RANDOMIZED DOUBLE-BLIND CONTROLLED TRIAL TO EVALUATE EFFICACY OF VITAMIN D SUPPLEMENTATION AMONG PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract

Objective/background: Patients with systemic lupus erythematosus (SLE) have a high prevalence of vitamin D deficiency. We aimed to assess the efficacy and safety of ergocalciferol combined with standard care among patients with SLE.

Methods: A randomized, double-blinded, placebo-controlled study was conducted among patients with SLE (N=104). The patients were randomized to receive either a higher dosage of ergocalciferol (100,000 IU of ergocalciferol weekly for 4 weeks followed by 40,000 IU of ergocalciferol weekly for 20 weeks, group A (N=52) or placebo (group B, N=52). All patients received 800 units of cholecalciferol daily for 24 weeks. Concurrent medications were adjusted as clinically required. We compared demographics, serum 25-Hydroxy vitamin D (25(OH) D) levels, SLE disease activity index (SLEDAI-2K) and treatment variables between the two groups. The outcomes were measured at baseline, 12 and 24 weeks follow-up. These outcomes included serum 25(OH) D, SLEDAI-2K, SLE flare event defined by an increase of SLEDAI-2K between 2 visits, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), urine protein creatinine ratio (UPCR), health assessment questionnaire (HAQ), the change of dosage of immunosuppressive drugs and glucocorticoids (GCS) and ergocalciferol related toxicity. Subgroup analyses were also undertaken among patients with lupus nephritis. Continuous variables between the 2 groups were compared using student's t-test whereas categorical groups were compared using the chi-square test.

Results: Of 104 patients, only 88 patients completed the study. Baseline characteristics between the 2 groups were similar. At 24 weeks, the mean ± standard difference (SD) of serum levels of 25(OH) D in group A was significantly higher than those in group B (41.2 ± 14.4 vs. 27.2 ± 10.1, $p < 0.001$). No difference was observed between groups A and B with respect to SLEDAI-2K, flare event, ESR, CRP and dosage of immunosuppressive drugs. However, at 12 and 24 weeks, the number of patients who could reduce GCS dosage in group A were significantly greater than group B (at 12 weeks, 39.6 vs. 17.6%, $p = 0.008$; at 24 weeks, 43.4 vs. 23.5%, $p = 0.013$). Subgroup analysis revealed no significant improvement of UPCR in group A compared with group B. Ergocalciferol related adverse reactions in both groups were similar. Serum calcium levels did not change within and between groups of treatment.

Conclusion: This study was inconclusive in demonstrating the efficacy of high dose ergocalciferol in controlling SLE disease activity. However, high dose ergocalciferol could be a safe adjunctive therapy that has a corticosteroid-sparing effect on patients with SLE.

Keywords: Vitamin D level, Systemic Lupus Erythematosus

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Introduction

Vitamin D is a secosteroid that carries a structure similar to a steroid. The main source of vitamin D is de novo synthesis in the skin through ultraviolet irradiation of 7 dehydrocholesterol. Vitamin D is related to mineral metabolism and skeletal health. Vitamin D enhances intestinal calcium, phosphate absorption stimulated osteoclast differentiation, calcium resorption from bone and promotes mineralization of bone matrix. [1, 2]

Over the last decade, several studies found vitamin D receptor (VDR) and vitamin D activating enzyme 1, α-hydroxylase (CYP27B1) expressed in many cell types especially cells of the immune system. Vitamin D deficiency has effects on innate and adaptive immune systems and possibly enhances the activity or occurrence of auto-immune disease. [3-6] It has been shown that 1, 25-dihydrovitamin D3 could inhibit dendritic cell maturation and expression of IFN-α gene among patients with Systemic Lupus Erythematosus (SLE).[7] A recent study also demonstrated patients with vitamin D-deficient SLE had higher serum IFN-α activity and B-cell activation compared with those patients with higher vitamin D levels.[8]

Several studies demonstrated a high prevalence of vitamin D deficiency among patients with SLE due to multiple risk factors such as sunlight avoidance, glucocorticoids and hydroxychloroquine exposure and chronic kidney disease.[9] Low serum vitamin D levels have been suspected as a risk factor in developing SLE, persistence of disease activity and increasing morbidity and mortality among patients with SLE (10-12). A recent study among Thai patients with SLE demonstrated a statistically significant inverse relationship between disease activity scores of SLE and serum levels of 25-hydroxyvitamin D and inverse relationship between urine creatinine ratio and serum levels of 25-hydroxyvitamin D. [13, 14] Two recent studies evaluating the efficacy of vitamin D supplementation among patients with SLE found that high dose vitamin D supplementation increased naive CD4+ T cells, Tregs and decreased effector Th1 and Th17 cells, memory B cells and anti-DNA antibodies. Another study also showed significantly improved levels of pro-inflammatory cytokines and hemostatic markers (fibrinogen, von Willebrand factor).[15, 16]

This study aimed to assess the efficacy and safety of high dose ergocalciferol combined with standard care among patients with SLE by measuring the level of 25-hydroxyvitamin D, an inflammatory marker, disease activity index, quality of life, adverse events and concurrent medications.

Methods

Study Design

A randomized double-blind controlled trial was conducted in the Rheumatic Department, Phramongkutklao Hospital. The study was approved by the Institutional Review Board of the Royal Thai Army Medical Department. All subjects provided informed consent and all procedures were performed under the ethics standard of the responsible committee on human experimentation. Following informed consent, eligibility criteria and clinical status were assessed at first visit.

Subjects were enrolled from November 2013 to January 2014. All subjects fulfilled at least 4 of the American College of Rheumatology (ACR) classification criteria for SLE, 1997. Inclusion criteria included patients with SLE at least 18 years of age. Female subjects were eligible to enter the study if they were not pregnant or nursing. All subjects had the ability to understand the requirements of the study to provide written informed consent and complied with the study protocol procedures. Subjects were excluded if they had other co-existing auto-immune diseases (except for secondary Sjogren's Syndrome), history of liver disease, history of renal stone, chronic inflammatory or infectious condition, active cancer or laboratory abnormality of the following conditions, i.e., serum creatinine >2.5 g/dl, serum calcium >10.5 mg/dl or serum 25 (OH) D <10 ng/ml.

All subjects and physicians were blinded to group assignment and treatment allocation. Subjects were randomized in 2 parallel groups, randomized by box of 4 using computer analysis at baseline of treatment. All subjects gave a detailed history and received a thorough physical examination. Clinical data recorded included disease duration, body mass index, medication use including mean daily dosage of corticosteroid, antimalarial and other immunosuppressive drugs. Subjects were randomized in 2 groups. The high dose (HD) group was assigned to receive 100,000 IU of

ergocalciferol weekly for 4 weeks followed by 40,000 IU of ergocalciferol weekly for 20 weeks. The placebo group received identical placebo 24 weeks and both groups received 800 units of cholecalciferol daily for 24 weeks. Both groups were allowed to adjust the dose of corticosteroid, antimalarial and immunosuppressive drugs followed by disease activity.

25 (OH) vitamin D level measurement and definitions

Serum samples for 25 (OH) vitamin D levels were obtained from all randomized subjects before administering ergocalciferol or placebo at the baseline visit and end of study (week 24). The 25 (OH) vitamin D level was measured using a chemiluminescence immunoassay. In accordance with the US Endocrine Society, vitamin D deficiency was defined as 25 (OH) vitamin D level of 20 ng/ml or less, vitamin D insufficiency as 21 to 29 ng/ml, and vitamin D sufficiency as 30 ng/ml or higher. [9, 16, 17] Biological markers and auto-antibodies measurements included complete blood count, erythrocyte sedimentation rate (ESR), blood urea nitrogen, creatinine, liver function test, serum calcium and phosphorus levels, C-reactive protein (CRP), autoantibodies levels (anti-dsDNA), C3, C4, lupus anticoagulant, serum anti-cardiolipin and B2glycoprotein. Urinary analysis included urine protein-creatinine ratio (UPCR). These biomarkers were measured at baseline and at weeks 12 and 24.

Disease activity assessments on SLE Disease activity index (SLEDAI) and SLE flare index were evaluated at baseline, weeks 12 and 24. Quality of life was evaluated at baseline and end of the study. Treatment-related adverse events reported by patients or observed by physicians were collected at every visit.

Efficacy endpoints and analysis

Primary efficacy endpoints included the change of inflammatory and disease activity markers (ESR, CRP, anti-dsDNA, C3, C4, lupus anticoagulant, serum anti-cardiolipin, B2glycoprotein) and disease activity index (SLEDAI, HAQ) at week 12 and the end of study. Secondary efficacy endpoints included the renal response in one patient with lupus nephritis at the end of the study. Lupus nephritis was determined by UPCR ≥ 0.5 and the renal response was determined by changes in proteinuria (UPCR below 0.5 and/or 25 to 50% reduced proteinuria) and the dose adjustment of prednisolone and other immunosuppressive drugs.

Statistical analysis

Data were analyzed using SPSS Software, Version 20. Values in the study were expressed as mean (SD), median (IQR) or number (percentage). Continuous variables between the 2 groups were compared using the student's t-test, and categorical groups were compared using the chi-square test. Statistical significance was defined as a 2-sided *p*-value of 0.05.

Results

The 104 eligible participants (91 woman, 13 men) were randomized in either high dose group (HD-groups, n=52) or placebo group (n=52). The mean age was 41.15 years in the high dose group and 43.67 years in the placebo group. Eighty-five patients (81%) completed the protocol at the end of 24 weeks of treatments.

The demographic characteristics of study groups are depicted in **Table 1.** Baseline characteristics were similarly distributed between the 2 treatment groups except only hypertension was more common in the placebo group. Mean 25 (OH) D levels, inflammatory, disease activity marker, renal response of vitamin D supplement of the study population at baseline and 24 weeks of treatment are shown in **Table 2.**

Table1. Baseline characteristics of study participants according to treatment groups

	High dose group	Placebo group	*p*-value
Sex, female/male, (n, %)	48 (90.57%)	43 (84.31%)	0.386
Age, years, mean (SD)	41.15 (13.31)	43.67 (13.19)	0.336
BMI, kg/m2, mean (SD)	22.01(5.49)	22.59 (5.59)	0.533
DM (n, %)	7 (13.21%)	4 (7.84%)	0.374
HT (n, %)	18 (33.96%)	28 (54.90%)	0.032
DLD (n, %)	14 (26.42%)	22 (43.14%)	0.073
CAD (n, %)	3 (5.56%)	3 (5.58%)	0.961
Hypothyroid (n, %)	2 (3.77%)	0	0.161
APS (n, %)	4 (7.55%)	6 (11.76%)	0.466
Disease duration (months), median (IQR)	72 (24, 144)	120 (48, 228)	0.052
Vitamin D Supplement IU/day, median (IQR)	800 (800, 2857)	800 (600, 2875)	0.632
Drug calcium (mg), mean (SD)	1301.89 (512.72)	1264.71 (550.94)	1.0
Prednisolone (mg / day), median (IQR)	8.75 (5, 15)	5 (2.5, 10)	0.257
CQ (mg/day), mean (SD)	207.63 (65.16)	197.5 (73)	0.669
HCQ (mg/day), mean (SD)	180 (40.82)	193.8 (102.6)	0.538
Azathioprine (mg/day), mean (SD)	55.25 (26.73)	59.1 (23.1)	0.699
CYC iv (mg/month), mean (SD)	1000 (200)	800 (163.3)	0.203
Cyclosporin A (mg/day), mean (SD)	-	100	NA
MTX (mg/week), mean (SD)	6.25 (1.77)	-	NA
MMF (mg/day), mean (SD)	1416 (664.58)	1647 (852.2)	0.609
SLEDAI, median (IQR)	4.0 (2, 6)	4.0 (1, 4)	0.544
c3 (g/l), mean (SD)	0.81 (0.34)	0.83 (0.34)	0.757
c4 (g/l), mean (SD)	0.20 (0.13)	0.19 (0.11)	0.869
Anti-dsDNA (U/ml), median (IQR)	135 (25.9, 408.5)	142.25 (29.43, 472)	0.797
ESR (mm/hour), mean (SD)	49.17 (26.47)	41.89 (21.62)	0.150
CRP (mm/hour), median (IQR)	1.6 (0.6, 3)	1.4 (0.6, 3.3)	0.892
25 (OH) D (ng/ml), mean (SD)	27.99 (9.24)	25.92 (10.57)	0.288
Ca (mg/dl), mean (SD)	9.16 (0.49)	9.07 (0.52)	0.396
po4 (mg/dl), mean (SD)	3.68 (0.6)	3.57 (0.66)	0.359
Alb (mg/ml), mean (SD)	4.06 (0.4)	4.12 (0.5)	0.520
UPCR, mean (SD)	0.35 (0.65)	0.47 (0.99)	0.470
Cardiolipin (U/ml), median (IQR)	1.8 (0.85, 2.86)	1.3 (0.7, 3.6)	0.479
b2gly (U/ml), median (IQR)	9.2 (4.4, 14.25)	7.9 (4.5, 12)	0.734
HAQ, mean (SD)	64.42 (20.93)	68.12 (33.8)	0.502

DLD: dyslipidemia; CAD: coronary artery disease; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; CQ: chloroquine; HCQ: hydroxychloroquine; MTX: methotrexate; CYC: cyclophosphamide; MMF: mycophenolate mofetil; Alb: serum albumin; UPCR: urine protein-creatinine ratio; HAQ: health assessment questionnaire.

Table 2. Vitamin D status and inflammatory and disease activity markers at baseline and 24 weeks of treatment

	High dose group	Placebo group	*p*-value
Serum vitamin D (ng/ml) (mean, SD)			
Baseline	27.99 (9.24)	25.92 (10.57)	0.288
24 weeks	41.17 (14.44)	27.16 (10.12)	<0.001
Anti-dsDNA (U/ml), median (IQR)			
Baseline	135 (25.9, 408.5)	142.25 (29.43, 472)	0.797
24 weeks	164.80 (40.55, 321.0)	102.3 (42.5, 260)	0.706
C3 (g, l) (mean, SD)			
Baseline	0.81 (0.34)	0.83 (0.34)	0.757
24 weeks	0.96 (0.35)	0.92 (0.36)	0.606
C4 (g, l) (mean, SD)			
Baseline	0.20 (0.13)	0.19 (0.11)	0.869
24 weeks	0.20 (0.11)	0.27 (0.28)	0.166
ESR (mm, hr) (mean, SD)			
Baseline	49.17 (26.47)	41.89 (21.26)	0.150
24 weeks	45.55 (25.99)	39.17 (20.27)	0.219
CRP (mm, hr) (median) (IQR)			
Baseline	1.6 (0.6, 3)	1.4 (0.6, 3.3)	0.892
24 weeks	0.9 (0.5, 2.0)	1.4 (0.55, 2.9)	0.442
Cardiolipin (U/ml) (median) (IQR)			
Baseline	1.8 (0.85, 2.86)	1.3 (0.7, 3.6)	0.479
24 weeks	1.1 (0.8, 2.5)	1.7 (0.8, 2.6)	0.284
B2 glycoprotein (U/ml) (median) (IQR)			
Baseline	9.2 (4.4, 14.25)	7.9 (4.5, 12)	0.734
24 weeks	8.4 (4.6, 18.2)	8.1 (3, 14)	0.478
Subgroup of subjects with UPCR ≥ 0.5 at baseline	N=36	N=33	
UPCR (mean) (SD)			
UPCR at baseline	1.28 (1.07)	2.67 (1.29)	0.028
UPCR at 24 weeks	0.83 (0.82)	0.55 (0.65)	0.561
Renal response (N, %)			
25 % decreased UPCR or UPCR < 0.5 at 24 weeks	19(57.6%)	11 (30.6%)	0.024
50 % decreased UPCR or UPCR < 0.5 at 24 weeks	11(33.3%)	8 (22.2%)	0.302

UPCR: urine protein-creatinine ratio.

Vitamin D status

Vitamin D status of the HD-group at baseline was similar to the placebo group (27.99±9.24 vs. 25.92±10.57ng/ml, p=0.288). At baseline, a small number of patients in the HD-group had vitamin D deficiency (<20ng/ml) compared with the placebo group (20.75 vs. 33.33%, p=0.148). At the end of the study, mean 25 (OH) D levels of the HD-group were significantly higher than

those of the placebo group (41.2 ± 14.4 vs. 27.2 ± 10.1, $p < 0.001$). In addition, a significantly lower number of subjects in the HD group had vitamin D insufficiency than that of the placebo group (7.55 vs. 21.57%, P = 0.035) at 24 weeks of treatment.

Inflammatory and disease activity markers

Inflammatory and disease activity markers including anti-dsDNA, C3, C4, CRP, ESR, B2-glycoprotein and anti-cardiolipin were similar between the HD and placebo groups during the study. Subgroup analysis was performed among subjects with 25 (OH) D levels below 30ng/ml at baseline. No significantly improved inflammatory and disease activity markers were found between the two treatment groups (data not shown).

Subgroup of patients with lupus nephritis

In all, 17 patients presented lupus nephritis at baseline (HD-group, n=10 and placebo group, n=7). Renal response among patients with lupus nephritis at the end of the study between the two groups is shown in **Table 2.** At baseline, the mean level of UPCR in the HD-group was significantly lower than that of the placebo group (1.28±1.07 vs. 2.67±1.29, p= 0.028). At 24 weeks of treatment, no significant difference was observed in the mean level of UPCR between two groups (0.83±0.82 vs. 0.55±0.65). However, the number of subjects presenting lupus nephritis with 25% reduced UPCR or UPCR below 500 mg/day and the number of subjects with lupus nephritis with 50% reduced UPCR or UPCR below 500 mg/day did not significantly differ between two groups.

Disease activity index

Efficacies of vitamin D supplement are shown in **Table 3**. In this study, no significant improvement was shown in both disease activity indexes (SLEDAI, flare index) and quality of life determined using a health assessment questionnaire (HAQ) between the two study groups.

Table 3. Variations in SLEDAI score, HAQ score and number of patients (n, %) with an improved flare index in the HD-group compared with those of the placebo group, values are mean (SD), median (IQR)

SLEDAI Median (IQR)	High dose group	Placebo group	*p*-value
At baseline	4.0 (2, 6)	4.0 (1, 4)	0.544
At 12 weeks of treatment	2.0 (0, 4)	2.0 (0, 2)	0.880
At 24 weeks of treatment	0.0 (0, 4)	2.0 (0, 2)	0.101
HAQ (mean, SD)			
At baseline	64.42 (20.93)	68.12 (33.8)	0.502
At 24 weeks of treatment	60.04 (22.42)	58.09 (21.3)	0.672
SLE not flare (N, %)			
At 24 weeks of treatment	39 (73.6%)	42 (82.4%)	0.266

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; UPCR: urine protein-creatinine ratio; HAQ: health assessment questionnaire.

Vitamin D as steroid-sparing effect and effect on immunosuppressant

Significantly more subjects could reduce the dose of prednisolone in the HD group compared with the placebo group at 12 weeks until the end of the study (12 weeks; 43.75% vs. 18.75%, $p = 0.008$ and 24 weeks; 52.27% vs. 26.66%, $p = 0.024$) and at 6 months of treatment (52.27% vs. 26.66%, $p = 0.024^*$). In addition, significant difference was found in the dose adjustment of immunosuppressive drugs between the two groups during the study. Data are shown in **Table 4**.

Table 4. Number of subjects with reduced prednisolone and immunosuppressive doses at 12 and 24 weeks of treatment.

The number of subjects with a reduced prednisolone dose	High dose group	Placebo group	*p*-value
At 12 weeks of treatment (n, %)	21 (39.62%)	9 (17.65%)	0.008
At 24 weeks of treatment (n, %)	23 (43.40%)	12 (23.53%)	0.013
The number of subjects with reduced immunosuppressive dose			
At 12 weeks of treatment (n, %)	2 (3.8%)	0	0.242
At 24 weeks of treatment (n, %)	4 (7.6%)	1 (2.0%)	0.203

Safety profile

One patient in the HD group withdrew from the study due to minor rash reaction and recovered after vitamin D discontinuation. One patient in the placebo group withdrew from the study due to weight gain. Serum calcium and phosphorus levels did not change within and between groups of treatment (data not shown).

Discussion

In the view of the potential beneficial effects of vitamin D on immunomodulation and high prevalence of vitamin D deficiency among patients with SLE [8, 10, 16, 18, 19], supplementation of vitamin D constitutes an important therapeutic strategy. Avoidance of sunlight, renal insufficiency, obesity, and use of medication such as glucocorticoids are major risk factors for vitamin D insufficiency in SLE. [14] This study showed the effect of high dose over low dose vitamin D supplementation on rising serum vitamin D levels among patients with SLE.

The immunomodulation of vitamin D is opposite that of the observed immunological aberrations among patients with SLE. A related study demonstrated that 1, 25-dihydroxy vitamin D and its analogs inhibited polyclonal and anti-dsDNA (IgG) production by stimulating peripheral blood mononuclear cells from patients with SLE. [20] Dihydroxy vitamin D3 has been shown to inhibit dendritic cell maturation and expression of the IFN-α gene (IFN signature) among patients with SLE. [1, 7, 25] A more recent study also demonstrated that vitamin D deficient patients with SLE had higher serum IFN-α activity and B-cell activation compared with those patients with higher vitamin D levels taken together. Strong evidence indicates that insufficient vitamin D may aggravate immunological abnormalities among patients with SLE. [8] Several studies have reported an inverse relationship exists between 25 (OH) D level and disease activity. [16, 21, 22] Abou-Raya et al. showed that high dose vitamin D supplementation provided a significant effect on the reducing autoantibodies levels (anti-sm, anti-dsDNA) and ESR with improved complement level and SLE-DAI score. [16] This study could not demonstrate improved inflammatory markers, immunological markers, disease activity or quality of life of patients with SLE. This could be explained by the small sample size, short duration of follow-up, a small number of patients with vitamin D deficiency and uncontrolled concurrent medications.

Regarding the subgroup analysis of patients with lupus nephritis, this study found no significantly improved UPCR among patients receiving high dose of vitamin D supplementation. According to a recent study of Petri M el al., vitamin D supplementation among patients with SLE with low level 25 (OH) D (<40 ng/ml) and 20 ng/ml increase in 25 (OH) D level were associated with a 21% decrease in the odds of having a high disease activity score and 15% decrease in the odds of having clinically improved proteinuria. [23] This could be explained by the small number of patients with lupus nephritis as well as short duration of follow-up.

Interestingly, our study was the first to find a steroid-sparing effect of high-dose vitamin D supplementation. A significantly improved de-escalating of corticosteroid among patients receiving high dose vitamin D supplementation was observed, despite no differences in adjusting immunosuppressive agents. Two cross-sectional studies found an inverse relationship between levels of vitamin D and corticosteroid use (both

current dose and cumulative dose) which might have supported corticosteroid-sparing effects in our study (14, 24). However, a future study controlling the dosage of immunosuppression is needed to confirm these findings.

The long term use of vitamin D is not completely safe, concerning hypercalcemia, hyperphosphatemia and renal stones, but the risks are extremely low. Long term follow-up is needed to ensure sufficient levels of 25 (OH) D leads to clinically improved disease activity. Finally, we recommend a routine assessment of vitamin D levels and adequate supplementation of vitamin D among patients with SLE.

Conclusion

This study could not demonstrate the efficacy of high dose ergocalciferol in controlling SLE disease activity. However, high dose ergocalciferol could improve vitamin D levels back to normal and constitute a safe adjunctive therapy exhibiting a steroid-sparing effect among patients with SLE.

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Disclosures None

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