V Curs d'Eritropatologia de la Societat Catalana d'Hematologia i Hemoteràpia
Actualització en malalties amb afectació eritrocitària i anèmies poc freqüents
Curs Societat Catalana d'Hematologia i Hemoteràpia

Tractament amb ferro endovenós des de la perspectiva de l'hematòleg.

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Introducción

- Hierro endovenoso: pasado y presente
- Ejemplo de la Epo: Reimbursement
- Fe iv: ¿Situación similar en el futuro?
- Papel del servicio de Hematología: ¿Qué nos jugamos?

Pfeffer MA, Burdmann EA, Chen CY et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009; 361: 2019–2032.
Charytan DM, Pai AB, Chan CT et al. Considerations and challenges in defining optimal iron utilization in hemodialysis. J Am Soc Nephrol 2015; 26: 1238–1247.
Rostoker G, Vaziri ND, Fishbane S. Iatrogenic Iron Overload in Dialysis Patients at the Beginning of the 21st Century. Drugs. 2016 May;76(7):741-57.

Cuándo tratar

Condiciones candidatas a tratar con Fe iv

- **IDA todos los casos serían susceptibles.**

- **FD: prevención de anemia**
- **Sintomatología no hematológica.**
- **ICC beneficio**

- **FD funcional: asociada a Epo**

- **IDA en ATC (diagnóstico complejo. Ratio RctF/Ft)**
- **ACD: (epo, etc.) Tto personalizado**

Camaschella C. Iron-deficiency anemia. N Engl J Med. 2015;372(19):1832-43

Anemia ferropénica: criterios de la OMS.

Table 1
Relative extent of iron stores on the basis of serum ferritin concentration

	Serum ferritin (µg/l)			
	Less than 5 years of age		5 years of age or older	
	Male	Female	Male	Female
Depleted iron stores	< 12	< 12	< 15	< 15
Depleted iron stores in the presence of infection	< 30	< 30	-	-
Severe risk of iron overload (adults)	-	-	> 200	> 150

http://www.who.int/nutrition/publications/micronutrients/anaemia_iron_deficiency/en/

Diagnóstico de la AF

Revisión de 27 guías terapéuticas para tratamiento de la FP, incluyendo nuevas indicaciones.

Todas recomiendan la Ferritina, y la mitad la Saturación como test alternativo o complementario.

En 18/27 recomiendan primero Fe v. oral (niños y mujeres, pre y post-embarazo).

En 13/27 suplementos con Fe iv (7 en IRC, 5 en QT-cancer).
Diana: Aumento de Hb a 100-120 g/l o normalización (8) y Ft sérica > 100 (n:7) ó > 200 (n:4).
En el caso de la IRC la Ft no debería exceder 500 (n=5) o 800 (n:5).
8 guías recomiendan la saturación como diana única desde 20 al 50%.

El cutoff más recomendado para el diagnóstico de FD es el de ferritina sérica de 100 microg/L y el de la saturación del 20%, incluyendo mujeres jóvenes con hipermenorrea.

Peyrin-Biroulet L,Williet N, Cacoub P. Guidelines on the diagnosis and treatment of iron deficiency across indications: a systematic review .Am J Clin Nutr 2015;102:1585–94.

Valor del cociente TFR/Ft en el diagnóstico de la AF.

Comparado con Gold standard Fe medular (49 IDA y 14 controles)
>80 años Rohovot, Israel.

Otros índices eritrocitarios.

	FE/SAT/Ft	TFR-Ft
Especificidad %	100	**92.9**
Sensibilidad	16,3	**87,7**
VPP %	100	**97,7**
VPN%	22,2	**68,4**

El cociente TFR/Ft es el que permite un mejor diagnóstico de anemia ferropénica

Rimon E, Levy S, Sapir A, Gelzer G, Peled R, Ergas D, Sthoeger ZM. Diagnosis of iron deficiency anemia in the elderly by transferrin receptor-ferritin index. Arch Intern Med 2002; 162:445-9.
Buttarello M. Laboratory diagnosis of anemia: are the old and new red cell parameters useful inclassification and treatment, how? Int J Lab Hematol 2016;38 Suppl 1:123-32.,
Shin DH, Kim HS, Park MJ, Suh IB, Shin KS. Utility of Access Soluble Transferrin Receptor (sTfR) and sTfR/log Ferritin Index in Diagnosing Iron Deficiency Anemia. Ann Clin Lab Sci 2015;45:396-402.

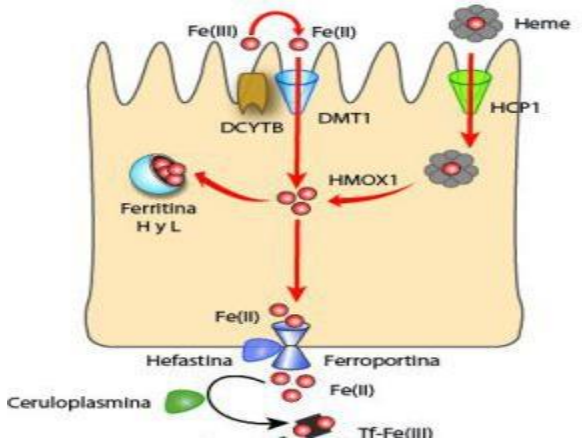
Con qué tratar

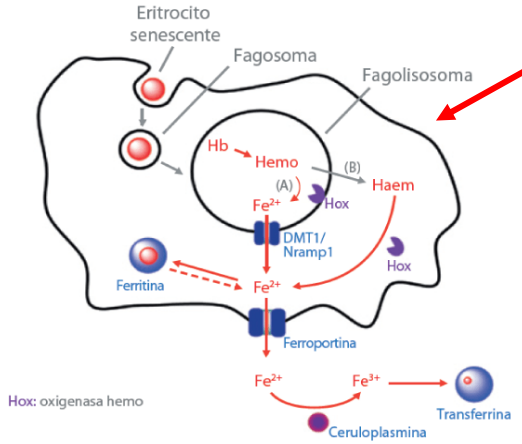
Fe oral

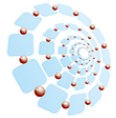
Fe iv

Farmacocinética Fe oral vs Fe iv

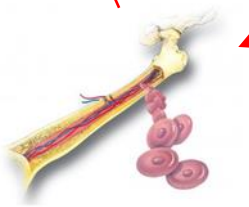
Fe oral







Fe carbohidratos iv



Tratamiento con Fe oral de la AF

- Tradicional y recomendado
- Sales ferrosas entre 60 y 200 mg de Fe elemental
  - Dosis divididas
  - Entre comidas
  - La dosis se puede individualizar.
- Problemas.
  - Efectos secundarios
  - Tratamiento prolongado
  - Toxicidad GI del Fe no absorbido
    - Macrobiota
    - Cáncer de colon.

- Novedades.
  - Dosis única vs dosis divididas
  - Tratamiento a días alternos o cada 3 días (inducción de hepcidina)
  - Nuevas formulaciones (Ferroglicina sulfato, Fe-liposomal)
  - Diferentes mecanismos de absorción.

Moretti D, Goede JS, Zeder C, Jiskra M, Chatzinakou V, Tjalsma H, Melse-Boonstra A, Brittenham G, Swinkels DW, Zimmermann MB. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood. 2015;126(17):1981-9
Constante M, Fragoso G, Lupien-Meilleur J, Calvé A, Santos MM. Iron Supplements Modulate Colon Microbiota Composition and Potentiate the Protective Effects of Probiotics in Dextran Sodium Sulfate-induced Colitis. Inflamm Bowel Dis. 2017 May;23(5):753-766.
Lee T, Clavel T, Smirnov K, Schmidt A, Lagkouvardos I, Walker A, Lucio M, Michalke B, Schmitt-Kopplin P, Fedorak R, Haller D. Oral versus intravenous iron replacement therapy distinctly alters the gut microbiota and metabolome in patients with IBD. Gut. 2017 May;66(5):863-871.
Ng O. Iron, microbiota and colorectal cancer. Wien Med Wochenschr. 2016 Oct;166(13-14):431-436.

Indicaciones de Fe iv: establecidas.

Condición	Ejemplos
Fallo del Fe oral	No adherencia, efectos adversos
Malabsorción	CEL,GI,HP,IRIDA,GT/GP(c.bariátrica)
AF severa	Hb < 80 g/l
IRC	(+ Epo)
Enf Inflam. Intestinal	AF en enf activa
Embarazo	AF severa (2-3 trimestre)
ICC*	IC sistólica (LVEF < 45%)

*ID (inclusos sin anemia) FT < 100 o < 300 microg/l si Sat < 20%)

Camaschella C. Iron-deficiency anemia. N Engl J Med. 2015;372(19):1832-43.

Bhandari S. Update of a comparative analysis of cost minimization following the introduction of newly available intravenous iron therapies in hospital practice. Therapeutics and Clinical Risk Management 2011:7 501–509.

Girelli D, Nemeth E, Swinkels DW. Hepcidin in the diagnosis of iron disorders. Blood. 2016 Jun 9;127(23):2809-13

Indicaciones de Fe iv: potenciales (extendidas).

Condición	Ejemplos
FD/IDA ancianos	No adherencia, comorbilidades,polifarmacia
Anemia perioperatoria	PBM strategies
AF en cáncer	(+/-Epo)
S. Piernas inquietas*	
Enfermedad de las alturas*	Prevención
Pérdidas uterinas severas*	

Camaschella C. Iron-deficiency anemia. N Engl J Med. 2015;372(19):1832-43

Girelli D, Nemeth E, Swinkels DW. Hepcidin in the diagnosis of iron disorders. Blood. 2016 Jun 9;127(23):2809-13

*Auerbach M, Deloughery T. Single-dose intravenous iron for iron deficiency: a new paradigm. Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):57-66.

Las diferentes formas de Fe endovenoso

Fármaco	Fe-Gluconato	Fe-sucrosa	Fe-dextrano BPM	Fe-carboximaltosa	Fe-dextrano APM	Fe-Isomaltosido 1000*	Ferumoxytol
Nombre	Ferrlecit	Venofer	Cosmofer	Ferrinject	Dexferrum	Monofer	Feraheme
Carbohidrato	monosacárido	disacárido	Polisacárido ramificado	Polisacárido ramificado	Polisacárido ramificado	Oligosacárido linear	Polisacárido ramificado
Complejo	III Lábil y débil	II Semirobusto y moderadamente lábil	I Robusto y fuerte	I Robusto y fuerte	I Robusto y fuerte	I Robusto y fuerte	I Robusto y fuerte
Pm (kd)	285-440	30-60	165	150	265	150	750
Vm (h)	1	6	20	16	60	20	15
Fe lábil	3+ (3,3%)	+/- (3,4%)	- (1,9%)	- (0,6%)	-	- (1%)	- (1%)
Fe donado a Tf (%)	5-6	4-5	1-2	1-2	1-2	<1	<1
Test	No	No	Sí	No	Si	No	No
Contenido de Fe mg/ml	12,5	20	50	50	50	100	30
Dosis máxima mg (DIT)	125 (no)	200 (no)	20 mg/kg (no)	20 mg/kg Max 1000 (sí)	20 mg/kg (sí)	20 mg/kg Max 1500 (sí)	510 (no)
EA x 10E9	0,9	0,6	3,3	Raros	11,3	Raros	Raros
Dosis recomendada	125-187,5 mg varias veces, 1 h	100-200 mg varias veces 15 – 30 min	Múltiplos de 100 1000 mg infusión única 1-4 h	2 dosis de 170 mg cada 7 d < 50 kg 2 dosis de 15 mg/kg o 100 mg cada 7 d > 50 kg	Múltiplos de 100 1000 mg infusión única 1-4 h	Una infusión 20 mg/kg hasta 1500 mg o hasta 3 veces 500 mg cada 7 d	2 infusiones 510 mg cada 3-8 d o dosis única de 1020 mg

Achebe MM, Gafter-Gvili A. How I treat anemia in pregnancy: iron, cobalamin, and folate. Blood. 2017 Feb 23;129(8):940-949.
Rostoker G, Vaziri ND, Fishbane S. Iatrogenic Iron Overload in Dialysis Patients at the Beginning of the 21st Century. Drugs. 2016 May;76(7):741-57.
Del Vecchio L, Longhi S, Locatelli F. Safety concerns about intravenous iron therapy in patients with chronic kidney disease. Clin Kidney J. 2016 Apr;9(2):260-7.
Cançado R, Muñoz M. Iron replacement options: oral and intravenous formulations. TATM 2012;12;3-4:103-114

* Fe isomaltosido pendiente resolver advertenciaAEMPS del 19 Julio 2017

Dosificación de Fe iv

Fórmula de Ganzoni:

Dosis de hierro total = Peso corporal (Kg) [a] x ($Hb_{objetivo}$ - Hb_{real})(g/dl) [b] x 2,4 [c] + Hierro para los depósitos[d] (500 mg)

[a]Se recomienda utilizar el peso corporal ideal del paciente o el peso antes del embarazo
[b]Para convertir Hb (mM) en Hb (g/dl) se debe multiplicar Hb (mM) por el factor 1,61145
[c]Factor 2,4 = 0,0034 x 0,07 x 10000; donde:
0,0034 es el contenido en hierro de la hemoglobina (0,34 %)
0,07 el volumen sanguíneo (70 ml/kg de peso corporal ≈ 7 % del peso corporal)
10000: Factor de conversión de g/dl a mg/l
[d]Para una persona con un peso corporal superior a 35 kg, los depósitos de hierro son de 500 mg o más.
Un defecto de esta fórmula es que no tiene en cuanta ni la ingesta de hierro ni las pérdidas de hierro, tampoco tiene en cuanta un tratamiento de mantenimiento.

Tabla simplificada

Peso corporal	35 kg a < 70kg		≥70kg	
Hb (g/dL)	≥10	<10	≥10	<10
Dosis total de hierro	1000 mg	1500 mg	1500 mg	2000 mg
Administración semana 1	1000 mg	1000 mg	1000 mg	1000 mg
Administración semana 2	–	500 mg	500 mg	1000 mg

Alternativa:

Hb < 100 g/l administrar 1 gramo o 1,5 g de Fe iv en total.
Hb > 100 g/l 500-600 mg
Control a las 4-6 semanas y valorar administración, generalmente a dosis más bajas (100 a 500 mg) RC (Hb > 120 o 130 g/l sin ferropenia).
Si AF crónica realizar un tratamiento de mantenimiento. Ajustar para Hb normal y una ferritina de 100 microg/l, nunca debería sobrepasar Ferritina de 500 microg/l.

Efectos adversos del Fe IV

Inmunogenicidad y reacciones adversas relacionadas con la infusión.

Efectos adversos del uso excesivo de Fe iv.

Van Buren P, Velez RL, Vaziri ND, Zhou XJ. Iron overdose: a contributor to adverse outcomes in randomized trials of anemia correction in CKD. Int Urol Nephrol. 2012 Apr;44(2):499-507.

Reacciones adversas relacionadas con la infusión.

Reacciones adversas relacionadas con la infusión. Historia del Fe iv.

1947 Fe-sacarido

1954 Fe-dextrano HPM

Riesgo Inaceptable Anafilaxia

1991 Fe-dextrano BPM

1999 Fe-Gluconato

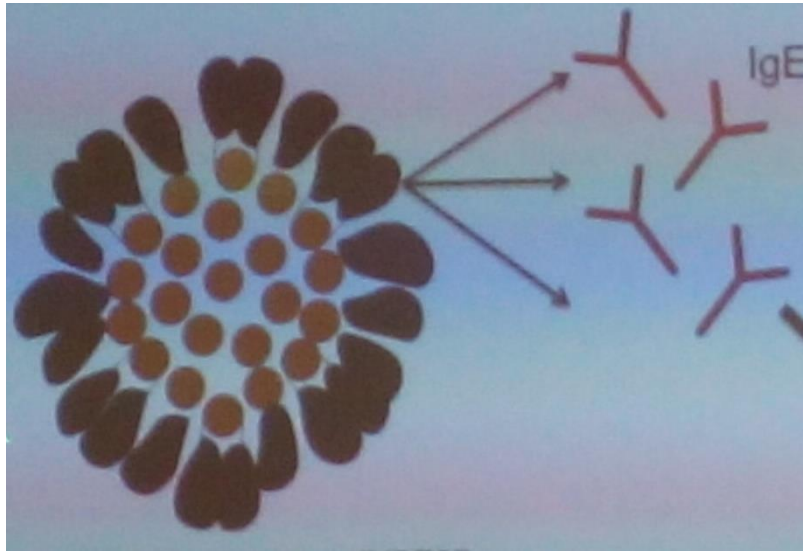
2000 Fe-sacarosa

nuevos

>2009:

Ferumoxytol
Fe-isomaltosido
Fe-carboximaltosa

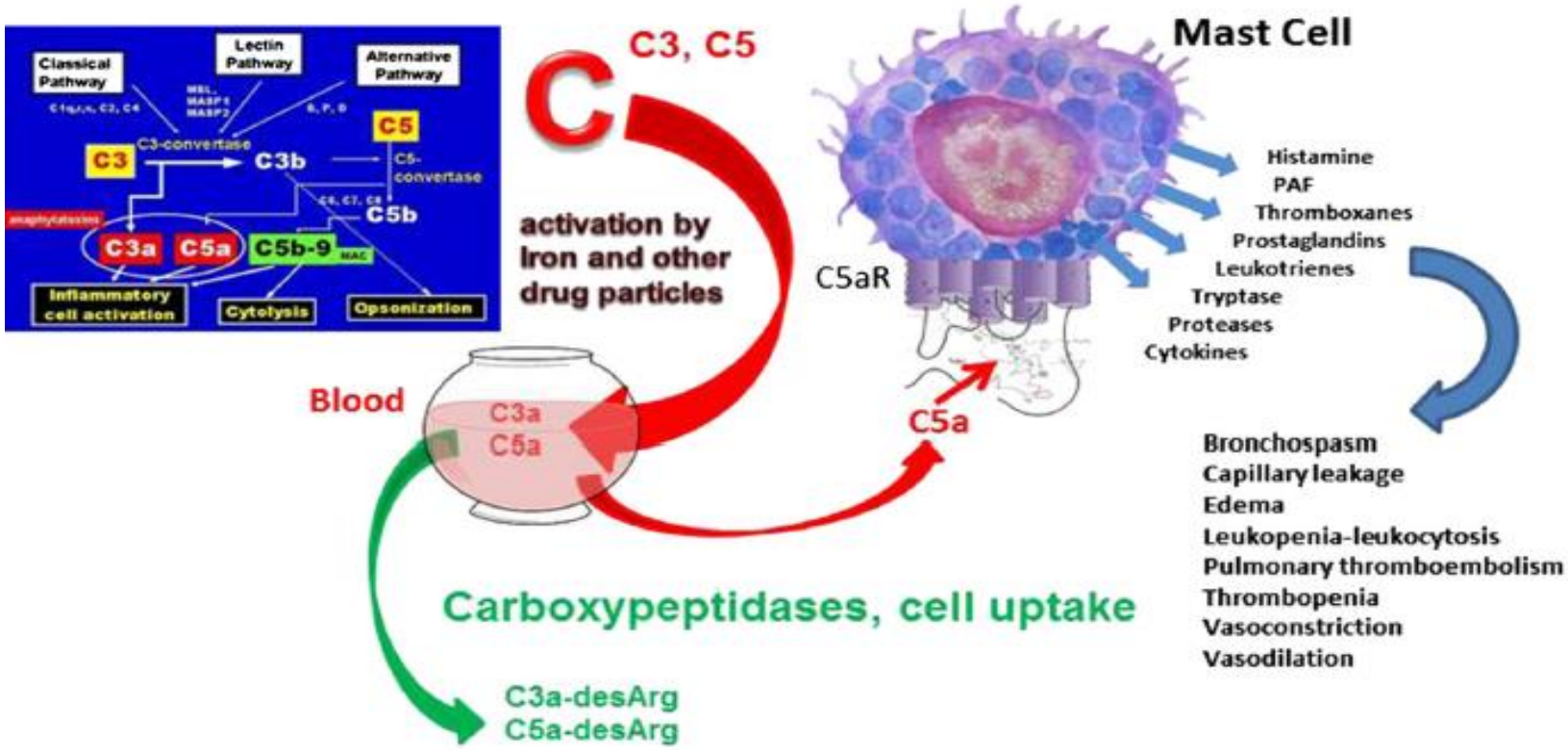
Diferencias claves en:
Inmunogenicidad
Estabilidad



Estudio retrospectivo > 30 millones dosis,
casi todas reacciones graves Fe-dextrano HPM
Retirado
EA graves: 11,3 x 10E9 infusiones.

Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmén J. Update on adverse drug events associated with parenteral iron. Nephrol Dial Transplant. 2006;21:378-82.

Reacciones de hipersensibilidad del Fe iv.



Pseudoalergia relacionada con la activación del complemento

Szebeni J, Fishbane S, Hedenus M, Howaldt S, Locatelli F, Patni S, Rampton D, Weiss G, Folkersen J. Hypersensitivity to intravenous iron: classification, terminology, mechanisms and management. Br J Pharmacol. 2015;172:5025-36.

Reacciones postinfusión de Fe iv: la mayoría mínimos efectos.

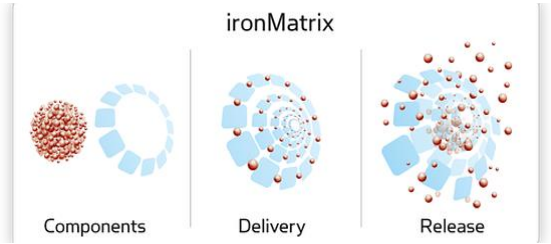
A

B

- Aprox 1 cada 200 infusiones.
- Flushing con/sin mialgias
- con/sin náuseas
- con/sin congestión nasal
- sin hipotensión.

- Autolimitadas
- Evitar antihistamínicos
- No suelen ser recurrentes.

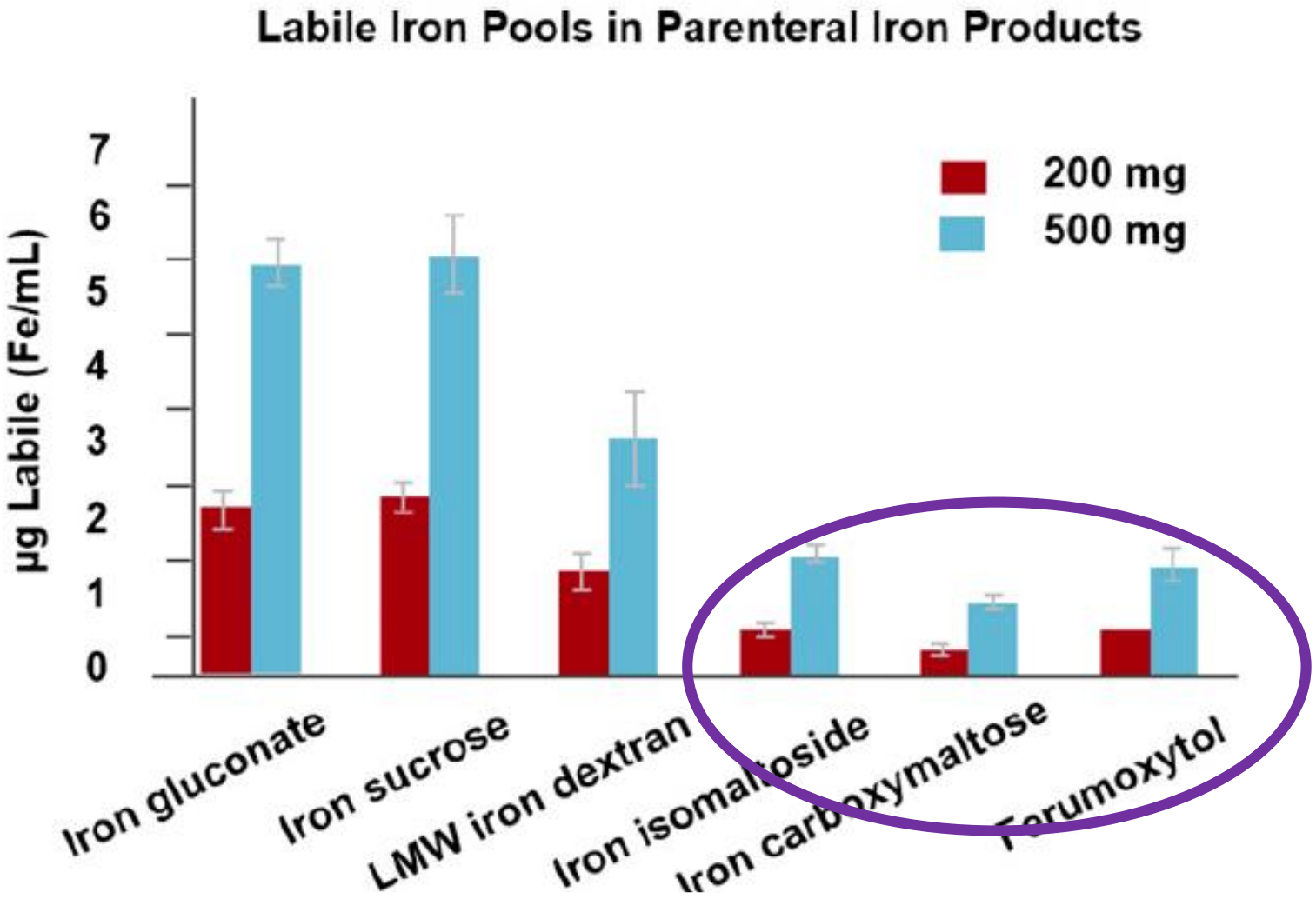
Toxicidad hemodinámica aguda



Liberación de Fe al plasma antes de la fagocitosis

Depende de la estabilidad y limita la cantidad de Fe a administrar en cada infusión

Auerbach M, Deloughery T. Single-dose intravenous iron for iron deficiency: a new paradigm. Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):57-66.



Jahn MR, Andreasen HB, F¨ utterer S, et al. A comparative study of the physicochemical properties of iron isomaltoside 1000 (Monofer), a new intravenous iron preparation and its clinical implications. Eur J Pharm Biopharm. 2011;78(3):480-491.

Auerbach M, Deloughery T. Single-dose intravenous iron for iron deficiency: a new paradigm. Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):57-66.

Recomendaciones de la EMA 2013 Committee for Medicinal Products for Human Use (CHMP) en el manejo del riesgo de las reacciones alérgicas con Fe iv.

1. All prescribers should inform patients of the risk and seriousness of a hypersensitivity reaction and the importance of seeking medical attention if a reaction occurs.

2. Patients need to be closely observed for any allergic reactions during and for at least 30 min after IV-iron injection.

3. IV-iron preparations should only be administered

   A. by staff trained to evaluate and manage anaphylactic and anaphylactoid reactions,

   B. in an environment where resuscitation facilities are available so that the patient can be treated immediately.

4. The current practice of first giving the patient a small test dose is not a reliable way to predict how the patient will respond when the full dose is given. A test dose is therefore no longer recommended, but instead, caution is warranted with every dose of IV-iron that is given, even if previous administrations have been well tolerated.

5. In case of hypersensitivity reactions, healthcare professionals should immediately stop the iron administration and consider appropriate treatment for the hypersensitivity reaction.

6. IV-iron medicines should not be used during pregnancy unless clearly necessary. Treatment should be confined to the second or third trimester, provided the benefits of treatment outweigh the risk to the unborn baby.

EMA-CHMP (2013). New recommendations to manage risk of allergic reactions with intravenous iron-containing medicines Vol.EMA/579491/2013, pp 1–3: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/IV_iron_31/WC500151308. pdf (accessed 10/11/2015).

Frecuencia de reacciones de hipersensibilidad en Fe IV.

Reaction rate	Drugs	Drug Type
Very high $P > 10\%$	Rituximab, infliximab	mAb
	Doxil (Caelyx), AmB (AmBisome)	Liposome-encapsulated
	Taxanes (paclitaxel, docetaxel), platinum	Micellarized anticancer
High $1\% < P < 10\%$	Natalizumab, cetuximab, trastuzumab, panitumumab, gentuzumab	mAb
	Amphotec, Myocet, Amphocyl, DaunoXome, Abelcet, Visudyne	Liposome
	Penicillin	Antibiotic
	Platinum compounds (cisplatin, carboplatin),	Anticancer drugs
Moderate $0.1 < P\ \% < 1$	Omalizumab	Monoclonal antibodies (mAbs)
	Alemtuzumab	
	Trastuzumab	
	Cephalosporins/carbapenems, aztreonam, imipenem	Antibiotics
	Iodinated contrast agents (loxaglate, lohexol, lopamidol, loversol, lopromide, loxilan)	Radiocontrast agents
low $0.01 < P\ \% < 0.1$	Bevacizumab	mAb
	Epipodophyllotoxins (teniposide, etoposide), asparaginase, procarbazine, doxorubicin, 6-mercaptopurine	Anticancer drugs
	Acetaminophen (paracetamol), aspirin, ibuprofen	Anaesthetics, analgesics antalgics, antipyretics and non-steroidal anti-inflammatory drugs
	Phenytoin, carbamazepine phenobarbital sodium Lamotrigine, primidone diphenylhydantoin, sulfonamides (procainamide), sulfonylureas	Anticonvulsants (antiepileptics)
	Iodinated contrast agents (ioxaglate, iohexol, iopamidol, ioversol, iopromide, ioxilan, iodixanol, Gd-GTPA	Contrast agents
	Venofer, Cosmofer, Ferinject, Monofer, Ferrlecit, Ferumoxytol	IV-iron[b]
Very low $P < 0.01$	SonoVue	Contrast agents
	Venofer, Cosmofer, Ferinject, Monofer, Ferrlecit, Ferumoxytol	IV-iron[b]

[a]All types of reactions regardless of severity. Rates were obtained from individual box labels, public (internet) information or Summaries of Product Characteristics.
[b]Data uncertain to select the exact category, P = prevalence.

Rampton G, Folkersen J, Fishbane S, Hedenus M, Howaldt S, Locatelli F et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimisation and management. Haematologica 2014; 99: 1671–1676.

Reacciones adversas con Fe iv. Resultados de Metanálisis

Tipo	RR
All studies	1.04 (0.93-1.17)
Mortality	1.06 (0.81-1.39)
By compound	
IS	1.33 (0.96-1.83)
FCM	0.82 (0.64-1.06)
FML	1.04 (0.71-1.53)
ISM or IPM	1.09 (0.43-2.80)
ID	1.05 (0.77-1.45)
FG	1.12 (0.96-1.30)
By infusion reaction	
All	2.47 (1.43-4.28)[b]
IS	1.75 (0.69-4.43)
FCM	1.47 (0.40-5.39)
FML	2.26 (0.19-26.22)
ISM or IPM	1.00 (0.99-1.01)
ID	3.10 (0.86-11.22)
FG	5.32 (1.49-18.99)[b]
Placebo comparator	2.96 (1.16-7.51)[b]
Hypotension	
Total	1.39 (1.09-1.77)[b]
Gastrointestinal	
Total	0.55 (0.51-0.61)[b]
ID	0.28 (0.14-0.53)[b]
FCM	0.57 (0.48-0.68)[b]
IS	0.38 (0.32-0.45)[b]
Placebo	1.39 (1.13-1.71)[b]
No iron	0.84 (0.72-0.92)[b]
Oral iron	0.33 (0.29-0.38)[b]
Infections	1.17 (0.83-1.65)

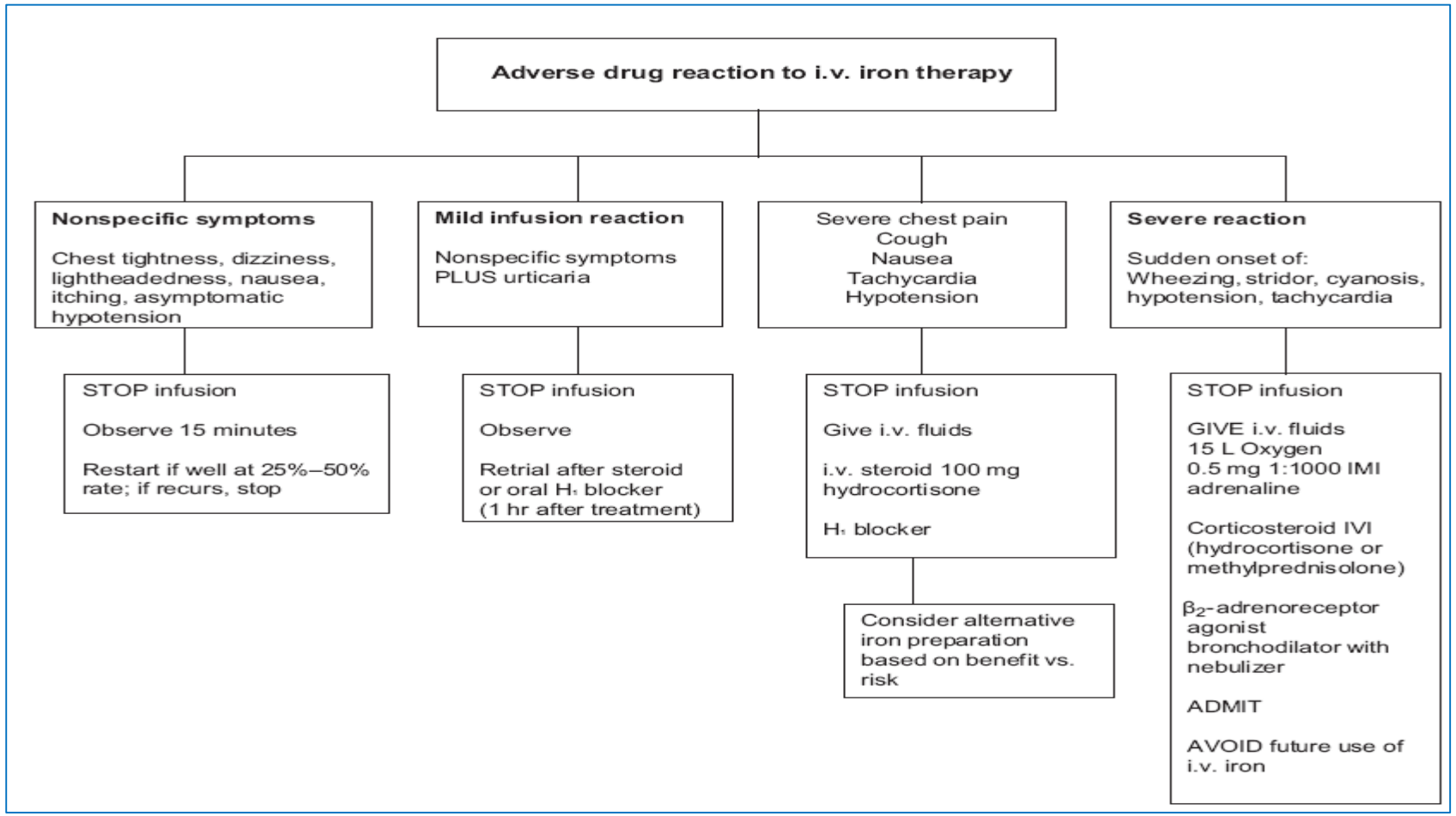
[a]FCM = ferric carboxymaltose; FG = ferric gluconate; FML = ferumoxytol; ID = iron dextran; IPM = iron polymaltose; IS = iron sucrose; ISM = iron isomaltoside; NA = not applicable; NNH = number needed to harm; NNP = number needed to prevent; RR = relative risk; SAE = severe adverse event.
[b]Indicates statistically significant results.

Morbilidad mayor.
Transfusiones: 1 en 21.413 infusiones.
FE iv: < 1/200.000 infusiones.

No diferencias con placebo.

Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A. The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo Clin Proc. 2015;90:12-23.
Auerbach M, Deloughery T. Single-dose intravenous iron for iron deficiency: a new paradigm. Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):57-66.

Manejo de las reacciones de hipersensibilidad en drogas iv, incluido el Fe iv.



Macdougall IC, Bircher AJ, Eckardt KU, Obrador GT, Pollock CA, Stenvinkel P, Swinkels DW, Wanner C, Weiss G, Chertow GM; for Conference Participants. Iron management in chronic kidney disease: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference. Kidney International 2016; 89: 28–39.

Efectos adversos del uso de Fe iv.

. Stress oxidativo (Arteriosclerosis)
. Disfunción endotelial. (Arteriosclerosis)
. Inflamación. (Arteriosclerosis)
. Disfunción inmune. (Infecciones)
. Empeoramiento de la función renal.

. Sobrecarga férrica.

.

Van Buren P, Velez RL, Vaziri ND, Zhou XJ. Iron overdose: a contributor to adverse outcomes in randomized trials of anemia correction in CKD. Int Urol Nephrol. 2012 Apr;44(2):499-507.
Silverberg DS, Wexler D, Schwartz D. Is Correction of Iron Deficiency a New Addition to the Treatment of the Heart Failure? Int J Mol Sci. 2015 Jun 18;16(6):14056-74
Ribeiro S, Belo L, Reis F, Santos-Silva A. Iron therapy in chronic kidney disease: Recent changes, benefits and risks. Blood Rev. 2016 Jan;30(1):65-72.
Del Vecchio L, Longhi S, Locatelli F. Safety concerns about intravenous iron therapy in patients with chronic kidney disease. Clin Kidney J. 2016 Apr;9(2):260-7.

Hipótesis: Fe iv se asocia en IRC con efectos adversos CV, infecciones, empeoramiento FR.

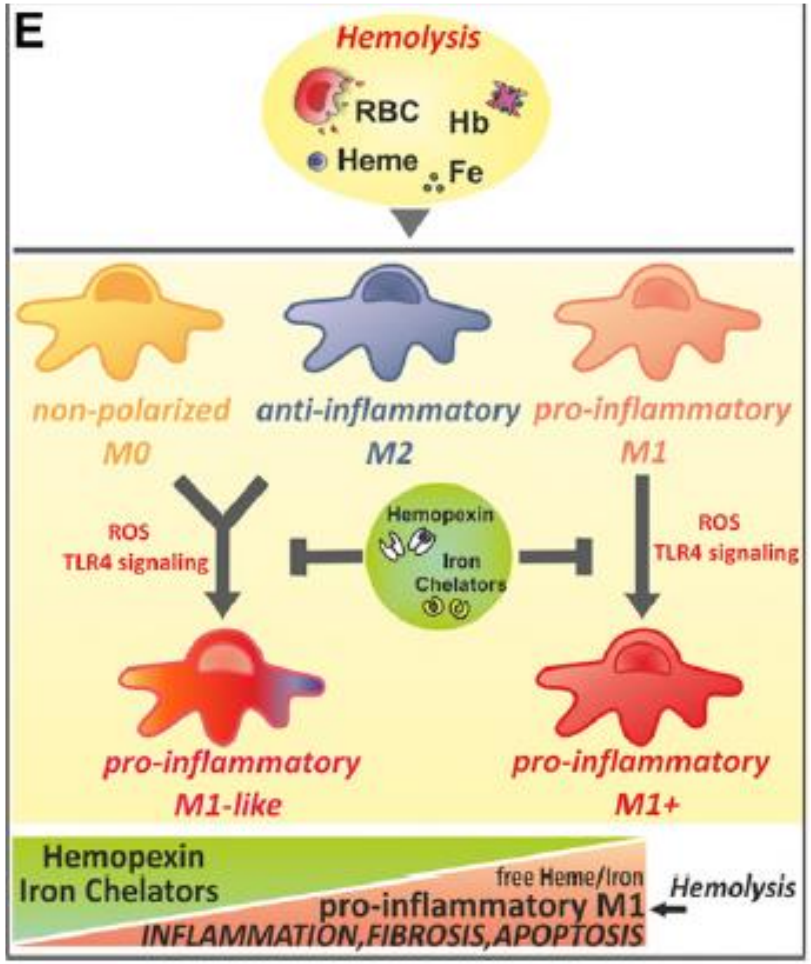
Estudios en humanos a favor y otros que no han demostrado esté efecto adverso. Problemas de diseño y calidad de los estudios.

Fe sacarosa agrava la disfunción endotelial (aumenta la adhesion c. mononucleadas a endotelio) y empeora la Arteriosclerosis.

Fe altera función c. inmunes (linfocitos T, neutrófilos, monocitos)

Kuo KL, Hung SC, Lee TS, et al. Iron sucrose accelerates early atherogenesis by increasing superoxide production and upregulating adhesion molecules in CKD. J Am Soc Nephrol. 2014;25:2596–2606.
Silverberg DS, Wexler D, Schwartz D. Is Correction of Iron Deficiency a New Addition to the Treatment of the Heart Failure? Int J Mol Sci. 2015 Jun 18;16(6):14056-74
Ribeiro S, Belo L, Reis F, Santos-Silva A. Iron therapy in chronic kidney disease: Recent changes, benefits and risks. Blood Rev. 2016 Jan;30(1):65-72.
Del Vecchio L, Longhi S, Locatelli F. Safety concerns about intravenous iron therapy in patients with chronic kidney disease. Clin Kidney J. 2016 Apr;9(2):260-7.

Efecto proinflamatorio del hierro



Macrófagos M1 inducen inflamación, fibrosis y apoptosis hepática

Fe, heme y Hb libre (hemólisis) es capaz de promover la diferenciación de los macrófagos hacia un fenotipo pro-inflamatorio (M1), vía producción de ROS y TLR4.
Promueve la diferenciación a M1 de M0 (no-polarizado) y M2 (anti-inflamatorio) y los M1 a formas más agresivas (M11).

Quelantes del Fe y hemopexina previene este efecto proinflamatorio.

Vinchi F, Costa da Silva M, Ingoglia G, Petrillo S, Brinkman N, Zuercher A, Cerwenka A, Tolosano E, Muckenthaler MU. Hemopexin therapy reverts heme-induced proinflammatory phenotypic switching of macrophages in a mouse model of sickle cell disease. Blood. 2016 Jan 28;127(4):473-86.

Efectos adversos del uso de Fe iv.

. Sobrecarga férrica.

IRC

Otras indicaciones.

.

Van Buren P, Velez RL, Vaziri ND, Zhou XJ. Iron overdose: a contributor to adverse outcomes in randomized trials of anemia correction in CKD. Int Urol Nephrol. 2012 Apr;44(2):499-507.
Silverberg DS, Wexler D, Schwartz D. Is Correction of Iron Deficiency a New Addition to the Treatment of the Heart Failure? Int J Mol Sci. 2015 Jun 18;16(6):14056-74
Ribeiro S, Belo L, Reis F, Santos-Silva A. Iron therapy in chronic kidney disease: Recent changes, benefits and risks. Blood Rev. 2016 Jan;30(1):65-72.
Del Vecchio L, Longhi S, Locatelli F. Safety concerns about intravenous iron therapy in patients with chronic kidney disease. Clin Kidney J. 2016 Apr;9(2):260-7.

Efectos adversos del uso excesivo de Fe iv.

. Sobrecarga férrica.

IRC

Excesivo Fe iv y riesgo de sobrecarga férrica.

Table 1. Indications for iron therapy in CKD patients

Organization	When to start	When to stop
KDIGO [5]	ESA naive • Serum ferritin < 500 ng/mL • TSAT < 30% ESA therapy • Serum ferritin < 500 ng/mL • TSAT < 30%	Serum ferritin ≥ 500 ng/mL TSAT ≥ 30%
ERBP [6]	ESA naive – CKD-ND • Serum ferritin < 200 ng/mL • TSAT < 25% – CKD-5D • Serum ferritin < 300 ng/mL • TSAT < 25% ESA therapy – CKD all stages • Serum ferritin < 300 ng/mL • TSAT < 30%	Serum ferritin ≥ 500 ng/mL TSAT ≥ 30%
KDOQI [7]	– CKD all stages • Serum ferritin < 500 ng/mL • TSAT < 30%	None (if high ferritin, weigh potential risks and benefits of persistent anaemia, ESA dosage, comorbid conditions and health-related quality of life)
Canadian Guidelines [8]	– CKD all stages • Serum ferritin < 500 ng/mL • TSAT < 30%	None
NICE [9]	– CKD all stages • Serum ferritin < 100 ng/mL • TSAT < 20% (unless ferritin > 800 ng/mL) • HRC <6% (unless ferritin > 800 ng/mL)	Serum ferritin 500–800 ng/mL

CKD-ND, non-dialysis CKD.

Considering that the benefits of IV iron in terms of Hb increase and decreased ESA doses become less evident for TSAT values ≥30% and high ferritin values,

we do believe that there is no need to use high doses of IV iron therapy, especially in CKD patients who are not on dialysis or in those who are ESA naive

Del Vecchio L, Longhi S, Locatelli F. Safety concerns about intravenous iron therapy in patients with chronic kidney disease. Clin Kidney J. 2016 Apr;9(2):260-7.

Iron Overload

Studies show that 30% with IO

It is crucial that we test to ensure we are not giving too much iron.

Serum ferritin remains the best test in routine use for this

Macdougall IC, Bircher AJ, Eckardt KU, Obrador GT, Pollock CA, Stenvinkel P, Swinkels DW, Wanner C, Weiss G, Chertow GM; Conference Participants.. Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int. 2016 Jan;89(1):28-3

Ratcliffe LE, Thomas W, Glen J, Padhi S, Pordes BA, Wonderling D, Connell R, Stephens S, Mikhail AI, Fogarty DG, Cooper JK, Dring B, Devonald MA, Brown C, Thomas ME. Diagnosis and Management of Iron Deficiency in CKD: A Summary of the NICE Guideline Recommendations and Their Rationale. Am J Kidney Dis. 2016 Apr;67(4):548-58.

Kliger AS, Foley RN, Goldfarb DS, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for anemia in CKD. Am J Kidney Dis. 2013;62(5):849-859.

ACHIEVING THE RIGHT BALANCE: IRON DEFICIENCY VERSUS IRON OVERLOAD

Iron overload and its impact on organ function and patient outcomes

There is no feasible method available to determine total body iron content.

Magnetic resonance imaging scans have been shown to provide a reliable estimate of tissue iron content in non-CKD populations, and measurements in unselected HD patients suggest that liver iron content is increased compared to reference values in the majority of patients.

However, the clinical relevance of increased liver iron content in the absence of elevated liver enzymes is unclear.

However, the magnitude, distribution, and duration of iron accumulation in CKD patients may be insufficient to produce toxicity similar to that observed in hemochromatosis. The exposure to higher amounts may not have accrued long enough to detect such toxicity.
At present one cannot exclude the toxicity potential of iron induced by repeated high-dose i.v. iron administration in CKD.

Macdougall IC, Bircher AJ, Eckardt KU, Obrador GT, Pollock CA, Stenvinkel P, Swinkels DW, Wanner C, Weiss G, Chertow GM; for Conference Participants. Iron management in chronic kidney disease: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference. Kidney International 2016; 89: 28–39.
Rostoker G, Griuncelli M, Loridon C, et al. Hemodialysis-associated hemosiderosis in the era of erythropoiesis-stimulating agents: a MRI study. Am J Med. 2012;125:991–999.

ACHIEVING THE RIGHT BALANCE: IRON DEFICIENCY VERSUS IRON OVERLOAD

Table 1. Overview of effectiveness of laboratory variables.

Parameter	n	Visit	Mean	Standard deviation	Minimum	Median	Maximum
Hemoglobin (g/dL)	638	Baseline	11.01	1.66	6.10	10.97	16.58
		Intermediate	11.56	1.62	7.10	11.50	16.70
		Final	11.55	1.63	6.80	11.47	16.20
		Difference*	0.53	1.98	–6.44	0.50	7.60
Hematocrit (%)	638	Baseline	33.96	5.03	19.20	33.90	52.00
		Intermediate	35.33	4.76	21.10	35.00	54.00
		Final	35.27	4.76	20.50	35.00	51.70
		Difference*	1.30	6.00	–18.40	1.30	21.40
s-iron (µg/dL)	459	Baseline	55.17	23.93	16.00	52.50	171.70
		Intermediate	71.42	31.80	17.00	68.00	276.32
		Final	72.92	32.19	15.50	68.24	235.00
		Difference*	17.75	36.27	–127.00	15.00	197.20
s-ferritin (µg/L)	589	Baseline	320.44	341.00	3.70	218.00	2,275.00
		Intermediate	509.71	420.43	9.00	418.00	3,011.40
		Final	641.47	673.81	7.20	507.20	8,795.00
		Difference*	321.03	616.68	–1,177.00	212.00	8,008.00
Transferrin saturation (%)	467	Baseline	19.39	9.08	3.90	18.00	77.00
		Intermediate	27.03	12.75	5.00	25.20	96.90
		Final	28.28	13.21	3.00	26.30	89.70
		Difference*	8.90	14.22	–30.80	7.00	71.90

*Difference from baseline to final examination. All differences were statistically significant ($p < 0.0001$).

Datos a los 3-9 meses de tto con Fe iv.
Dosis acumulada (2,574 mg isomaltoside)

Hb de 110 a 116 g/L,
SAT de 19.4% a 28.3%
Ferritina de 320 µg/L a 642 µg/L

Reducción de AEE
(epoetin α de 40,688 IU/m a 35,665 IU/mes, –13.7%, $p < 0.001$).

Biggar P, Leistikow F, Walper A. A prospective observational study of effectiveness and safety of iron isomaltoside in patients with chronic renal failure and iron deficiency anemia. Clin Nephrol. 2016 Dec;86 (2016)(12):310-318.

ferumoxytol

Schiller B, Bhat P, Sharma A. Safety and effectiveness of ferumoxytol in hemodialysis patients at 3 dialysis chains in the United States over a 12-month period. Clin Ther. 2014;36:70-83.
Lu M, Cohen MH, Rieves D, Pazdur R. FDA report: Ferumoxytol for intravenous iron therapy in adult patients with chronic kidney disease. Am J Hematol. 2010;85:315-9.

Sobrecarga férrica y riesgo de mortalidad en IRC en diálisis en tratamiento con Fe Iv.

	Year	Patients	Iron dose/Follow-up time	Outcome	Ref.
Iron overload	2012	HD patients (n=119)	100 mg of iron sucrose (2-3x/w - induction phase; 1x/w every 4 w - maintenance phase) 60 mo follow-up	• 84 % of patients with hepatic iron deposition, 30% of them with severe iron overload • Iron liver content correlates with infused iron	[54]
	2012	HD patients (n=21)	100 mg (ferric saccharate) 1-3x/w 12 mo follow-up	• 90% of patients with mild-to-severe hepatic iron deposition • 95% of patients with splenic iron deposition • 14% patients with pancreatic iron deposition	[53]
	2011	CKD patients (n=25)	50 to 200 mg/mo for 12 mo	• Liver iron concentration: 60% of patients > 60 umol/g; 13% of patients > 130 umol/g (reference value 30 umol/g)	[49]
	2004	HD patients (n=40)	31.25 mg ferric gluconate complex 10 patients: maintenance iron at least 6 mo 30 patients: without iron therapy at least 2 mo (after ferritin > 500 ug/L)	• 70% of patients with mild-to-severe hepatic iron overload • 70% of patients with ferritin < 500 ng/mL	[52]
Mortality	2015	HD patients (n=32 435)	4 month-follow up of IV iron dose: < 300 mg/mo *versus* ≥ 300 mg/mo	• ↑ mortality among patients with higher doses of IV iron (≥ 300 mg/mo over 4 months), regardless serum ferritin or CRP values	[60]
	2014	dialysis patients (n=235)	7.6 years-follow up with continuous maintenance iron therapy once/w in varying doses: 12.5 mg (minimum dose) to 62.5 mg (maximum dose)	• ↑ mortality with ferritin levels > 800 ng/mL in case of concomitant inflammation (CRP > 0.5 mg/dL)	[59]
	2013	HD patients (n=117 050)	3 mo-follow up after 1 mo exposure to: high dose (> 200 mg) *versus* low dose (1-200 mg) bolus (consecutive doses ≥ 100 mg exceeding 600 mg during one month) *versus* maintenance dose	• no significant associations of bolus versus maintenance dose or high dose *versus* low dose IV iron with increased short-term cardiovascular morbidity and mortality	[58]
	2005	HD patients (n=58 058)	Iron gluconate effect in a 2 year-follow up, with different iron dose categories: 0 mg/mo; 1 to 199.9 mg/mo; 200 to 399.9 mg/mo; > 400 mg/mo	• ferritin 200-1200 ng/mL, TSAT 30-50% and IV iron dose < 400 mg/mo associated with improved survival	[57]
	2004	HD patients (n= 27 280)	Effect of iron administration in a 2 year follow-up, with iron doses categories at each 6 mo: >0 to 700 mg; > 700 to 100 mg; > 1000 to 1800 mg; > 1800mg	• no association between iron administrated and mortality • association between iron dose and mortality at 12 to 18 months of treatment, for doses > 1800 mg • association between mortality and ferritin > 800 ng/mL in the 6 months prior to death	[56]
	2002	HD patients (n= 10 169)	number of 100-mg vials of iron during 6 mo	• ↑ risk of death and hospitalization with IV iron > 1000 mg	[55]

CRP – C reactive protein; HD – hemodialysis; IV – intravenous; mo - month; w – week.

Ribeiro S, Belo L, Reis F, Santos-Silva A. Iron therapy in chronic kidney disease: Recent changes, benefits and risks. Blood Rev. 2016 Jan;30(1):65-72.

Excesivo Fe iv y riesgo de sobrecarga férrica en IRC en HD y tto con Fe iv y AEE.

Sobrecarga férrica : 84%; 36% severa (> 201 micromol/g).

Table 2 Biochemical Markers of Iron Metabolism in the 119 Hemodialysis Patients Included in the Cross-sectional Study (Classified According to Hepatic Nonheme Iron Stores, as Measured by Hepatic MRI)

	Positive Control Group (n = 9)	Normal (≤50 μmol/g) (n = 19)	Mild Overload (51-100 μmol/g) (n = 42)	Moderate Overload (101-200 μmol/g) (n = 22)	Severe Overload (>201 μmol/g) (n = 36)	*P* Value Kruskal-Wallis Test
Hemoglobin (g/dL) Optic cytometry, Abbott normal range in dialysis patients: 10-12 g/dL	ND	11.58 (8.85-13.42)	11.41 (8.43-14.13)	12.34 (9.50-14.10)	12.39 (9.80-15.12)	<.001
C-reactive protein (mg/L) Immunoturbidimetry using latex particles, Roche Diagnostics; normal range: (<5 mg/L)	ND	6.97 (0.90-38.38)	4.70 (0.30-75.93)	1.80 (1-38.95)	3.68 (0.60-20.70)	.089
Serum ferritin (μg/L) Immunoturbidimetry using latex particles, Roche Diagnostics; normal range: (M: 30-400 μg/L, F: 15-150 μg/L)	524 (335-828)	99.33 (27.67-631.30)	205.80 (37-1383)	215.20 (15-949.50)	446.10 (55.25-1299)	<.0001
Serum iron (μmol/L) Colorimetric test, Roche Diagnostics; normal range: (M: 11-28, F: 6.6-26 μmol/L)	23.75 (8.60-32.90)	8.54 (3.95-22.08)	8.69 (3.59-22.31)	11.05 (4.40-17.11)	11.86 (4.21-26.27)	<.05
Serum transferrin (g/L) Immunoturbidimetry, Roche Diagnostics; normal range: (2-3.6 g/L)	1.90 (1.7-2.0)	1.83 (1.07-2.70)	1.69 (1.23-2.50)	1.75 (1.35-2.77)	1.60 (1.07-2.43)	.094
Transferrin saturation (TSAT) (%) serum iron/ total iron-binding capacity ratio; normal range: (20%-40%)	43.80 (19.10-77.40)	21.33 (7.83-40)	19.25 (7.67-47.70)	24.32 (6.33-41.33)	30.87 (8-72.16)	<.001
Soluble transferrin receptor (sTfr) (mg/L) Immunoturbidimetry, Roche Diagnostics; normal range: (M: 2.2-5; F: 1.9-4.40 mg/L)	ND	4.93 (2.08-12.60)	3.82 (1.99-12.13)	5.13 (1.59-13.02)	3.99 (1.43-9.19)	.331
sTfr/Ferritin ratio	ND	42.25 (5.62-248.60)	26.63 (1.65-327.80)	21.51 (4.94-732.70)	6.71 (2.60-166.30)	<.0001
Hepcidin (ng/mL) Enzyme innumoassay, Peninsula Laboratories, USA; normal range: (1.71-175.9 ng/mL)	ND	52.33 (0.76-554.80)	102.80 (6.53-421.40)	87.90 (1.10-250.20)	162.70 (5.29-1036)	<.01

MRI — magnetic resonance imaging; ND — not done.
Values are given as median and (range).

Rostoker G, Laroudie M, Blanc R, Galet B, Rabaté C, Griuncelli M, Cohen Y. Signal-intensity-ratio MRI accurately estimates hepatic iron load in hemodialysis patients. Heliyon. 2017 Jan 5;3(1):e00226.
Rostoker G, Griuncelli M, Loridon C, Magna T, Machado G, Drahi G, Dahan H, Janklewicz P, Cohen Y. Reassessment of Iron Biomarkers for Prediction of Dialysis Iron Overload: An MRI Study. PLoS One. 2015 Jul 16;10(7):e0132006.
Rostoker G, Griuncelli M, Loridon C, Magna T, Janklewicz P, Drahi G, Dahan H, Cohen Y. Maximal standard dose of parenteral iron for hemodialysis patients: an MRI-based decision tree learning analysis. PLoS One. 2014 Dec 15;9(12):e115096.
Rostoker G, Griuncelli M, Loridon C, Couprie R, Benmaadi A, Bounhiol C, Roy M, Machado G, Janklewicz P, Drahi G, Dahan H, Cohen Y. Hemodialysis-associated hemosiderosis in the era of erythropoiesis-stimulating agents: a MRI study. Am J Med. 2012 Oct;125(10):991-999.

SF en HD: impacto de abandonar el Fe iv.

De 115 casos en 21 ferritina (SF) > 1000 ng/mL (2688 ± 1489 ng/mL).

RMI: SF moderada a severa en 19 de 21 en hígado (8 en pancreas, ninguno cardiaca).

Se para Fe IV durante 12 meses y se sigue con AEE
Ferritina disminuyó a 1682 ng/mL, no cambio en Hb.

Ghoti H, Rachmilewitz EA, Simon-Lopez R, Gaber R, Katzir Z, Konen E, Kushnir T, Girelli D, Campostrini N, Fibach E, Goitein O. Evidence for tissue iron overload in long-term hemodialysis patients and the impact of withdrawing parenteral iron. Eur J Haematol. 2012 Jul;89(1):87-93.

SF en HD: impacto de abandonar el Fe iv.

Caso clínico:
47 a varón. Tte renal. Tto previo (89 m) con HD y recibió 100–300 mg de Fe iv/semana y transfusion de 8 u.
Pérdida de peso y alt p. hepáticas.
Hb 13.1 g/dL and platelets 190,000/mm3.
Portal Doppler ultrasound: signos de cirrosis incipiente.
Ferritina: 5300 ng/mL, SAT: 82%.
Biopsia hepatica: hemosiderosis + fibrosis portal.
Flebotomías: 19 u. Mejoría p.hepaticas y Ft, ganancia de peso.

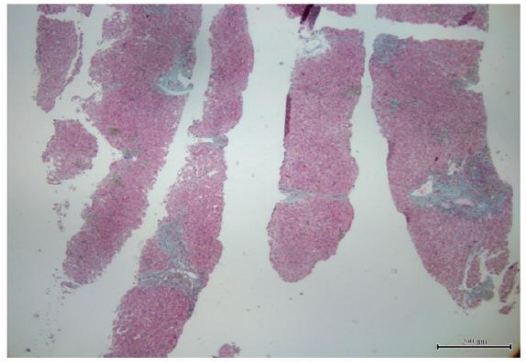


Figure 3. There is portal fibrous enlargement and septae formation (Masson trichrome ×100).

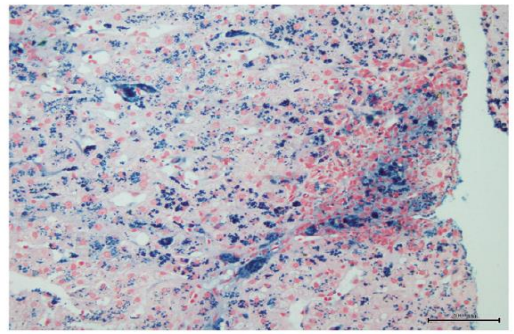


Figure 2. There is marked iron deposition (Grade 3) that is most prominent in portal macrophages and zone 1 hepatocytes and Kupffer cells (Perls stain ×200).

Yaprak M, Çeltik A, Turan İ, Nart D, Turan MN, Sezer TÖ, Hoşçoşkun C, Töz H. Rare cause of weight loss in a kidney transplant recipient: iron overload. Ren Fail. 2014 Feb;36(1):119-22.

Prevención de la SF en pacientes con HD.

Estudio prospectivo 8 m en unidad HD. 45 casos.

Reducir dosis de Fe iv:
Fe iv si SAT < 20% y Ft < 200 µg/L.
AEE igual.

Media de Fe iv de 77.8 ± 87.6 a 24.4 ± 52.9 mg (p = 0.0003).
Ft de 947.7 ± 1056.4 a 570.7 ± 424.4 µg/L (p = 0.0001).

Hb estable (11.13 ± 1.05 vs. 11.00 ± 1.16 g/dL, p = 0.54) y dosis de AEE (126.4 ± 91.9 vs. 108.2 ± 112.7 µg/28 d, p =0.07).

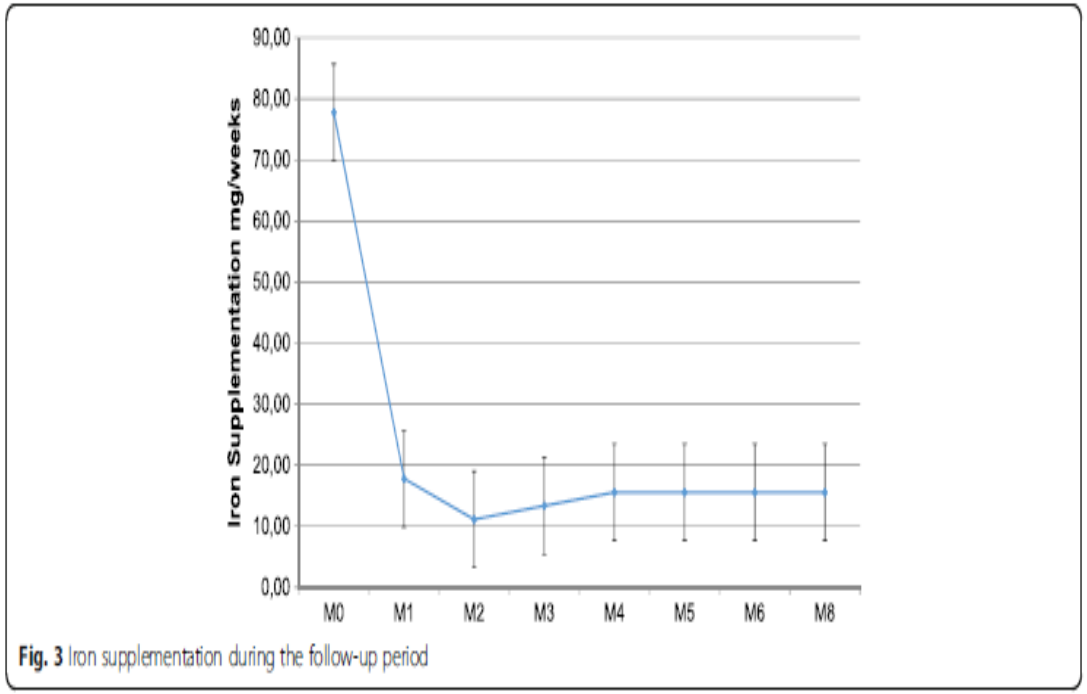


Fig. 3 Iron supplementation during the follow-up period

Se puede reducir la dosis de Fe iv, sin cambios en cifra de Hb y dosis de AEE, pero se reduce la sobrecarga férrica.

Peters NO, Jay N, Cridlig J, Rostoker G, Frimat L. Targets for adapting intravenous iron dose in hemodialysis: a proof of concept study. BMC Nephrol. 2017 Mar 20;18(1):97.

FE iv: otras condiciones

Fe iv en cáncer

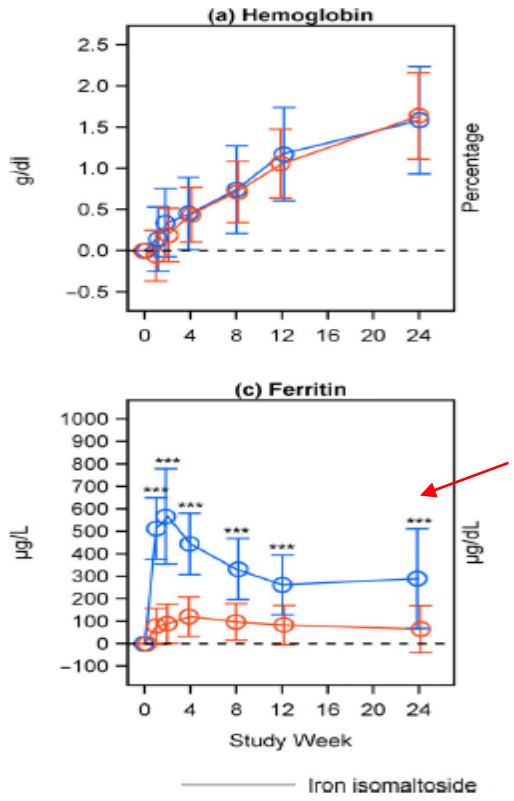


Table 3. Changes in Hemoglobin and Iron Variables

Laboratory variables, time point (no. of patients)	Iron isomaltoside (group A), least-square mean estimate[a]	Iron sulfate (group B), least-square mean estimate[a]	Difference estimates (95% CI)	p value
Hemoglobin, g/dl: full analysis set				
Week 1 (group A: 215, group B: 110)	0.14	−0.06	0.20 (−0.024–0.43)	0.08
Week 2 (group A: 210, group B: 100)	0.34	0.19	0.15 (−0.10–0.40)	0.24
Week 4 (group A: 192, group B: 99)	0.45	0.44	0.02 (−0.26–0.29)	< 0.001, 0.91[b]
Week 8 (group A: 181, group B: 84)	0.74	0.71	0.03 (−0.33–0.38)	0.88
Week 12 (group A: 164, group B: 81)	1.17	1.06	0.12 (−0.29–0.52)	0.58
Week 24 (group A: 157, group B: 72)	1.58	1.64	−0.05 (−0.60–0.49)	0.85
Hemoglobin, g/dl: per protocol analysis set				
Week 4 (group A: 184, group B: 89)	0.46	0.47	−0.007 (−0.29–0.28)	< 0.001, 0.96[b]
Serum iron, µg/dl[c] full analysis set				
Week 1 (group A: 216, group B: 109)	21.5	2.92	18.6 (3.95–33.2)	0.01
Week 2 (group A: 210, group B: 100)	12.3	12.3	−0.008 (−16.3–16.2)	0.99
Week 4 (group A: 194, group B: 98)	5.45	5.89	−0.45 (−13.8–12.9)	0.95
Week 8 (group A: 182, group B: 84)	−4.26	1.67	−5.93 (−19.3–7.46)	0.38
Week 12 (group A: 163, group B: 81)	−4.04	7.43	−11.5 (−26.1–3.18)	0.12
Week 24 (group A: 156, group B: 72)	−6.97	−4.89	−2.08 (−16.1–11.9)	0.77
Serum ferritin, ng/ml: full analysis set				
Week 1 (group A: 216, group B: 109)	513	78	435 (378–492)	< 0.001
Week 2 (group A: 209, group B: 100)	567	89	478 (374–582)	< 0.001
Week 4 (group A: 193, group B: 98)	445	121	324 (254–394)	< 0.001
Week 8 (group A: 182, group B: 84)	332	97	235 (175–295)	< 0.001
Week 12 (group A: 164, group B: 81)	262	83	179 (112–246)	< 0.001
Week 24 (group A: 220, group B: 72)	290	65	225 (103–347)	< 0.001
Transferrin saturation, %: full analysis set				
Week 1 (group A: 216, group B: 109)	6.83	0.69	6.14 (2.18–10.10)	0.003
Week 2 (group A: 210, group B: 100)	4.92	3.12	1.79 (−2.95–6.54)	0.46
Week 4 (group A: 194, group B: 98)	3.38	1.89	1.49 (−2.52–5.50)	0.47
Week 8 (group A: 182, group B: 84)	0.45	0.60	−0.16 (−4.24–3.92)	0.94
Week 12 (group A: 163, group B: 81)	−0.41	1.14	−1.56 (−5.65–2.54)	0.45
Week 24 (group A: 155, group B: 72)	−1.65	−2.43	0.77 (−3.75–5.30)	0.74
Total iron binding capacity, µmol/L: full analysis set				
Week 1 (group A: 216, group B: 109)	−3.90	−1.34	−2.57 (−4.25 to −0.88)	0.003
Week 2 (group A: 210, group B: 100)	−6.12	−2.33	−3.79 (−5.60 to −1.99)	< 0.001
Week 4 (group A: 194, group B: 98)	−7.65	−2.98	−4.67 (−6.90 to −2.43)	< 0.001
Week 8 (group A: 182, group B: 84)	−6.68	−3.50	−3.18 (−6.00 to −0.35)	0.03
Week 12 (group A:163, group B: 81)	−4.81	−2.99	−1.83 (−4.42–0.77)	0.17
Week 24 (group A: 155, group B: 72)	−3.76	−0.52	−3.24 (−6.33 to −0.16)	0.04

CI = confidence interval.
[a]Least-square means from the repeated measures model with the inclusion of treatment, visit, treatment × visit interactions, platinum-based chemotherapy (yes/no), and country as factors and baseline hemoglobin level as the covariate.
[b]The first p value represents the noninferiority test, and the second p value represents the superiority test.
[c]Conversion factor for serum iron: µmol/L/0.179 = µg/dl.

Riesgo de SF, si repetidas infusiones a dosis altas

Birgegård G, Henry D, Glaspy J, Chopra R, Thomsen LL, Auerbach M. A Randomized Noninferiority Trial of Intravenous Iron Isomaltoside versus Oral Iron Sulfate in Patients with Nonmyeloid Malignancies and Anemia Receiving Chemotherapy: The PROFOUND Trial. Pharmacotherapy. 2016 Apr;36(4):402-14.

Fe IV. Artroplastia de rodilla

1,000 mg of iron isomaltoside 1000 intravenously. Because the maximal daily dose of iron isomaltoside 1000 is 20 mg/kg and the current study included patients weighing under 50 kg, the total dose was administered in two separate doses. The day before surgery, 600 mg iron isomaltoside 1000 was given in 100 mL normal saline; the remaining 400 mg were administered in 100 mL normal saline 1 week later.

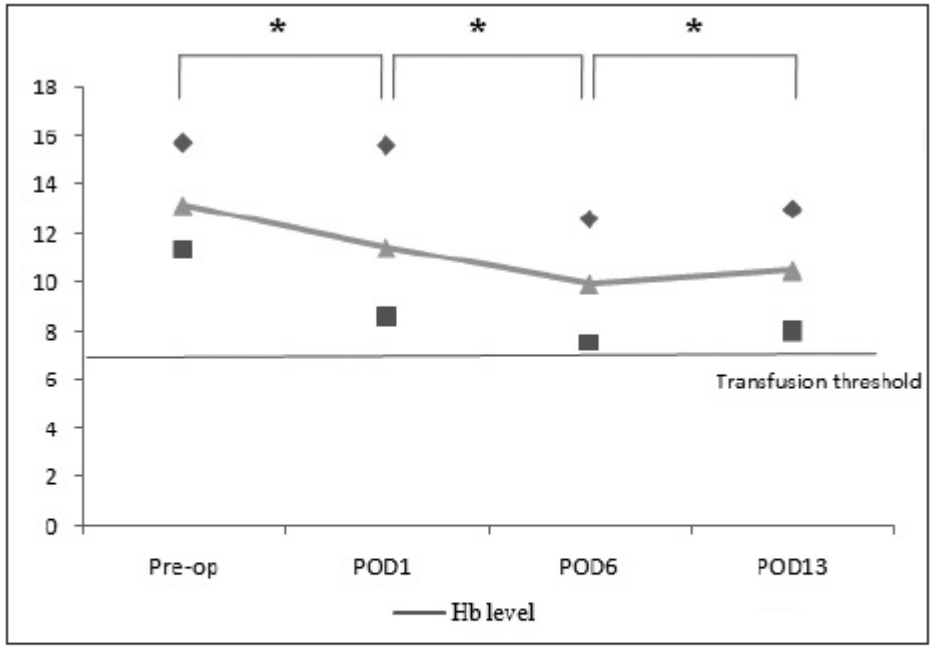


Figure 1 - Post-operative Hb levels.
Mean, ▲, and range: min, ■, and max, ◆. The Hb level was decreased on POD1 and POD6, and had begun to recover by POD13; *p-value <0.05 by Wilcoxon's signed rank test. Hb: haemoglobin.

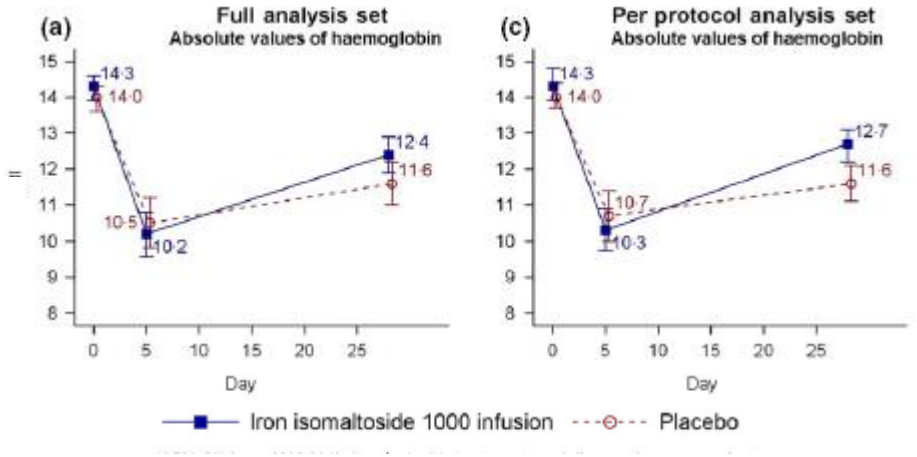
Riesgo de SF (moderada)

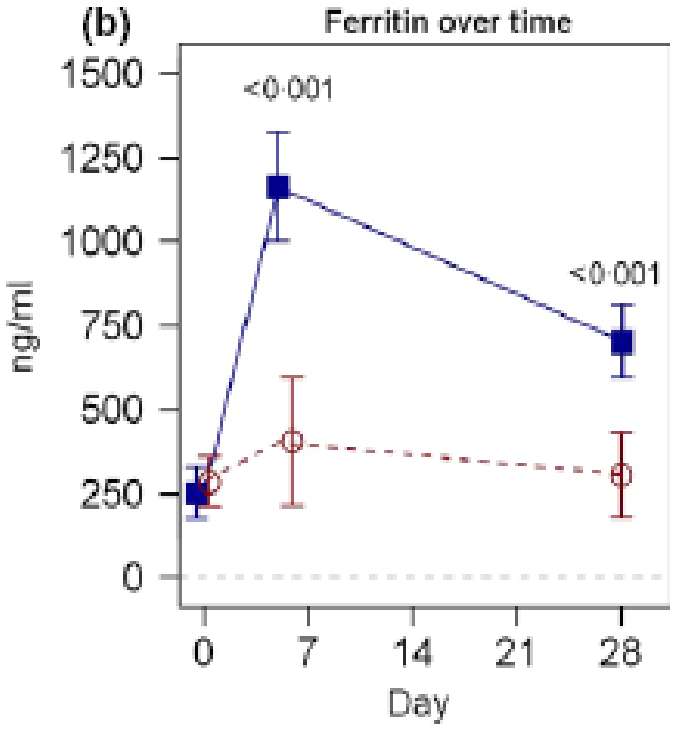
FT y SAT no reportados.

Suh DW, Han SB, Park JH, Cheong K, Kyung BS. Intravenous iron supplementation with intra-articular administration of tranexamic acid reduces the rate of allogeneic transfusions after simultaneous bilateral total knee arthroplasty. Blood Transfus. 2016 Jul 22:1-6.

Fe IV. Cirugía cardíaca

Statistics/Category	Treatment group: Iron isomaltoside 1000 (n = 30)	Treatment group: Placebo (n = 30)
Biochemistry at baseline		
Haemoglobin (g/dl)	14·25	13·98
Transferrin saturation (%)	19	21
Ferritin (ng/ml)	254	286

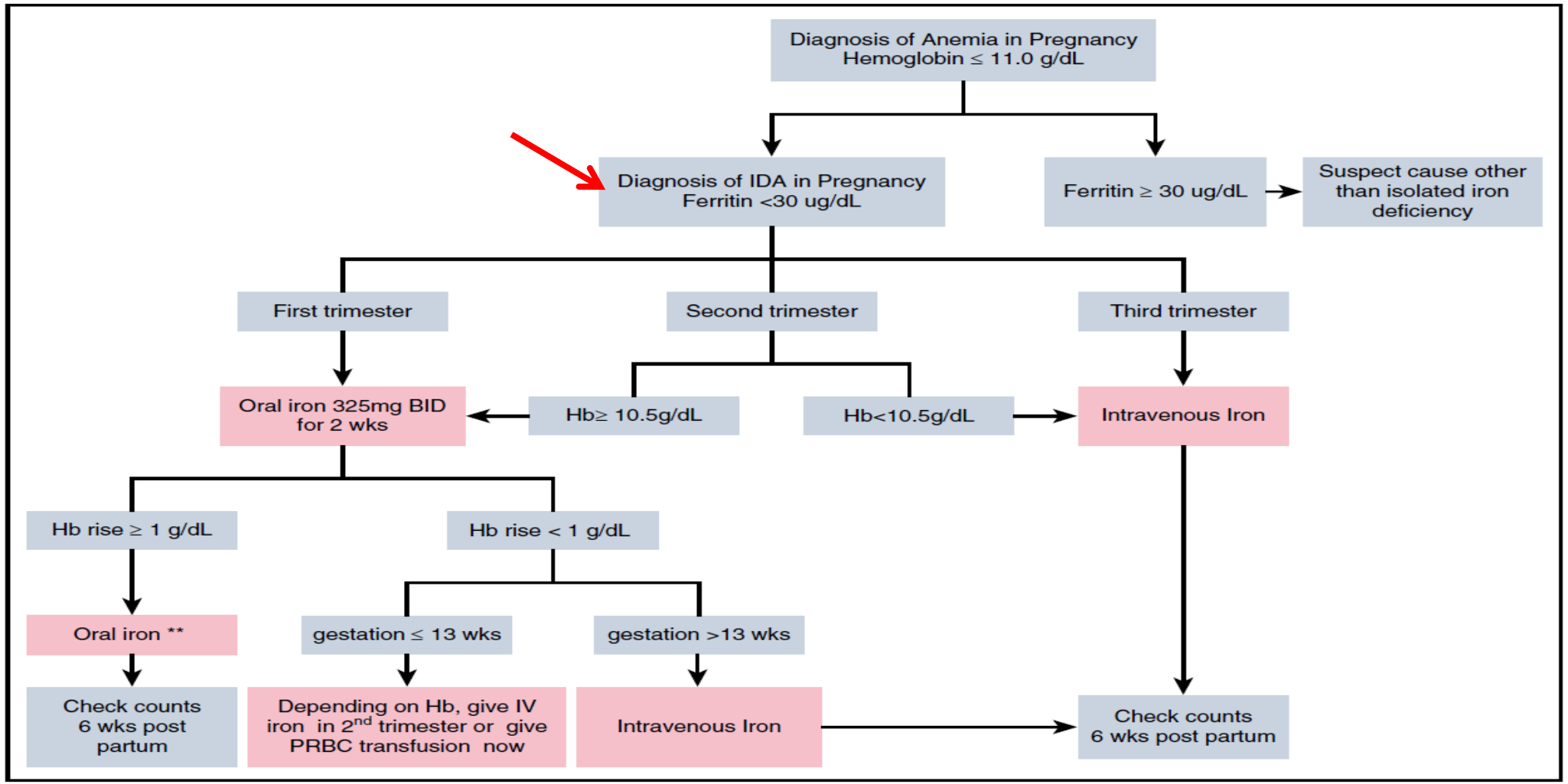




Riesgo de SF (moderada)

Johansson PI, Rasmussen AS, Thomsen LL. Intravenous iron isomaltoside 1000 (Monofer®) reduces postoperative anaemia in preoperatively non-anaemic patients undergoing elective or subacute coronary artery bypass graft, valve replacement or a combination there of: a randomized double-blind placebo-controlled clinical trial (the PROTECT trial). Vox Sang. 2015 Oct;109(3):257-66.

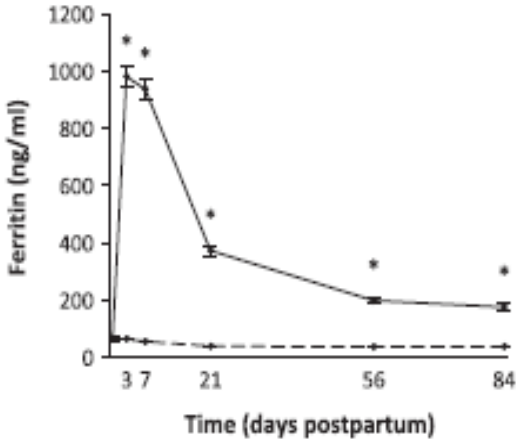
Fe iv en embarazo



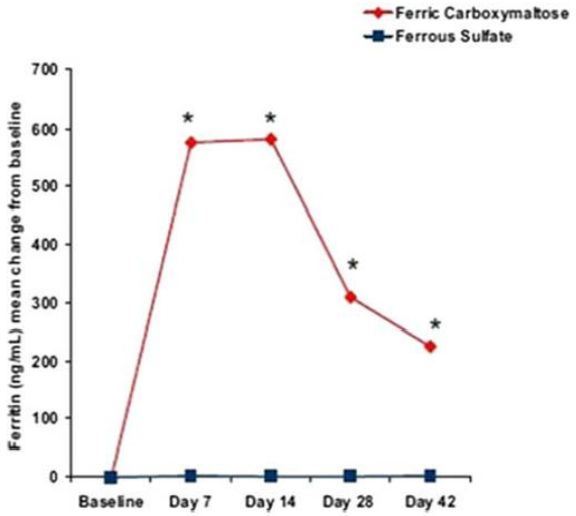
Achebe MM, Gafter-Gvili A. How I treat anemia in pregnancy: iron, cobalamin, and folate. Blood. 2017 Feb 23;129(8):940-949.

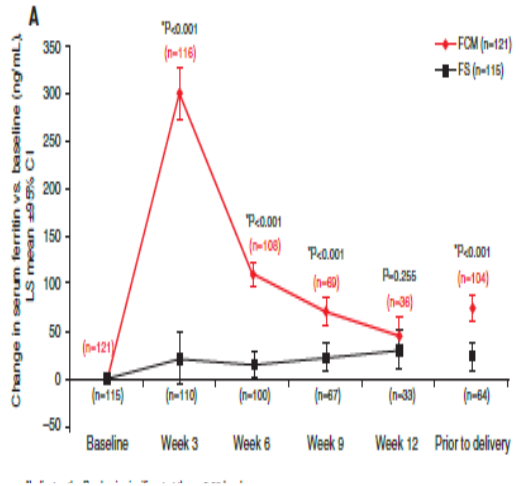
Poco riesgo de SF

Fe iv en postparto. Dosis total o única



Single-dose intravenous iron infusion





Ferric iron carboxymaltose (Ferinject®) 1,000–2,500 mg iron

Poco riesgo de SF

Holm C, Thomsen LL, Norgaard A, Langhoff-Roos J. Single-dose intravenous iron infusion or oral iron for treatment of fatigue after postpartum haemorrhage: a randomized controlled trial. Vox Sang. 2017;112(3):219-228.
Holm C, Thomsen LL, Norgaard A, Langhoff-Roos J. Single-dose intravenous iron infusion versus red blood cell transfusion for the treatment of severe postpartum anaemia: a randomized controlled pilot study. Vox Sang. 2017;112(2):122-131.
Milman N. Postpartum anemia II: prevention and treatment. Ann Hematol. 2012 Feb;91(2):143-54.
Breymann C, Milman N, Mezzacasa A, Bernard R, Dudenhausen J; FER-ASAP investigators.. Ferric carboxymaltose vs. oral iron in the treatment of pregnant women with iron deficiency anemia: an international, open-label, randomized controlled trial (FER-ASAP). J Perinat Med. 2016 Jun 8. pii: /j/jpme.ahead-of-print/jpm-2016-0050/jpm-2016-0050.xml

Fe iv en postparto. Fe iv vs oral

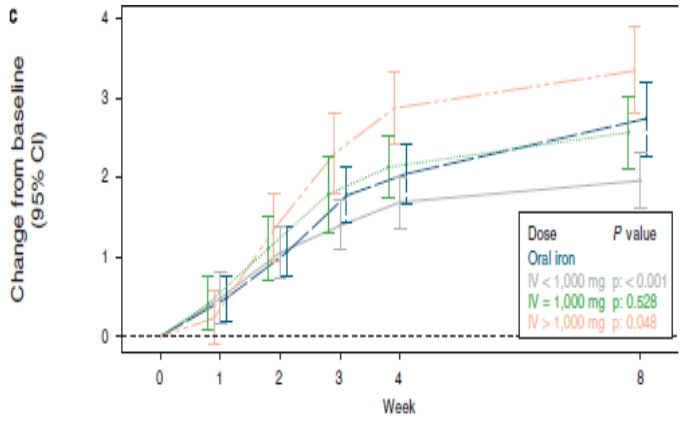
Table 3 Treatment of postpartum IDA with oral vs. i.v. iron and effect on serum ferritin: summary of studies

Reference	Women (n)	Iron treatment	Ferritin at inclusion (µg/l)	Outcome		*p*-Value
Breymann et al. [56]			Mean, ~32	Mean SF day 14		
	20	80 mg Fe^{2+}/day oral 14 days		22±10 µg/l		<0.01
	40	800 mg iron sucrose i.v.		81±30 µg/l		
Bhandal and Russell [57]			<15	Mean SF day 14	Mean SF day 40	
	21	400 mg Fe^{2+}/day oral 40 days		16±4 µg/l	15±3 µg/l	<0.01
	22	400 mg iron sucrose i.v.		38±5 µg/l	42±7 µg/l	
Van Wyck et al. [55]				Mean increase SF day 14	Mean increase SF day 42	
	169	195 mg Fe^{2+}/day oral 42 days		0 µg/l	0 µg/l	<0.001
	168	~1,400 mg ferric carboxymaltose i.v.		560 µg/l	210 µg/l	
Westad et al. [60]			Mean, 24	Mean SF day 28	Mean increase SF day 28	
	70	200 mg Fe^{2+}/day oral 84 days		25±15 µg/l	4 µg/l	<0.001
	58	600 mg iron sucrose i.v. + 200 mg Fe^{2+}/day oral iron, 56 days		40±23 µg/l	14 µg/l	
Seid et al. [59]			Mean, 24	Mean increase SF day 14	Mean increase SF day 42	
	148	195 mg Fe^{2+}/day oral 42 days		0 µg/l	0 µg/l	<0.0001
	168	~1,400 mg ferric carboxymaltose i.v.		595 µg/l	215 µg/l	
Giannoulis et al. [58]			<10	Mean increase SF day 28		
	26	800 mg Fe^{3+}/day oral 28 days		68 µg/l		<0.001
	78	300 mg iron sucrose i.v.		105 µg/l		

SF. serum ferritin

Milman N. Postpartum anemia II: prevention and treatment. Ann Hematol. 2012 Feb;91(2):143-54.

Fe iv en enfermedad inflamatoria intestinal.



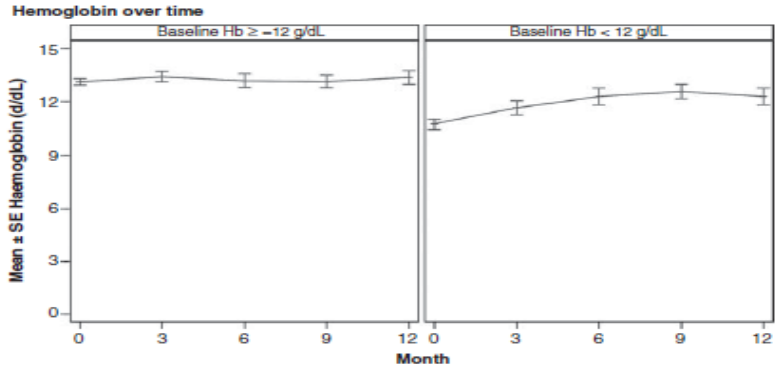


Figure 2. Hemoglobin over time.

Table 2. Number of patients with adverse events

	Iron isomaltoside 1,000						Oral iron sulfate (group B)	
	Total		Infusion (group A1)		Bolus (group A2)			
	N	%	*N*	%	*N*	%	*N*	%
Safety analysis set	223	100	110	100	113	100	109	100
Any AEs	88	39	46	42	42	37	38	35
Related AEs	31	14	17	15	14	12	11	10
Not related AEs	69	31	36	33	33	29	29	27
SAEs	8	4	3	3	5	4	1	<1
Related SAE	1	0.4	1	0.9	—	—	—	—

AE, adverse event; SAE, serious AE.

Poco riesgo de SF
Fe oral?

analysis set.

Visits	*S*-iron (µg/dl)	Concentration/Cha *S*-ferritin (mcg/L)
At baseline		
n	35	35
Median (range: min:max)	45.00 (11:191)	32.00 (5:514)
Change in concentration from baseline to		
3 months		
n	34	34
Median (range: min:max)	10.50 (−133:170)	46.00 (−207:464)
6 months		
n	27	27
Median (range: min:max)	23.00 (−34:101)	117.00 (−12:734)
9 months		
n	25	25
Median (range: min:max)	19.00 (−45:98)	102.00 (−10:568)
12 months (end of study)		
n	26	26
Median (range: min:max)	17.00 (−43:115)	132.50 (−36:660)
p-Value	0.003	<0.001

Abbreviations: Max: Maximum; Min: Minimum; TIBC = Total iron binding capacity

high-dose intravenous iron

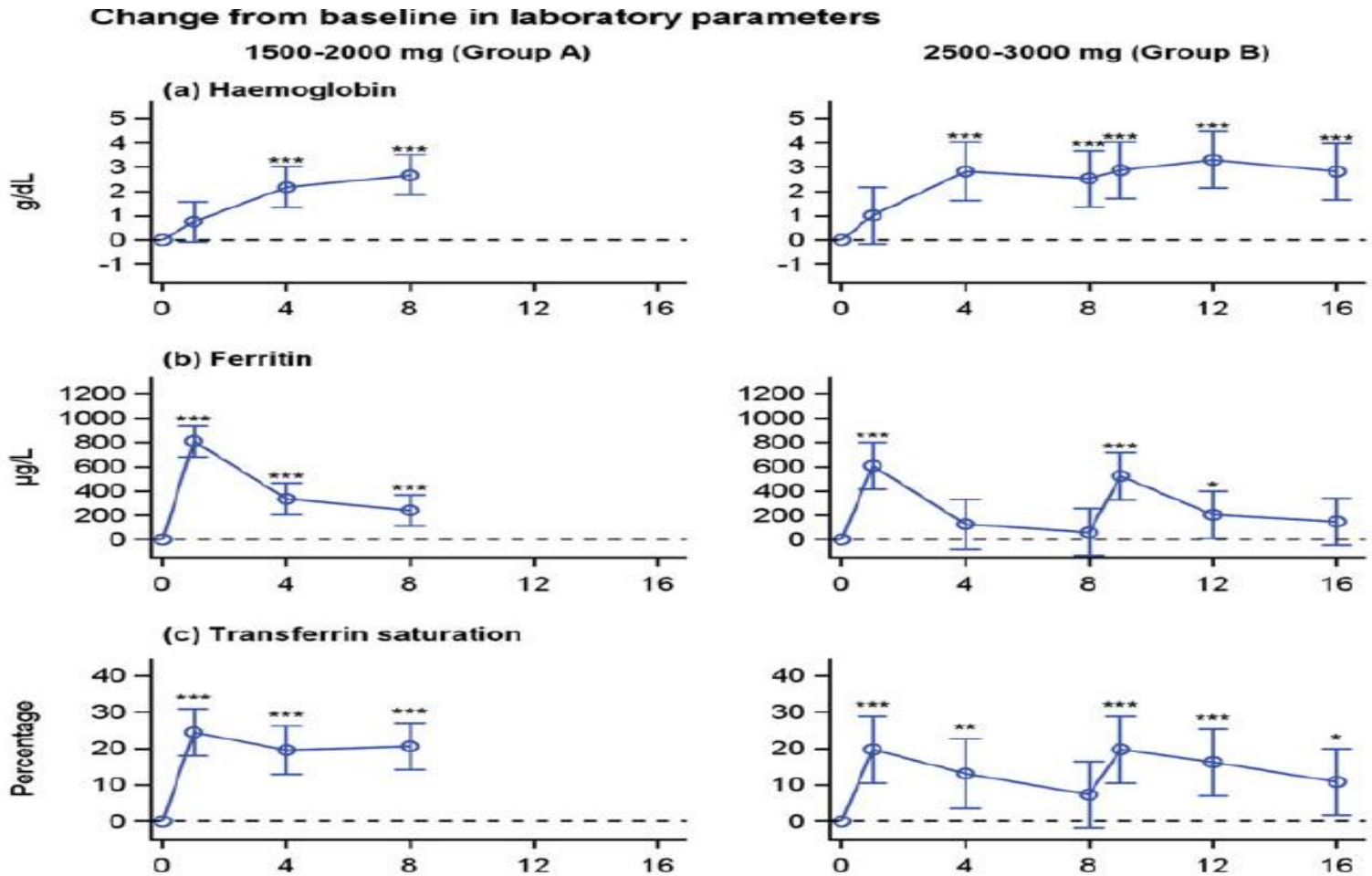
Reinisch W, Altorjay I, Zsigmond F, Primas C, Vogelsang H, Novacek G, Reinisch S, Thomsen LL. A 1-year trial of repeated high-dose intravenous iron isomaltoside 1000 to maintain stable hemoglobin levels in inflammatory bowel disease. Scand J Gastroenterol. 2015;50:1226-33.
Reinisch W, Staun M, Tandon RK, Altorjay I, Thillainayagam AV, Gratzer C, Nijhawan S, Thomsen LL. A randomized, open-label, non-inferiority study of intravenous iron isomaltoside 1,000 (Monofer) compared with oral iron for treatment of anemia in IBD (PROCEED). Am J Gastroenterol. 2013;108:1877-88
Dahlerup JF, Jacobsen BA, van der Woude J, Bark LÅ, Thomsen LL, Lindgren S. High-dose fast infusion of parenteral iron isomaltoside is efficacious in inflammatory bowel disease patients with iron-deficiency anaemia without profound changes in phosphate or fibroblast growth factor 23. Scand J Gastroenterol. 2016 Nov;51(11):1332-8.
Vadhan-Raj S, Ford DC, Dahl NV, Bernard K, Li Z, Allen LF, Strauss WE. Safety and efficacy of ferumoxytol for the episodic treatment of iron deficiency anemia in patients with a history of unsatisfactory oral iron therapy: Results of a phase III, open-label, 6-month extension study. Am J Hematol. 2016;91(2):E3-5.
Ford DC, Dahl NV, Strauss WE, Barish CF, Hetzel DJ, Bernard K, Li Z, Allen LF. Ferumoxytol versus placebo in iron deficiency anemia: efficacy, safety, and quality of life in patients with gastrointestinal disorders. Clin Exp Gastroenterol. 2016;9:151-62
Derman R, Roman E, Modiano MR, Achebe MM, Thomsen LL, Auerbach M. A randomized trial of iron isomaltoside versus iron sucrose in patients with iron deficiency anemia. Am J Hematol. 2017;92:286-291.

High-dose fast infusion of parenteral iron isomaltoside is efficacious in inflammatory bowel disease

Table 1. Intravenous dosing regimen of iron isomaltoside in IBD patients with iron deficiency anaemia.

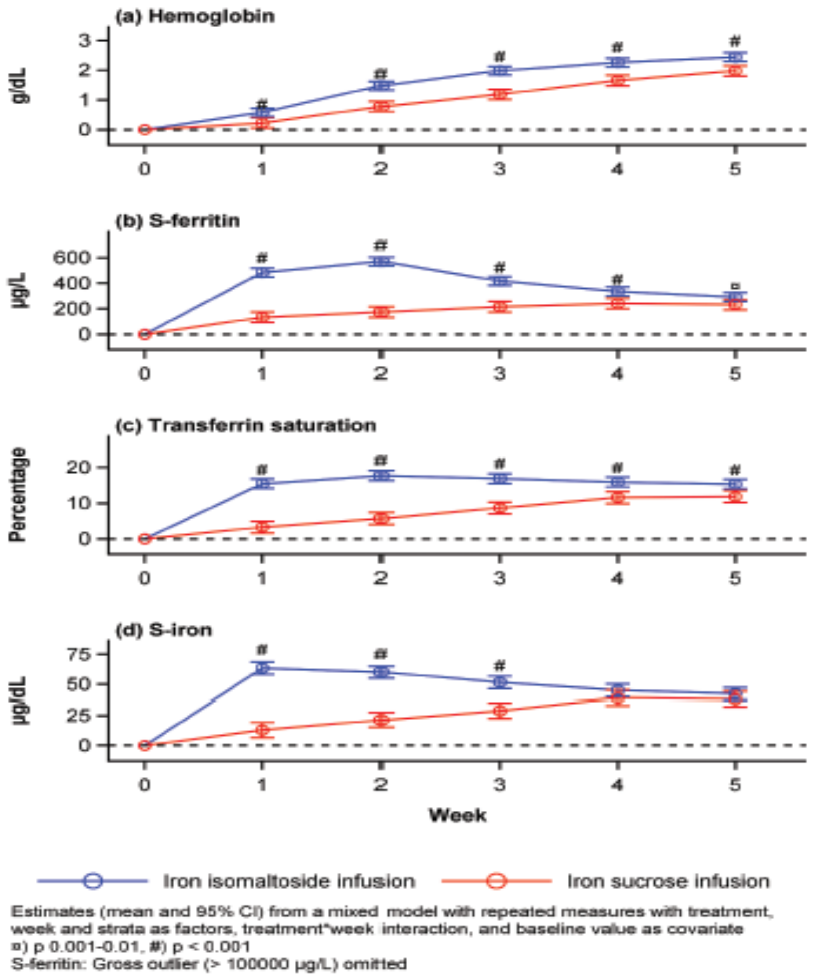
Treatment group	Haemoglobin (Hb)	Iron isomaltoside	
		Body weight <70 kg	Body weight ≥70 kg
A	Women: 10 ≤ Hb <12 g/dL Men: 11 ≤ Hb <13 g/dL	1500 mg	2000 mg[a]
B	Women: Hb <10 g/dL Men: Hb <11 g/dL	2500 mg[b]	3000 mg[b]

[a]Dose administered over one or two visits.
[b]Dose administered over two visits.



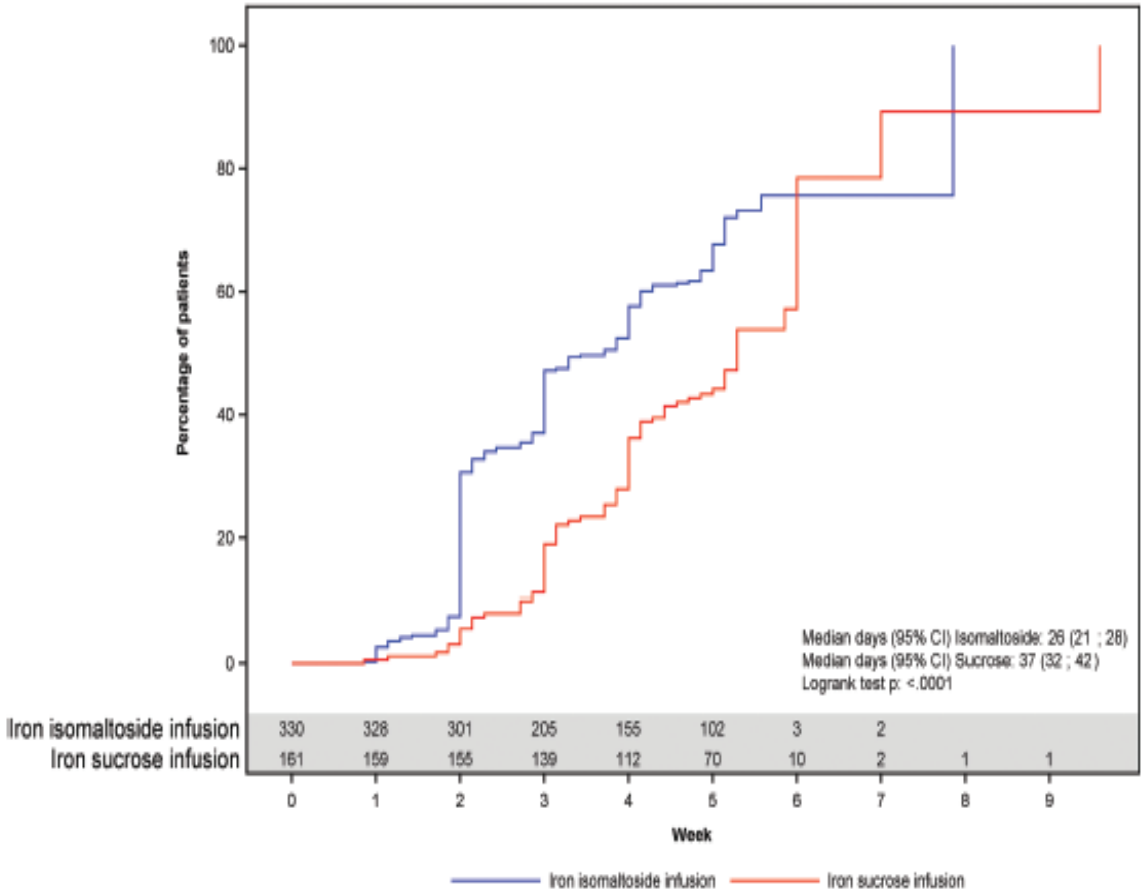
Dahlerup JF, Jacobsen BA, van der Woude J, Bark LÅ, Thomsen LL, Lindgren S. High-dose fast infusion of parenteral iron isomaltoside is efficacious in inflammatory bowel disease patients with iron-deficiency anaemia without profound changes in phosphate or fibroblast growth factor 23. Scand J Gastroenterol. 2016 Nov;51(11):1332-8.

A randomized trial of iron isomaltoside versus iron sucrose in patients with iron deficiency anemia



Estimates (mean and 95% CI) from a mixed model with repeated measures with treatment, week and strata as factors, treatment*week interaction, and baseline value as covariate
¤) p 0.001-0.01, #) p < 0.001
S-ferritin: Gross outlier (> 100000 µg/L) omitted

FIGURE 2 Hemoglobin, *s*-ferritin, transferrin saturation, and *s*-iron over time by treatment group, full analysis set.



Both treatments were well tolerated; 0.6% experienced a serious adverse drug reaction In the iron isomaltoside group, 75 (22.5%) reported 137 ADRs (i.e., treatment-related adverse event), and in the iron sucrose group 29 (17.3%) reported 86 ADRs (p>0.05).. Iron isomaltoside was more effective than iron sucrose in achieving a rapid improvement in Hb. In both treatment groups, the SF-36 scores in the eight health domains as well as for the two composite scores improved from baseline to weeks 2 and 5, and there were no differences between the treatment groups.

The mean cumulative dose of iron isomaltoside was 1640.2 (standard deviation (SD): 357.6) mg and of iron sucrose 1127.9 (SD: 343.3) mg.

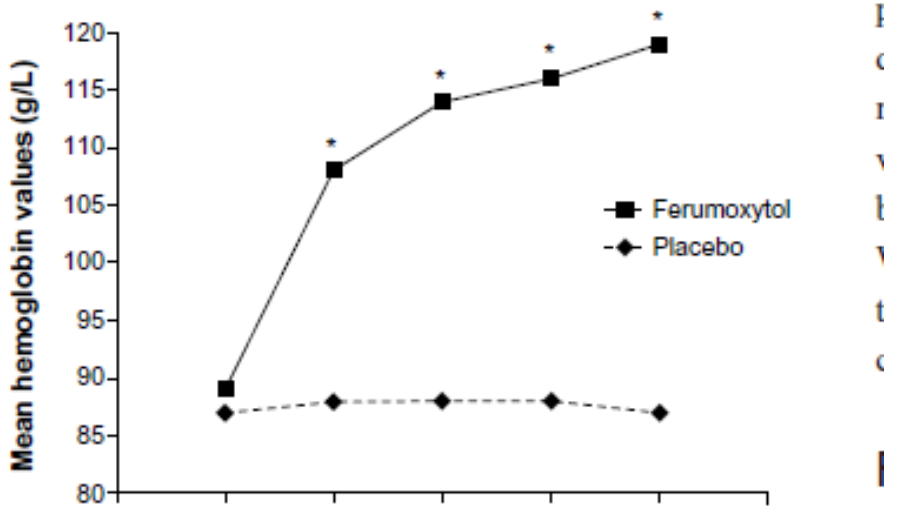
Derman R, Roman E, Modiano MR, Achebe MM, Thomsen LL, Auerbach M. A randomized trial of iron isomaltoside versus iron sucrose in patients with iron deficiency anemia. Am J Hematol. 2017;92:286-291.

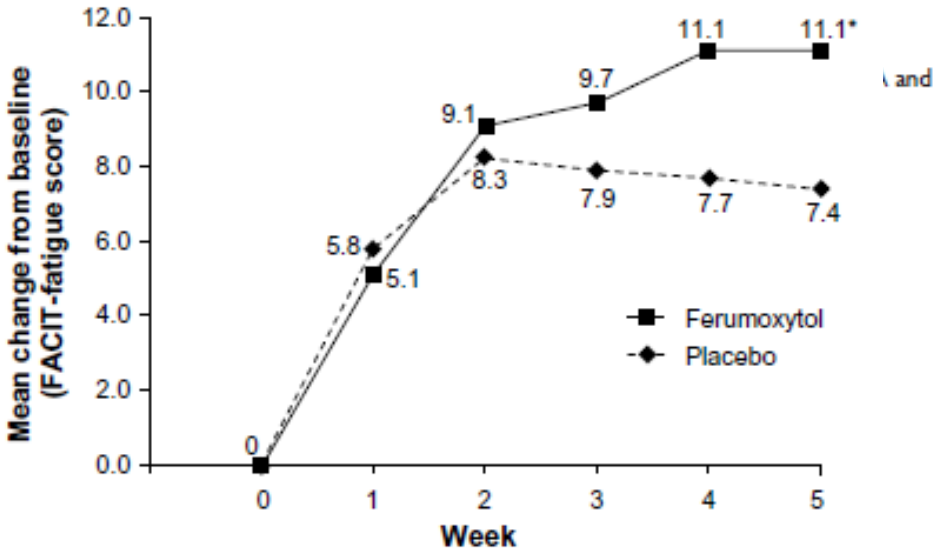
Fe iv en enfermedad inflamatoria intestinal.

Ferumoxytol versus placebo in IDA in patients with gastrointestinal disorders

Table I Baseline characteristics of the subgroup of patients with IDA and GI disorders (intent-to-treat population)

Baseline characteristics	GI disorders subgroup			Overall IDA group
	Ferumoxytol (n=173)	Placebo (n=58)	Total (n=231)	Total (N=808)
Demographics				
Age (years), mean (SD)	47.4 (16.85)	52.1 (15.93)	48.6 (16.72)	45.1 (13.76)
Clinical, mean (SD)				
Baseline Hgb level (g/L)	89 (8.9)	87 (7.3)	88 (8.5)	89 (8.9)
Baseline TSAT (%)	6.5 (12.97)	4.7 (3.53)	6.0 (11.67)	6.6 (11.51)
Baseline FACIT-Fatigue	22.4 (11.7)	22.1 (11.4)		





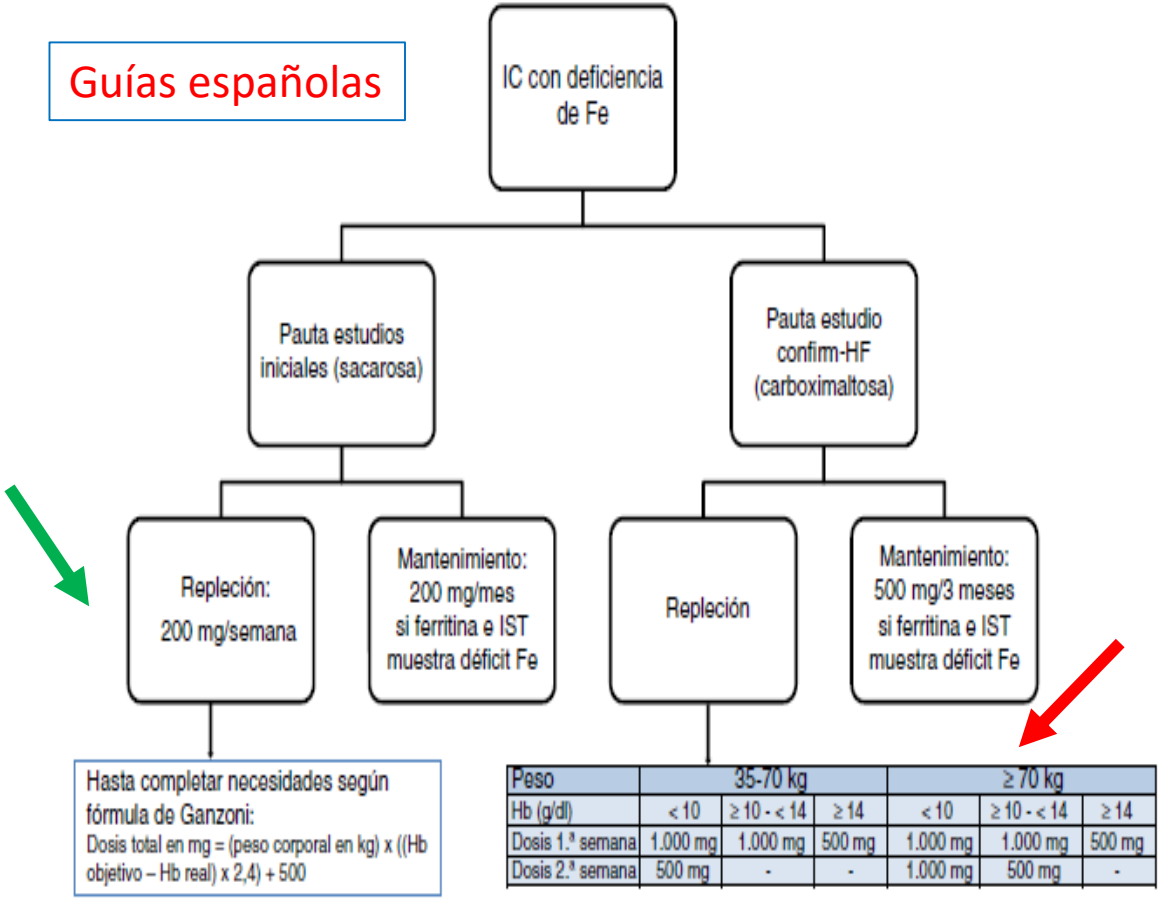
Following a 2-week screening period, patients with IDA were randomized 3:1 to receive a 510 mg dose of ferumoxytol (AMAG Pharmaceuticals, Waltham, MA, USA) (volume: 17 mL) or normal saline placebo at the baseline visit (Day 1), followed by a second dose 2–8 days later (Week 1). Patients were observed weekly until the end of the 5-week treatment period (Weeks 2–5).

Vadhan-Raj S, Ford DC, Dahl NV, Bernard K, Li Z, Allen LF, Strauss WE. Safety and efficacy of ferumoxytol for the episodic treatment of iron deficiency anemia in patients with a history of unsatisfactory oral iron therapy: Results of a phase III, open-label, 6-month exte study. Am J Hematol. 2016;91(2):E3-5.

Ford DC, Dahl NV, Strauss WE, Barish CF, Hetzel DJ, Bernard K, Li Z, Allen LF. Ferumoxytol versus placebo in iron deficiency anemia: efficacy, safety, and quality of life in patients with gastrointestinal disorders. Clin Exp Gastroenterol. 2016;9:151-62

Fe iv en ICC

Guías españolas



Peso	35-70 kg			≥ 70 kg		
Hb (g/dl)	< 10	≥ 10 - < 14	≥ 14	< 10	≥ 10 - < 14	≥ 14
Dosis 1.ª semana	1.000 mg	1.000 mg	500 mg	1.000 mg	1.000 mg	500 mg
Dosis 2.ª semana	500 mg	-	-	1.000 mg	500 mg	-

Figura 3 Opciones de tratamiento en la IC con déficit de hierro.
Fe: hierro; Hb: hemoglobina; IC: insuficiencia cardíaca; IST: índice de saturación de la transferrina.

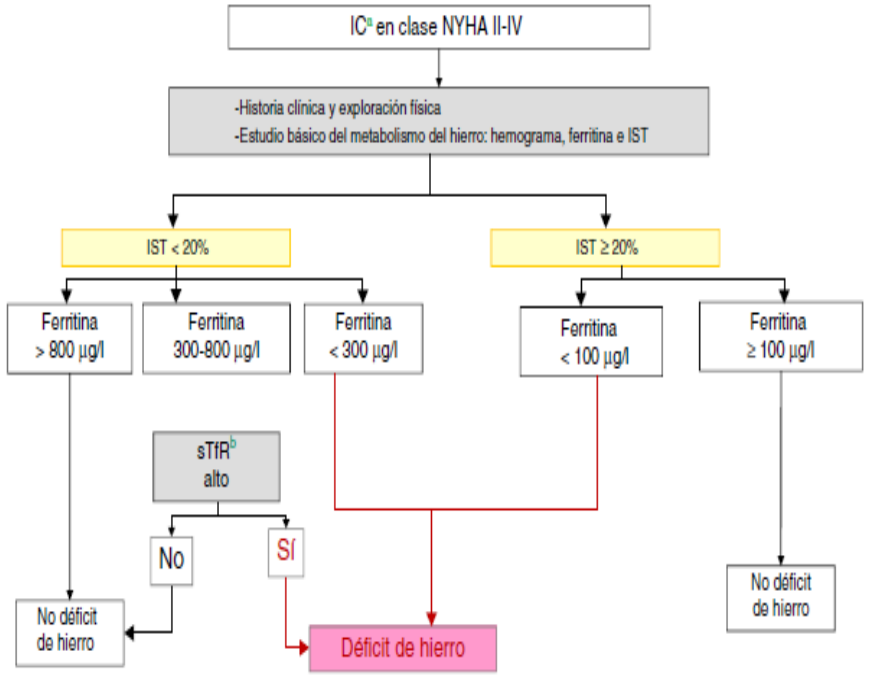


Figura 2 Algoritmo diagnóstico del déficit de hierro en la insuficiencia cardiaca.
IC: insuficiencia cardiaca; IST: índice de saturación de transferrina; sTfR: receptor soluble de transferrina.
[a] Comienzo: seguimiento o descompensación.
[b] En IC aguda con diagnóstico dudoso tras determinación de ferritina e IST podría ser útil la determinación de hepcidina y sTfR.
Fuente: Jankowska et al.[31].

Manito N, Cerqueiro JM, Comín-Colet J, García-Pinilla JM, González-Franco A, Grau-Amorós J, Peraira JR, Manzano L. Consensus Document of the Spanish Society of Cardiology and the Spanish Society of Internal Medicine on the diagnosis and treatment of iron deficiency in heart failure. Rev Clin Esp. 2017;217:35-45

Tim Goodnough L, Comin-Colet J, Leal-Noval S, Ozawa S, Takere J, Henry D, Javidroozi M, Hohmuth B, Bisbe E, Gross I, Shander A. Management of anemia in patients with congestive heart failure. Am J Hematol. 2017 Jan;92(1):88-93.

Puntos clave

- La corrección del DH por sí mismo es un objetivo terapéutico en la IC, aun sin la presencia de anemia.
- El tratamiento del DH está indicado siempre que el paciente presente síntomas (NYHA ≥II) a pesar de la optimización terapéutica de la IC.
- El tratamiento del DH mediante el uso de HCM está recomendado en las guías de práctica clínica de IC del 2016 de la European Society of Cardiology con una recomendación clase IIa, nivel de evidencia A.
- En los pacientes asintomáticos con IC debe considerarse la corrección del DH cuando se asocie a anemia.
- Los pacientes han de encontrarse euvolémicos y con tratamiento médico óptimo antes de evaluar el tratamiento del DH.

- El beneficio del tratamiento del DH solo se ha evidenciado en pacientes con función sistólica deprimida.
- Los enfermos con IC e insuficiencia renal crónica que no estén en diálisis, con cifras bajas de hemoglobina y reingresos por IC se benefician especialmente de la reposición de hierro[64].
- En pacientes con IC y FEVI preservada diversos estudios observacionales sugieren que el impacto del DH en el pronóstico, capacidad funcional y calidad de vida es similar al observado en pacientes con FEVI reducida[43,65,66].
- Según los protocolos de los estudios FAIR-HF[10] y CONFIRM-HF[13], disponemos de dos esquemas de tratamiento del DH (fig. 3): a) 200 mg/semana hasta corregir el déficit calculado por la fórmula de Ganzoni, seguido de 200 mg/mes como mantenimiento[10], o b) 1.000 mg como dosis inicial, más 500 mg a los 7 días en algunos casos según el déficit calculado en la fórmula simplificada, seguidos de 500 mg cada 3 meses[13]. En ambos casos la dosis de mantenimiento se basará en los valores del hemograma y la ferrocinética previos a la nueva dosis.

Manito N, Cerqueiro JM, Comín-Colet J, García-Pinilla JM, González-Franco A, Grau-Amorós J, Peraira JR, Manzano L. Consensus Document of the Spanish Society of Cardiology and the Spanish Society of Internal Medicine on the diagnosis and treatment of iron deficiency in heart failure. Rev Clin Esp. 2017;217:35-45

Metanálisis Fe iv en ICC

Tabla 2 Estudios con preparados de hierro realizados en pacientes con insuficiencia cardiaca y anemia o déficit de hierro

Autor	Tipo estudio	Formulación Fe iv	N.° pacientes		Edad media (años)	FEVI media % (ambos grupos)	Hb media g/dl (ambos grupos)	Semanas tratamiento	Semanas seguimiento	Resultados (Fe iv *vs.* placebo)
			Fe iv	Control placebo						
Bolger 2006[58]	Abierto	Sacarosa	16	–	68 ± 11,5	26	11,2 ± 0,7	1,7	12	↑ Hb a 12,6 ± 1,2 g/dl Mejoría NYHA -14 en el MLFHQ +44 m T6M
Toblli 2007[51]	Doble ciego	Sacarosa	20	20	75 ± 7	31	10,3	5	24	↑ Hb (11,8 *vs.* 9,8 g/dl) ↓ 333,4 pg/ml NT-ProBNP ↓ PCR (2,3 *vs.* 6,5 mg/dl) ↑ FEVI (35,7 *vs.* 28,8%) Mejoría NYHA (2 *vs.* 3,3) ↓ 18 en el MLFHQ +56 m T6M
Okonko 2008[42] (FERRIC-HF)	Ciego simple	Sacarosa	24	11	64 ± 13	30	12,5	16	18	↑ Hb (13 *vs.* 12,6 g/dl) Mejoría NYHA (2,1 *vs.* 2,6) ↑ O2 tisular
Usmanov 2008[67]	Abierto	Sacarosa	32	–	49,4 ± 5,7	32	10,2	26	6 meses	↑ Hb en 3 g/dl Mejoría NYHA si clase III ↑ FEVI si clase III
Anker 2009[10] (FAIR-HF)	Doble ciego	Carboximaltosa	304	155	68	32	11,9	24	-	↑ Hb (13 *vs.* 12,5 g/dl) +7 en el KCCQ +35 ± 8 m Test 6 min.
Ponikowski 2014[13] (CONFIRM-HF)	Doble ciego	Carboximaltosa	152	152	69	36,5	12,4	24		Mejoría NYHA +33 m Test 6 min. −0,6 escala disnea +1,3 en el KCCQ +2,8 en EQ-5D
								52		+36 m T6M -0,7 Escala disnea +4,5 en KCCQ +2,6 en EQ-5D

EQ-5D: EuroQoL-5D Health Questionnaire; Fe iv: hierro intravenoso; FEVI: fracción eyección ventrículo izquierdo; Hb: hemoglobina; KCCQ: Kansas City Cardiomyopathy Questionnaire; MLFHQ: Minnesota Living With Heart Failure Questionnaire; NT-ProBNP: propéptido natriurético cerebral N-terminal; NYHA: New York Heart Association; PCR: proteína C reactiva; T6M: test de 6 min.

No estudia la sobrecarga férrica.

Jankowska EA, Tkaczyszyn M, Suchocki T, Drozd M, von Haehling S, Doehner W, Banasiak W, Filippatos G, Anker SD, Ponikowski P. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. Eur J Heart Fail. 2016 Jul;18(7):786-95

Table 1. Baseline Demographic and Clinical Characteristics of the Study Patients in the Intention-to-Treat Population, According to Study Group.*

Laboratory measurements		
Hemoglobin — g/liter	119±13	119±14
Mean corpuscular volume — μm^3	91.6±8.1	91.7±6.7
Serum ferritin — μg/liter	52.5±54.5	60.1±66.5
Transferrin saturation — %§	17.7±12.6	16.7±8.4
C-reactive protein — mg/liter	7.46±5.34	9.12±5.48
Sodium — mmol/liter	141±3	141±3
Potassium — mmol/liter	4.65±0.61	4.58±0.52
Alanine aminotransferase — U/liter	20.5±12.3	18.8±8.1
Aspartate aminotransferase — U/liter	23.1±10.4	22.4±7.2
Creatinine — mg/dl	1.2±0.6	1.2±0.6
Estimated glomerular filtration rate — ml/min/1.73 m^2 of body-surface area¶	63.8±21.2	64.8±25.3

Table 3. Levels of Iron-Metabolism Markers and Hemoglobin at Week 24 According to Study Treatment.*

Variable	Ferric Carboxymaltose (N=305)	Placebo (N=154)	P Value
All patients			
Ferritin (μg/liter)	312±13	74±8	<0.001
Transferrin saturation (%)†	29±1	19±1	<0.001
Hemoglobin (g/liter)	130±1	125±1	<0.001
Mean corpuscular volume (μm^3)	97±0	94±1	<0.001
Patients with anemia (hemoglobin ≤120 g/liter)			
Ferritin (μg/liter)	275±18	68±11	<0.001
Transferrin saturation (%)†	29±1	17±1	<0.001
Hemoglobin (g/liter)	127±1	118±2	<0.001
Mean corpuscular volume (μm^3)	98±1	93±1	<0.001
Patients without anemia (hemoglobin >120 g/liter)			
Ferritin (μg/liter)	349±19	80±11	<0.001
Transferrin saturation (%)†	30±1	22±1	<0.001
Hemoglobin (g/liter)	133±1	132±1	0.21
Mean corpuscular volume (μm^3)	96±1	95±1	0.91

* Plus–minus values are means ±SE. The P value is for the mean treatment effect, adjusted for the baseline value. One patient who had been randomly assigned to the placebo group received ferric carboxymaltose.
† The percent transferrin saturation was calculated as iron (in micromoles per liter) ÷ transferrin (in grams per liter) × 25.1.

Riesgo de SF, si repetidas infusiones a dosis totales

Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Lüscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, von Eisenhart Rothe B, Pocock SJ, Poole-Wilson PA, Ponikowski P; FAIR-HF Trial Investigators.. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med. 2009;361:2436-48.

Conclusiones

- Hierro endovenoso es el presente
- Terapia en ascenso, recomendada cada día en más condiciones.

- Reacciones relacionadas con la infusión raras.

- Problema emergente; Sobrecarga férrica
- IR problema actual.
- Candidatos: ICC ?
- Hematología: Uso racional y no descontrolado (dosis altas)

Manejo de las reacciones de hipersensibilidad en drogas iv, incluido el Fe iv.

	Symptoms	Treatment options
Mild HSRs	Itching, urticaria, flushing, sensation of heat, slight chest tightness, hypertension and back/joint pains	Stop infusion temporarily and watch symptoms and signs. If symptoms improve the infusion can be restarted cautiously.
Moderate HSRs	As in mild reaction + cough, chest tightness, nausea, shortness of breath, tachycardia and hypotension	Stop infusion and consider IV-fluids and IV-corticosteroids.
Severe HSRs = life-threatening anaphylaxis	As in moderate + sudden onset and rapid aggravation of symptoms + wheezing, stridor, periorbital oedema, cyanosis, loss of consciousness and cardiac/respiratory arrest	As for moderate HSRs + IM or IV adrenaline (epinephrine) + consider β_2-adrenoceptor agonist inhaler, O_2 by facemask, act according to local standard anaphylaxis guidelines.

Rampton G, Folkersen J, Fishbane S, Hedenus M, Howaldt S, Locatelli F et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimisation and management. Haematologica 2014; 99: 1671–1676.

KDIGO: Recomendaciones prácticas en las reacciones por Fe iv.

Table 3 | Practical tips for management of hypersensitivity reactions to i.v. iron

- The first dose (either in a CKD or dialysis setting) should be administered in a clinical facility.
- Although total-dose iron infusions have not been demonstrated to have significant risk,[119] i.v. doses of iron gluconate or iron sucrose should not exceed 125 or 200 mg/dialysis, respectively, because of the potential risk for iron not binding immediately to transferrin and resulting in a reaction due to labile iron.
- There is no physiological basis to recommend that patients should be observed for 30 minutes after an infusion of iron is completed, since i.v. iron delivery should not be associated with a severe delayed reaction (as is observed with subcutaneous antigen presentation in vaccination or allergen immune therapy).
- There is no evidence that pretreatment with corticosteroids or antihistamines (H_1 channel blockers) reduces the risk of severe reactions to i.v. iron. Paradoxically, i.v. antihistamines may be associated with unwanted side effects, particularly drowsiness or flushing upon rapid infusion.[120] Hence no pretreatment with corticosteroids or antihistamines is recommended in patients identified as being at potential risk of a hypersensitivity reaction. Desensitization protocols to limit hypersensitivity reactions are not established and, therefore, not recommended.
- Jurisdictional requirements regarding the use of i.v. iron vary and thus, should be followed closely. For example, in 2013 the EMA made recommendations following reports of several hypersensitivity reactions in 3 pregnant women receiving low–molecular weight iron dextran compounds,[121] all of whom made a complete recovery. The recommendations were extrapolated to all patient groups receiving any i.v. iron compounds. This conference agreed with the current position of the EMA that all i.v. iron preparations can rarely cause hypersensitivity reactions, though the total number of life-threatening reports is low. Although the data show a clear association of iron medications and hypersensitivity reactions, the data cannot be used to detect differences in the safety profiles of different formulations. The attendees concurred that i.v. iron should not be administered in the first trimester of pregnancy. It was also agreed that a test dose was not useful in any circumstance to predict the risk of hypersensitivity to i.v. iron.

CKD, chronic kidney disease; EMA, European Medicines Agency.

Macdougall IC, Bircher AJ, Eckardt KU, Obrador GT, Pollock CA, Stenvinkel P, Swinkels DW, Wanner C, Weiss G, Chertow GM; for Conference Participants. Iron management in chronic kidney disease: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference. Kidney International 2016; 89: 28–39.