Superiority of a High Loading Dose of Cholecalciferol to Correct Hypovitaminosis D in Patients with Inflammatory/Autoimmune Rheumatic Diseases

PIER PAOLO SAINAGHI, MATTIA BELLAN, ALESSANDRA NERVIANI, DANIELE SOLA, ROSSELLA MOLINARI, CHIARA CERUTTI, and MARIO PIRISI

ABSTRACT. ***Objective.*** To compare 3 different cholecalciferol supplementation regimens in patients with rheumatic diseases.

Methods. One hundred fifty-four patients who completed a 6-month course of cholecalciferol supplementation, of whom 111 had an autoimmune/inflammatory rheumatic disease (ARD) and 43 osteoarthritis (NARD), were retrospectively identified from a database of 872 consecutive adult patients who attended a tertiary level immuno-rheumatology clinic from 2007 to 2010. Patients with renal failure or primary hyperparathyroidism were excluded. Plasma 25-hydroxy vitamin D [25(OH)D] and parathyroid hormone (PTH) concentrations were evaluated at baseline and after completion of treatment with (i) a single oral dose of cholecalciferol 300,000 IU, followed by oral cholecalciferol 800–1000 IU daily for 6 months [high-dose loading treatment (HLT) group; n = 40]; (ii) a single oral dose of cholecalciferol 100,000 IU, followed by daily oral cholecalciferol as above [low-dose loading treatment (LLT) group; n = 30]; or (iii) daily oral cholecalciferol as above but without the loading dose [standard therapy (ST); n = 84].

Results. The rates of serum 25(OH)D and PTH normalization (defined as values > 75 nmol/l and < 72.9 pg/ml, respectively) were as follows: HLT, 52.5% (95% CI 37.5–68.5) and 69.2% (95% CI 54.7–83.3); LLT, 36.7% (95% CI 19.7–54.3) and 53.8% (95% CI 36.2–71.8); ST, 31.0% (95% CI 21.1–40.9) and 35.0% (95% CI 14.1–55.9). All regimes increased 25(OH)D ($p < 0.001$) but only HLT reduced PTH ($p < 0.01$) in comparison to baseline. The ARD group had a similar 25(OH)D increase but a smaller PTH reduction than the NARD ($p < 0.05$).

Conclusion. An HLT cholecalciferol regimen is needed to correct hypovitaminosis D of patients with rheumatic diseases, with superior 25(OH)D normalization and PTH suppression rates at 6 months. (J Rheumatol First Release Dec 15 2012; doi:10.3899/jrheum.120536)

Key Indexing Terms:
HYPOVITAMINOSIS D 25–HYDROXYVITAMIN D SUPPLEMENTATION
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From the Internal Medicine and Rheumatology Unit, Department of Translational Medicine, Università del Piemonte Orientale A. Avogadro and AOU Maggiore della Carità; and the Interdisciplinary Research Center of Autoimmune Diseases (IRCAD), Novara, Italy.

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P.P. Sainaghi, MD, PhD, Internal Medicine and Rheumatology Unit, Department of Translational Medicine, Università del Piemonte Orientale A. Avogadro, AOU Maggiore della Carità, and IRCAD; M. Bellan, MD; A. Nerviani, MD; D. Sola, MD; R. Molinari, MD; C. Cerutti, MD, Internal Medicine and Rheumatology Unit, Department of Translational Medicine, Università del Piemonte Orientale A. Avogadro, AOU Maggiore della Carità; M. Pirisi, MD, Internal Medicine and Rheumatology Unit, Department of Translational Medicine, Università del Piemonte Orientale A. Avogadro, AOU Maggiore della Carità, and IRCAD.

Dr. Sainaghi and Dr. Bellan contributed equally to this report.

Address correspondence to Dr. P.P. Sainaghi, Internal Medicine and Rheumatology Unit, AOU Maggiore della Carità, Corso Mazzini 18, 28100 Novara, Italy. E-mail: pierpaolo.sainaghi@med.unipmn.it

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Hypovitaminosis D is a highly prevalent condition[1], associated with an increase in plasma parathyroid hormone (PTH) concentration (secondary hyperparathyroidism). Since PTH is frequently suppressed when plasma 25-hydroxy vitamin D [25(OH)D] concentration is higher than 75–80 nmol/l (30–32 ng/ml), this threshold is considered the desirable 25(OH)D value granting bone health[2,3,4]. Full correction of hypovitaminosis D is important in the management of patients with rheumatic diseases, in particular in those with an inflammatory/autoimmune disease, because they are at higher risk for osteoporosis[5,6]. Indeed, normalization of 25(OH)D concentration increases bone mass density[7] and reduces the risk of falls[8]. According to the US Institute of Medicine, a daily dietary intake of 600–800 IU cholecalciferol is needed in adults[9]. However, which is the best cholecalciferol supple-

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mentation regimen to correct hypovitaminosis D is uncertain. It has been suggested that oral cholecalciferol supplementation with 800 IU/day can improve vitamin D status and suppress plasma PTH concentration[10]. According to others, high loading doses with 100,000 or 300,000 IU are safe and should be preferred to increase compliance to treatment, which is lower in the case of daily regimens[11,12,13]; in other studies, a weekly supplementation regimen was tested[14]. Finally, a personalized regimen based on baseline plasma 25(OH)D concentration and body weight has been proposed[15]. To our knowledge, no supplementation regimen has been studied in the specific setting of inflammatory/autoimmune (ARD) or noninflammatory/autoimmune rheumatic diseases (NARD).

The relationship between vitamin D and inflammation is hotly debated in rheumatology. Indeed, vitamin D metabolites have been shown to have immune modulatory properties. *In vitro*, 1,25(OH)$_2$ vitamin D promotes differentiation of monocytes into antigen-presenting cells and limits inflammatory cytokine production and the activation of CD4+ T-lymphocytes, favoring a Th2 phenotype[16,17,18,19]. Further, in epidemiological studies, hypovitaminosis D was linked to an increased prevalence of multiple sclerosis[20], type I diabetes mellitus[21], systemic lupus erythematosus, systemic sclerosis, polymyositis/dermatomyositis, and rheumatoid arthritis (RA)[22,23,24]. We recently demonstrated that hypovitaminosis D is very common in patients with rheumatic diseases, among whom those with an ARD show an altered vitamin D metabolism evidenced by a relative refractoriness of PTH to suppression[25,26].

In this retrospective observational study, we compared 3 different supplementation regimens of cholecalciferol in rheumatic patients with ARD or NARD. Our aim was to identify the supplementation regimen most appropriate to increase plasma 25(OH)D concentration and to suppress PTH concentration in these categories of patients.

MATERIALS AND METHODS

We retrospectively evaluated 872 clinical records of consecutive adult patients attending a tertiary level immuno-rheumatology clinic from June 2007 to December 2010. We included any patient older than age 18 years with a diagnosis of ARD [RA, spondyloarthritis (SpA), polymyalgia rheumatica (PMR), and other connective tissue diseases (CTD)] or NARD (osteoarthritis) who underwent at least a 6-month course of one of the following supplementation regimens: (i) a single oral 300,000 IU loading dose, followed by 800–1000 IU oral daily dose of cholecalciferol (high-dose loading treatment, HLT); (ii) a single oral 100,000 IU loading dose, followed by 800–1000 IU oral daily dose of cholecalciferol (low-dose loading treatment, LLT); or (iii) an 800–1000 IU oral daily dose of cholecalciferol with no loading dose (standard treatment, ST).

We excluded all patients with renal failure, primary hyperparathyroidism, or liver failure because of possible interference in vitamin D metabolism. We also excluded all patients already receiving vitamin D supplementation. No patient had a history of malabsorption.

Out of 872 eligible patients, 649 were not included because they were already receiving cholecalciferol supplementation (n = 522) or because of the unavailability of either 25(OH)D or PTH measurement (n = 127). Out of the remaining 223 patients, 154 satisfied inclusion and exclusion criteria, while 69 were excluded (10 with renal failure, 5 liver failure, 3 primary hyperparathyroidism, and 51 who had received a lower dose cholecalciferol regimen).

Plasma 25(OH)D and PTH concentrations, bone biomarkers (calcium, phosphorus), and markers of inflammation (C-reactive protein, erythrocyte sedimentation rates) together with other clinical data were recorded at baseline and after 6 months of treatment.

All assays were performed at the same central laboratory. A chemiluminescence method (Liaison; Diasorin) was used to measure both 25(OH)D and PTH. The 25(OH)D assay had a lower limit of detection (LLD) of 10 nmol/l, and the PTH assay had LLD of 1 pg/ml. Plasma PTH concentration was considered normal when lower than 72.9 pg/ml, the cutoff applied at our laboratory (this reference value was established by modifying the normality range proposed by the manufacturer, identifying the 95% CI for local healthy subjects). Calcium and phosphate were measured with a spectrophotometric method (Advia 2400 system; Siemens). This retrospective analysis was performed according to the local code of conduct for clinical studies and data protection rules. Local ethical committee approval was not required.

Statistical analysis. Data were recorded in a database and analyzed using Statistica (release 7; StatSoft). The Shapiro and Wilk test was performed to assess normality. Because of non-normal distribution of data in continuous variables, the measures of central tendency and dispersion are medians (95% CI). Data were analyzed with the Mann-Whitney U test for independent samples, the Wilcoxon test for paired samples, and the Kruskal-Wallis test, as appropriate. Categorical variables were analyzed with the Pearson chi-squared test. The 2-tailed 0.05 level was chosen to indicate statistical significance.

RESULTS

In total, 154 patients were included after the application of exclusion criteria: 111 with ARD (51 RA, 24 SpA, 25 PMR, 11 CTD) and 43 with NARD; 54.3% had unsuppressed PTH. Eighty-four received the ST, 30 the LLT, and 40 the HLT. Plasma 25(OH)D had a non-normal distribution (Shapiro-Wilk $p < 0.05$) and thus a nonparametric analysis was chosen. Table 1 shows details of the study population. Demographic (age and sex distribution; chi-square, $p \geq 0.12$) and clinical features (plasma calcium, phosphate, PTH, C-reactive protein, and erythrocyte sedimentation rates; Kruskal-Wallis ANOVA, $p \geq 0.34$) were similar among the groups, and so was the distribution of ARD/NARD and glucocorticoid treatments (chi-square, $p = 0.27$ and 0.20, respectively). However, patients who received HLT had significantly lower plasma 25(OH)D concentrations (posthoc test, $p < 0.0001$).

Figure 1 presents the changes of 25(OH)D concentrations before and after the 6-month course of cholecalciferol supplementation. At baseline, plasma 25(OH)D concentration was similarly low in the NARD group (median 27.2 nmol/l, IQR 13.0–48.4) and in the ARD group (median 28.9 nmol/l, IQR 16.5–43.4) (Mann-Whitney U test, $p = 0.95$). After ST, plasma 25(OH)D increased significantly in comparison to baseline, both in ARD (median 59.4 nmol/l, IQR 44.7–81.1) and in NARD (median 61.6 nmol/l, IQR 48.2–76.4; $p = 0.77$). The reference value for 25(OH)D (75 nmol/l) was demonstrated by 31.0% of patients (95% CI 21.1–40.9), while plasma PTH suppression (below 72.9 pg/ml) was shown by 35.0% (95% CI 14.1–55.9). Similarly,

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Table 1. Main demographic and clinical features of patients receiving different cholecalciferol supplementation regimens at baseline.

Characteristic	ST, n = 84	LLT, n = 30	HLT, n = 40	p
Age, yrs	68 (60–74)	70 (62–74)	67 (56–69)	0.12†
25 (OH)D, nmol/l	30.8 (18.9–47.4)	30.0 (14.3–46.8)	20.3 (10.1–26.1)	< 0.001†
PTH, pg/ml	89.4 (77.7–129.0)	98.5 (70.0–118.0)	92.3 (79.1–124.0)	0.36†
Calcium, mg/dl	9.1 (8.8–9.5)	9.2 (8.8–9.5)	9.0 (8.7–9.4)	0.35†
Phosphate, mg/dl	3.1 (2.8–3.5)	3.1 (2.5–3.4)	3.2 (2.8–3.5)	0.37†
Body mass index, kg/m^2	24.9 (21.8–28.6)	24.6 (23.0–26.9)	23.9 (21.7–27.5)	0.81†
Season of specimen collection* (S/S/A/W)	16/22/23/23	11/5/5/9	12/10/8/10	0.48††
Male/female	13/71	3/27	9/31	0.36††
ARD/NARD	65/19	20/10	26/14	0.27††
Osteoporosis** (Yes/No)	19/65	11/19	11/29	0.32††
Glucocorticoids (Yes/No)	43/41	13/17	14/26	0.23††
CRP, mg/dl	0.6 (0.3–1.0)	0.3 (0.1–0.9)	0.4 (0.1–1.0)	0.34††
ESR, mm/h	23 (12–33)	15 (9–27)	22 (9–34)	0.44 ††

* Spring/summer/autumn/winter. ** Bone mineral density with dual-energy X-ray absorptiometry T-score ≤ –2.5. † ANOVA, Kruskal-Wallis test. †† Pearson chi-square. ST: standard treatment; LLT: low-dose loading treatment; HLT: high-dose loading treatment; PTH: parathyroid hormone; ARD: autoimmune/inflammatory rheumatic disease; NARD: nonautoimmune/inflammatory rheumatic disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

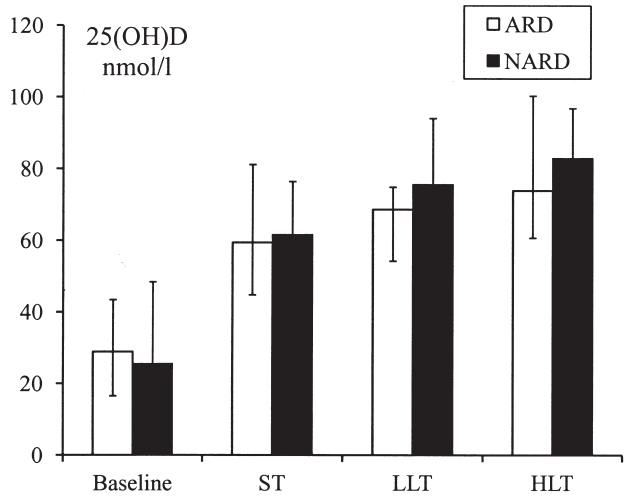

Figure 1. Plasma 25(OH)D concentration at baseline and 6 months after oral cholecalciferol treatment in patients with inflammatory/autoimmune (ARD) or noninflammatory/autoimmune rheumatic diseases (NARD). Standard treatment (ST), 800–1000 IU daily; low-dose loading therapy (LLT), single 100,000 IU dose, followed by 800–1000 IU daily; high-dose loading therapy (HLT), single 300,000 IU dose, followed by 800–1000 IU daily. None of the comparisons between ARD and NARD reached statistical significance.

patients who received the LLT had a significant increase in median plasma 25(OH)D concentration, with no differences between the ARD and NARD groups (68.6 pg/ml, IQR 54.2–74.9, vs 75.6 pg/ml, IQR 60.4–94.0, respectively; p = 0.15). In this LLT group, 36.7% (95% CI 19.7–54.3) and 53.8% (95% CI 36.2–71.8) of patients achieved the above targets for 25(OH)D and PTH, respectively. Finally, patients who received HLT had a significant increase in 25(OH)D concentrations, with no differences between the ARD (73.9 pg/ml, IQR 60.7–100.3) and NARD groups (82.9 pg/ml, IQR 66.4–96.8; p = 0.36). Among them, 52.5% (95% CI 37.5–68.5) and 69.2% (95% CI 54.7–83.3), respectively, were on target with regard to 25(OH)D and PTH. Body mass index was similar between patients who reached 25(OH)D normalization and those with subnormal concentrations after treatment: 23.9 kg/m^2 (range 21.7–27.5) and 25.0 kg/m^2 (range 22.0–27.5), respectively (Mann-Whitney U test, p = 0.49). Figure 2 shows the rates of 25(OH)D and PTH normalization according to the supplementation regimen received.

As shown in Figure 3, the 3 supplementation regimens resulted in a significant increase in plasma 25(OH)D in comparison to baseline (p < 0.001 for all), but only HLT brought about a significant reduction in median plasma PTH (p < 0.01).

Finally, while increments of 25(OH)D from baseline were not different between patients with ARD and NARD (Mann-Whitney U test, p = 0.15), median reduction of PTH was significantly lower in ARD compared to NARD (Mann-Whitney U test, p < 0.05; Figure 4). Patients with ARD who were receiving glucocorticoids had similar 25(OH)D increments and PTH reduction compared to those who were not receiving steroids: Δ25(OH)D 13.8 nmol/l (range 8.7–22.4) versus 13.2 nmol/l (range 6.5–21.1), respectively (Mann-Whitney U test, p = 0.80); and ΔPTH –13.7 pg/ml (range 32.9 to 0.0) versus –3.4 pg/ml (range –23.6 to 11.0; Mann-Whitney U test, p = 0.31).

As for safety concerns, none of the patients had hypercalcemia, independently of the supplementation regimen

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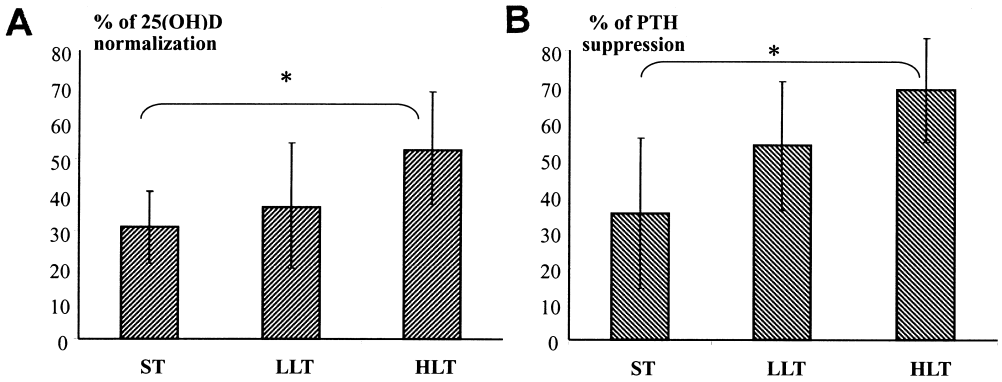

Figure 2. Proportion of patients achieving normalization of (A) plasma 25(OH)D or (B) parathyroid hormone (PTH) after administration of 3 cholecalciferol supplementation regimens. Reference values 75 nmol/l for 25(OH)D, 72.9 ng/ml for PTH. *Chi-square > 5.3, p < 0.02. ST: standard treatment; LLT: low-dose loading therapy; HLT: high-dose loading therapy.

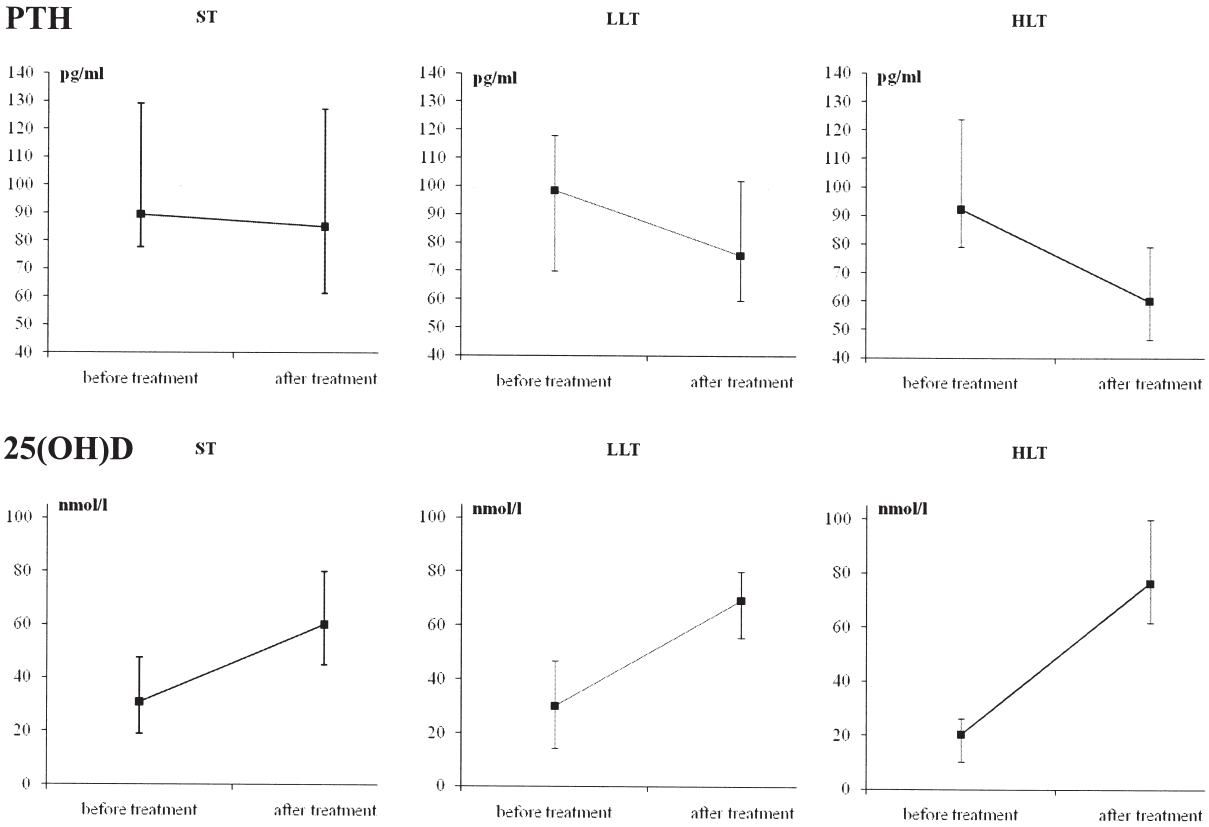

Figure 3. Median plasma concentration of 25(OH)D (lower panels) and PTH (upper panels), before and after treatment with cholecalciferol in standard therapy (ST), low-dose loading therapy (LLT), and high-dose loading therapy (HLT). See text for statistical comparisons.

received: the median plasma calcium concentrations recorded at 6 months were 9.0 mg/dl (range 8.8–9.5) in the ST group, 9.3 mg/dl (range 8.8–9.6) in LLT, and 9.0 mg/dl (range 8.7–9.3) in HLT (Kruskal-Wallis H test: 2.3, p = 0.32). Within the limitations of self-report management, compliance to treatment was good, and all patients were able to complete the 6-month treatment period as scheduled without significant side effects.

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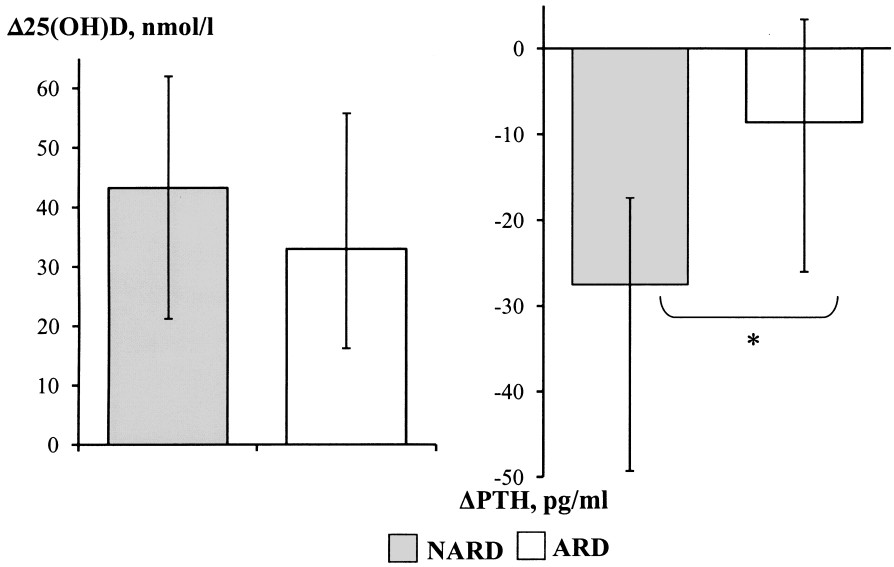

Figure 4. Plasma 25(OH)D and PTH concentrations after cholecalciferol treatments in patients with inflammatory/autoimmune (ARD) or noninflammatory/autoimmune rheumatic disease (NARD); data from all treatment regimens are pooled. *Mann-Whitney U test, $p < 0.05$.

DISCUSSION

Vitamin D, a secosteroid derived either from dietary intake or skin production, plays an important role in bone homeostasis: it favors intestinal calcium and phosphate absorption and stimulates bone mineralization[27]. In addition, vitamin D inhibits both directly and indirectly the actions of parathyroid glands. Low plasma 25(OH)D levels are associated with a secondary hyperparathyroidism due to increased PTH synthesis and secretion[28,29,30] that cause a deleterious stimulation of bone turnover. Although the definition of "normal" 25(OH)D concentration remains a matter of debate, plasma values above the 75 nmol/l (30 ng/ml) threshold, leading to suppression of secondary hyperparathyroidism, are considered sufficient for bone health[4]. The prevalence of hypovitaminosis D is very high worldwide, in different clinical settings[1,31], including rheumatic diseases[5]. Severe hypovitaminosis D can lead to osteomalacia in adults, while mild deficiency can cause muscle weakness and pain and increased bone turnover, contributing to the development of osteoporosis[32]. In patients with hypovitaminosis D, cholecalciferol supplementation is reported to increase bone mineral density in osteopenic patients[7] and to reduce the nonvertebral fracture risk at a daily dose of 400 IU[33]. The effect of vitamin D supplementation on the risk of falls in the elderly is controversial; in particular, Sanders, *et al*[34] reported an increase in falls and fractures in patients treated with high-dose (500,000 IU) cholecalciferol, while in a metaanalysis, the same supplementation was efficient in the prevention of falls and fractures[35]. Falls were not reported in our clinical records after cholecalciferol intake; however, the retrospective design of our study did not allow a reliable collection of side effects, and thus further data in rheumatic patients are required. Overall, it is prudent to affirm that correcting hypovitaminosis D is desirable in particular in patients at high risk for osteoporosis, as for those with rheumatic diseases. However, the optimal supplementation regimen in this setting has not been defined to date. We analyzed the results obtained in clinical practice using 3 oral regimens, a "standard" daily dose of 800–1000 IU cholecalciferol (ST) and 2 other regimens in which ST was preceded by a loading dose of 100,000 IU (LLT) and 300,000 IU (HLT), respectively.

There were no differences in clinical and epidemiological features between the 3 groups at baseline (i.e., male/female ratio, ARD and NARD distribution, season of supplementation, body mass index, and glucocorticoid treatment). We observed lower plasma 25(OH)D concentration at baseline in the HLT group; because the study was performed in a retrospective way we presume this was related to prescription of higher cholecalciferol doses in patients with the lowest 25(OH)D concentrations. However, it is very unlikely this influenced our conclusions. It did limit the proportion of 25(OH)D normalization in the HLT group. While we observed an increase in plasma 25(OH)D concentration with all regimens, PTH suppression was achieved in the majority of patients (69.2% of patients at 6 months) only in the HLT group, despite the lower median 25(OH)D concentration at baseline. All 3 regimens of cholecalciferol supplementation tested seemed to be safe during the

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6-month followup period: no patient in any treatment group had hypercalcemia and none reported significant side effects, in agreement with the excellent safety record for cholecalciferol supplementation acknowledged in the literature. However, the retrospective design affected the collection of definitive data about possible adverse effects; indeed, we retrospectively recorded the incidence of falls and nephrolithiasis but these clinical data were not specifically requested during the visit, so their prevalence might be underestimated.

Our results compare favorably with those in other studies. For example, von Restorff and colleagues demonstrated a significant increase in plasma 25(OH)D concentration after a single high dose of cholecalciferol, but with a suboptimal concentration after 6 months[11]. In another study in a nonrheumatic disease setting, 100% of patients treated with 300,000 IU had a plasma 25(OH)D concentration > 50 nmol/l after 6 weeks, while the rate of normalization in 25(OH)D concentration decreased to 89% after 12 weeks, and data were not provided at 6 months[12]. The shortcoming of these studies was that a maintenance dose was not provided after the single loading dose. Our results suggest that both a high loading dose and a daily maintenance dose of oral cholecalciferol are needed to correct hypovitaminosis D and to suppress plasma PTH in the long term in the majority of patients. This concept was supported by practice guidelines[36] suggesting administration of a loading dose of 400,000 IU, divided into 8 weekly doses, followed by a maintenance treatment program similar to our HLT regimen.

In our study we based the assessment of vitamin D status on PTH concentrations and on measurement of 25(OH)D, rather than its active form, 1,25$(OH)_2$ vitamin D, because 25(OH)D has a longer half-life (3 weeks vs 4 hours, respectively), providing a better indication of vitamin D stores. Further, liver production of 25(OH)D is mainly dependent on substrate concentration, while 1,25$(OH)_2$ vitamin D production is tightly regulated by calcium needs[37].

Reports link hypovitaminosis D with autoimmunity[20,21,22,23,24]. Therefore, one may ask whether correction of hypovitaminosis D is beneficial for control of the autoimmune process. Our study was not designed to test this hypothesis; however, we observed that the increase in plasma 25(OH)D concentration was similar in patients with ARD and NARD, independent of the supplementation regimen. Nevertheless, PTH reduction after cholecalciferol supplementation was greater in the NARD group and was not influenced by concomitant treatment such as glucocorticoids, in agreement with findings by our group that patients with ARD had higher plasma PTH levels despite similar 25(OH)D concentrations[26]. Our current data give further support to the hypothesis that patients with ARD may be more refractory to PTH suppression by vitamin D than those with NARD. Autoimmune/inflammatory diseases may determine a functional impairment of vitamin D that is poorly indicated by 25(OH)D measurement in isolation, which may reflect vitamin D consumption by macrophages, resulting in lower availability of 1,25$(OH)_2$ vitamin D to parathyroid cells, which is insufficient to suppress PTH. However, our study was not designed to verify this hypothesis, which could only be addressed by the prospective evaluation of 25(OH)D, 1,25$(OH)_2$ vitamin D, and PTH changes after cholecalciferol supplementation in patients with ARD versus patients with NARD.

Our study has several limitations, principally because of its retrospective design. In particular, this design did not allow collection of reliable information about patients' compliance with cholecalciferol supplementation, which was based on patient self-reporting. This may have underestimated the side effects of this treatment. However, differences in longterm adherence and persistence between the 3 different regimens are unlikely, since all patients received the same maintenance dose. Moreover, because we included ARD with different etiologies, we could not correlate PTH suppression with disease-specific measures: a disease-specific prospective study is required to address this issue. Finally, the nonrandomized treatment allocation almost certainly led to a selection bias, evidenced by the fact that patients who received HLT had a more severe hypovitaminosis D compared to the other groups; however, this should have limited the extent of 25(OH)D and PTH normalization in this group, while the opposite effect was observed. Hypothetically, the superior results of HLT might be further magnified in a properly designed prospective study.

According to our data, cholecalciferol supplementation preceded by a high loading dose was effective in normalizing plasma 25(OH)D and suppressing PTH concentrations in patients with rheumatic disease, and should be preferred in particular for those patients with an inflammatory/autoimmune disease. Prospective studies are warranted to confirm these results.

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