

Low Iron Is Biomarker, Treatment Target in HF

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EXPERT ANALYSIS FROM THE ANNUAL CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY

STOCKHOLM – Iron deficiency in patients with heart failure is common, occurs independently of anemia, and is strongly associated with exercise intolerance and increased risk of death or need for heart transplantation.

Moreover, iron deficiency in heart failure is not merely an independent predictor of poor outcomes, it's also emerging as an attractive target for treatment, Dr. Piotr Ponikowski said at the congress.

"Iron deficiency is pretty new stuff for cardiologists," he observed in a press conference. "Cardiologists should start to become more aware of the importance of iron deficiency in chronic heart failure patients and be able to eval-

uate iron status using a combination of simple, clinically applicable biomarkers of iron metabolism."

Dr. Ponikowski, president of the Heart Failure Association of the European Society of Cardiology, was senior author of a prospective observational study in which 546 patients with stable systolic heart failure were tested for iron deficiency.

Thirty-seven percent of subjects were found to be iron deficient based on either

a serum ferritin level below 100 mcg/L, or 100-300 mcg/L with a transferrin saturation below 20%. One-third of the iron-deficient patients were nonanemic. Iron deficiency was significantly more common in women, in subjects with C-reactive protein or plasma N-terminal pro type B natriuretic peptide levels above the median values, and in those with New York Heart Association (NYHA) class III-IV heart failure, although it was also found in 31% of patients who were class I-II (Eur. Heart J. Aug. 2010; 31:1872-80).

The mean 2-year survival rate free of heart transplantation was 53% in iron-deficient patients, significantly worse than the 67% in non-iron-deficient patients. In a multivariate analysis, the adjusted risk of death or heart transplantation in nonanemic heart failure patients with iron deficiency was 60% greater than in subjects without iron deficiency, noted Dr. Ponikowski, professor of cardiology

• 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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It's safe to treat iron deficiency in patients with symptomatic heart failure, but it's 'not in the guidelines yet.'

DR. PONIKOWSKI

at Wroclaw (Poland) Medical University.

He was also a coauthor of the first major treatment study, the Ferinject Assessment in Patients With Iron Deficiency and Chronic Heart Failure (FAIR-HF). In that double-blind, placebo-controlled, randomized trial, intravenous iron repletion of patients with heart failure resulted in significant improvement of all primary and secondary study end points, including exercise tolerance, self-reported patient global assessment scores, quality of life, and NYHA functional class (N. Engl. J. Med. 2009;361:2436-48). The improvement was apparent early, after two of the biweekly injections.

Asked whether it is now appropriate to prescribe iron therapy in iron-deficient patients with symptomatic heart failure, Dr. Ponikowski replied that he routinely screens symptomatic heart failure patients for iron deficiency and treats those who are deficient. "It's fairly safe and fairly straightforward. But we in the ESC [European Society of Cardiology] are very guideline-oriented people, and it's not in the guidelines yet," he added.

He recommended intravenous iron over oral formulations. The bioavailability of iron from oral intake is poor, only 3-4 mg per dose. He and his colleagues have estimated that the total amount of iron that needs to be replaced in iron-deficient heart failure patients is on average 800-1,200 mg. That would require close to a year of daily oral therapy, which would be poorly tolerated gastrointestinally.

Dr. Ponikowski has received lecture and consulting fees from Vifor Pharma, which sponsored the FAIR-HF trial, as well as from Amgen. ■