Caroline Chang, MD (Pediatrics PGY 3)
ICCR Rotation
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The Effect of Vitamin D Supplementation on Disease Activity in Pediatric Patients with Systemic Lupus Erythematosus: A Randomized Controlled Trial

A. Study Purpose and Rationale

Vitamin D is a pro-hormone that has a clear role in maintenance of bone health and calcium homeostasis. However, recent studies have shown that vitamin D may have an additional role in immune health. Vitamin D has been shown to affect B cells, T cells, and dendritic cells, and deficiency has been shown to be associated with increased risk of developing autoimmune diseases such as type 1 diabetes and multiple sclerosis.[5] Protective effects of vitamin D supplementation against rheumatoid arthritis and inflammatory bowel disease have also been demonstrated.[4,6]

In Systemic Lupus Erythematosis (SLE), vitamin D has been shown to decrease Th1 CD4 T cells and cytokines, increase regulatory T cells, down-regulate T cell driven IgG production, inhibit dendritic cell differentiation, and prevent activated B cell proliferation. However, patients with SLE also have an increased risk of vitamin D deficiency. This occurs for a number of reasons, including prolonged steroid use, avoidance of sunlight exposure due to its effect on disease flares, and possibly from the disease process itself.[3] In addition, Amital et al showed that serum vitamin D levels were inversely related to overall disease activity. Thus, it is postulated that vitamin D supplementation may have a significant beneficial clinical effect on patients with SLE.[1]

Additionally, in adults, recent studies have shown that a serum 25-hydroxyvitamin D (25[OH]D) level of 32ng/ml is a more appropriate threshold for vitamin D sufficiency compared to the previous threshold of 20ng/ml. However, in children, there have not been enough studies to justify changing the definition of vitamin D sufficiency and deficiency.[4] Therefore, even though pediatric patients with SLE may be getting vitamin D supplementation, many patients may not be getting the maximum potential benefit of vitamin D supplementation if they are following the current guidelines.

Several studies have investigated the effect of vitamin D supplementation on SLE activity. However, these studies have predominantly been observational studies in adults, and have been based on dose of vitamin D administered rather than serum levels of vitamin D. To date there have not yet been any randomized controlled studies showing an improvement in disease activity with vitamin D supplementation in adults or children. Therefore, the purpose of this study will be to determine via a randomized controlled trial whether vitamin D supplementation to a level higher than the current recommended levels will improve SLE activity in pediatric patients.

B. Study Design and Statistical Analysis

This is a multi-center, prospective randomized double-blind trial that will enroll patients with vitamin D insufficiency/deficiency defined as a 25[OH]D level <20ng/ml. Once a subject has entered the study, we will use computer generated randomization to assign them to one of two arms: 1) target 25[OH]D level of 20ng/ml 2) target 25[OH]D level of 60 ng/ml.

Primary Outcome:
Overall change in disease activity as measured by SLEDAI scores over the course of 1 year.

Secondary Outcomes:
Number of flares, number of hospital admissions

Variables to be collected:
1. Demographic information
    a) Age
    b) Gender
    c) Ethnicity
2. Laboratory Data
    a) Vitamin D status--25[OH]D levels, calcium, PTH
    b) SLEDAI variables-CBC, C3, C4, anti-DS DNA, urinalysis and urine protein
3. Medications
    a) Current lupus medications (type, duration)
    b) Current vitamin D supplementation
4. Hospitalizations during the course of the study (Number, reason for admission)
5. SLEDAI scores

Estimation of required study size was performed assuming a standard deviation of 7, which was calculated based on a change in SLEDAI of 3 with a SEM of 0.5 in lupus flares in a study of 185 patients.[8] In order to be powered to 80% to determine a difference of 3 points or more on the SLEDAI scale at a significance level of 0.05 using an unpaired t-test and assuming a 10% loss to follow-up, we will enroll a total of 200 study subjects. Analysis of the primary and secondary outcomes will be performed via intention to treat method using an unpaired t-test.

C. Study Procedure
Patients age 1-18 with a diagnosis of SLE (defined below) and vitamin D insufficiency/deficiency will be eligible for the study. Patients will be recruited from January 1, 2011 through December 31, 2014. Written informed consent from parents/legal guardians will be obtained. Data will be collected from the patients for a total of 12 months from their enrollment in the study, and will include demographic information, lab values, number of hospital stays, and disease activity as measured by SLEDAI scores.

Within 1 week of the blood draw showing a 25[OH]D level <20ng/ml, the patient will be randomized to either the standard or higher target serum 25[OH]D level. A baseline SLEDAI score will be determined. For the course of the study, patients will be required to take one pill per day of the study drug. The dosage of vitamin D3 contained in the study drug will be determined base on the serum level as described below. Serum 25[OH]D levels, calcium, and PTH levels will be checked every 2 months to monitor vitamin D status. Vitamin D levels will be measured using radioimmunoassay for all patients in the NYPH lab. Additionally, labs required for the SLEDAI score (CBC, C3, C4, anti-DS DNA, UA, and urine protein) will be measured every 2 months. The number of venipunctures will not be more than the standard of care for baseline lupus management, but 25[OH]D, calcium, and PTH levels will be measured more frequently than the standard of care. All patients will also be given calcium per recommended dosing during treatment for vitamin D deficiency. Disease activity will be evaluated by the patients' rheumatologists via SLEDAI score at the beginning, end and every 2 months throughout the course of the study. To minimize variability, practitioners will receive a short training course on how to calculate the SLEDAI.

D. Study Drugs

Vitamin D3 (cholecalciferol) is a drug approved by the FDA for treatment of vitamin D deficiency in all age groups and rickets in children.[7] It has been shown to be more potent and efficient than other forms of vitamin D at replenishing the body's stores of vitamin D. It is extremely safe and has been used by many people for vitamin D supplementation.[4]

In the study, vitamin D3 will be administered by mouth, which is the standard route of administration. Repletion will be given according to standard recommendations for vitamin D deficiency, which is 5,000-10,000IU by mouth daily for 2-3 months.[4] Patients will initially receive 5,000IU and 10,000IU of vitamin D3 orally in the 20ng/ml arm and 60ng/ml arms respectively. If subjects are still not at their target level of vitamin D after the first 2 months, they will repeat the same regimen for another 2 months and have their level rechecked, and continue this in 2-month intervals until the goal serum level is reached. Once subjects reach their target level, they will be changed to a maintenance dose of 400IU daily. If patients subsequently fall below their goal serum level, they will go back to treatment dosing.

Side effects of elevated vitamin D are not seen unless serum levels of 25[OH]D are >100ng/ml, and only if calcium levels are concurrently elevated. Toxicity is rare. Its effects are those of hypercalcemia, secondary to hypervitaminosis D. Signs include QT shortening, sinus tachycardia, confusion, lethargy, nausea, vomiting, abdominal pain, soft tissue calcinosis, calciuria, and nephrocalcinosis.[7]

E. Medical Device

None

F. Study Questionnaires
We will use the SLEDAI, a weighted, cumulative index of lupus disease activity that has been shown to be a valid and reliable disease activity measure in multiple patient groups, including children. This scale provides a total score between 0 and 105, with higher scores representing increased disease activity, an increase of 3 points representing a relative flare, and decrease of 3 points representing relative improvement.[2] (see attached)

G. Study Subjects

Inclusion Criteria:
Patients age 1-18 who have:

1) A diagnosis of Systemic Lupus Erythematosus as defined by the American College of Rheumatology (ACR) classification criteria (see attached)

AND

2) A serum 25[OH]D level <20ng/ml within the past 1 week.

Exclusion Criteria:

1) Inability to tolerate vitamin D supplementation for any reason
2) Hypercalcemia

H. Recruitment of Subjects
A study coordinator will review the paper and electronic records of new and existing SLE patients weekly in the pediatric rheumatology lupus clinic. If a patient meets the inclusion criteria and lacks exclusion criteria, the study coordinator, after obtaining permission from the patient's rheumatologist, will approach the patient's parent/legal guardian to obtain written informed consent for inclusion in the study.

I. Confidentiality of Study Data
All written data regarding study participants will be kept in a locked room and all electronic data will be kept on a secure computer in a password protected file. Blood samples will be collected in similar tubes and each tube labeled with a non identifying umber. Only study personnel will have access to the file linking study sample number with patient name and medical record number.

J. Potential Conflict of Interest
None

K. Location of Study
Morgan Stanley Children's Hospital of NewYork-Presbyterian Pediatric Rheumatology Clinic as well as three other sites yet to be determined.

L. Potential Risks
Potential risks include vitamin D toxicity.

M. Potential Benefits
Patients may benefit from the study by having improved vitamin D levels, which would benefit bone health. They may or may not have additional personal benefits including improvement (decrease) in disease activity. There also may or may not be benefits to society in elucidating the role of vitamin D in immune health.

N. Alternative Therapies
If a patient chooses not to participate in the study, they can be treated for vitamin D deficiency per the current guidelines to a goal serum level of 20ng/ml, using either daily or stoss therapy. Stoss therapy may be beneficial for patients with compliance issues, as it is only a 5-day treatment course followed by daily maintenance dosing.

O. Compensation to Subjects
None

P. Costs to Subjects
There is no monetary cost to any patient or family enrolled in the study. The patient's family will be asked to provide written informed consent for a total of 7 blood draws of 10 milliliters of blood and 7 urine samples from their child throughout the study when blood and urine is already being collected for clinical purposes.

Q. Minors as Research Subjects
To be submitted to the Department of Pediatrics Committee on Human Investigation.

R. Radiation or Radioactive Substances
None

References
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3. Kamen, D and Aranow, C. The Link Between Vitamin D Deficiency and Systemic Lupus Erythematosus. Current Rheumatology Reports 2008, 10: 273 – 280
4. Madhusmita Misra et al. Vitamin D Deficiency in Children and Its Management: Review of Current Knowledge and Recommendations. Pediatrics 2008;122;398-417
5. Munger KL, Zhang SM, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. Neurology 2004;62:60–5.
6. Merlino LA, Curtis J, Mikuls TR, et al. Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. Arthritis Rheum 2004;50:72–7.
7. Pediatric Lexi-Drugs Online. http://online.lexi.com/crlsql/servlet/crlonline
8. Petri M, et al. Definition, incidence, and clinical description of flare in systemic lupus erythematosus. A prospective cohort study. Arthritis Rheum. 1991 Aug;34(8):937-44.

ACR Classification Criteria for Diagnosis of SLE

Having 4 out of the 11 following criteria either simultaneously or serially on 2 separate occasions qualifies as a diagnosis of SLE (sensitivity 75%, specificity 95%):

a) Serositis	-pleuritis or pericarditis
b) Oral Ulcers	
c) Arthritis	-nonerosive arthritis of 2 or more peripheral joints, with tenderness, swelling, or effusion
d) Photosensitivity	-exposure to UV light causes rash or other symptoms of SLE
e) Hematologic Disorder	-hemolytic anemia, leukopenia (< 4,000/L), lymphopenia (<1500/L), or thrombocytopenia (<100,000/L) in the absence of an offending drug
f) Renal disorder	-More than 0.5g per day or 3+ in urine or cellular casts
g) Antinuclear Antibody	
h) Immunologic Disorder	-positive anti-smith, anti-ds DNA, anti-phospholipid antibody, or false positive test for syphilis
i) Neurologic Disorder	-seizures or psychosis without other causes
j) Malar rash	
k) Discoid rash	

Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)

8 Seizure	Recent onset. Exclude metabolic, infectious or drug cause
8 Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Excluded uremia and drug causes.
8 Organic Brain Syndrome	Altered mental function with impaired orientation,memory or other intelligent function, rapid onset fluctuating clinical features: clouding of consciousness, reduced capacity to focus, plus 2: perceptual disturbance, incoherent speech, insomnia, or change in psychomotor activity. Exclude metabolic, infectious or drug causes
8 Visual Disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages serious exodate or hemorrhages in the choroids, or optic neuritis. Exclude hypertension, infection, or drug causes.
8 Cranial Nerve Disorder	New onset of sensory or motor neuropathy involving cranial nerves
8 Lupus Headache	Severe persistent headache: may be migrainous, but must be nonresponsive to narcotic analgesia.
8 CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis
8 Vasculitis	Ulceration, gangrene, tender finger nodules, periungual, infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis
4 Arthritis	More than 2 joints with pain and signs of inflammation
4 Myositis	Proximal muscle aching/weakness, with elevated CPK/adolase or electromyogram changes or biopsy showing myositis.
4 Urinary Casts	Heme-granular or red blood cell casts
4 Hematuria	>5 red blood cells/hpf. Exclude stone, infection or other cause.
4 Proteinuria	>0.5 gm/24 hours. New onset or recent increase >0.5 gm/24 hours.
4 Pyuria	>5 white blood cells/high power field. Exclude infection.
2 New Rash	New onset/recurrence of inflammatory type rash.
2 Alopecia	New onset/recurrence of abnormal, patchy or diffuse loss of hair.
2 Mucosal Ulcers	New onset or recurrence of oral or nasal ulcerations
2 Pleurisy	Pleuritic chest pain with pleural rub/effusion, or pleural thickening.
2 Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram confirmation.
2 Low Complement	Decrease in CH50, C3, or C4 <lower limit of normal for testing lab
2 Increased DNA	>25% binding by Farr assay or above normal range for testing lab
1 Fever	>38°C. Exclude infectious cause
1 Thrombocytopenia	<100,000 platelets/mm3
1 Leukopenia	<3,000 White blood cell/mm3. Exclude drug causes.
0-3 Physicians Global	
Assessment	0 None, 1 Mild, 2 Medium, 3 Severe