SHORT COMMUNICATION

Efficacy of high-dose intravenous iron in middle-aged to elderly iron-deficient patients

Dheeraj Khiatani, MBBS[1], Hui Sian Tay, MBBS[2], Timothy Robert Cushway, BSc[1,3]

[1]Integrative Medical Centre, Singapore, [2]Pantai Hospital Ayer Keroh, Malacca, Malaysia, [3]Compai Pharma, Singapore

ABSTRACT

Iron deficiency (ID) impacts about fifty percent of elderly patients with many symptoms present before iron deficiency anaemia . If left untreated, ID may increase morbidity and mortality. Oral iron is often not tolerated or the absorption is suboptimal. We describe our initial experiences of using high-dose intravenous ferric derisomaltose (Monofer®) infusions of 500 and 1000mg for iron deficiency and iron deficiency anaemia respectively in the outpatient setting. Rapid correction of laboratory parameters and improvement in common symptoms (such as fatigue) were observed. Intravenous iron may be an option for symptomatic iron deficient patients unsuitable for oral iron.

INTRODUCTION

Iron deficiency (ID) may result when there is a negative imbalance between iron intake and loss.[1] ID impacts 58% of women and 20% of men (mean age 56.9 years) in Singapore.[2] Common signs and symptoms of ID include hair loss, fatigue, and brain fog (Figure 1)[1,5,10]. Middle aged and the elderly are at increased risk for ID due to poor diet, reduced intestinal absorption, concomitant medications such as proton-pump inhibitors, blood loss secondary to chronic disease, and increased incidence of surgeries with associated blood loss.

Data from the English Longitudinal Study of Ageing assessing 4451 patients demonstrated a mortality hazard ratio (HR) in ID patients of 1.58 (95% confidence interval (CI) 1.29–1.93) over a 14-year period.[3] The key drivers of mortality were increased respiratory deaths (HR 2.14, 95% CI 1.30–3.50) and cancer (HR 1.58, 95% CI 1.14–2.20).

In Taiwan, a longitudinal study of 32,390 patients (median observational period 5.43 years) suggested iron deficiency anaemia (IDA) increased the risk of developing cancer (Standardised Incidence Ratio of 2.15 (95% CI 2.06–2.25))[4]. The authors hypothesised that cancer development was due, among other reasons, to ID impairing the molecular and metabolic functions of cells. They also highlighted that IDA alters immune activities and may create a microenvironment permissive for carcinogenesis.

Ironically, treating ID is considered simple yet the high ID prevalence suggests otherwise. In elderly, oral iron may be ineffective (if tolerated) due to upregulated hepcidin or interference with concomitant medications. Whilst many misconceptions remain, there have been strong advancements in the safety and usability of parenteral iron.[5] Parenteral iron complexes have an iron core with a carbohydrate shell. Whilst administering similar cumulative doses results in similar efficacy, the ability of newer formulations to reduce the number of infusions with higher doses may improve patient compliance and hospital resources.[6]

Ferric derisomaltose (Monofer®; FDI), previously iron isomaltoside, and ferric carboxymaltose (Ferinject®; FCM) permit administration of doses of 500, 1000, or 1500–2000mg iron (for FDI) as a single infusion over 15–30 minutes. Despite having similar effectiveness, symptomatic and severe hypophosphataemia have been ascribed to FCM.[7-9] In a randomized controlled study, 11.3% of FCM patients (versus 0% for FDI) developed severe hypophosphataemia (serum phosphate level ≤1.0mg/dL).[7] A pharmacokinetic study demonstrated that FCM reduces serum phosphate in a dose-dependent manner.[8] The phosphate nadir appears at approximately day 14 and whilst initially believed to be benign and short acting, increasing cases with significant clinical symptoms (and studies demonstrating long lasting hypophosphataemia) have resulted in revision of this understanding and subsequent updates to global labels (i.e. USA, Australia, and Europe).[9] Patients are at increased risk for developing hypophosphataemia with age.

MATERIALS AND METHODS

We performed a retrospective review on 11 middle-aged to elderly patients treated with FDI at either Pantai Hospital Ayer Keroh, Malaysia or the Integrative Medical Centre, Singapore. We described our first experiences from a practical, effectiveness, and outcomes perspective. Whilst significant data has been published with FDI, there is little or no publications of use in the local population.

Dosing of FDI was 500mg iron (for patients with ID only) or 1000mg (for patients with IDA). ID was diagnosed with serum ferritin <30ng/mL or, when anaemic (haemoglobin (Hb)<12g/dL), with ferritin <100ng/mL and/or transferrin saturation (TSAT)<20%. FDI was administered after careful setting of a cannula (first pass technique to minimise risk for extravasation) and iron then infused over 15–30 minutes (in 10–100mL normal saline) followed by a 30-minute observation.

RESULTS

The average age of patients was 67.3 (51–89) years old. All were of Asian descent and complained of commonly

This article was accepted: 19 June 2022
Corresponding Author: Hui Sian Tay
Email: huisiantay@yahoo.co.uk

Table I: Summary of patient laboratory data pre/post ferric derisomaltose administration

Patient Information			Iron	Timing (days)	Hb (g/dL)		Ferritin (ng/mL)		TSAT (%)	
Age	Sex	Med History	(mg)	Post Tx labs	B/L	Post Tx	B/L	Post Tx	B/L	Post Tx
75	F	Hypertension	1000	42	8.7	13.6	9	108	4	17
55	F	Endometrial cancer; uterine fibroids	1000	38	8.7	11.9	6	247	4	26
73	F	Hypertension and osteoporosis	1000	43	9.3	12.8	106	438	7	39
68	F	CKD	1000	42	10.3	11.4	67	443	20	28
75	F	Stroke, hypertension, and CKD	1000	41	10.3	11.6	134	509	13	13
80	F	CKD	1000	43	10.4	11.1	44	297	10	28
65	F	TKR planned*	500	91	11.1	10.6	74	292	15	33
89	F	Hypertension andosteoporosis	1000	35	11.4	11.9	94	422	6	36
56	F	Nil**	500	57	12.4	12.8	10	165	22	32
53	F	HMB***	500	115	12.7	12.3	6	50	26	39
51	M	ADHD; GERD	500	64	14.5	14.7	25	178	17	22
		Average	**818**	**56**	**10.9**	**12.2**	**52**	**286**	**13**	**29**

ADHD: attention deficit hyperactivity disorder; CKD: chronic kidney disease; HMB: heavy menstrual bleeding; GERD: gastroesophageal reflux disease; TKR: total knee replacement.

* Patient underwent a total knee replacement the day following administration of IV iron with significant blood loss and suffers from anaemia of chronic disease.
** Patient was a vegetarian with sub-optimal dietary habits leading to iron deficiency.
***Patient required a second dose of 500mg iron to resolve symptoms. Post second infusion (cumulatively 1000mg iron) the serum ferritin concentration increased to 149ng/mL

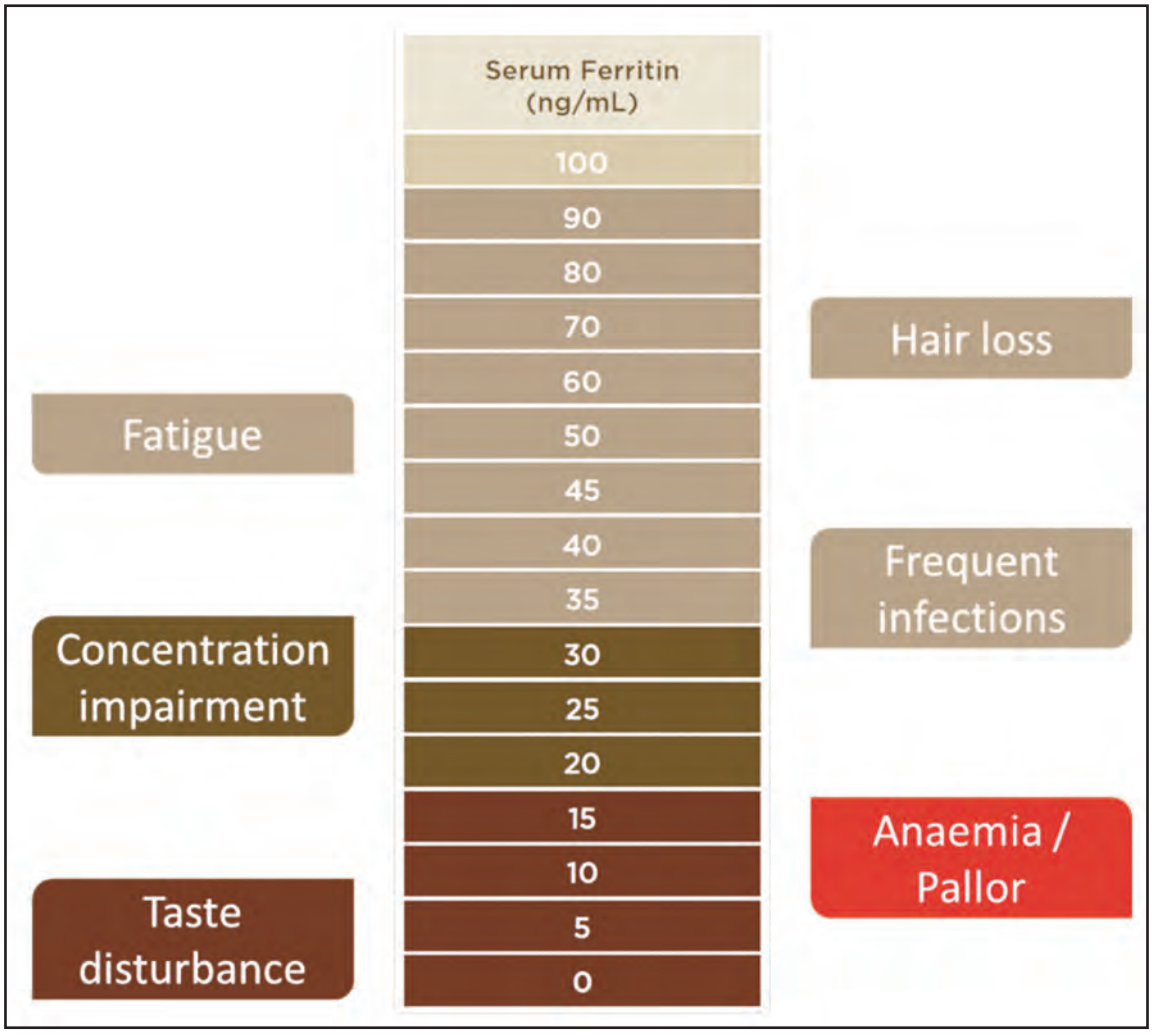

Fig. 1: Relationship of serum ferritin concentration and common symptoms of iron deficiency (in patients without underlying inflammatory conditions)

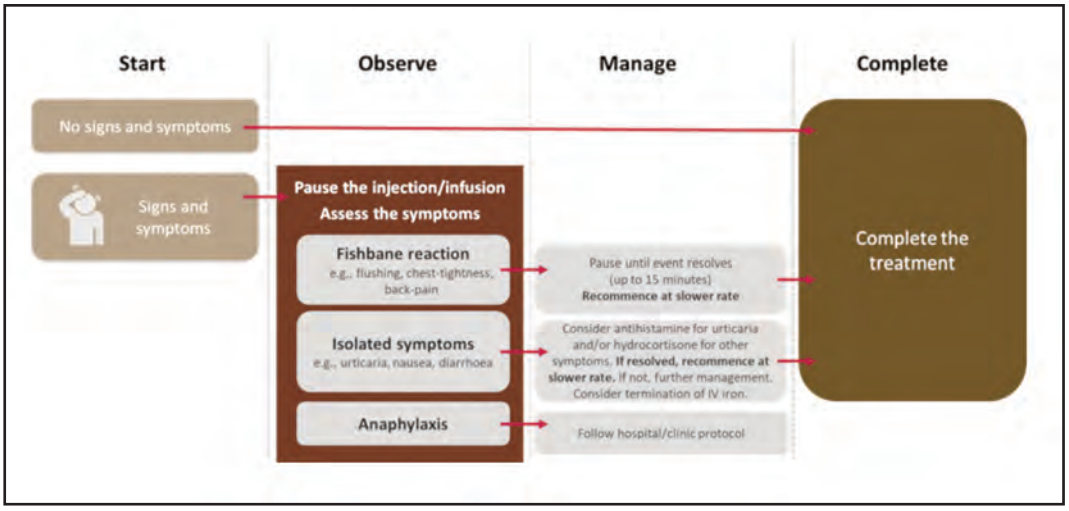

Fig. 2: Clinic protocol for the management of adverse events. *Adapted from Lim et. al., Vox Sanguinis (2019) 114*

expressed symptoms of ID (namely fatigue) with an average baseline ferritin of 52ng/mL and TSAT of 13% and for anaemic subjects, the average Hb was 10g/dL. Repeat labs were performed on average 56 (35–115) days later with clinically significant increases in all laboratory parameters post-infusion and ID(A) resolution (Table I).

Patients generally reported feeling less fatigued 1–2 weeks post-infusion and a patient undergoing surgery after receiving IV iron had an uneventful recovery with no significant decrease in Hb concentration or need for a blood transfusion.

All patients have at least 3 months of follow-up and only one patient, with recent history of heavy menses, required additional iron. Pre-infusion Hb was 12.7g/dL and she was administered 500mg iron. Several months post-infusion she complained of fatigue and the repeat ferritin was 50ng/mL. A second dose of FDI resulted in the resolution of symptoms with ferritin improving to 149ng/mL. No adverse events were recorded with reported cases.

DISCUSSION

Iron formulations can be associated with acute chest and back tightness and these reactions, potentially related to "free" or "labile" iron, normally resolve spontaneously without any medical therapy (within minutes of pausing the infusion) and rarely recur when IV administration recommences.[5] Expert reviews estimate serious adverse event rates at <1:250,000 administrations.[5] Figure 2 illustrates our protocol for managing side effects.

The promising results of this local data combined with the ease of administration and improved symptoms in patients should encourage clinicians to conduct regular iron studies in middleaged and elderly patients with and without anaemia.[2] Treatment of symptomatic ID(low ferritin) prior to anaemia with IV iron may rapidly improve quality of life whilst potentially reducing consequences of other comorbidities (e.g., development of cancer, heart failure or infections).

CONCLUSION

IV iron rapidly corrects IDA and early treatment may aid in recovery for those planned or requiring surgical intervention and reduce the chances of requiring red cell transfusions.

REFERENCES

1. Camaschella C. Iron-deficiency anemia. N Engl J Med. 2015 7; 372(19): 1832-43.
2. Yeo TJ, Yeo PS, Ching-Chiew Wong R, Ong HY, Leong KT, Jaufeerally Fet al. Iron deficiency in a multi-ethnic Asian population with and without heart failure: prevalence, clinical correlates, functional significance and prognosis. Eur J Heart Fail. 2014; 16(10): 1125-32.
3. Philip KEJ, Sadaka AS, Polkey MI, Hopkinson NS, Steptoe A, Fancourt D. The prevalence and associated mortality of non-anaemic iron deficiency in older adults: a 14 years observational cohort study. Br J Haematol. 2020; 189(3): 566-72.
4. Hung N, Shen CC, Hu YW, Hu LY, Yeh CM, Teng CJ, et al. Risk of cancer in patients with iron deficiency anemia: a nationwide population-based study. PLoS One. 2015; 17; 10(3): e0119647. Erratum in: PLoS One. 2015; 10(4): e0125951.
5. Muñoz M, Gómez-Ramírez S, Besser M, Pavía J, Gomollón F, Liumbruno GM, et al. Current misconceptions in diagnosis and management of iron deficiency. Blood Transfus. 2017; 15(5): 422-37.
6. Auerbach M, Gafter-Gvili A, Macdougall IC. Intravenous iron: a framework for changing the management of iron deficiency. Lancet Haematol. 2020; 7(4): e342-e350.
7. Wolf M, Rubin J, Achebe M, Econs MJ, Peacock M, Imel EA, et al. Effects of iron isomaltoside vs ferric carboxymaltose on hypophosphatemia in iron-deficiency anemia: two randomized clinical trials. JAMA. 2020; 4; 323(5): 432-43.
8. Ikuta K, Shimura A, Terauchi M, Yoshii K, Kawabata Y. Pharmacokinetics, pharmacodynamics, safety, and tolerability of intravenous ferric carboxymaltose: a dose-escalation study in Japanese volunteers with iron-deficiency anemia. Int J Hematol. 2018; 107(5): 519-27.
9. Glaspy JA, Wolf M, Strauss WE. Intravenous iron-induced hypophosphatemia: an emerging syndrome. Adv Ther. 2021; 38(7): 3531-3549.
10. Park SY, Na SY, Kim JH, Cho S, Lee JH. Iron plays a certain role in patterned hair loss. J Korean Med Sci. 2013; 28(6): 934-8.