

Lupus Patients Need 2,000 IU Daily Vitamin D

VITALS

Major Finding: Five of six black lupus patients who were given 2,000 IU vitamin D daily repleted serum 25-hydroxyvitamin D to 30 ng/mL or more at 3 months.

Data Source: A phase 1 study of 18 patients.

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BY M. ALEXANDER OTTO

FROM THE INTERNATIONAL CONGRESS
ON SYSTEMIC LUPUS ERYTHEMATOSUS

VANCOUVER, B.C. — A daily dose of at least 2,000 IU of vitamin D is required to elevate serum 25-hydroxyvitamin D levels above 30 ng/mL, the minimum threshold for optimal immune health, according to results from an open-label, phase

I study of vitamin D repletion in 18 black patients with lupus.

Starting from a baseline mean 25-hydroxyvitamin D (25[OH]D) level of 13.3 ng/mL, six patients received 800 IU vitamin D once daily; six received 2,000 IU once daily; and six received 4,000 IU once daily, reported Dr. Diane Kamen, a rheumatologist at the Medical University of South Carolina in Charleston.

After 12 weeks, 67% (four patients) in the 800-IU group, 83% (five) in the 2,000-IU group, and 67% (four) in the 4,000-IU group repleted to 30 ng/mL or greater.

In the 4,000-IU group, levels in 33% (two patients) rose above 40 ng/mL. That level was not reached at the lower doses.

The results are important, Dr. Kamen said in an interview after the meeting, because although there is growing awareness that such high doses of vitamin D are needed to restore 25(OH)D levels in patients with autoimmune disease, the rheumatology literature still contains recommendations for doses of 600-800 IU/day.

“That’s just not going to cut it; 2,000 IU a day is the minimum effective dose for repletion,” especially if patients avoid the sun to prevent lupus flares, Dr. Kamen said.

Physicians “need to know to recommend those higher doses, and to monitor levels” of 25(OH)D to make sure they are maintained, she said.

The 18 patients were enrolled from a population of blacks living on the Sea Islands of South Carolina and Georgia, a population known as the Gullah in whom there is a high incidence of lupus.

An earlier Gullah study found that 43% of 187 subjects had 25(OH)D levels below 10 ng/mL; in some, levels were undetectable.

Lower levels correlated with higher SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) scores and higher anti-dsDNA antibody levels, Dr. Kamen said.

The mean age in the phase I study was 44 years; the mean prednisone dose 4.3 mg/day, and the mean SLEDAI score 2.4. In all, 17 of 18 of the subjects were women, 50% (9) took hydroxychloroquine, and 50% (9) were anti-dsDNA antibody positive.

Compliance with the treatment regimen was 99%, by pill count. The doses were very well tolerated and safe, Dr. Kamen said.

Although 2,000 IU per day elevated 25(OH)D levels in most patients to at least 30 ng/mL, there’s debate about whether target blood levels should be higher in lupus patients.

“We know that 30 ng/mL is the minimum accepted as normal,” Dr. Kamen said, noting that secondary hyperparathyroidism can begin below that level.

“I tell my patients at high risk for conditions influenced by vitamin D, such as osteoporosis and inflammatory conditions, that we want them to stay between 40 and 60 ng/mL,” she said, but “it’s a gray zone” that awaits further research.

Levels of 25(OH)D are known to be low in lupus patients, but no one can say for sure whether that is a cause or a consequence of the disease, or if it results from the medications that are used to treat it, such as prednisone and hydroxychloroquine. ■

• Insulin initiation and intensification of glucose control

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

• Lipodystrophy

Long-term use of insulin, including LANTUS, can cause lipodystrophy at the site of repeated insulin injections. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy. [See *Dosage and Administration* (2.1)].

• Weight gain

Weight gain can occur with insulin therapy, including LANTUS, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

• Peripheral Edema

Insulin, including LANTUS, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

• Allergic Reactions

Local Allergy

As with any insulin therapy, patients taking LANTUS may experience injection site reactions, including redness, pain, itching, urticaria, edema, and inflammation. In clinical studies in adult patients, there was a higher incidence of treatment-emergent injection site pain in LANTUS-treated patients (2.7%) compared to NPH insulin-treated patients (0.7%). The reports of pain at the injection site did not result in discontinuation of therapy.

Rotation of the injection site within a given area from one injection to the next may help to reduce or prevent these reactions. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique. Most minor reactions to insulin usually resolve in a few days to a few weeks.

Systemic Allergy

Severe, life-threatening, generalized allergy, including anaphylaxis, generalized skin reactions, angioedema, bronchospasm, hypotension, and shock may occur with any insulin, including LANTUS and may be life threatening.

• Antibody production

All insulin products can elicit the formation of insulin antibodies. The presence of such insulin antibodies may increase or decrease the efficacy of insulin and may require adjustment of the insulin dose. In phase 3 clinical trials of LANTUS, increases in titers of antibodies to insulin were observed in NPH insulin and insulin glargine treatment groups with similar incidences.

6.2 Postmarketing experience

The following adverse reactions have been identified during post-approval use of LANTUS.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate reliably their frequency or establish a causal relationship to drug exposure.

Medication errors have been reported in which other insulins, particularly short-acting insulins, have been accidentally administered instead of LANTUS [See *Patient Counseling Information* (17) in the full prescribing information]. To avoid medication errors between LANTUS and other insulins, patients should be instructed to always verify the insulin label before each injection.

7. DRUG INTERACTIONS

A number of drugs affect glucose metabolism and may require insulin dose adjustment and particularly close monitoring.

The following are examples of drugs that may increase the blood-glucose-lowering effect of insulins including LANTUS and, therefore, increase the susceptibility to hypoglycemia: oral anti-diabetic products, pramlintide, angiotensin converting enzyme (ACE) inhibitors, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, propoxyphene, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

The following are examples of drugs that may reduce the blood-glucose-lowering effect of insulins including LANTUS: corticosteroids, niacin, danazol, diuretics, sympathomimetic agents (e.g., epinephrine, albuterol, terbutaline), glucagon, isoniazid, phenothiazine derivatives, somatropin, thyroid hormones, estrogens, progestogens (e.g., in oral contraceptives), protease inhibitors and atypical antipsychotic medications (e.g. olanzapine and clozapine).

Beta-blockers, clonidine, lithium salts, and alcohol may either potentiate or weaken the blood-glucose-lowering effect of insulin. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

The signs of hypoglycemia may be reduced or absent in patients taking sympatholytic drugs such as beta-blockers, clonidine, guanethidine, and reserpine.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 7 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m². In rabbits, doses of 0.072 mg/kg/day, which is approximately 2 times the recommended human subcutaneous starting dose of 10 Units/day (0.008 mg/kg/day), based on mg/m², were administered during

LANTUS®

(insulin glargine [rDNA origin] injection) solution for subcutaneous injection

organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

There are no well-controlled clinical studies of the use of LANTUS in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. Insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients.

8.3 Nursing Mothers

It is unknown whether insulin glargine is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when LANTUS is administered to a nursing woman. Use of LANTUS is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

The safety and effectiveness of subcutaneous injections of LANTUS have been established in pediatric patients (age 6 to 15 years) with type 1 diabetes [see *Clinical Studies* (14) in the full prescribing information]. LANTUS has not been studied in pediatric patients younger than 6 years of age with type 1 diabetes. LANTUS has not been studied in pediatric patients with type 2 diabetes.

Based on the results of a study in pediatric patients, the dose recommendation when switching to LANTUS is the same as that described for adults [see *Dosage and Administration* (2.3) and *Clinical Studies* (14) in the full prescribing information]. As in adults, the dosage of LANTUS must be individualized in pediatric patients based on metabolic needs and frequent monitoring of blood glucose.

8.5 Geriatric Use

In controlled clinical studies comparing LANTUS to NPH insulin, 593 of 3890 patients (15%) with type 1 and type 2 diabetes were ≥65 years of age and 80 (2%) patients were ≥75 years of age. The only difference in safety or effectiveness in the subpopulation of patients ≥65 years of age compared to the entire study population was a higher incidence of cardiovascular events typically seen in an older population in both LANTUS and NPH insulin-treated patients.

Nevertheless, caution should be exercised when LANTUS is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemic reactions. Hypoglycemia may be difficult to recognize in the elderly [See *Warnings and Precautions* (5.3)].

10. OVERDOSAGE

An excess of insulin relative to food intake, energy expenditure, or both may lead to severe and sometimes prolonged and life-threatening hypoglycemia. Mild episodes of hypoglycemia can usually be treated with oral carbohydrates. Adjustments in drug dosage, meal patterns, or exercise may be needed.

More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. After apparent clinical recovery from hypoglycemia, continued observation and additional carbohydrate intake may be necessary to avoid recurrence of hypoglycemia.

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