

Medication Duo Scores Big Against *P. acnes*

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FROM THE ANNUAL CONGRESS OF THE EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY

GOTHENBURG, SWEDEN – Multimodal therapy with adapalene 0.1% and benzoyl peroxide 2.5% in a fixed-dose combination gel plus oral doxycycline proved safe, effective, and well tolerated for severe acne vulgaris in a large, dou-

ble-blind, multicenter randomized trial.

Indeed, the combination therapy's favorable safety profile makes it a compelling first-line treatment for all but the most severe, recalcitrant cases of nodular acne, where oral isotretinoin, despite its problematic safety profile, remains the treatment of choice because of its unequalled efficacy, Dr. Alma Cruz said at the meeting.

The mechanism of benefit for adapa-

lene 0.1%–benzoyl peroxide 2.5% fixed-dose combination gel (Epiduo) plus oral doxycycline in patients with severe acne appears to involve, at least in part, the combination therapy's ability to achieve a rapid and sustained reduction in *Propionibacterium acnes* as documented in the trial by serial fluorescent photography, according to Dr. Cruz, a dermatologist in Carolina, P.R.

At week 4 in the 12-week trial, pa-

tients in the combination therapy arm had a mean 60% reduction from baseline in *P. acnes* compared with a 22% decrease in the vehicle plus doxycycline group.

At weeks 8 and 12, the combination therapy group had 73% and 74% reductions from baseline in *P. acnes*, compared with reductions of 16% and 14% in controls.

The reduction in *P. acnes* correlated with clinical efficacy. At week 2, one-third of the ultimate reduction in total lesion count in the combination treat-

• 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 lipoatrophy (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.

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

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 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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VITALS

Major Finding: At weeks 8 and 12, the combination therapy group had 73% and 74% reductions from baseline in *Propionibacterium acnes*, compared with reductions of 16% and 14% in controls.

Data Source: A large, double-blind multicenter trial involving 459 patients with severe acne who were randomized to once-daily application of Epiduo in the evening plus 100 mg/day of doxycycline hyclate for 12 weeks, or to vehicle plus doxycycline.

Disclosures: Dr. Cruz said he had received a research grant from Galderma Laboratories, which funded the clinical trial.

ment arm had already been achieved, with a mean 21% reduction from baseline, compared with a 13% decrease in controls.

At week 12, patients on Epiduo plus doxycycline had a mean 64% decrease from baseline in total acne lesions, compared with a 41% reduction in controls. The combined therapy outperformed doxycycline plus vehicle in treating both inflammatory and noninflammatory lesions.

The treatment success rate as defined by a rating of clear or almost clear on the investigator's global assessment scale was 9.9% and 31.5% at weeks 8 and 12 in the combined therapy group, versus 2.6% and 8.4% in the controls.

The trial involved 459 patients with severe acne who were randomized to once-daily application of Epiduo in the evening plus 100 mg/day of doxycycline hyclate for 12 weeks, or to vehicle plus doxycycline.

The overall safety and tolerability of the combination therapy was similar to that of the vehicle plus doxycycline. Just under 10% of patients in both study arms reported gastrointestinal complaints believed to be due to the doxycycline.

A week-12 patient satisfaction survey showed 76% of patients in the combined therapy arm were satisfied or very satisfied overall with their treatment, compared with 50% of the controls. Sixty-seven percent of patients in the combination therapy group indicated they felt a lot better or much better about themselves since starting their therapy, as did 48% of the controls. ■