High-Dose Vitamin D Does Not Prevent Postoperative Recurrence of Crohn's Disease in a Randomized Placebo-Controlled Trial

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Q7 **BACKGROUND & AIMS:** **Vitamin D deficiency is common in Crohn's disease (CD). High-dose vitamin D had anti-inflammatory effects in preclinical studies and trials of patients with CD. We performed a randomized trial to determine whether high-dose vitamin D prevents postoperative recurrence of CD after ileocolonic resection.**

METHODS: **Patients with CD after ileocolonic resection with ileocolonic anastomosis were assigned randomly to groups given weekly 25,000 IU oral vitamin D (n = 72) or placebo (n = 71) for 26 weeks, at 17 hospitals in The Netherlands and Belgium, from February 2014 through June 2017. Patients were assessed at baseline and at weeks 2, 6, 12, and 26 for laboratory and clinical parameters, and underwent ileocolonoscopy at 26 weeks. The primary end point was endoscopic recurrence (modified Rutgeerts score, ≥i2b, as assessed by blinded readers) at 26 weeks. Secondary end points included clinical recurrence (Crohn's disease activity index, ≥220), quality of life (measured by the 36-Item Short Form Health Survey, Inflammatory Bowel Disease Questionnaire, and EuroQol, a 5-dimension questionnaire), and outcomes associated with the baseline serum concentration of vitamin D.**

RESULTS: **In the vitamin D group, serum levels of 25-hydroxy vitamin D increased from a median of 42 nmol/L at baseline to 81 nmol/L at week 26 ($P < .00001$), whereas levels did not change significantly in the placebo group and remained unchanged at 43 nmol/L. In the intention-to-treat analysis, the proportion of patients with endoscopic recurrence at 26 weeks did not differ significantly between the vitamin D vs the placebo group (58% vs 66%; $P = .37$). The cumulative rate of clinical recurrence did not differ significantly between the groups (18.1% in the vitamin D group vs 18.3% in the placebo group; $P = .91$). Quality of life improved slightly over time in both groups, but did not differ significantly between groups ($P = .07$). There were few adverse events in either group.**

Abbreviations used in this paper: 25-OH vitamin D, 25-hydroxy vitamin D; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; IBD, Inflammatory bowel disease; IQR, interquartile range; OR, odds ratio; VDR, vitamin D receptor.

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CONCLUSIONS: **High-dose vitamin D, compared with placebo, did not reduce the incidence of postoperative endoscopic or clinical recurrence of CD in patients who underwent ileocolonic resection with ileocolonic anastomosis. ClinicalTrials.gov no: NCT02010762.**

Keywords: Inflammatory Bowel Disease; Neoterminal Ileitis; Chemoprevention; Surgery; Complication.

The majority of patients suffering from Crohn's disease (CD) and other immune-mediated diseases have low serum concentrations of 25-hydroxy vitamin D (25-OH vitamin D).[1–4] National guidelines differ significantly on normal serum concentrations. Vitamin D has anti-inflammatory and antifibrotic properties in the gut.[5–7]

Calcitriol, the active form of vitamin D, down-regulates several proinflammatory cytokines.[8–10] Furthermore, in vitamin D–deficient interleukin 10 knockout mice, diarrhea and wasting improved significantly after 2 weeks of vitamin D treatment.[11]

Binding of calcitriol to the vitamin D receptor (VDR) stimulates transcription of vitamin D–responsive genes. VDR expression is down-regulated considerably in inflammatory bowel disease (IBD) patients regardless of inflammation, compared with healthy controls.[12] Furthermore, a murine VDR knockout model is more susceptible to experimental colitis.[13]

In CD patients, serum 25-OH vitamin D levels less than 50 nmol/L have been associated with an increased risk of surgery compared with levels greater than 75 nmol/L.[14] One prospective trial with 104 patients randomized 1:1 to receive vitamin D3 or placebo showed that the clinical relapse rate of CD patients in medical remission was lower in patients treated with daily 1200 IU vitamin D compared with placebo (13% vs 29%).[15] Endoscopy was not performed in this trial and clinical outcomes just failed to reach statistical significance ($P = .06$).

CD recurs in 50% to 80% of patients after ileocolonic within 6 to 12 months.[16,17] Because the majority of CD patients require surgery during their disease course,[18] it is important to develop therapeutic interventions that alter the 'natural course' of CD recurrence. To date, medical treatments to prevent recurrence have had limited success.[19–23]

Because vitamin D has potential disease-modulating effects and it is safe and inexpensive, we investigated the anti-inflammatory effect of high-dose oral vitamin D on the recurrence of postoperative CD in a placebo-controlled, double-blind, randomized, multicenter trial.

Methods

Patients

Patients undergoing ileocecal or ileocolonic resection with ileocolonic anastomosis for CD were recruited across 17 regional and academic hospitals in The Netherlands and Belgium between February 2014 and June 2017. The Institutional Board and Medical Ethical Committee at each site approved the trial, and patients provided written informed consent.

Patients had established ileal or ileocolonic CD, were 18 years of age or older, and underwent a first or second ileocecal or ileocolonic resection with ileocolonic anastomosis or had closure of a loop ileostomy after a previous ileocecal or ileocolonic resection. Patients with normal serum calcium levels not exceeding the upper limit of normal were enrolled within 14 days after surgery.

Exclusion criteria included the presence of macroscopic evidence for CD at the proximal or distal resection margin. Patients with an ileorectal anastomosis or active perianal fistulae were excluded. Patients with an extensive small-bowel resection (>60 cm small bowel removed), additional stricturoplasty or other small-bowel resections, a postoperative definite stoma, primary hyperparathyroidism, sarcoidosis or tuberculosis, and pregnant/breastfeeding patients were ineligible. Postoperatively, all CD medication was stopped except for ongoing steroids, which were tapered gradually in the weeks after surgery according to local guidelines. No multivitamin or open-label vitamin D preparations were allowed during the study period and patients were not allowed to use tanning beds.

Study Design

Patients were randomized 1:1 to receive weekly 25,000 IU of vitamin D3 (cholecalciferol in 1-mL oral vials, D-Cura; Laboratoires SMB, Brussels, Belgium) or comparable placebo vials (Laboratoires SMB). Randomization was performed at the pharmacy of the Amsterdam University Medical Center within 2 weeks after surgery, and subjects were stratified by baseline 25-OH vitamin D level (<75 or ≥75 nmol/L).[24] Patients, attending physicians, and all other study personnel were blinded to the treatment regimen and laboratory results. Cholestyramine and/or loperamide were allowed for the treatment of bile acid diarrhea. In that case, patients were instructed to take the study drug at least 6 hours after the intake of cholestyramine to prevent interaction. The vitamin D dosage was selected based on the balance between potential benefits and risks, taking into account previously published data.[15,25,26]

Patients were assessed at baseline and at weeks 2, 6, 12, and 26 after randomization. Laboratory assessment included hematology, liver, and kidney function tests, as well as C-reactive protein (CRP), serum albumin, 25-OH vitamin D, calcium and parathyroid hormone, and fecal

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calprotectin levels. Determination of 25-OH vitamin D was performed using the chemiluminescent immunoassay technology (Liaison; DiaSorin, Stillwater, MN). The Crohn's Disease Activity Index (CDAI) was measured at each visit based on 7-day scoring by the patient before this visit.[27] Moreover, quality-of-life questionnaires were administered at each visit: the EuroQol, a 5-dimension questionnaire, the 36-Item Short Form Health Survey, and the Inflammatory Bowel Disease Questionnaire.[28–30] At week 26, an ileocolonoscopy was performed. Central readers scored the ileocolonoscopy for the modified Rutgeerts score.[31]

All authors had access to the study data and reviewed and approved the final manuscript.

End Points

The primary end point was the proportion of patients with significant endoscopic recurrence in the neoterminal ileum 6 months after surgery, defined as a modified Rutgeerts score of i2b or higher.[31]

Secondary end points included endoscopic recurrence at week 26, defined as a Rutgeerts score of i2a or higher and i1 or higher, the proportion of patients with clinical recurrence (CDAI, ≥220) at any time during follow-up evaluation, differences in recurrence among all patients with low 25-OH vitamin D levels at baseline, quality of life as measured by each of the questionnaires, and adverse events.

Patients who developed symptoms of CD recurrence earlier than 6 months after surgery underwent fecal calprotectin and CRP testing. If the fecal calprotectin concentration was 250 μg/g or greater and the CRP was 5 mg/L or greater, patients underwent an earlier ileocolonoscopy. If this procedure was fewer than 6 weeks before the primary end point, the endoscopic score was used for the primary end point (last observation carried forward). If the ileocolonoscopy was more than 6 weeks before the primary end point and showed recurrence (Rutgeerts score of ≥i2b by the local investigator), the patient was considered to have failed treatment and received alternative treatment at the discretion of the local investigator.

Central Reading of Endoscopies

All videotapes of the ileocolonoscopies were blinded and scored independently at the end of the trial by 2 experienced IBD endoscopists (G.D. and P.B.). The videos with disagreement in scoring were reviewed during a second round by the 2 readers together during an adjudication meeting, after which the agreed score was used for analysis.

Sample Size Calculation and Statistical Analysis

As a basis for sample size calculation, we reviewed the endoscopic recurrence rates of CD patients after ileocolonic resection with anastomosis at the Amsterdam University Medical Center between 2007 and 2013 who had not received postoperative CD therapy (n = 105). Of these, 55% had significant endoscopic recurrence (≥i2b) after 6 to 12 months.[32] Based on this we estimated the rate of endoscopic recurrence on placebo to be 55%. At the time the study was designed, 1 randomized placebo-controlled trial with vitamin D in CD was published using clinical relapse as the primary end point.[15] Risk reduction of relapse with vitamin D in this trial was 45%. We decided to power the trial for an absolute effect size of 25% for significantly less endoscopic recurrence in the vitamin D group.

To attain a power of at least 80% in a 2-sided test model with an α error of less than .05, inclusion of 61 patients in each group was necessary. With an estimated loss to follow-up evaluation of 15%, the target sample size was 144. Endoscopic recurrence rates were analyzed by the Pearson chi-square test. The time to clinical recurrence was analyzed using Kaplan–Meier curves and the log-rank test. The association between recurrence and risk factors of recurrence was analyzed using logistic regression. Logistic regression also was used to evaluate whether the vitamin D treatment effect on recurrence rate differed between subgroups of patients. Change of quality of life was analyzed using linear mixed-effect regression models with time and treatment as fixed factors. The interaction test between time and treatment was used to test the null hypothesis that the averaged change patterns in the 2 treatment groups did not differ. In addition, we compared the averaged quality-of-life levels at 26 weeks, estimated from the mixed-effects models. The effect of treatment on serum 25-OH vitamin D levels and other

What You Need to Know

Background

Vitamin D deficiency is common in patients with Crohn's disease (CD). Some studies have reported anti-inflammatory effects of vitamin D in models of or patients with CD.

Findings

Weekly 25,000 IU of vitamin D doubled serum 25-hydroxy vitamin D levels in patients randomized to vitamin D after 6 weeks of treatment and remained stable thereafter. However, there was no difference in the incidence of endoscopic or clinical recurrence at week 26 in the vitamin D vs the placebo groups. Outcome was not affected by baseline serum vitamin D level, season of inclusion, or ethnicity.

Implications for patient care

Oral high-dose vitamin D (25,000 IU) weekly is well tolerated and normalizes serum concentrations in patients with CD. However, it does not prevent postoperative recurrence of CD after ileocolonic resection.

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laboratory parameters were analyzed with similar linear mixed-effects regression models, after logarithmic transformation for some parameters to improve goodness-of-fit to the mixed-effects regression models. Drop-out and adverse event rates were compared between the 2 treatment groups with the Pearson chi-square test. A *P* value of .05 or less was used to indicate a statistically significant difference. Both an intention-to-treat analysis (in patients receiving at least 1 dose of trial medication) and a per-protocol analysis were performed.

Results

Demographic and Baseline Disease Characteristics

In total, 143 patients were randomized, of whom 72 patients received vitamin D and 71 patients received placebo. Patient characteristics are shown in Table 1. Fifty-seven men and 86 women were included, with a median age of 32 years (interquartile range [IQR], 25–43 y). Twenty-five patients had an inflammatory disease phenotype, 75 patients had stricturing disease, and 36 patients had a penetrating phenotype as based on the Montreal classification at the time of surgery.[33] Twenty-nine patients underwent previous surgical resections. The 2 groups were well balanced with respect to demographic and disease characteristics (Table 1) (all data nonsignificantly different).

In the placebo group, all but 1 patient received at least 1 dose of trial medication (Supplementary Figure 1). Hence, the entire intention-to-treat population consisted of 72 patients randomized to vitamin D and 70 patients to placebo. Because not all patients underwent the week 26 endoscopy, we analyzed a modified intention-to-treat population of patients who underwent colonoscopy, consisting of 63 patients on vitamin D and 55 on placebo. In both groups, 3 patients discontinued trial medication before month 6 because of clinical disease exacerbation, of whom 2 patients in the placebo group needed repeat surgery. The other 4 patients with early clinical relapse underwent colonoscopy and this score was used for the primary end point. In total, 58 patients completed the full study in the vitamin D group and 54 patients in the placebo group (per-protocol population). Three patients discontinued treatment for adverse events (2 in the vitamin D group, and 1 in the placebo group). The total drop-out rate was 18.2% (26 of 143). Drop-out rates did not differ significantly between both groups (13 of 72 vs 13 of 71; $P = .999$).

Treatment Effect on Serum 25-Hydroxy Vitamin D Levels

The 25-OH vitamin D serum median concentrations at baseline were 42 nmol/L (IQR, 10–119 nmol/L) and 43 nmol/L (IQR, 7–108 nmol/L) for patients on vitamin D treatment and placebo, respectively (Figure 1). There was a clear and highly significantly different change pattern of 25-OH vitamin D levels between the 2 treatment groups ($P < .00001$). 25-OH vitamin D concentrations were stable in the placebo group throughout the duration of the trial (average change, 3 nmol/L; SE, 4; $P = .74$) and increased significantly by an average of 40 nmol/L (SE, 5; $P < .00001$) by week 6 in the vitamin D treatment group, further remaining at this increased level for the remaining duration of the trial. This effect represented an increase of 101% (95% CI, 72%–135%) of the median 25-OH vitamin D levels. Concomitant cholestyramine had no effect on median serum 25-OH vitamin D levels.

The effect of vitamin D treatment on other biochemical parameters is shown in Supplementary Table 1. There were no significantly different change patterns between the 2 treatment groups, except for parathyroid hormone levels that increased slightly more in patients treated with placebo (from slightly lower baseline levels). Fecal calprotectin levels decreased between baseline and week 6 in the placebo group, but increased slightly thereafter and were not significantly different at week 26.

Endoscopic Recurrence

Table 2 summarizes the consensus scoring of the endoscopic findings.

For the primary outcome analysis of endoscopic recurrence, all patients who discontinued the trial before week 26 without having an endoscopy were considered to have failed the treatment (Rutgeerts score, ≥i2b). In this pure intention-to-treat population, 42 of 72 (58%) patients in the vitamin D group vs 46 of 70 (66%) in the placebo group had endoscopic recurrence (odds ratio [OR]; 95% CI; $P = .37$) (Figure 2*A*).

In the modified intention-to-treat population (patients with week 26 endoscopy), 33 of 63 (52%) patients had a Rutgeerts score of i2b or higher in the vitamin D group, and 31 of 55 (56%) in the placebo group ($P = .71$) (Figure 2*B*). With a different cut-off value for recurrence of Rutgeerts score of i2a or higher, recurrence rates were 87% vs 82% in the vitamin D and placebo groups, respectively ($P = .45$), and with a Rutgeerts score of i1 or higher recurrence rates were 94% and 86%, respectively ($P = .22$). Comparing the distribution of all 63 and 55 patients over the 6 endoscopic recurrence categories, the *P* value was .61.

In the per-protocol analysis, there were 29 of 58 (50%) patients with a Rutgeerts score of i2b or higher in the vitamin D group and 31 of 54 (57%) in the placebo group ($P = .43$). A Rutgeerts score of i2a or higher recurrence rates were 86% vs 82% in the vitamin D and placebo groups, respectively ($P = .50$), and by defining a Rutgeerts score of i1 or higher the recurrence rates were 93% and 87%, respectively ($P = .28$). Comparing the

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Table 1. Demographic and Baseline Disease Characteristics of the Intention-to-Treat Population

	Vitamin D (n = 72)	Placebo (n = 71)
Demographics		
Sex, male, n (%)	28/72 (39)	29/71 (41)
Age, *y*, median (IQR)	31 (25–46)	33 (25–46)
Age >40 y, n (%)	17/72 (24)	26/71 (36)
Ethnic background, Caucasian, n (%)	68/72 (94)	57/71 (79)
Behavioral risk factors		
Current smoker, n (%)	13/70 (19)	13/67 (19)
BMI, *kg/m²*, mean (SD)	23.7 (4.8)	23.0 (4.6)
Disease characteristics		
Age at diagnosis, n (%)		
≤16 y, A1	9/72 (13)	12/71 (17)
17–40 y, A2	57/72 (79)	45/71 (64)
>40 y, A3	6/72 (8)	13/71 (18)
Disease location at surgery, n (%)		
Ileum only, L1	28/72 (39)	39/71 (56)
Colon only, L2	1/72 (1)	2/71 (3)
Ileum and colon, L3	43/72 (60)	29/71 (41)
Disease phenotype at surgery, n (%)		
Inflammatory, B1	11/72 (15)	17/71 (24)
Stricturing, B2	40/72 (56)	36/71 (51)
Penetrating, B3	21/72 (29)	17/71 (24)
Perianal disease, p	0/72 (0)	0/71 (0)
Previous surgical resections	17/72 (24)	14/70 (20)
CDAI at study entry, median (minimum–maximum)	165 (19–394)	136 (1–463)
CDAI, 150–199, n (%)	13/54 (24)	8/53 (15)
CDAI, 200–219, n (%)	1/54 (2)	2/53 (4)
CDAI, ≥220, n (%)	17/54 (31)	14/53 (26)
Steroid use		
Prednisone	45/71 (63)	43/67 (64)
Budesonide	35/71 (49)	34/67 (51)
Mesalamine	22/71 (31)	17/67 (25)
Immunomodulators, n (%)		
Azathioprine	47/71 (66)	40/67 (59)
6-Mercaptopurine	13/71 (18)	20/67 (30)
Methotrexate	8/71 (11)	6/67 (9)
Previous anti-TNFα, n (%)		
Infliximab	12/71 (17)	21/67 (31)
Adalimumab	13/71 (18)	11/67 (16)
Any anti-TNF	19/71 (27)	10/67 (15)
Biochemical parameters, median (minimum–maximum)		
CRP, *mg/L*	37 (1–251)	34 (1–318)
25-OH vitamin D, *nmol/L*, n (%)	42 (10–119)	43 (7–108)
≤25 nmol/L	15/67 (22)	12/63 (19)
26–50 nmol/L	30/67 (45)	27/63 (43)
51–74 nmol/L	11/67 (16)	17/63 (27)
≥75 nmol/L	11/67 (16)	7/63 (11)
Serum albumin, *g/L*, median (minimum–maximum)	36 (23–51)	37 (19–46)

BMI, body mass index; CDAI, Crohn's disease activity index; CRP, C-reactive protein; IQR, interquartile range; 6-MP, 6-mercaptopurine; TNFα, tumor necrosis factor α; 25-OH vitamin D, 25-hydroxy vitamin D.

distribution of all 58 and 54 patients over the 6 Rutgeerts categories, the *P* value was .52.

Clinical Recurrence

The incidence of clinical recurrence, measured with CDAI scores, is summarized in Supplementary Table 2 and Figure 2*C*. There was no significant difference between the 2 treatment groups with respect to the distribution of the patient numbers over the CDAI categories ($P > .065$) at any time point.

Risk Factors for Endoscopic Recurrence

The ORs of 'established' risk factors for endoscopic recurrence are listed in Table 3. Previous surgery was associated with a lower risk of endoscopic recurrence (OR, 0.35; 95% CI, 0.15–1.00; $P = .049$). Current smoking was associated with a higher risk of recurrence but just did not reach significance (OR, 3.1; 95% CI, 0.98–9.67; $P = .054$). Higher 25-OH vitamin D levels (>50 nmol/L) at baseline were associated numerically with a lower recurrence risk, but this trend also failed to reach significance ($P = .3$). Moreover, there was no difference in endoscopic recurrence based on an increase of vitamin D levels from pretreatment to post-treatment. Patients with endoscopic recurrence (Rutgeerts score, ≥i2b) had a significantly higher calprotectin level at week 26 than patients with a Rutgeerts score of i2a or less (mean, 448 μg/g; SD, 354; vs 236 μg/g; SD, 265; $P = .002$). Moreover, patients with an increased CRP level (>5 mg/L) at week 26 had endoscopic recurrence more often compared with patients with normal CRP levels (75% vs 49%; OR, 1.15; $P = .019$).

Quality of Life

Quality of life was measured by changes in the EuroQol, a 5-dimension questionnaire, the SF-36, and the Inflammatory Bowel Disease Questionnaire during the trial. In general, the scores of all questionnaires improved slightly during the trial, but at none of the visits was there a statistically significant difference between the vitamin D and placebo groups ($P > .07$) (Supplementary Table 3).

Subgroups

The treatment effect on endoscopic and clinical recurrence was analyzed by subgroups of patients defined by baseline 25-OH vitamin D levels, low baseline calcium levels, low baseline parathyroid hormone levels, calprotectin at week 26, ethnic background, and season of inclusion (autumn/winter). Treatment effects are shown in Supplementary Figure 2. No differential effect was statistically significant.

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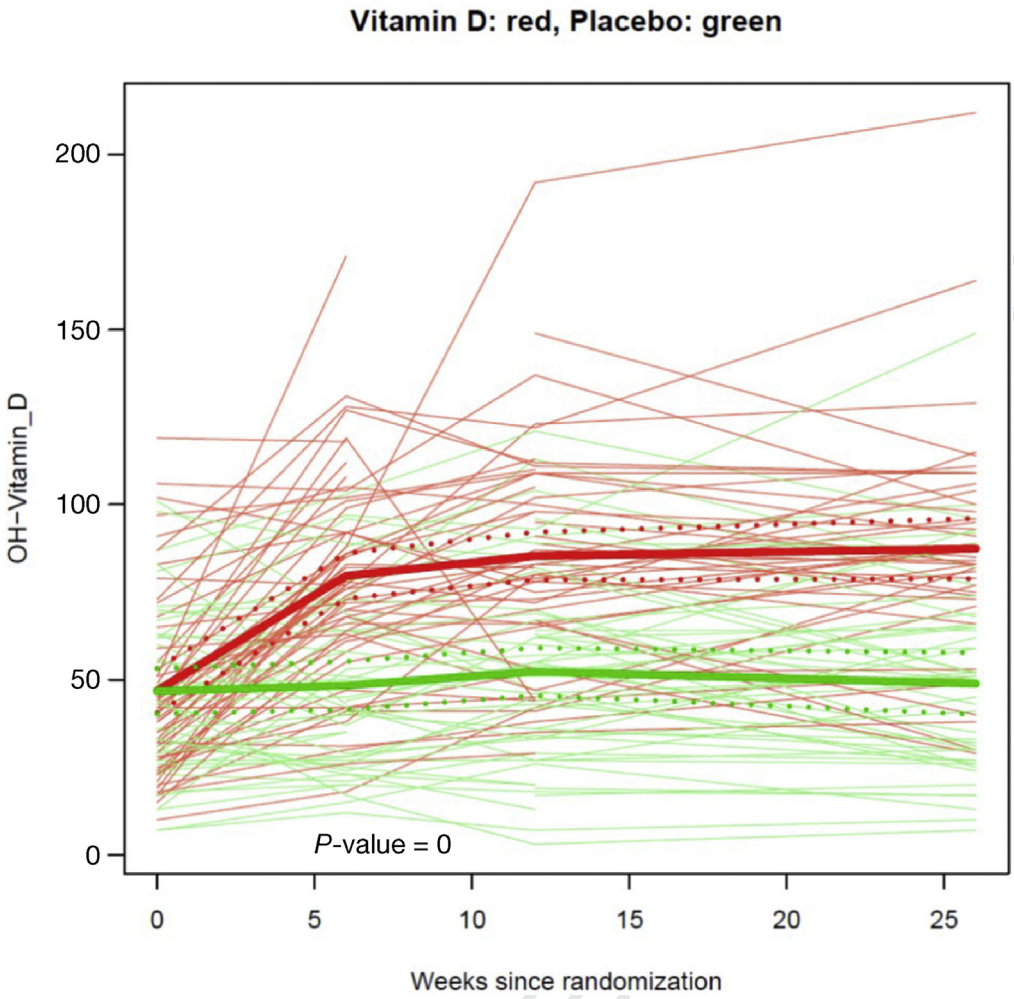

Figure 1. Treatment effect on 25-hydroxyvitamin D serum concentrations. The observed serum vitamin D levels for all patients are shown (**dark lines** represent the patients in the vitamin D group, **light lines** represent the patients in the placebo group). The **bold lines** indicate the estimated mean levels from the mixed-effects regression model with time as a factor (0, 6, 12, and 26 wk) and treatment and their interaction as fixed effects and a random intercept and slope of time as random patient effects. The **dotted lines** indicate the estimated 95% CIs of the estimated regression lines. The reported *P* value is for the interaction term of time with treatment. OH vitamin D, hydroxy vitamin D.

Table 2. Endoscopic Findings of All Available Colonoscopies, Central Adjudicated Reading

Outcome	Vitamin D	Placebo
Intention-to-treat analysis	n = 72 (%)	n = 70 (%)
i0	4 (5.6)	8 (11.4)
i1	4 (5.6)	2 (2.9)
i2a	22 (27.7)	14 (20)
i2b	22 (27.7)	20 (28.9)
i3	2 (2.8)	3 (4.3)
i4	9 (12.5)	8 (11.4)
Modified intention-to-treat analysis	n = 63 (%)	n = 55 (%)
i0	4 (6.3)	8 (14.5)
i1	4 (6.3)	2 (3.6)
i2a	22 (34.9)	14 (25.5)
i2b	22 (34.)	20 (36.4)
i3	2 (3.2)	3 (5.5)
i4	9 (14.3)	8 (14.5)
Per-protocol analysis	n = 58 (%)	n = 54 (%)
i0	4 (6.9)	7 (13.0)
i1	4 (6.9)	3 (5.6)
i2a	21 (36.2)	13 (24.0)
i2b	21 (36.2)	20 (37.0)
i3	1 (1.7)	3 (5.6)
i4	7 (12.1)	8 (14.8)

NOTE. Results of the primary intention-to-treat analysis concerned the modified intention-to-treat analysis.

Adverse Events

In total, 337 adverse events were reported, 182 in the vitamin D group and 155 in the placebo group. The proportion of patients reporting 1 or more adverse events was 59 (82%) and 53 (74%) for the vitamin D and placebo groups, respectively ($P = .32$). Twenty-five percent of all adverse events were related to surgery. Thirty-eight were reported as serious adverse events (15 patients receiving vitamin D and 23 patients receiving placebo). One patient receiving placebo was diagnosed with colonic adenocarcinoma, all other events were related to hospitalization. No deaths occurred. Most adverse events were considered to be unrelated to treatment.

Discussion

In this study we investigated the effect of high-dose vitamin D treatment to prevent postoperative recurrence of CD after an ileocolonic resection with ileocolonic anastomosis. Vitamin D at a dose of 25,000 IU/wk orally did not reduce endoscopic or clinical recurrence compared with placebo, despite doubling of the serum concentrations.

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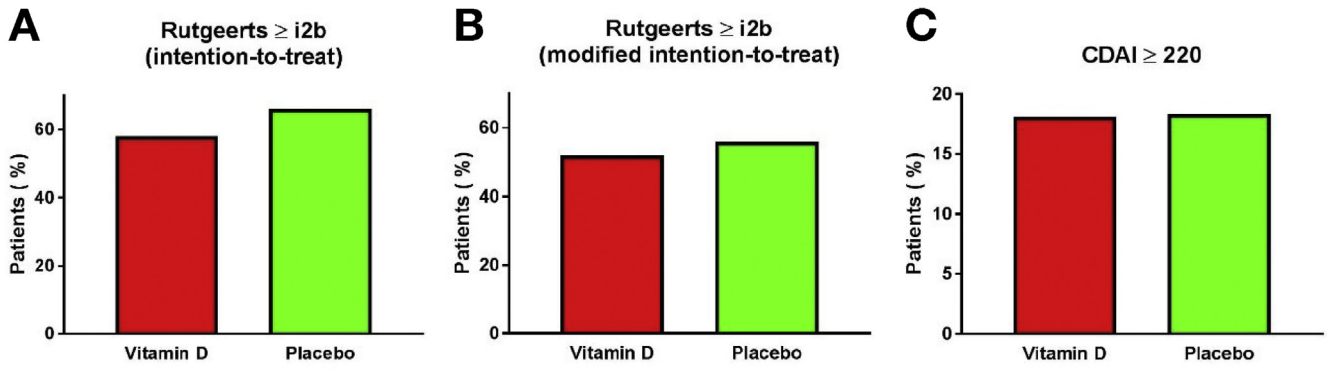

Figure 2. Endoscopic and clinical recurrence. (*A*) Percentage of patients with endoscopic recurrence at 26 weeks, defined as a Rutgeerts score of i2b or greater in the intention-to-treat analysis (58% vs 66%; $P = .37$). (*B*) Percentage of patients with endoscopic recurrence at 26 weeks, defined as a Rutgeerts score of i2b or greater in the modified intention-to-treat analysis (52% vs 56%; $P = .71$). (*C*) Percentage of patients with clinical recurrence at any time point during follow-up evaluation, defined as a Crohn's disease activity index (CDAI) score of 220 or higher (18% vs 18%; $P = .93$).

There is an ongoing debate whether vitamin D deficiency in CD is a cause for or consequence of active disease because vitamin D deficiency is common in CD patients. Interventional trials with vitamin D have, to date, not provided conclusive answers to this enigma. One of the weaknesses has been the exclusive use of symptom-based end points, which is known to be associated poorly with objective evidence of inflammation.[34] Two prospective trials in IBD patients receiving vitamin D evaluated clinically significant relapse based on CDAI scores, serum CRP level, and/or quality of life[15,35,36] and observed fewer relapses in patients treated with vitamin D. However, in another small clinical trial in CD patients in remission, there was no difference in clinical remission rates.[37] In our study, we decided to use a more robust end point (blinded centrally read endoscopic recurrence) as an outcome measure in an established clinical model in which other interventions were shown to be beneficial.

Because the endoscopic appearance 6 months after surgery is a predictor of the clinical disease course, follow-up evaluation of studies on postoperative recurrence often do not exceed 6 months. With a clinical end point longer follow-up evaluation may be recommended, as it was performed in the PREVENT trial.[17] The incidence of endoscopic recurrence that we observed in the current trial (56%) was comparable with that in other studies.[17,19,22] Hence, the population in our trial can be considered as representative.

In our risk factor analysis we observed that current smoking was associated with a higher, although not significant, risk for postoperative recurrence, which is in line with previous studies.[38] Conversely, previous surgery was associated with a lower risk for endoscopic recurrence. A possible explanation could be that patients with active perianal fistulas were excluded from this study, and patients with perianal disease phenotype usually have higher recurrence rates.[39] In addition, the indication for which patients undergo a first resection may have changed over the years. Current treatment algorithms now have positioned limited ileocecal resection as a valid alternative for biologic treatment after failure of immunomodulators, predominantly in patients with fibrostenotic disease,[40,41] and patients with this disease phenotype typically have lower recurrence rates.[42]

There is an ongoing debate about the minimal or optimal serum concentration of 25-OH vitamin D in normal individuals and in patients with chronic inflammatory diseases. Reference levels, however, are based mainly on the skeletal effects of vitamin D, whereas the effect of vitamin D on extraskeletal functions remains uncertain. Levels higher than 75 nmol/L are considered to be necessary for immunomodulatory and nonskeletal effects,[43] although certain investigators have suggested levels greater than 100 nmol/L may be needed.[44] Because the patients on vitamin D in our study reached serum concentration levels greater than 75 nmol/L, we believe that they received sufficient doses to benefit from an anti-inflammatory effect should there be any. None of our vitamin D–treated patients developed hypercalcemia, so the weekly dose of 25,000 IU vitamin D also can be considered safe. Furthermore, seasonal variations of serum concentration of 25-OH vitamin D are significant in Western populations.[45] Because we included patients over a time period of 3 years with a stable inclusion rate through all seasons, seasonal influence was minimalized. Moreover, the season in which a patient was included had no effect on endoscopic recurrence.

The current study was a multicenter, double-blind, randomized, placebo-controlled, clinical trial. The patient cohort was well characterized and monitored closely. We studied CD activity during treatment with vitamin D using endoscopy. Given all of these factors, we could not observe any anti-inflammatory effect with this regimen in postoperative CD.

Our study had a few limitations that probably did not have an impact on the final results. First, we observed a higher drop-out rate than anticipated (18.2%). The higher loss to follow-up evaluation rate could be owing

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Table 3. Risk Factors for Endoscopic Recurrence

		95% CI	
	OR	Lower limit	Upper limit
Age at diagnosis			
≤16 y, A1	1.00	–	–
17–40 y, A2	2.32	0.78	6.83
>40 y, A3	3.67	0.85	15.84
Number of previous surgical resections			
≥1	0.38	0.15	1.00
Smoking			
Current smoker	3.08	0.98	9.67
Ex-smoker	2.13	0.90	5.04
Never smoked	1.00	–	–
Previous anti-TNF treatment			
Infliximab	0.74	0.35	1.53
Adalimumab	0.87	0.42	1.83
Any anti-TNF treatment	1.06	0.50	2.23
Disease phenotype at surgery			
Penetrating, B3	1.08	0.47	2.46
25-OH vitamin D at baseline			
Vitamin D, ≤50 nmol/L	1.00	–	–
Vitamin D, >50 to ≤75 nmol/L	0.74	0.29	1.86
Vitamin D, >75 nmol/L	0.55	0.17	1.76
Calcium level at baseline			
<2.2 mmol/L	1.40	0.58	3.36
PTH level at baseline			
<2 pmol/L	NA		
Calprotectin level at week 26			
0–50 μg/g	1.00	–	–
50–250 μg/g	5.1	1.2	21.9
>250 μg/g	7.3	1.8	30.6
Ethnic background			
Caucasian	1.63	0.56	4.71
Season of inclusion date			
Autumn/winter	1.66	0.79	3.47

NA, not applicable; OR, odds ratio; PTH, parathyroid hormone; TNF, tumor necrosis factor; 25-OH vitamin D, 25-hydroxyvitamin vitamin D.

in part to the fact that the study patients often received no treatment at all but "watchful-waiting" for 6 months postoperatively. Because the patients usually were free of symptoms, the motivation to adhere to the trial requirements was suboptimal. Because of this higher loss to follow-up rate, the targeted sample size was not reached. However, in all analyses there was no significant difference in outcome. Second, we treated all patients with 25,000 IU vitamin D irrespective of serum vitamin D level. It could be argued that a treat-to-target study design to reach serum 25-OH vitamin D levels greater than 75 nmol/L would have been more optimal because it recently was performed in a small clinical trial in patients with active IBD.[44] However, in our patient cohort those levels were reached at fixed doses in every patient. Nevertheless, a postoperative trial, in our opinion, is an excellent model for truly investigating the anti-inflammatory effect of, in this case, vitamin D, because after resection the disease could be considered as a "reset to zero," thereby diminishing possible confounding factors as concomitant immunomodulating medication and disease activity.

In conclusion, high-dose vitamin D treatment, reaching adequate vitamin D levels 6 weeks after ileocolonic resection, did not reduce endoscopic and clinical CD recurrence.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2020.05.037.

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Supporting; Investigation: Supporting; Writing – review & editing: Supporting); Esmé Clasquin (Project administration: Equal); Jarmila D. van der Bilt (Investigation: Supporting; Writing – review & editing: Supporting); Tim Tollens (Investigation: Supporting; Writing – review & editing: Supporting); Willem A. Bemelman (Investigation: Equal; Writing – review & editing: Equal); Andre D'Hoore (Investigation: Equal; Writing – review & editing: Equal); Marjolijn Duijvestein (Data curation: Equal; Formal analysis: Equal; Investigation: Equal; Methodology: Equal; Supervision: Equal; Writing – review & editing: Equal); Geert R. D'Haens (Conceptualization: Lead; Data curation: Equal; Formal analysis: Equal; Methodology: Equal; Supervision: Lead; Validation: Lead; Writing – review & editing: Lead).

Data analysis was performed by a clinical statistician (Professor A. H. Zwinderman) who was not involved in the clinical study. Vitamin D and placebo vials were kindly provided by SMB Pharma. SMB Pharma, BROAD Medical Research Program–Crohn's and Colitis Foundation, and the International Organization for Inflammatory Bowel Diseases were not involved in the data collection or analysis. The authors wish to thank the pharmacy of the Amsterdam University Medical Center for all the help involved in this trial. Moreover, the authors thank Evelyne Joos for the rigorous monitoring of this trial and Professor R. Bouillon (KU Leuven) for his support in the trial design. The authors would like to thank the members of the Belgian Inflammatory Bowel Research and Development Group and Initiative on Crohn's and Colitis for patient inclusion.

Members of the DETECT study group (The Effect of Vitamin D3 to Prevent Postoperative Relapse of Crohn's Disease: a Placebo-controlled Randomized Trial) are listed in the Supplementary Appendix.

Conflicts of interest

The authors disclose no conflicts. Q5

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Supplementary Appendix

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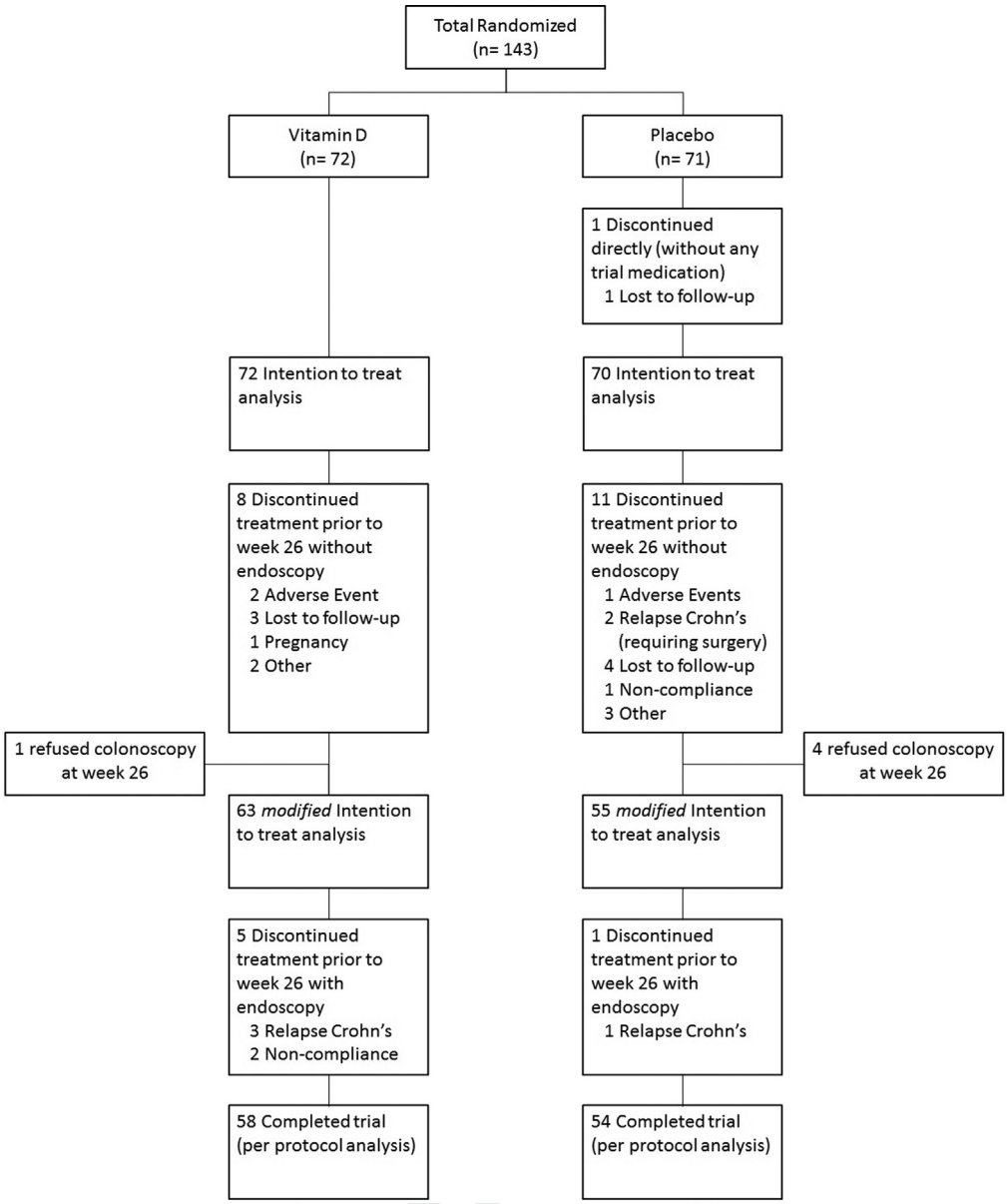
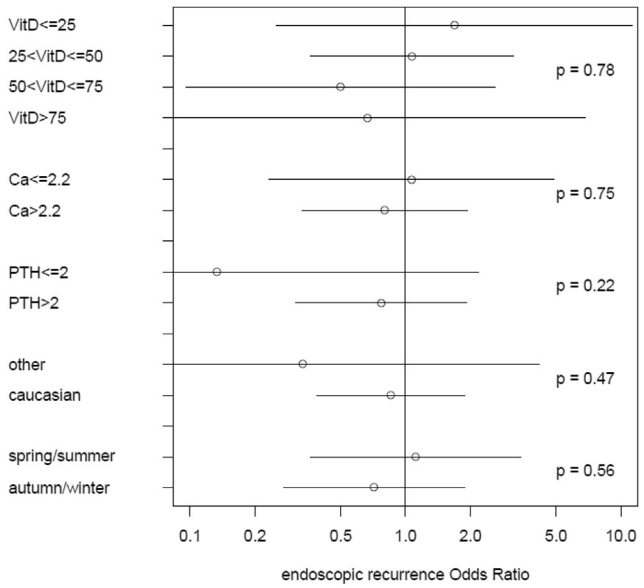
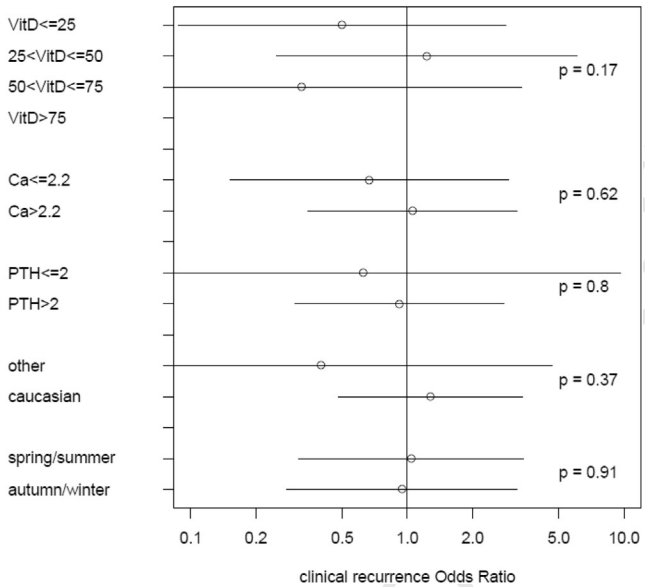


Supplementary Figure 1. Patient flow diagram.





Supplementary Figure 2. Endoscopic and clinical odds ratio (95% CI) of vitamin D (VitD) treatment in patient subgroups: baseline levels of serum 25-hydroxy vitamin D, baseline calcium (Ca) levels, baseline parathyroid hormone (PTH) levels, ethnic background (Caucasian/other), and season of inclusion (spring/summer vs autumn/winter). The *P* value refer to the treatment by subgroup interaction in the logistic regression model.

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Supplementary Table 1. Average Baseline Levels (SD) and Estimated Average Change Between Baseline and 26 Weeks (SE) of Various Laboratory Parameters

	Baseline		Change at 26 weeks from baseline		
	Vitamin D, mean (SD)	Placebo, mean (SD)	Vitamin D, mean (SE)	Placebo, mean (SE)	*P* value
25-OH vitamin D, *nmol/L*	47.0 (25.9)	46.3 (24.1)	40.3 (5.32)	3.19 (4.13)	<.0001
Calcium, *mmol/L*	2.28 (0.15)	2.27 (0.14)	0.04 (0.02)	0.07 (0.02)	.31
PTH, *pmol/L*	4.78 (3.75)	3.81 (2.20)	-0.22 (0.62)	1.29 (0.45)	.042
Fecal calprotectin, *μg/g*	570 (404)	567 (400)	-203 (54)	-150 (54)	.48
Serum albumin, *g/L*	37 (7)	36 (6)	6.3 (0.7)	6.6 (0.7)	.73
Hemoglobin, *mmol/L*	7.4 (1.0)	7.1 (1.1)	0.9 (0.1)	0.7 (0.2)	.41
CRP, *mg/L*	57.7 (62.1)	67.6 (75.8)	-49.9 (8.0)	-53.8 (8.8)	.51

CRP, C-reactive protein; PTH, parathyroid hormone; 25-OH vitamin D, 25-hydroxyvitamin vitamin D.

Supplementary Table 2. CDAI Scores During The Trial

CDAI score	Vitamin D	Placebo
Baseline	n = 54 (%)	n = 53 (%)
0–50	5 (9.3)	4 (7.5)
50–150	18 (33.3)	26 (49.1)
150–200	13 (24.1)	8 (15.1)
200–220	1 (1.9)	1 (1.9)
>220	17 (31.5)	14 (26.4)
Week 6	n = 60 (%)	n = 51 (%)
0–50	15 (25.0)	10 (19.6)
50–150	27 (45.0)	27 (52.9)
150–200	9 (15.0)	7 (13.7)
200–220	4 (6.7)	3 (5.9)
>220	5 (8.3)	4 (7.8)
Week 12	n = 53 (%)	n = 55 (%)
0–50	17 (32.1)	16 (29.1)
50–150	22 (41.5)	31 (56.4)
150–200	10 (18.9)	2 (3.6)
200–220	1 (1.9)	0 (0.0)
>220	3 (5.7)	6 (10.9)
Week 26	n = 54 (%)	n = 52 (%)
0–50	15 (27.8)	21 (40.4)
50–150	31 (57.4)	27 (51.9)
150–200	4 (7.4)	3 (5.8)
200–220	0 (0.0)	0 (0.0)
>220	4 (7.4)	1 (1.9)

CDAI, Crohn's disease activity index.

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Supplementary Table 3. Average Baseline Levels (SD) and Estimated Average Change Between Baseline and 26 Weeks (SE) of Various Questionnaire Parameters

		Baseline		Change at 26 weeks from baseline		
		Vitamin D, mean (SD)	Placebo, mean (SD)	Vitamin D, mean (SE)	Placebo, mean (SE)	*P* value
CDAI		172 (98)	158 (101)	-62 (12)	-82 (12)	.24
EQ-5D	Total	57 (18)	61 (15)	15.5 (2.3)	13.1 (2.4)	.48
SF-36	PCS	36 (10)	36 (10)	10.9 (1.3)	11.4 (1.4)	.77
	MCS	42 (13)	41 (12)	6.3 (1.4)	5.0 (1.5)	.53
IBDQ	Bowel	48 (10)	48 (9)	4.6 (1.1)	7.2 (1.2)	.12
	Systemic	19 (7)	18 (6)	4.9 (0.7)	6.7 (0.8)	.08
	Social	21 (8)	22 (7)	8.3 (1.0)	7.9 (1.0)	.73
	Emotional	56 (16)	55 (13)	6.9 (1.4)	10.4 (1.5)	.09
	Total	147 (36)	146 (30)	24.9 (3.7)	31.1 (3.8)	.25

CDAI, Crohn's disease activity index; EQ-5D, EuroQol, 5-dimension questionnaire; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, mental component summary; PCS, physical component summary; SF-36, 36-Item Short Form Health Survey.

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