Drugs and Therapeutic Backgrounder:

Iron therapy and congestive heart failure

Anemia is a significant concern in congestive heart failure (CHF) patients. Parenteral iron is reserved for patients with symptomatic heart failure with reduced ejection fraction (LVEF ≤ 40%) and iron deficiency (ferritin <100 mg/L or ferritin 100-299 mg/L and transferrin saturation <20%). Oral iron therapy should be used for iron deficiency anemia in other heart failure patients.

Background

In patients with heart failure, small reductions in hemoglobin (Hb) may be associated with worsening symptoms, a higher New York Heart Association (NYHA) classification, and an impairment in functional capacity and quality of life[1]. Anemia is an independent predictor of mortality and number of hospitalizations[1]. Canadian Cardiovascular Society (CCS) guidelines recommend initiating iron treatment in heart failure with reduced ejection fraction (HFrEF) patients who are iron deficient (ID) prior to diagnosis of anemia to improve exercise tolerance, quality of life, and to reduce hospitalizations[1].

The majority of evidence available supports the use of parenteral iron replacement over oral in patients with heart failure[2-4]. The studies included HFrEF patients with LVEF <45%. Further research is warranted in heart failure patients with preserved ejection fraction (HFpEF) as few trials with oral iron have taken place in this population, with limited evidence suggesting oral iron is effective when taken over a longer period of time (similar findings to general population)[5].

Efficacy

The evidence is mixed regarding iron therapy in heart failure patients. One study in HFrEF patients with ID demonstrated that after 16 weeks high dose oral iron compared to placebo produced minimal improvement in clinical outcomes and quality of life[5]. Parenteral iron has been shown to improve iron stores, clinical outcomes, and quality of life in HFrEF patients with ID, although no benefit to mortality has been shown [2-4,7].

Guidance The following does not replace clinician judgment[1,12].

Scenario	Recommended Intervention
Ferritin >100 mg/L **and** LVEF >40% **and/or** TSAT >20%	• Oral iron therapy for 3-6 months (consider intermittent dosing schedule) • Educate patient on high iron diet. Dietician referral.
HFrEF (LVEF <40%) **and** Ferritin <100 mg/L **or** Ferritin 100-299 mg/L **and** TSAT <20% **or** No response after 3 months oral therapy **or** Intolerance to oral therapy	• Parenteral iron therapy
Failure to respond to parenteral iron therapy	• Consider 1 unit red blood cell (RBC)

Alberta Health Services

Safety

Oral iron therapy is associated with gastrointestinal (GI) adverse effects including nausea, heartburn, constipation, diarrhea, and darkened stools. The occurrence of these events can be reduced with an alternative day or intermittent (e.g. every other day) dosing schedule[8]. Parenteral iron has less GI adverse effects than oral iron therapy, but potential reactions include: cardiovascular side effects (hypotension, hypertension, edema), headache, upper respiratory tract infections, and anaphylaxis reactions[9, 13].

Two meta-analyses demonstrated that there was no increase in adverse events with parenteral iron therapy[10, 11]. Further evidence is required for parenteral iron repletion and major cardiovascular event rates in HFpEF patients and patients who have heart failure and are non-anemic[1].

References

1. Ezekowitz, JA. et al. 2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure. Canadian Journal of Cardiology, Volume 33, Issue 11, 1342 – 1433 https://www.onlinecjc.ca/article/S0828-282X(17)30973-X/pdf
2. Ponikowski P, van Veldhuisen D, Comin-Colet J, Ertl G, Komajda M, Mareev V, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J 2014. http://dx.doi.org/10.1093/ eurheartj/ehu385.
3. Anker S, Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, et al. Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency. N Engl J Med 2009;361:2436–48.
4. Okonko D, Grzeslo A, Witkowski T, Mandal A, Slater R, Roughton M, et al. Effect of Intravenous Iron Sucrose on Exercise Tolerance in Anemic and Nonanemic Patients With Symptomatic Chronic Heart Failure and Iron Deficiency. J Am Coll Cardiol 2008;51:103–12.
5. Lewis GD, Malhotra R, Hernandez AF, McNulty SE, Smith A, Felker GM, et al.Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: the IRONOUT HF randomized clinical trial JAMA, 317 (19) (2017), pp. 1958-1966, 10.1001/jama.2017.5427
6. Niehaus E, Malhotra R, Cocca-Spofford D, Semigran M, Lewis, G. Repletion of Iron Stores with the Use of Oral Iron Supplementation in Patients with Systolic Heart Failure. J Card Fail 2015; 21(8): 694-7
7. Ponikowski P, van Veldhuisen D, Comin-Colet J, Ertl G, Komajda M, Mareev V, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J 2014. http://dx.doi.org/10.1093/ eurheartj/ehu385.
8. Peña-Rosas JP, De-Regil LM, Gomez Malave H, Flores-Urrutia MC, Dowswell T. Intermittent oral iron supplementation during pregnancy. Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD009997. DOI: 10.1002/14651858.CD009997.pub2.
9. Muñoz M, Gómez-Ramírez S & Bhandari S. The safety of available treatment options for iron-deficiency anemia, Expert Opinion on Drug Safety, 2018;17:2, 149-159, DOI: 10.1080/14740338.2018.1400009
10. Avni T, Leibovici L, Gafter-Gvili A. Iron supplementation for the treatment of chronic heart failure and iron deficiency: systematic review and meta-analysis. Eur J Heart Fail 2012;14:423-9.
11. Qian C, Wei B, Ding J, Wu H, Wang Y. The efficacy and safety of iron supplementation in patients with heart failure and iron deficiency: a systematic review and meta-analysis. Can J Cardiol 2016;32:151-9.
12. Toward Optimized Practice Iron Deficiency Anemia Committee. 2018 March. Iron deficiency anemia clinical practice guideline. Edmonton, AB: Toward Optimized Practice. Available from: http://www.topalbertadoctors.org
13. Lexicomp. Parenteral iron monograph. Accessed October 2019.

Revised on January 20, 2020