Correct Anemia to Improve Heart Failure Outcomes

BY MITCHEL L. ZOLER
Philadelphia Bureau

BARCELONA — Researchers moved a step closer toward proving that correcting the anemia that often occurs in patients with heart failure improves outcomes, with results from three phase II studies that tested two different ways to boost hemoglobin levels.

Reports from two controlled studies that compared darbepoetin alfa with placebo in 475 patients showed that the treatment was safe, that it produced improvements in patients' exercise capacity that were tied to boosts in hemoglobin levels, and that the drug could cut the rate of death or hospitalization for heart failure at a rate that approached statistical significance, Dr. William T. Abraham reported at a joint meeting of the European Society of Cardiology and the World Heart Federation.

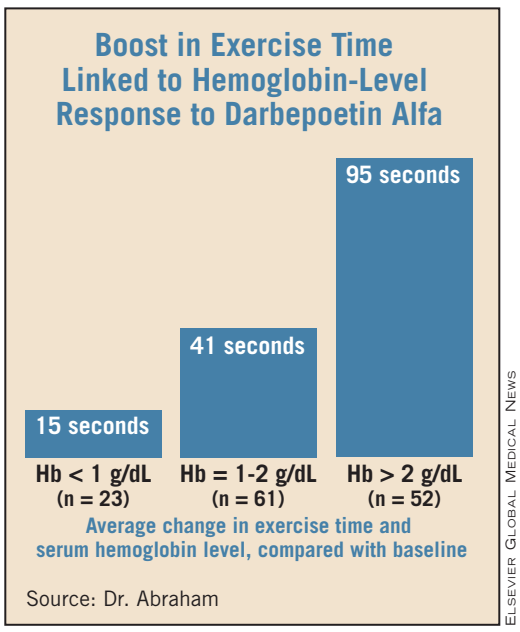
And results from the first randomized, observer-blinded test of intravenous iron in 35 patients with heart failure and low iron levels supported the idea that iron repletion is safe and associated with improvement in exercise capacity and heart failure symptoms, Dr. Stefan D. Anker said in a separate report at the meeting.

Anemia is a common complication of heart failure, but just how common depends on how it's defined. In data collected from one recent, large heart failure treatment trial, 30% of women and 16% of men had anemia if it was defined as a serum hemoglobin level of less than 12.5 g/dL. With a more conservative definition of less than 11.5 g/dL, the prevalence was 10% among women and 8% among men, said Dr. Anker, a cardiologist and professor of medicine at Charité University in Berlin.

These hemoglobin levels would not be severe enough to warrant drug interventions if they occurred in otherwise healthy people, in whom the hemoglobin level would have to be less than 10 g/dL to make drug intervention reasonable, Dr. Anker said in an interview. But in the context of heart failure, experts have hypothesized that higher hemoglobin levels might lead to clinically important improvements in exercise capacity and quality of life, and to a significant drop in heart failure hospitalizations. The two most obvious ways to correct anemia are treatment with an erythropoietin agent and treatment with iron supplementation, which could also be used together.

Three phase II studies of darbepoetin alfa, a long-acting erythropoietin, were recently completed, and results from the two largest of these studies were reported at the meeting. All three studies were sponsored by Amgen, which markets darbepoetin (Aranesp). Dr. Abraham has received research support from Amgen.

One trial involved 319 patients with New York Heart Association class II-IV heart failure and a serum hemoglobin level of 9.0-12.5 g/dL; their average baseline hemoglobin level was 11.35 g/dL. Of the 319 patients, 157 were randomized to receive placebo and 162 received darbepoetin alfa at a starting dosage of 0.75 mcg/kg administered subcutaneously every 2 weeks. The dosage was titrated to produce a rise in hemoglobin of 0.5-1.5 g/dL every 3 weeks and then to maintain a hemoglobin level of 13.0-15.0 g/dL. All patients also received supplemental iron, given as an oral dosage of 200 mg/day. The primary end point for this study was the change in exercise capacity from baseline after 6 months of treatment, measured as time spent walking on a treadmill.



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The regimen produced an average hemoglobin level of 13.5 g/dL in patients treated with darbepoetin alfa and no change in the patients treated with placebo.

The change in treadmill-exercise time was an average of 46.5 seconds in placebo patients and 57.3 seconds in the darbepoetin alfa–treated patients, a nonsignificant difference, reported Dr. Abraham, professor of medicine and director of the division of cardiovascular medicine at Ohio State University, Columbus.

However, a post hoc analysis of these data showed a promising and statistically significant link between the rise in serum hemoglobin level and improvements in exercise time (see table). More than 80% of patients treated with darbepoetin alfa had a "robust response to treatment," with a hemoglobin rise of more than 1 g/dL, and these patients had substantial improvements in their exercise time, noted Dr. Abraham.

A prespecified end point for the two largest of the trials was a combined analysis to assess safety and efficacy measured by the incidence of all-cause death or first hospitalization for heart failure after 1 year of treatment. This combined the results from the 319-patient study described above and the results from a study with 165 patients. The second study randomized 55 patients to placebo, 56 to a weight-based dosage of darbepoetin that was the same as was used in the larger study, and 54 patients to a fixed-dosage regimen of the drug that used 50 mcg every 2 weeks. The results showed no difference between the effects of the weight-based and fixed dosages. Data for the combined analysis were available for 209 patients who received placebo and 266 who received darbepoetin alfa. The 1-year incidence of death or hospitalization for heart failure was reduced by 33% in the patients treated with darbepoetin, compared with those who received placebo, a difference that neared statistical significance. Darbepoetin alfa treatment was also associated with trends in improved quality of life and patients' global self-assessment.

The incidence of serious adverse events was similar in the placebo and drug-treated arms, and treatment with darbepoetin alfa showed no evidence of any increases in the events that are of particular concern in patients who receive erythropoietin-type drugs, such as hypertension or thrombotic events.

Supplementation with oral iron in patients with anemia is often ineffective in routine practice, because the supplements taste bad and patients stop taking them, which makes an intravenous supplement an attractive alternative, said Dr. Anker. The results he reported were collected from 18 heart failure patients with anemia (hemoglobin less than 12.5 g/dL) and 17 patients with no anemia (hemoglobin 12.5-14.5 g/dL) but with iron deficiency as measured by their serum ferritin or transferrin saturation levels. Twelve patients from each of these two subgroups were randomized to treatment with weekly infusions of iron sucrose (Venofer), and the remaining 11 were treated with placebo. Patients were treated for 3 months. The study's primary end point was the change from baseline to the end of the study in peak oxygen consumption.

In anemic patients, iron supplementation was associated with a significant 204-mL/min greater increase in oxygen consumption over baseline, compared with the placebo group. In nonanemic patients, supplementation did not lead to a notable change in oxygen consumption, compared with the placebo group, reported Dr. Anker. By other measures, iron supplementation was also linked to improvements in exercise duration and heart failure class. The treatment was also safe, with no difference in adverse event rates between the intervention and control groups. ■

Heart Failure Patients Should Be Screened for Sleep Apnea

BY SHERRY BOSCHERT
San Francisco Bureau

SEATTLE — There is no standard way to screen for sleep apnea in patients with heart failure, but there are several screening models to choose from, Dr. Steven M. Scharf said at the annual meeting of the Heart Failure Society of America.

Sleep apnea commonly accompanies heart failure, and can be treated, though there's little high-quality evidence that treatment alters mortality or quality of life. Still, "you certainly should screen all your heart failure patients," said Dr. Scharf, professor of medicine and director of the sleep disorders lab at the University of Maryland, Baltimore.

One good clinical screening tool is the Berlin Questionnaire, which asks about symptoms in three categories: excessive sleepiness or sleepiness while driving; wild, disturbing snoring or gasping; and either obesity or heart failure (Ann. Intern. Med. 1999;131:485-91). Primary care patients with symptoms from two of the three categories have a high risk for obstructive sleep apnea, but the sensitivity and specificity of the Berlin Questionnaire in patients with heart failure is unknown, he said.

Other screening schemes stratify patients by neck circumference, with larger necks increasing the risk for sleep apnea (N. Engl. J. Med. 2002;347:498-91). Various other scoring systems combine clinical findings such as male gender, body mass index, a snoring index, and a choking index to rate the likelihood of sleep apnea. Many of these screening models may be useful, Dr. Scharf suggested.

If a heart failure patient seems to have a high probability of having sleep apnea (perhaps based on the Berlin Questionnaire and neck circumference), schedule a full polysomnograph evaluation, he advised.

Patients with symptoms from two of the three Berlin Questionnaire categories are at high risk for apnea.

DR. SCHARF

Consider doing overnight pulse oximetry testing in heart failure patients who don't meet your threshold for high risk for apnea, he added. A recent meta-analysis of 79 studies that used pulse oximetry for screening suggests that if you have a strong clinical suspicion for obstructive sleep apnea and testing shows fewer than 15 desaturations per hour, diagnostic polysomnography may be warranted (Chest 2001;120:625-33). With more than 15 desaturations/hour, a full evaluation for sleep apnea or treatment with titrated continuous positive airway pressure may be reasonable.

Two articles suggest that an algorithm assessing heart rate variability might help screen for apnea in heart failure patients, but practice parameters don't exist and would need to be developed, he said (Eur. Respir. J. 2006;27:571-7).

One small study suggests the PAT100 Watch, which measures peripheral arterial tone, also might help screen for sleep apnea. Portable polysomnography (outside sleep labs) is not recommended by the American Thoracic Society and other organizations.

Dr. Scharf has no affiliation with companies that sell the tools he discussed. ■