Heart Failure Improved With Iron Repletion

BY MITCHEL L. ZOLER

VITALS

Major Finding: At 24 weeks, Patient Global Assessment scores improved in 50% of the 304 heart failure patients receiving intravenous iron and in 28% of the 155 patients on placebo, a statistically significant difference.

Source of Data: FAIR-HF, placebo-controlled phase III study of 459 patients, from 75 sites in 11 countries, randomized to iron or placebo.

Disclosures: The study was sponsored by Vifor Pharma, a Swiss company that markets Ferinject in Europe. Dr. Jessup disclosed that she is a speaker for, or consultant to, Boston Scientific, Medtronic, Ventracor, and ACORN. Dr. Cleland received research support from several drug and cardiac device companies.

ORLANDO — The clinical benefits from intravenous iron in chronic heart failure seen in a placebo-controlled study of 459 patients abruptly made iron repletion a new, plausible treatment for a sizable fraction of heart failure patients.

"This is a new therapeutic concept. When patients [with heart failure] are symptomatic, physicians should think about iron deficiency," Dr. Stefan D. Anker said at the annual scientific sessions of the American Heart Association. The study results also showed that the boost from iron occurred regardless of whether patients were anemic before starting treatment, a finding that suggests iron helps patients by a mechanism that does not involve hemoglobin.

The study findings "are very intriguing. Iron deficiency hasn't been on our radar screen," commented Dr. Mariell L. Jessup, professor of medicine and associate chief of clinical affairs in the division of cardiovascular medicine at the University of Pennsylvania in Philadelphia. "I think this is something that people will start to act on quickly. I wouldn't be surprised if some physicians start to say, 'You're iron deficient? Let's give you some iron.' Iron supplements by injection are clearly [already] out there in the nephrology world."

"Iron deficiency is extremely common in this population if you look for it. Intravenous iron is probably the way to go," commented Dr. John G.F. Cleland, professor and chairman of cardiology at the University of Hull, England.

Dr. Cleland, who has studied oral iron supplements in heart failure patients, and has found that by that route repletion lags and clinical benefits are lacking, possibly because many heart failure patients have impaired iron absorption in their gut, he said in an interview.

Despite the promising new results, Dr. Anker stressed that the study was not powered to adequately address safety or efficacy end points such as survival and hospitalization. Further study is needed to build up a larger experience with the tested agent, ferric carboxymaltose, in heart failure patients, although Dr. Anker's study included 150 patient-years of treatment with this drug with no hint of excess adverse events aside from an expected, modest increase in gastrointestinal disorders. Dr. Anker also expressed eagerness to test this strategy in patients with diastolic dysfunction: heart failure with preserved left ventricular function.

About 20%-30% of heart failure patients likely have iron deficiency, said Dr. Anker, professor in the Center for Cardiovascular Research at Charité University in Berlin.

The Ferinject Assessment in Patients With Iron Deficiency and Chronic Heart Failure (FAIR-HF) trial enrolled patients during June 2007–December 2008 at 75 sites in 11 countries. Dr. Anker and his associates screened more than 950 patients to find the 459 who fulfilled the study's criteria for heart failure and serum ferritin level. Eligible patients had either New York Heart Association class III heart failure and a left ventricular ejection fraction of 45% or less, or class II heart failure and an ejection fraction of 40% or less. Their hemoglobin at enrollment could be 95-135 g/L, and so the study included nearly equal numbers of patients with anemia (hemoglobin of 120 g/L or less) and those without (more than 120 g/L). Their average age was 68, and 82% had class III heart failure.

The researchers randomized patients on a two-to-one basis to receive an intravenous, bolus injection of ferric carboxymaltose equivalent to 200 mg iron weekly or placebo. Once iron repletion occurred, after 8 or 12 weeks, the iron dosage scaled back to one injection every 4 weeks.

The study was sponsored by Vifor Pharma, a Swiss company that markets a formulation of ferric carboxymaltose (Ferinject) in Europe but which does not have U.S. approval. Dr. Anker said that he has received fees from Vifor for consulting, lecturing, and serving on the study's executive committee, and he also has received fees from Roche and Amgen.

After 24 weeks, the self-reported Patient Global Assessment was at least moderately improved in 50% of the 304 patients receiving iron and in 28% of the 155 patients on placebo, a statistically significant difference for this primary end point. New York Heart Association heart failure class improved in 47% of the patients on iron and in 30% of the control patients, also a significant difference in the second primary end point. The results appeared in an article published online (N. Engl. J. Med. 2009 Nov. 17 [doi:10.1056/NEJMoa0908355]) concurrently with Dr. Anker's report at the meeting.

Dr. Anker said the fast action may relate to his hypothesis to explain how iron supplementation exerts a benefit that is apparently independent of a hemoglobin effect. "Iron is needed for the proper function of mitochondria to generate energy in both the heart and in peripheral muscles," Dr. Anker said. "I think intravenous iron is a powerful intervention; it's a legal way to do doping."

During the study, mortality rates were 3% in the iron group and 6% in the control patients, a nonsignificant difference. Hospitalization for any cardiovascular reason occurred in 10% of the iron patients and 20% of the controls, a difference that came close to, but did not reach, statistical significance. Cardiac disorders of any type were significantly more common in the control patients, 50%, than in those on iron, 28%. The most notable adverse event more common in the iron patients was gastrointestinal disorder, in 17% of the iron patients and 7% of the controls, a difference that just missed statistical significance.

Dr. Anker noted that his findings show no suggestion of a safety concern, but he conceded that the current experience is limited and the drug needs testing in more patients. Vifor Pharma is currently discussing what further steps it will take in studying its ferric carboxymaltose formulation in patients with heart failure, said Dr. David R. Ebsworth, Vifor's chief executive officer. ■

MY TAKE

'The Effect Occurs So Quickly'

This is a remarkable result. I am especially impressed that the separation in the primary end points between the patients receiving iron and those on placebo began to be statistically significant after the first 4 weeks on treatment and then continued to separate further.

The effect occurs so quickly. This is probably the fastest separation we've seen in a clinical trial in heart failure.

MILTON PACKER, M.D., *is professor of medicine at the University of Texas Southwestern Medical Center in Dallas. He has been an adviser to Actelion, Pfizer, and United Therapeutics.*

Congenital Heart Disease Survival to Adulthood Hits 89%

BY MITCHEL L. ZOLER

VITALS

Major Findings: Survival to adulthood has significantly improved for persons born with congenital heart disease, from 82% in those born in the 1970s to 89% in those born in the 1990s.

Data Source: Clinical database of 17,044 patients in the congenital heart disease program at Catholic University, Leuven, Belgium.

Disclosures: Dr. Moons had no financial conflicts of interest to report.

ORLANDO — Infants born with a congenital heart disease during 1990-1999 who underwent care at a tertiary center had an 89% actuarial survival rate to age 18 or older, data on more than 3,800 patients at one Belgium center showed.

That was a significant improvement over 85% survival to adulthood for infants born during 1980-1989 and managed at the same center, and the 82% rate in those born during 1970-1979, Philip Moons, Ph.D., said at the annual scientific sessions of the American Heart Association.

The 89% rate improved on the 85% rate from the 32nd Bethesda Conference in a report based on outcomes of congenital heart disease patients born in the 1980s, Dr. Moon said (J. Am. Coll. Cardiol. 2001;37:1170-5).

Dr. Moons and his associates analyzed survival data from the clinical database of the congenital heart disease program at Catholic University, Leuven, Belgium. It included 17,044 patients born with gross structural abnormalities of the heart or intrathoracic great vessels with actual or potential functional significance. The subset of these patients born during 1990-1999 was 23%; 24% were born before 1970, 10% during 1970-1979, 21% during 1980-1989, and 17% in 2000 or later.

The most common congenital diseases for the entire group was ventricular septal defect (22%), followed by atrial septal defect (15%), and pulmonary valve abnormality (10%).

Among infants born in 1990-1999, mortality from congenital heart disease was due to cardiac failure in 56%, postoperative complications in 22%, and perioperative complications in 9%. In the 1990-1999 subgroup, survival during follow-up was 99% in patients with mild congenital heart disease, 90% in those with moderate disease, and 59% in patients with a complex abnormality, said Dr. Moons, a health services researcher at Catholic University. ■