1\) decreased by 20% [PC\(_{20}\)] ≤8 mg/mL if not receiving inhaled corticosteroids or ≤16 mg/mL if receiving inhaled corticosteroids). All participants received stable asthma controller therapy for 2 weeks or longer and had a predicted FEV\(_1\), of 50% or greater. The VIDA (Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma) study protocol was approved by the institutional review board at each participating institution, all participants provided written informed consent, and a data and safety monitoring board monitored the study. The full study protocol and additional information appears in eMethods, eAppendix 1, and eAppendix 2 in the Supplement.

Study Design and Treatment

The study was a randomized, double-masked, parallel group trial (eFigure 1 in Supplement), with each eligible participant randomly assigned to either placebo or high-dose vitamin D\(_3\) (100 000 IU once, followed by 4000 IU/d for 28 weeks) (BioTech Pharmacal) added to inhaled ciclesonide (320 μg/d; 2 puffs twice daily) and levalbuterol. Eligible participants were screened from April 2011 to May 2013 and enrolled if they met the inclusion criteria. After completing a 4-week run-in period of treatment with only ciclesonide and levalbuterol (prior asthma treatments were discontinued), participants were randomized. Participants were excluded if they did not meet study criteria at entry or during run-in (Figure 1).

Computer-generated randomization was stratified by clinical center, body mass index (BMI), calculated as weight in kilograms divided by height in meters squared; ≤25 vs >25), and race (blacks vs all others), with treatment assignments made in random permuted blocks of size 2. The placebo vitamin D

Figure 1. Participant Flow of VIDA Trial

VIDA indicates Vitamin D Add-on Therapy Enhances Corticosteroid Responsiveness in Asthma. Postrandomization dropouts were included in the analysis as censored observations.

* Details for those screened but ineligible were not collected.

K The most common reasons were predicted forced expiratory volume in the first second of expiration (FEV\(_1\)) greater than 90% (n = 286; a subsequent protocol modification removed this criteria), did not have a provocative concentration of methacholine at which FEV\(_1\) decreased by 20% or did not qualify for challenge (n = 60), too few symptoms (n = 52), and predicted FEV\(_1\) of less than 50% (n = 41).
soft gelatin capsules matched in appearance those containing vitamin D₃. To assess responsiveness to corticosteroids, 40 mg of prednisone was added to each participant’s daily regimen for 1 week at the end of the run-in; a change in FEV₁ of 5% or greater was considered significant.¹⁵,¹⁶

After randomization, participants entered a 12-week inhaled corticosteroids stability phase, in which they continued to receive 320 μg/d of ciclesonide. This was followed up by 2 phases in which inhaled corticosteroids were tapered by 50% if the participant’s asthma symptoms were controlled. During the first phase at 12 weeks, patients were tapered to 160 μg/d of ciclesonide for 8 weeks, and during the second phase at 20 weeks, patients were tapered to 80 μg/d for 8 weeks. Participants were terminated or withdrawn from the study if they had more than 2 treatment failures or exacerbations. The last participant completed follow-up in January 2014.

Adherence to dosing with ciclesonide and vitamin D capsules was monitored electronically (DOSER device [MediTrack] for ciclesonide and MEMS 6 monitor [Aardex] for capsules), and symptoms and peak expiratory flows were recorded in a device that was both an electronic diary and a peak flow meter (Spirotel [Medical International Research]).

Outcome Measures

The primary end point was time to first asthma treatment failure during the 28-week study period. Treatment failure was defined as 1 or more of the following: peak expiratory flow of 65% or less of baseline measurement on 2 of 3 consecutive measurements; FEV₁ of 80% or less of baseline measurement on 2 consecutive measurements; increase in levalbuterol dose of 8 puffs/d or more for 48 hours (vs baseline); additional use of inhaled corticosteroids or use of oral or parenteral corticosteroids for asthma; emergency department or hospitalization for asthma with systemic corticosteroids or use of oral or parenteral corticosteroids for asthma; participant lack of satisfaction with treatment; and physician clinical judgment for safety reasons.⁷⁻⁹

There were 14 prespecified secondary outcomes. Of these, 9 have been analyzed and are presented herein: asthma exacerbations, lung function, airway hyperresponsiveness, asthma symptoms, asthma control, asthma-specific quality of life,¹⁰ achieving vitamin D sufficiency (25-hydroxyvitamin D level ≥ 30 ng/mL), total inhaled corticosteroids dose, and airway inflammation (eTable 1 in Supplement). Asthma exacerbations were defined by meeting criteria for treatment failure and 1 or more of the following: failure to respond to rescue algorithm within 48 hours; FEV₁ of less than 50% of baseline measurement on 2 consecutive measurements; FEV₁ of less than 40% of predicted level on 2 consecutive measurements; use of 16 puffs/d or more of as-needed levalbuterol for 48 hours; experiencing an exacerbation of asthma according to physician opinion; and use of oral or parenteral corticosteroids due to asthma.¹⁸,¹⁹,²²

Asthma symptoms were measured using an electronic diary and the Asthma Symptom Utility Index (ASUI).²³ Participants were instructed to complete the electronic diary every morning and evening and asked to grade the following symptoms: shortness of breath, chest tightness, wheezing, cough, and phlegm or mucus. Symptoms were graded as 0 (absent; no symptom present), 1 (mild; symptom was minimally troublesome or not sufficient to interfere with normal daily activity or sleep), 2 (moderate; symptom was sufficiently troublesome to interfere with normal daily activity or sleep), or 3 (severe; symptom was so severe as to prevent normal activity or sleep, or both). The scores on the ASUI range from 0 to 1; a higher score indicates better symptom control (0.88, mild; 0.64, moderate; and 0.47, severe asthma) and the minimal clinically important difference is 0.09.²⁴

Asthma control was measured using the Asthma Control Test (ACT).²⁵ The proportion of days in which a participant had no asthma symptoms or use of levalbuterol was recorded in the electronic diary. The scores on the ACT range from 5 to 25; higher scores indicate better asthma control and the minimal clinically important difference is 3.²⁶ Asthma-specific quality of life was measured using the Asthma Bother Profile questionnaire.²⁶ The scores on the Asthma Bother Profile range from 0 to 75 and higher scores indicate poorer quality of life. Serum 25-hydroxyvitamin D level was measured at baseline and at the end of each ciclesonide treatment phase using the DiaSorin LIAISON vitamin D assay. Vitamin D responder status was defined as vitamin D₃–treated participants who achieved a 25-hydroxyvitamin D level of 30 ng/mL or greater.

Airway inflammation was measured by performing a differential cell count from induced sputum samples collected at the end of the 4-week run-in and at 12 weeks. Race was assessed...
Table 1. Baseline Characteristics of Randomized Participants (continued)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 207)</th>
<th>Vitamin D3 (n = 201)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)*</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>39.5 (12.7)</td>
<td>39.9 (13.1)</td>
</tr>
<tr>
<td>Asthma, y</td>
<td>25.0 (12.8)</td>
<td>24.9 (13.3)</td>
</tr>
<tr>
<td>Body mass index**</td>
<td>31.53 (9.51)</td>
<td>32.00 (8.19)</td>
</tr>
<tr>
<td>Positive skin test, median (IQR)</td>
<td>3.0 (2.0 to 6.0)</td>
<td>3.0 (2.0 to 6.0)</td>
</tr>
<tr>
<td>Symptom score*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning</td>
<td>0.41 (0.36)</td>
<td>0.41 (0.34)</td>
</tr>
<tr>
<td>Afternoon and evening</td>
<td>0.43 (0.40)</td>
<td>0.44 (0.35)</td>
</tr>
<tr>
<td>Asthma Symptom Utility Index score*</td>
<td>0.82 (0.12)</td>
<td>0.83 (0.11)</td>
</tr>
<tr>
<td>Asthma control, median (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test score*</td>
<td>20.0 (17.0 to 22.0)</td>
<td>19.0 (17.0 to 22.0)</td>
</tr>
<tr>
<td>Proportion of days*</td>
<td>7 (0 to 31)</td>
<td>0 (0 to 29)</td>
</tr>
<tr>
<td>Asthma-related quality of life, median (IQR)*</td>
<td>18.0 (12.0 to 28.0)</td>
<td>19.0 (12.0 to 26.0)</td>
</tr>
<tr>
<td>Level of 25-hydroxyvitamin D, median (IQR), ng/mL</td>
<td>18.8 (13.4 to 23.7)</td>
<td>19.9 (14.5 to 25.0)</td>
</tr>
<tr>
<td>Peak flow, L/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morning</td>
<td>393.6 (107.0)</td>
<td>394.4 (103.9)</td>
</tr>
<tr>
<td>Afternoon and evening</td>
<td>399.4 (109.2)</td>
<td>399.2 (103.9)</td>
</tr>
<tr>
<td>FEV1 before albuterol use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level, L</td>
<td>2.62 (0.83)</td>
<td>2.63 (0.78)</td>
</tr>
<tr>
<td>% Predicted</td>
<td>80.5 (14.2)</td>
<td>80.7 (13.8)</td>
</tr>
<tr>
<td>Ratio of FEV1 to forced vital capacity</td>
<td>0.71 (0.09)</td>
<td>0.72 (0.09)</td>
</tr>
<tr>
<td>After prednisone, % change*</td>
<td>-0.49 (8.25)</td>
<td>-0.88 (7.14)</td>
</tr>
<tr>
<td>FEV1 after albuterol use, % predicted</td>
<td>92.09 (13.65)</td>
<td>91.32 (13.83)</td>
</tr>
<tr>
<td>Maximum albuterol reversibility, % change</td>
<td>18.41 (11.84)</td>
<td>16.63 (11.56)</td>
</tr>
<tr>
<td>Methacholine PC20, geometric mean (CV), mg/mL</td>
<td>1.85 (1.67)</td>
<td>2.05 (1.61)</td>
</tr>
<tr>
<td>Sputum eosinophils, median (IQR), %</td>
<td>0.40 (0 to 1.30)</td>
<td>0.30 (0 to 1.30)</td>
</tr>
</tbody>
</table>

Abbreviations: CV, coefficient of variation; ED, emergency department; FEV1, forced expiratory volume in the first second of expiration; IQR, interquartile range; PC20, provocative concentration at which FEV1 decreased by 20%.

* Unless otherwise indicated.

** Included American Indian, Alaskan Native, or participant-selected “other” category.

† Dosage of 40 mg for 5 to 7 days.

‡ Calculated as weight in kilograms divided by height in meters squared.

§ Indicates the average score for shortness of breath, chest tightness, wheezing, cough, and phlegm or mucus (0 = absent, 1 = mild, 2 = moderate, 3 = severe).

∥ Score range is 0 to 1 (a higher score indicates better symptom control).

(§) Score is sum of questions 1 through 5 (score range for individual questions is 1 to 5; higher values indicate better asthma control).

‖ Based on use of levalbuterol or any symptoms reported during the 14 days prior to the end of run-in.

∥∥ Score is sum of scores across 18 questions on the Asthma Bother Profile Scale (score range, 0–5; response range, “no bother” to “makes my life a misery”).

Results

Enrollment and Study Completion
A total of 1523 participants were enrolled and 408 were randomized (n = 201 in the vitamin D3 group and n = 207 in the placebo group). Overall, the completion rate was similar in both groups (89% [95% CI, 85%-93%] in the vitamin D3 group vs 87% [95% CI, 83%-92%] in the placebo group), with a median duration of follow-up of 28.1 weeks (interquartile range [IQR], 27.6-28.7 weeks). The most common reasons for study discontinuation postrandomization were withdrawal of consent and loss to follow-up (Figure 1).

Baseline Characteristics
At baseline, there were no significant differences in participant characteristics between the groups (Table 1). The study enrolled adult participants with symptomatic asthma (median asthma control days, 0% [IQR, 0%-31%]; median ACT

by participant self-report, using National Institutes of Health race/ethnicity reporting standards and categories.

Statistical Analysis
The primary analysis was intent-to-treat, comparing treatment groups in a Cox proportional hazards regression model that estimated a hazard ratio (HR) for events across the entire 28-week treatment period, as well as within each of the treatment phases. The trial was designed to have a sample size of 400 for 90% power to detect an HR for treatment failures of 0.56 (a reduction from 40.0% in the placebo group and 24.5% in the vitamin D3 group based on data from the Asthma Clinical Research Network Salmeterol or Corticosteroids study and Salmeterol + Inhaled Corticosteroids trials), assuming an overall P value of .05, 2-sided test, and 15% withdrawal. The model included dropouts as censored observations, and was adjusted for clinical center, BMI, and race. An additional model incorporated the ability to taper inhaled corticosteroids during the treatment phases as a time-dependent covariate. The overall rates of treatment failures and exacerbations were evaluated in proportional hazards regression models for recurrent events.

Repeated-measures analysis of covariance models were used for secondary outcomes, with adjustment for the baseline stratification factors of clinical center, BMI, and race. Total inhaled corticosteroids dose was compared between the treatment groups in a repeated-measures analysis of variance model. The difference in inhaled corticosteroids dose was evaluated for each of the 2 taper phases with a Bonferroni correction applied to the significance criterion. The ability to taper was evaluated with χ2 tests. Prespecified subgroup analyses involving BMI and race were evaluated using interaction terms in the relevant models. A prespecified exploratory responder analysis was performed that evaluated outcomes in those participants treated with vitamin D3 who achieved a serum 25-hydroxyvitamin D level of 30 ng/mL or greater vs placebo. Baseline 25-hydroxyvitamin D level was evaluated as a predictor of achieving 25-hydroxyvitamin D of 30 ng/mL or greater in a logistic regression model. All tests were 2-sided and based on a significance criterion of P < .05. Without formal adjustment for the number of secondary analyses that were performed, the secondary results should be considered exploratory. All analyses were performed using SAS version 9.3 (SAS Institute Inc.).
score, 20 [IQR, 17-22]) and mild spirometric impairment. Health care use, corticosteroid courses, and days of school or work missed due to asthma did not differ significantly between groups. The mean baseline 25-hydroxyvitamin D level was 18.8 ng/mL (95% CI, 18.2-19.5 ng/mL). Of the participants, 54 (13%) had 25-hydroxyvitamin D levels of less than 10 ng/mL and 217 (53%) had levels of less than 20 ng/mL. Of the participants, 13% in the vitamin D group and 18% in the placebo group reported taking supplements containing vitamin D at baseline. Of the participants, 18% met FEV1 criteria for oral corticosteroid response. Following the run-in with inhaled ciclesonide, adherence was 96% (IQR, 90%-99%) in those receiving placebo (vitamin D3) and 94% (IQR, 90%-98%) in the placebo group (P = .56).

Serum 25-Hydroxyvitamin D Levels
In the vitamin D group, 82% of participants achieved a serum 25-hydroxyvitamin D level of 30 ng/mL or greater. The mean serum 25-hydroxyvitamin D level in the vitamin D group was 41.9 ng/mL (95% CI, 40.1-43.7 ng/mL) at 12 weeks (range, 6.3-97.3 ng/mL), an effect which persisted at 20 weeks (42.6 ng/mL; 95% CI, 40.8-44.3 ng/mL) and 28 weeks (41.8 ng/mL; 95% CI, 39.8-43.7 ng/mL). Median serum 25-hydroxyvitamin D levels remained less than 20 ng/mL in the placebo group, although 9% of participants treated with placebo were observed to have 25-hydroxyvitamin D levels of 30 ng/mL or greater at 12 weeks (range, 4.4-52.2 ng/mL). Among the participants, 13% in the vitamin D group and 15% in the placebo group reported taking supplements containing vitamin D at the end of the trial. In those treated with vitamin D3, baseline serum 25-hydroxyvitamin D level was associated with vitamin D sufficiency at 12 weeks (odds ratio, 2.1; 95% CI, 1.2-3.8) for achieving 25-hydroxyvitamin D level of 30 ng/mL or greater observed for each 10-ng/mL increment. Median adherence was 96% (IQR, 90%-99%) in those receiving vitamin D3 and 96% (IQR, 89%-99%) in those receiving placebo (P = .85).

Median ciclesonide adherence was 95% (IQR, 90%-98%) in the vitamin D group and 94% (IQR, 90%-98%) in the placebo group (P = .56).

Primary Outcome of Asthma Treatment Failures
The addition of vitamin D3 to ciclesonide did not significantly reduce the rate of first treatment failure compared with placebo; 28% (95% CI, 21%-34%) and 29% (95% CI, 23%-35%) of participants in each group, respectively, experienced at least 1 treatment failure during 28 weeks (adjusted HR, 0.9 [95% CI, 0.6-1.3]; P = .54; Figure 2). The overall treatment failure rate was not reduced in the vitamin D group at 0.58/person-year (95% CI, 0.47-0.69/person-year) vs 0.74/person-year (95% CI, 0.61-0.87/person-year) in the placebo group (adjusted HR, 0.8 [95% CI 0.6-1.1]; P = .17; Table 2). These estimates did not change significantly when taper status was included in the

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Table 2. Primary Treatment Failure and Exacerbation for Intent-to-Treat Vitamin D3 vs Placebo

<table>
<thead>
<tr>
<th>Treatment Failure*</th>
<th>Vitamin D3 (n = 201)</th>
<th>Placebo (n = 207)</th>
<th>Unadjusted HR (95% CI)</th>
<th>P Value</th>
<th>Adjusted HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First, No. of events (%) [95% CI]</td>
<td>53 (28) [21-34]</td>
<td>58 (29) [23-35]</td>
<td>0.9 (0.6-1.3)</td>
<td>.57</td>
<td>0.9 (0.6-1.3)</td>
<td>.54</td>
</tr>
<tr>
<td>Overall, No. of events (rate/person-year) [95% CI]*</td>
<td>63 (0.58) [0.47-0.69]</td>
<td>83 (0.74) [0.61-0.87]</td>
<td>0.8 (0.5-1.1)</td>
<td>.17</td>
<td>0.8 (0.6-1.1)</td>
<td>.17</td>
</tr>
<tr>
<td>Exacerbation*</td>
<td>28 (13) [8-18]</td>
<td>37 (19) [13-24]</td>
<td>0.7 (0.5-1.2)</td>
<td>.24</td>
<td>0.7 (0.4-1.2)</td>
<td>.21</td>
</tr>
<tr>
<td>Overall, No. of events (rate/person-year) [95% CI]*</td>
<td>28 (0.26) [0.18-0.33]</td>
<td>45 (0.40) [0.30-0.50]</td>
<td>0.6 (0.4-1.0)</td>
<td>.06</td>
<td>0.63 (0.39-1.01)</td>
<td>.05</td>
</tr>
</tbody>
</table>

Abbreviation: HR, hazard ratio.
* Adjusted for center, black race, and body mass index greater than 25.
* Defined as 1 or more of the following: peak expiratory flow of 65% or less of baseline measurement on 2 of 3 consecutive measurements; forced expiratory volume in the first second of expiration (FEV1) of 80% or less of baseline measurement on 2 consecutive measurements; increase in levibuterol dose of 8 or more puffs/day for 48 hours (vs baseline dose); additional use of inhaled corticosteroid, or use of oral or parenteral corticosteroids for asthma; emergency department or hospitalization for asthma with systemic corticosteroid use; participant lack of satisfaction with treatment; or physician clinical judgment for safety reasons.

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Figure 2. Primary Treatment Failure Outcome

Vertical bars represent censored events. The adjusted hazard ratio for time from randomization to first treatment failure was 0.9 (95% CI, 0.6-1.3) for the vitamin D3 vs placebo treatment groups (P = .54).
Ultimately, 96% (95% CI, 93%-99%) of the vitamin D3 group
cicled a 75% reduction in the starting dose of ciclesonide
(95% CI, 84%-93%) vs 80% (95% CI, 75%-86%), respectively,
achieved a 50% reduction in the starting dose of ciclesonide
(95% CI, 0.4-1.2), P = .21. The addition of vitamin D2 also did not signifi-
cantly reduce the overall exacerbation rate (0.26/person-year [95% CI, 0.18-0.33/person-year] in the vitamin D2 group
vs 0.40/person-year [95% CI, 0.30-0.50/person-year] in the placebo
group; adjusted HR, 0.63 [95% CI, 0.39-1.01], P = .05; Table 2 and Figure 3). These estimates did not change signific-
antly when taper status was included in the model (eTable 2 in Supplement).

Secondary Outcomes

Asthma Exacerbations

The addition of vitamin D3 to ciclesonide did not significa-
cantly reduce the rate of first asthma exacerbation compared
with placebo; 13% (95% CI, 8%-18%) and 19% (95% CI, 13%-24%)
of participants in each group, respectively, experienced at
least 1 exacerbation during 28 weeks (adjusted HR, 0.7 [95% CI,0.4-1.2], P = .21). The addition of vitamin D2 also did not signifi-
cantly reduce the overall exacerbation rate (0.26/person-year [95% CI, 0.18-0.33/person-year] in the vitamin D2 group
vs 0.40/person-year [95% CI, 0.30-0.50/person-year] in the placebo
group; adjusted HR, 0.63 [95% CI, 0.39-1.01], P = .05; Table 2 and Figure 3). These estimates did not change signific-
antly when taper status was included in the model (eTable 2 in Supplement).

Ciclesonide Dosing

Ultimately, 96% (95% CI, 93%-99%) of the vitamin D3 group
and 91% (95% CI, 87%-95%) of the placebo group achieved a
50% reduction in the starting dose of ciclesonide (P = .07); 89%
(95% CI, 84%-93%) vs 80% (95% CI, 75%-86%), respectively,
achieved a 75% reduction in the starting dose of ciclesonide
(P = .03). During the third treatment phase (phase 2b), a dif-
cference of 14.9 μg/d (95% CI 2.1-27.7 μg/d) in cumulative cicle-
sonide dosing was observed between the groups (the vita-
mim D3 group received 111.3 μg/d [95% CI, 102.2-120.4 μg/d] of
ciclesonide and the placebo group received 126.2 μg/d [95% CI,
117.2-135.3 μg/d] (P = .02; Bonferroni-adjusted P = .03 for the 2 taper phases).

Other Secondary Outcomes and Subgroup Comparisons

Treatment with vitamin D3 had no significant effect on lung
function or airway hyperreactivity (eTable 4 and eFigure 3 in
Supplement). Neither asthma quality of life nor asthma con-
control improved with vitamin D3 (eTable 4 in Supplement).
Sputum eosinophilia did not change after treatment with vi-
tamin D3.

Black race was associated with lower baseline 25-
hydroxyvitamin D levels, with a mean of 15.6 ng/mL (95% CI,
14.4-16.8 ng/mL) vs 20.4 ng/mL (95% CI, 19.6-21.1 ng/mL) in all
other races (P < .001). Although nonblack participants demon-
strated a significant reduction in the rate of first asthma exac-
beration with vitamin D3 (HR, 0.49 [95% CI, 0.25-0.96], P = .04),
there was no significant interaction between race and treat-
ment for this outcome (P = .07) or any other outcomes (eTable
5 in Supplement). Increased BMI was not associated with an in-
creased risk of treatment failures or exacerbations in either treat-
group, and no interactions were significant.

Exploratory Vitamin D3 Responder Analyses

When vitamin D3–treated participants who achieved a 25-
hydroxyvitamin D level of 30 ng/mL or greater (n = 157 of 201)
were compared with all placebo-treated participants (n = 207),
the rate of first treatment failure was not reduced: 25% (95% CI,
18%-32%) vs 29% (95% CI, 23%-35%), respectively, during
28 weeks (adjusted HR, 0.8 [95% CI, 0.5-1.2], P = .20; eTable 6 in
Supplement). The rate of first exacerbation was lower for the
vitamin D3 group (11%; 95% CI, 6%-16%) compared with the
placebo group (19%; 95% CI, 13%-24%) (adjusted HR, 0.57
[95% CI, 0.33-0.99], P = .05). Among participants who re-
sponded to treatment, the overall rates were lower for treat-
ment failures (adjusted HR, 0.6 [95% CI, 0.4-0.9], P = .02) and
exacerbations (adjusted HR, 0.5 [95% CI, 0.3-0.8], P = .01). The
change in serum 25-hydroxyvitamin D level from baseline to
12 weeks was significantly associated with the rate of treat-
ment failures and exacerbations. Each 10-ng/mL increase in
serum 25-hydroxyvitamin D level was associated with a re-
duction in the overall rate of treatment failures (HR, 0.88 [95%
CI, 0.78-0.99], P = .04) and overall rate of exacerbations (HR,
0.80 [95% CI, 0.67-0.96], P = .02).

Adverse Events

Nonasthma adverse events did not differ significantly be-
tween the treatment groups. The ratio of urine calcium to cre-
atinine exceeded 0.37 in 14 participants, all of which resolved
on repeat measurement. No instances of nephrolithiasis were
reported.

Discussion

In this randomized clinical trial of vitamin D3 added to cicle-
sonide in patients with symptomatic asthma, supplemental vi-
tamin D3 did not result in a significant reduction in the rate of
first treatment failure or exacerbation. There was also no sig-
ificant reduction in the secondary end points related to
asthma control, airway function, quality of life, or airway inflam-
ination.
Of the 9 secondary end points assessed, the only significant association observed was with dose of inhaled corticosteroids. Vitamin D$_3$ allowed participants to taper inhaled corticosteroids to as little as 25% of the original dose, but the absolute difference in inhaled corticosteroids dose was small (14.9 µg/d). Given that concern has been raised with the safety of both long-acting β-agonists and anticholinergics<sup>26,29</sup> (these agents are commonly added when inhaled corticosteroids are not optimally efficacious), this small effect of add-on vitamin D$_3$ might be important over time, but this would require further investigation. Because of the large number of secondary outcomes and lack of adjustment for multiple comparisons, this finding needs to be considered exploratory and interpreted with caution.

Our study must be interpreted in the context of a number of potential limitations. First, although vitamin D$_3$ did not reduce the treatment failure rate, it is possible that the failure to observe an effect is attributable to inadequate power. There was a lower than expected event rate (29%) in the control group, which could have limited the ability to detect a significant difference. The study was powered appropriately for detecting relatively moderate size population effects, but it was not designed for establishing the existence of smaller effects. Thus, it is possible that studies of larger sample size and longer duration will be needed to fully resolve the question of vitamin D$_3$ efficacy on asthma. Second, although we demonstrated significant increases in serum 25-hydroxyvitamin D level after 12 weeks, there was a wide range of observed 25-hydroxyvitamin D levels in the study population at this time point, suggesting that variable response to vitamin D$_3$ may have occurred. If associated with delayed onset of maximal 25-hydroxyvitamin D level in some participants, this may have underestimated the effect of vitamin D$_3$ and could explain the differences we observed between time-dependent outcomes and total numbers of treatment failures or exacerbations.

Third, during the course of designing and conducting the VIDA trial, consensus definitions of asthma exacerbations have changed, resulting in our primary outcome of treatment failure being different from the currently recommended definition of an asthma exacerbation for asthma clinical trials.<sup>27</sup> Although this does not directly affect the internal validity of the trial, it does affect the generalizability of our findings. Fourth, although vitamin D insufficiency may induce a proinflammatory state, we did not observe any association between the sputum differential cell counts and vitamin D status and do not have data to determine whether vitamin D$_3$ treatment altered sputum inflammatory biomarkers; thus, the effect of vitamin D$_3$ treatment on airway inflammation in asthma remains unknown. Fifth, although we did not observe any adverse events associated with vitamin D$_3$ treatment in the context of our trial, we cannot generalize beyond what was observed with regard to the long-term safety of vitamin D$_3$ treatment in asthma. Long-term risks of vitamin D$_3$ could be similar, less than, or greater than what we observed, and long-term studies will be needed to shed further light on this issue.

Conclusions

In adults with persistent asthma and lower vitamin D levels, treatment with vitamin D$_3$ did not reduce the rate of first treatment failure or exacerbation. These findings do not support a strategy of therapeutic vitamin D$_3$ supplementation in patients with symptomatic asthma.
Vitamin D$_3$ and Asthma Treatment Failures

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REFERENCES