

Door Opened to Biomarker-Guided HF Therapy

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CHICAGO – Using N-terminal pro-hormone brain natriuretic peptide levels to guide therapy in patients with systolic heart failure proved superior to standard-of-care management in terms of cardiovascular event rates, quality of life, and echocardiographic parameters in the randomized prospective PROTECT trial.

“If duplicated in larger cohorts, treatment guided by NT-proBNP may represent a new paradigm for heart failure care,” Dr. James L. Januzzi Jr. said at the meeting.

PROTECT (the ProBNP Outpatient Tailored Chronic Heart Failure Therapy study) was a single-center unblinded trial of 151 patients with systolic heart failure and a mean left ventricular ejection fraction of 27%. They were randomized to standard guideline-driven management on the basis of heart failure signs and symptoms or to the same approach with the added goal of reducing NT-proBNP levels to 1,000 pg/mL or less, a threshold previously shown to predict risk in heart failure patients.

Participants were scheduled for quarterly clinic visits, with extra ones as need-

ed to achieve therapeutic goals, said Dr. Januzzi, director of the cardiac intensive care unit at Massachusetts General Hospital, Boston.

The study was halted early for ethical reasons after 10 months. At that point, a total of 100 cardiovascular events – worsening heart failure, heart failure hospitalization, acute coronary syndrome,



The NT-proBNP-guided arm had a lower likelihood of worsening heart failure or heart failure hospitalization.

DR. JANUZZI

ventricular arrhythmias, cerebral ischemia, or cardiovascular death – had occurred in the standard-treatment group, compared with 58 events in patients on NT-proBNP-guided therapy

The major difference between the two study arms was the sharply lower likelihood of worsening heart failure or heart failure hospitalization in the NT-proBNP-guided arm.

Importantly, the reduction in cardiovascular events was similar in patients

over age 75 and in those who were younger, Dr. Januzzi said.

The secondary outcome of quality of life, assessed using the Minnesota Living with Heart Failure Questionnaire, also showed significantly greater improvement in the guided-treatment arm. In all, 61% of subjects in the NT-proBNP-guided arm achieved at least a 10-point improvement over baseline, considered clinically meaningful, compared with 39% on standard management.

The guided-treatment group also did significantly better in terms of secondary echocardiographic end points, with larger improvements in left ventricular ejection fraction and in ventricular remodeling as reflected by changes in LV end-systolic and end-diastolic volume index, the cardiologist continued.

NT-proBNP-guided therapy proved safe and was well tolerated, with no significant increase in adverse events.

Patients in the guided-treatment arm had a median of six clinic visits, compared with five with standard management. The median baseline NT-proBNP level in the guided-therapy arm was 2,344 pg/mL. It fell to 1,125 pg/mL, with 44% of subjects in the guided-therapy arm attaining an NT-proBNP of 1,000 pg/mL or less.

Session cochair Dr. Gregg C. Fonarow

said in an interview that he views PROTECT as a successful proof-of-concept study. But before biomarker-guided treatment of heart failure becomes part of guideline-recommended, routine outpatient care, it will be necessary to see if the Massachusetts General Hospital experience can be extended to other settings, including primary care practices, where many patients with heart failure receive their treatment. This will require a large multicenter trial with a diverse group of clinicians; randomization by site; and hard clinical end points, including mortality.

A proposal for such a study has been presented to the National Heart, Lung, and Blood Institute for funding consideration.

“It’s a large and expensive trial, but the impact is potentially profound,” said Dr. Fonarow, professor of medicine and director of the Ahmanson-UCLA Cardiomyopathy Center, Los Angeles. “Given the costs of heart failure and the tremendous number of outpatient visits for this disease, if we truly had a well-validated guide using biomarkers, that would be a phenomenal advance.”

The PROTECT trial was sponsored in part by Roche Diagnostics. Dr. Januzzi declared he serves as a consultant to and speaker for the company. ■

observed in an additional 22 patients 12 to 17 years of age who were treated with DULERA in another clinical trial. The safety and efficacy of DULERA have not been established in children less than 12 years of age.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately 1 cm per year (range 0.3 to 1.8 per year) and appears to depend upon dose and duration of exposure. This effect was observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for “catch up” growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

The growth of children and adolescents receiving orally inhaled corticosteroids, including DULERA, should be monitored routinely (e.g., via stadiometry). If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including DULERA, each patient should be titrated to his/her lowest effective dose [see *Dosage and Administration* (2.2)].

8.5 Geriatric Use

A total of 77 patients 65 years of age and older (of which 11 were 75 years and older) have been treated with DULERA in 3 clinical trials up to 52 weeks in duration. Similar efficacy and safety results were observed in an additional 28 patients 65 years of age and older who were treated with DULERA in another clinical trial. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other products containing beta₂-agonists, special caution should be observed when using DULERA in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta₂-agonists. Based on available data for DULERA or its active components, no adjustment of dosage of DULERA in geriatric patients is warranted.

8.6 Hepatic Impairment

Concentrations of mometasone furoate appear to increase with severity of hepatic impairment [see *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

10.1 Signs and Symptoms

DULERA: DULERA contains both mometasone furoate and formoterol fumarate; therefore, the risks associated with overdosage for the individual components described below apply to DULERA.

Mometasone Furoate: Chronic overdosage may result in signs/symptoms of hypercorticism [see *Warnings and Precautions* (5.7)]. Single oral doses up to 8000 mcg of mometasone furoate have been studied on human volunteers with no adverse reactions reported.

Formoterol Fumarate: The expected signs and symptoms with overdosage of formoterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the following signs and symptoms: angina, hypertension or hypotension, tachycardia, with rates up to 200 beats/min., arrhythmias, nervousness, headache, tremor, seizures, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, hypokalemia, hyperglycemia, and insomnia. Metabolic acidosis may also occur. Cardiac arrest and even death may be associated with an overdose of formoterol.

The minimum acute lethal inhalation dose of formoterol fumarate in rats is 156 mg/kg (approximately 63,000 times the MRHD on a mcg/m² basis). The median lethal oral doses in Chinese hamsters, rats, and mice provide even higher multiples of the MRHD.

10.2 Treatment

DULERA: Treatment of overdosage consists of discontinuation of DULERA together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of DULERA. Cardiac monitoring is recommended in cases of overdosage.

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