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An Evaluation of High-Dose Vitamin D for Rheumatoid Arthritis

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Key Indexing Terms

Bone Mineral Density; Clinical Trial; Cytokines; Rheumatoid Arthritis; Quality of Life; Vitamin D

INTRODUCTION

Vitamin D receptors (VDR) are present in T-lymphocytes, macrophages, chondrocytes, and synovial cells of patients with rheumatoid arthritis (RA) but not healthy individuals [1]. As recently reviewed [1], $1,25(OH)_2D$ inhibits T-cell proliferation and cytokine secretion in vitro, and ameliorates murine RA [2, 3]. We hypothesized that correction of hypovitaminosis D in subjects with RA would decrease parathyroid hormone (PTH), increase bone mineral density (BMD), improve functional capacity (Health Assessment Questionnaire, HAQ) and down-regulate inflammatory cytokines, thereby diminishing RA disease activity (RA-DAS) scores and improving quality of life.

METHODS

We recruited subjects from local rheumatology clinics for a randomized, double-blind, placebo-controlled study to evaluate the effect of vitamin D in patients with RA. Eligible subjects had RA [4] and serum 25(OH)D levels of 6.1–24.9 ng/mL [5]. We excluded subjects with hypercalcemia, hypercalciuria [6], calcium intake >2 g/day, nephrolithiasis, creatinine >2.0 mg/dL, Paget's disease, hyperthyroidism, pregnancy, and women 45–55 years old or within 5 years of menopause. Subjects taking osteoporosis medication, estrogen or a spine or hip T-score <−3.0 were also excluded. The local institutional review board

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approved the study and participants provided written consent (ClinicalTrials.gov Identifier NCT00423358).

Ergocalciferol 50,000 IU and matching placebo were manufactured (Tishcon Corporation, Westbury, NY) with content verified independently prior to use. The research pharmacy randomized eligible subjects using a 1:1 block to placebo or vitamin D_2 50,000 IU three times weekly for four weeks, then 50,000 IU twice monthly for 11 months. All subjects received calcium 500 mg three times daily throughout the study, and were asked to apply sunscreen (Sun Protection Factor 65) between May and September.

Study visits occurred at 0, 2, 5 and 12 months. If a vitamin D-treated subject's 25(OH)D was <25 ng/mL after randomization, pharmacy prescribed vitamin D 50,000 IU weekly for 8 weeks, with 10% on placebo receiving sham adjustments. Pill counts assessed adherence. Subjects underwent fasting phlebotomy before 10 am to measure serum 25(OH)D, PTH, bone-specific alkaline phosphatase, calcium, albumin, creatinine and cytokines (IL1β, IL4, IL6, IL12p40, IL12p70 and TNFα). We also measured second void urine calcium, creatinine and N-telopeptide. Subjects underwent a joint exam (28 joints, KEH) and completed HAQ and Short-Form 36 surveys at each visit. We measured BMD at 0 and 12 months using one Prodigy bone densitometer (GE Lunar Corporation, Madison, WI). 25(OH)D was measured by HPLC [5] with between run coefficients of variation (CV) of 2.6%–4.9% for 25(OH)D_3 and 3.2%–13% for 25(OH)D_2. Vitamin D Quality Assessment Scheme [7] participation confirmed measurement accuracy.

Statistical Analysis

The primary outcome was the change in PTH between treatment arms. Secondary outcomes were changes in BMD, DAS-28, HAQ and SF-36 scores and cytokines. Based on a 35% decline in PTH with an identical vitamin D dose [8], a sample size of 37 subjects per group provided 80% power to detect a 25 ng/ml decrease in PTH, using the independent t-test with a two-sided 5% level. We analyzed all study outcomes by intention to treat with repeated measures analysis of variance (ANOVA) using SAS version 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Between 2004 and 2009, 711 individuals were contacted; 98 were eligible for and underwent a screening visit. Of 33 subjects with eligible 25(OH)D levels, six were excluded due to abnormal screening tests (n=2) or inability to verify the diagnosis of RA (n=4), and five declined further participation. We randomized 22 subjects (see Supplemental Digital Content 1 which summarizes baseline characteristics). Ergocalciferol achieved universal vitamin D repletion by month 2 although two patients required additional vitamin D at month 5. Vitamin D/placebo adherence was 97% and 96% in placebo and vitamin D arms respectively; calcium adherence was 74% and 69% respectively.

Vitamin D had no significant effect on PTH, N-telopeptide or BMD but did increase bone formation reflected by bone specific alkaline phosphatase (Table). TNF-α levels increased in the vitamin D arm (Table). DAS-28 scores were unaffected, but patient's global health

and RA assessments worsened (see Supplemental Digital Content 2, which summarizes these data), and the physical function domain of the SF-36 survey declined 6 points (mean) in vitamin D-treated subjects (p-value 0.03).

No subject experienced fracture, nephrolithiasis, hypercalcemia or hypercalciuria. At 12 months, 45% of placebo and 18% of vitamin D-treated subjects correctly guessed treatment assignments.

DISCUSSION

Based upon unique expression of VDR in RA synovial cells [1] and $1,25(OH)_2D$ immunomodulation in vitro [1] and in murine RA [2, 3] we hypothesized a role for vitamin D therapy in patients with RA. In this small study, we did not detect improvement in health outcomes following high-dose vitamin D for one year in RA patients, although power limited firm conclusions.

Previously, two un-blinded studies reported improved RA disease activity or pain following vitamin D [11, 12], while a third open-label study [13] demonstrated no improvement in arthritis. A double-blind, placebo-controlled trial of 117 subjects [14] detected no change in RA following 12 weeks of vitamin D, but baseline repletion (mean 25(OH)D 43 ng/mL) might explain the null effect. Observationally, among 499 RA golimumab clinical trial subjects [15], baseline vitamin D status was unrelated to DAS-28, erosions, C-reactive protein or therapeutic response. To date, the largest body of evidence suggesting vitamin D's effects on immune function come from in vitro studies [1].

Several study limitations preclude concluding that vitamin D has no benefit for RA. Recently the Institute of Medicine [9] redefined vitamin D repletion as 25(OH)D levels ≥20 ng/mL. Since half of subjects had 25(OH)D levels >20 ng/mL at randomization, null findings might reflect vitamin D adequacy among many. Second, calcium supplementation could obviate benefits of vitamin D on PTH or BMD, since one trial found that calcium reduced PTH while vitamin D had no effect [10]. Third, we studied vitamin D_2 rather than vitamin D_3 or $1,25(OH)_2D$. Due to a longer half-life, vitamin D_3 might have prevented nadir serum levels at month 5. Use of $1,25(OH)_2D$ might elicit greater immunomodulation than vitamin D. Small sample size is our greatest weakness; despite contacting >700 potential subjects, few were eligible for the study.

In conclusion, our randomized, double-blind placebo-controlled vitamin D study did not demonstrate improvements in PTH levels, BMD, disease activity or cytokines in RA patients, although sample size limits conclusions. Additional studies are needed to clarify the role of vitamin D for patients with RA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table

Changes in Study Outcomes by Treatment

Variable	Treatment	Randomization	Month 2	Month 5	Month 12	Effect of Vitamin D	Pooled p-value
25(OH)D, ng/mL	Placebo	21 ± 9	22 ± 10	21 ± 7	23 ± 11	+12 ± 14	**0.005**
	Vitamin D	25 ± 24[†]	41 ± 10	31 ± 12	30 ± 11		
Parathyroid Hormone, pg/mL	Placebo	25 ± 11	22 ± 9	24 ± 12	20 ± 11	−3 ± 10	0.84
	Vitamin D	21± 8	18 ± 8	19 ± 10	19 ± 11		
N-telopeptide, nM/BCE	Placebo	14 ± 6	12 ± 6	12 ± 4	12 ± 5	−0.5 ± 7	0.92
	Vitamin D	16 ± 6	14 ± 6	14 ± 6	14 ± 5		
Bone specific alkaline phosphatase, U/L	Placebo	28 ± 10	25 ± 6	23 ± 5	23 ± 7	+6 ± 8	**0.02**
	Vitamin D	29 ± 10	28 ± 11	29 ± 10	30 ± 10		
TNF-α, pg/mL	Placebo	6 (3, 59)	9 (4, 20)	12 (4, 21)	9 (4, 20)	+13 (−5, 84)	**0.04**
	Vitamin D	20 (6, 69)	21 (7, 36)	22 (9, 49)	32 (8, 45)		
L1–L4 BMD, g/cm^2	Placebo	1.291 ± 0.214	-	-	1.307 ± 0.241	−0.020 ± 0.043	0.24
	Vitamin D	1.230 ± 0.178	-	-	1.226 ± 0.190		
Mean total hip BMD, g/cm2	Placebo	1.139 ± 0.163	-	-	1.151 ± 0.168	−0.011 ± 0.020	0.16
	Vitamin D	0.968 ± 0.135	-	-	0.970 ± 0.140		

Data are summarized using the mean ± standard deviation except TNFα levels which are summarized using the median (interquartile range).

[†]One individual in the vitamin D arm had a screening vitamin D level of 18 ng/mL and, presumably from casual sun exposure, her level was 96 ng/mL at randomization; this subject's outlier value is not included in the effect calculations for change in serum 25(OH)D levels. All laboratory studies were collected in the fasting state, prior to 10 am. We measured bone mineral density (BMD) using a single Lunar Prodigy bone densitometer. The effect of vitamin D was the average change between vitamin D and placebo arms ± the standard deviation for the change. Aside from changes in 25(OH)D levels, the effect of vitamin D was based on the intent to treat principle.