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REVIEW

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Intravenous Iron-Carbohydrate Nanoparticles and Their Similars. What Do We Choose?

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ABSTRACT

Anemia is highly prevalent worldwide and iron deficiency is the first cause. Iron deficiency has not only hematologic effects but also non-hematologic effects – immune, metabolic, cognitive dysfunctions and poor cardiovascular and renal outcomes – which generally precede anemia. Iron therapy not only significantly improves the hematological parameters but also has non-hematologic benefits. Given that its efficacy and safety has been revealed over the years, intravenous (IV) iron therapy is frequently used.

Intravenous iron products are nanoparticles largely consisting in an iron core surrounded by a carbohydrate shell. They are classified as non-biological complex molecules, being different from small commonly used molecules, with properties and biological behavior impossible to be completely characterized only by physicochemical analysis.

To date, there is no appropriate regulatory evaluation system for these medicines and several follow-on versions of the IV iron originators (e.g., iron sucrose) were approved using the same regulatory pathway as for generics. Because of this vulnerability in an adequate pathway for approval, both non-clinical and clinical studies suggested no therapeutic equivalence (thus no interchangeability) between iron sucrose originator (Venofer®), and iron sucrose similars.

In this review we aimed to underline the importance of intravenous iron therapy as well as raise awareness regarding the differences between nanomedicines and their intended similar but not identical copies. The potential implications of these differences impact patients (safety, efficacy) but also the medical system (higher costs).

Keywords: anemia, intravenous iron, nanoparticles, nanosimilar.

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INTRODUCTION

Anemia has a high prevalence globally (22.8% in 2019), despite a decreasing trend over the last 20 years (1). Women and children under five years of age are most frequently affected. Iron deficiency is its first cause, in both low and high income countries (2). Even in the absence of anemia, iron deficiency is commonly seen among children, women of childbearing age and patients with chronic kidney disease (CKD), heart failure (HF), neoplasia or inflammatory bowel disease (IBD) (3).

Not only iron deficient anemia (IDA) but also iron deficiency (ID) is associated with metabolic, immune, thyroid and cognitive function impairment, pregnancy complications, HF and ischemic heart disease exacerbations, kidney and cardiovascular poor outcomes (3, 4).

Moreover, it was showed that iron therapy non-hematological effects – on fatigue, restless legs syndrome, cognitive functions, exercise capacity, functional status and quality of life in HF, CV risk in HF and CKD – exceeded the effect on erythropoiesis (5-7). Intravenous (IV) iron therapy is the preferred option when oral iron therapy is not tolerated or ineffective, or when rapid correction is required.

Intravenous iron preparations are nanomedicines containing a polynuclear iron(III)-oxyhydroxide core stabilized in a carbohydrate shell (8). Numerous formulations are available, with different complex structures, both in the core and shell. The fate of the nanoparticle in the biological environment depends not only on the size of the nanoparticle, the nature of the core size or the characteristics of the shell, but essentially also on the manufacturing process (9). Any subtle change in this unique process can affect the stability of these complex drugs (10). For some of these products, follow-on versions are approved. However, there are plenty of data not supporting the interchangeability and substitutability between original nanomedicines and their similars, with both clinical safety and efficacy repercussions (9).

In this review we aim to emphasize the multidimensional impact of ID and IDA as well as the significance of iron therapy. At the same time, we intend to raise awareness about the concept of nanomedicines, focusing on IV iron products, highlighting the distinction between them and the small molecular drugs, and accentuating the complexity of their manufacturing process, which seems impossible to replicate.

Why is intravenous iron therapy needed?

Non-CKD patients. Importance and clinical impact of ID and IDA. Efficacy and safety of IV iron therapy

Pregnancy

In pregnancy, anemia has a prevalence of almost 50%, with ID being the most common cause, as the iron requirements gradually increase, unfulfilled by the usual diet intake. Iron deficiency anemia is associated with maternal and fetal morbidity both on short- and long-term (preterm birth, low-birth-weight, maternal and child mortality, altered mother-child interactions, development impairment in infants) (11, 12). Because its correction alleviates some of these outcomes (13, 14), many authorities recommend routine iron supplementation in pregnancy (15).

Generally, oral iron therapy is the first line reserved in early pregnancy, while IV iron therapy is recommended after the 13th week (16). Still, comparing oral with IV iron therapy efficacy in pregnancy, a meta-analysis including 11 randomized controlled trials (RCTs) – nine with iron sucrose (IS), one with iron carboxymaltose (FCM) and one with low molecular weight iron dextran – reported superiority of IV iron and lesser adverse effects (17).

However, few data are available regarding comparison between IV iron formulations in treating IDA of pregnancy. The possibility to administer a larger amount of iron at a time gives an advantage to FCM. In this respect, recently published data reported that FCM was not only safe and non-inferior to IS (the most used and studied IV iron product), but also lead to an earlier rise in hemoglobin level and a reduced total cost (as higher amount of iron can be delivered at once, there were fewer visits and equipment used, and less discomfort for the patients) (18).

Children

Up to 42% of children under five years of age are anemic worldwide (19), with an even higher prevalence being noted in Africa (63%) (20).

In Europe, the prevalence of ID in infants (6-12 months) was reported between 2–25% (more frequent in those who were socially vul-

TABLE 1. Benefits of iron therapy in different conditions

	Condition	Benefit		Efficacy IV *vs.* oral therapy
		ID	IDA	
Pregnancy	Preterm birth	+(13, 14)	+(26)	
	Low-birth weight	+(13, 14)		
	Preeclampsia		+(26)	
Children	Cognitive impairment	+(27)	+(27)	
	Attention and concentration	+(28)	+(28)	
	ADHD	+(23-25)		
	Restless leg syndrome	+(23-25)		
Heart failure	LVEF	+(29)	+(29)	IV superior (30)
	NYHA functional class	+(29)	+(29)	
	Quality of life	+(29)	+(29)	
IBD	Quality of life		+(31)	IV superior (32)
Oncology	Quality of life	+(33)	+(33)	
Planed surgery	Need for transfusion		+(34)	IV superior (34)
	Short-term mortality		+(35)	
	Postoperative infections		+(36)	

ADHD=attention-deficit/hyperactivity disorder; ID=iron deficiency; IBD=inflammatory bowel disease; IDA=iron deficiency anemia; IV=intravenous; LVEF=left ventricular ejection function.

nerable or fed with milk cow) and between 3% to 48% in older children (12-36 months). In both groups of age, a higher prevalence of IDA was noted in Eastern comparing to Western Europe (50% *versus* 5%) (21). In children, both ID and IDA are associated with altered behavior, impaired neurocognitive development and growth, and reduced immune function (22). Moreover, ID was related with the restless leg syndrome, attention deficit hyperactivity disorder and febrile seizures, all of which reflecting an altered brain excitability probably enhanced by ID (23-25).

Oral iron therapy is generally used in children with IDA, IV iron being often limited to children with chronic conditions such as CKD or IBD. Iron sucrose was the first choice because of its higher availability and better safety profile. In addition to efficacy in correcting ID and IDA, IS also improved fatigue and quality of life in non-anemic ID deficient menstruating adolescent females (37). Still, the low dose that can be safely administered one time makes IS therapy more inconvenient and has a higher total cost. Other IV products approved for children are ferric gluconate (used in children with CKD on hemodialysis) and low-molecular weight iron dextran (test dose needed) (38, 39). Ferric carboxymaltose was recently approved for children aged one year or older suffering from IDA with intolerance or inadequate response to oral iron. It is safe and highly effective in children with diverse ages and ID etiologies (gastrointestinal disorders, nutritional IDA) (40).

Heart failure

Iron deficiency is found in as much as 55% of HF patients, regardless of the presence of anemia. The prevalence of ID is higher with worsening NYHA functional class (41). Numerous studies showed that ID was associated with fatigue, lower exercise capacity, impaired quality of life, higher rates of hospitalization and higher mortality, regardless of the presence of anemia (42-44).

Data about iron oral supplementation on clinically significant outcomes in HF patients with ID are limited, suggesting a lower efficacy (30). Meanwhile, there are numerous studies supporting the superiority of IV iron therapy. To date, there are seven published RCTs investiga-

ting IV iron in HF (five in HF with reduced ejection fraction and two in acute HF) (29). Iron sucrose was safely used in two of the HF with reduced ejection fraction (HFrEF) studies, lowering the NT-proBNP level, improving left ventricular ejection function, NYHA functional class, exercise capacity and quality of life (45, 46). Ferric carboxymaltose was safely used in three of the HFrEF studies, with improvement of patient global assessment, NYHA functional class, six-minute walk test, quality of life (47, 48) and functional capacity (49). Moreover, in acute HF, FCM was safely administrated, reduced the risk of HF-related hospitalizations (50) and improved functional capacity compared to placebo (51). There are ongoing studies exploring IV iron therapy in HF with preserved ejection fraction and assessing the benefit of other IV iron products (iron (III) isomaltoside) (52).

Inflammatory bowel diseases

Anemia is one of the most frequent extraintestinal manifestation of inflammatory bowel diseases (IBD). Its prevalence was reported to vary between 10.2-72.7% in Crohn's disease and 8.8-66.6% in ulcerative colitis (53), being more frequent in children than adults (54). The etiology is multifactorial, but IDA is the first cause and it is resulting not only from chronic gastrointestinal blood loss, but also from a limited iron bioavailability (poor oral intake, reduced iron absorption because of mucosal inflammation involving small bowel, especially in Crohn's disease) (53). Chronic fatigue secondary to IDA had a significant impact on IBD patients' quality of life, similar to other symptoms such as abdominal pain or diarrhea (31).

Oral iron therapy was the first line in the management of ID and IDA in IBD, but gastrointestinal effects and an enhanced intestinal inflammation supported the use of IV iron therapy (55, 56). Data on both IS and FCM shows safety and efficacy (55). Furthermore, FCM was superior to IS in correcting anemia and also overall less expensive (real data, not estimations) (57). Additionally, recent data from IBD and IDA children who received IV iron (IS or FCM) showed similar profiles of safety and efficacy to adults, pointing to the same advantage of FCM regarding dosing schedule (58). Also, it seems that correcting IDA has a favorable impact on the quality of life in IBD patients, similar to controlling diarrhea (31). Regarding other IV iron formulations used in IBD ID or IDA data are sparse (55).

Oncology

Over half of oncologic patients have anemia, with a prevalence reaching 90% after chemotherapy (59, 60), and ID is reported in up to 60%; the etiology is multifactorial, depending on the tumor location and stage, and on the chosen threshold (61). Apart from the association of anemia with physical function impairment and poorer quality of life, data also suggest a reduced response to cancer therapy and an overall survival (62).

Oral therapy was insufficient to overcome iron-restricted erythropoiesis in cancer patients with chemotherapy-related anemia receiving ESA, as compared to IV iron therapy (63). Conversely, IV iron therapy was clinically successful in ID patients with or without anemia, improving their quality of life and functional capacities on both the short- and long-term (33). Moreover, IV iron therapy improves the response to ESA and reduces both ESA doses and the need of red blood cells transfusions in anemic patients with lymphoproliferative malignancies (64).

Planed surgery

The prevalence of pre-operative anemia is up to 75%, depending on age, gender (higher in women), comorbidities, type of surgery (highest in gynecologic surgery, colorectal cancer resection, cardiac surgery, liver metastasis resections and orthopedic surgery) and the cut-off used for the definition (65). Iron deficiency is the leading cause (66). Preoperative anemia is associated with poor postoperative outcomes (nosocomial infections, prolonged hospitalization, more intensive care admissions, mortality) (65, 66).

Oral iron therapy may be considered when usually there are more than six weeks until surgery (67). Still, in case of intolerance or poor response to oral iron, or if surgery is an emergency, IV iron therapy is the first choice. Intravenous iron therapy was found superior to oral therapy in both decreasing the need of blood transfusions and improving hematologic parameters in perioperative anemia in cardiac surgery (34). Meanwhile, in patients with anemia who received normal saline *versus* 1000 mg ferric carboxymaltose 10-42 days prior to elective major abdominal surgery, there was no advantage from

iron therapy before the operation (68). Conversely, IV iron therapy for postoperative IDA improved the scores of usual activities (orthopedic surgery) (69) as well as the quality of life (post-partum) (70). Moreover, IV postoperative iron therapy reduced the short-term mortality risk in older patients with IDA undergoing hip fracture surgery (35). Similar benefits on short-term (30 days) mortality but also on postoperative infections were reported in acute major non-cardiac surgery (36).

Chronic kidney disease patients. Importance and clinical impact of ID and IDA. Efficacy and safety of IV iron therapy

Chronic kidney disease is a global public health problem with a prevalence of 10-15%. Anemia is one of the most common complications in CKD. Its prevalence is higher as kidney function declines (from 14.9% in CKD stage 1 to 60.6% in CKD stage 5), being even more pronounced in patients with an increasing level of proteinuria and those with diabetes (71). Iron deficiency is the main mechanism involved even in non-dialysis CKD patients (72).

There is an abundance of data about the clinical impact of anemia in CKD. Not only the quality of life is affected, but also CKD progression and incidence of major CV events and mortality, which were the adverse outcomes associated with anemia (73). Yet, information regarding the impact of ID on clinical outcomes in CKD is limited. Still, there are some recently reported data that revealed an association between ID and lower physical health-related quality of life (74). Also, ID predicted all-cause mortality in non-dialysis CKD patients (75). The KDIGO guidelines recommendations for the management of anemia in CKD included iron supplementation for correcting IDA targeting the rise of hemoglobin and reduction of ESA doses (76). However, recent evidence revealed that IV iron administered proactively was clinically beneficial for hemodialysis CKD patients and this advantage seems to be due to ID correction, hence the non-hematological mechanisms (77).

Non-dialysis CKD patients

Oral iron therapy might be an option for non-dialysis CKD patients who can tolerate it and have no substantial iron-restricted erythropoiesis. However, the results of the largest study comparing oral iron with IV iron therapy in non-dialysis CKD patients with IDA showed the superiority of IV iron therapy in reaching and maintaining hemoglobin levels and a reduced need of ESA. Moreover, neither increased nephrotoxicity nor higher rates of infectious or cardiovascular events were observed in patients receiving IV iron therapy (78). Additionally, CKD-subgroup analyses from clinical trials in HF ID-patients showed similar benefits on clinical outcomes of IV iron therapy as in those without CKD in both acute and chronic HF (47, 48, 50). Even if evidence of functional benefits of IV iron in ID CKD patients without anemia is lacking, recent data showed a trend towards an improved quality of life (79).

Dialysis CKD patients

Intravenous iron therapy has become part of the standard care of anemia in CKD patients on maintenance HD (76). A high number of controlled studies sustain the superiority of IV *versus* oral iron therapy in increasing hemoglobin and reducing ESA doses in both HD and peritoneal dialysis, with IS being the most studied (80).

Still, recent data from the largest randomized prospective study (Proactive IV Iron Therapy in Hemodialysis Patients, PIVOTAL) assessing the impact of different dosing regimens (proactive as "high dose" and reactive as "low dose") of IV iron (IS) on clinical outcomes in HD patients revealed more than the improvement in anemia management with the proactive approach (77). The novelty was that there was a lower rate of recurrent hospitalizations for HF and a reduced proportion of myocardial infarctions (fatal and non-fatal) in the "proactive" regimen arm (81). Thus, the non-hematological effects of iron therapy also exist in CKD patients on dialysis.

Moreover, similar to other reported data from a recent meta-analysis (82), both "proactive" and "reactive" regimes exhibited comparable infection rates, indicating the safety of IV iron in dialysis patients (83).

Why is it essential to choose the best suitable product of IV iron?

Intravenous iron molecule structure and properties

Intravenous iron formulations are medicines produced using nanomaterials and nanotechnology

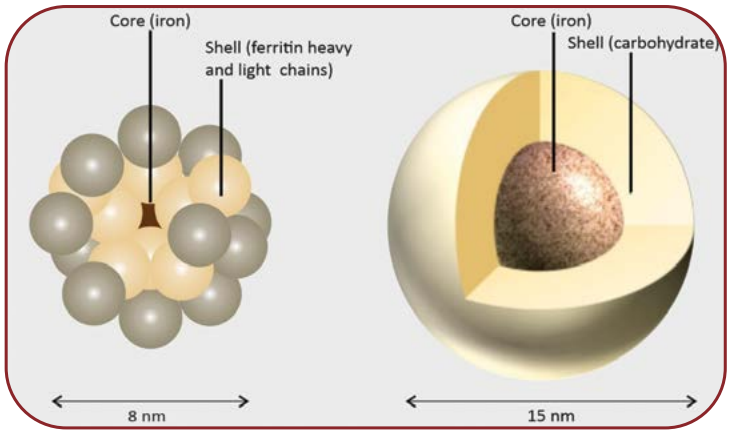

FIGURE 1. Serum ferritin and iron-carbohydrate complexes have similar structure [adapted from (86)]

(nanomedicines or nanodrugs). They are created as colloidal dispersions consisting of a core of polynuclear Fe(III)-oxyhdroxide surrounded by a carbohydrate shell. The reason is that ferric iron salts are unstable in an aqueous solution at a pH over 3 and the association with a carbohydrate ligand increases the stability of the complex and prevents polynuclearization and precicpitation of the nanoparticle (84). Furthermore, the design of the iron-carbohydrate complex intends to avoid a too fast release of iron (thus a high amount of labile iron) in circulation. Thus, existent IV iron-carbohydrate complexes are designed similar to serum ferritin which securely stores and releases iron when as necessary (85), with the protein ligand being replaced by a carbohydrate to avoid anaphylactic reactions (Figure 1). Over the last 90 years, numerous IV iron formulations were developed with the main purpose to improve safety, efficacy and to increase the amount of administered iron. The innovation primarily targeted the surface features of the carbohydrate shell (85).

Currently, the main IV iron products available on the market (in order of the year of market entry) include IS, sodium ferric gluconate, low molecular weight iron dextran, iron isomaltoside, FCM and ferumoxytol (Table 2). They have different kinetic profiles and different thermodynamic properties as they vary in shape and size, molecular weight, structure, surface characteristics, total iron content, iron core crystal structure and reactivity (85).

Their carbohydrate ligands are complex and structurally heterogeneous. Depending on the carbohydrate shell, influences are seen on the stability of the polymeric iron complex but also on the pharmacokinetics, immunogenicity and reactivity of the nanoparticle *in vivo* (87). Smaller nanoparticles, such as IS and sodium ferric gluconate that keeps elemental iron less tightly, are associated with higher amounts of labile iron released than low molecular weight iron dextran, FCM, ferumoxytol or iron isomaltoside (88).

After parenteral administration, iron nanoparticles interact with the innate immune system. The rates and extent of uptake by macrophages and the rate of biodegradation are also operated by the surface of the entire nanoparticle upon the carbohydrate shell characteristics (89).

In terms of efficacy or safety, there are no significant differences between the main currently

TABLE 2.
Intravenous iron formulations [adapted from (85)]

	Iron sucrose	**Iron gluconate**	**LMWID**	**Iron isomaltoside**	**FCM**	**Ferumoxytol**
Brand name	Venofer®	Ferrlecit®	Cosmofer®	Monofer®	Ferinject® Injectafer®	FeraHeme®
Carbohydrate shell	Sucrose	Gluconate and sucrose	Dextran	Isomaltoside	Carboxymaltose	Polyglucose sorbitol
Molecular weight (kDa)	34-60	37.5	165	69	150	185
Plasma half-life (h)	6	1	30	20	7-12	15
Iron content (mg/mL)	20	12.5	50	100	50	30
Maximal single dose (mg)	300	125	20 mg/kg BW	20 mg/kg BW	20 mg/kg BW	510
LMWID=low molecular weight iron dextran; IS=iron sucrose; FCM=ferric carboxymaltose; BW=body weight.						

used IV iron formulations (90) (data from clinical perspective presented above).

Manufacturing process and post-manufacturing issues

Intravenous iron formulations have been recently included in the category of medicinal products named non-biological complex drugs (NBCD), as they share similarity with biologics regarding molecular complexity and inability to be fully characterized (91).

A standardized manufacturing process of these unique nanomedicines is crucial to prevent different toxicities in different batches. Likewise, it was demonstrated that a subtle change in either the alkali or carbohydrate content, or the pH of the precipitation point determines different safety profiles even in otherwise identical manufacturing conditions (92).

The safety and stability of different IV iron nanoparticles might be affected not only by the production process but also by storage, transportation, handling and even the clinical way of application (type, speed, dosage, number of IV administrations) (86).

The NBCD manufacturing process starts by producing the iron core through the reaction of water-soluble iron (III) salts with a weak base and precipitation of iron (III)-oxyhydroxide cores in the reaction mixture. Thereafter, the cores can react with the carbohydrate solution under very strict conditions. Once synthetized, the product is isolated and then purified by different processes (filtration, centrifugation, distillation or lyophilization) (93). Any fine variation in this process affects the physicochemical properties of the molecule, which in turn influences the stability, iron release rate, extent of cellular uptake and tissue distribution, hence the safety and efficacy of the final product (94).

Autoclaving conditions and the primary packaging material can also impact the safety and efficacy of IV iron complexes (86).

Furthermore, transport and storage are other links in the chain that can affect the final products, since nanomedicines are susceptible to change in their physicochemical features and also to accelerated aging when stored under improper conditions (95).

Lastly, the way these products are handled (how is the product diluted and which is the diluting agent) is also of great importance as it can destabilize the carbohydrate shell, thus releasing a high amount of labile iron, which can increase the rate of adverse effects (91).

Challenges in characterization of IV iron nanoparticles

Non-biological complex molecules should be analyzed physiochemically, biologically and clinically.

The physicochemical assessment consists of examination of size (dynamic light scattering, transmission electron microscopy, atomic force microscopy), iron core crystallinity (X-ray diffraction, Fourier-transform infrared spectroscopy and Mössbauer spectroscopy), molecular weight (gel permeation chromatography), colloidal nature (lyophilic or lyophobic), amount of labile iron (bleomycin and ferrozine assays), iron content, viscosity and surface charge (96). However, only few of these characteristics are available from published data for all IV iron formulations, of which only iron sucrose is broadly described (86).

The biological evaluation of NBCD includes in vitro and in vivo studies to check for uptake mechanism, toxicity and efficacy. In contrast with classical medicines, nanoparticles have a different biological behavior, which is difficult to describe using chemical concepts alone (97). There are notable differences between IV iron products in this regard (86).

Finally, to avoid any significant differences with clinical impact that were not detected in the anterior steps, clinical trials must be performed. Unfortunately, for the majority of IV nanoparticles, these clinical trials have a short duration.

Challenges in authorization of IV iron nanosimilars

Generally, after the patent of a common drug expires and the therapeutic equivalence with the original product is established, generic products (a termed used for describing follow-on version of small classical molecules) receive marketing authorizations.

Conversely, for complex molecules like biologics, therapeutic equivalence is difficult to demonstrate and Food and Drug Administration (FDA) usually implements a weight-of-evidence approach, through a case-by-case tactic (98). On the other side, the European Medicines Agency (EMA) gives authorization for a follow-on pro-

	Common drugs	Biologics	Non-biologic complex drugs
Examples	Reducing blood pressure drugs NSAIDs	ESA	Iron-carbohydrate complexes Liposomes, glatiramoids
Molecular weight	Low (<500 Da)	High (range 5-900 kDa)	
Structure	Well defined	Complex, heterogeneous, defined by manufacturing process	
Production process	Chemical synthesis	In living cells or organisms	Synthetic technologies (nanotechnology)
Physicochemical characterization	Complete	Incomplete	
Generic production	Identical generics can be made	Impossible to create identical copy versions	

NSAIDs=non-steroidal anti-inflammatories; ESA=erythropoietin stimulating agents.

TABLE 3. Characteristics of small molecules, biologics and non-biologic complex drugs [adapted from (106)]

duct of a nanomedicine originator in an abridged applications process as a generic or a hybrid (99). To date, neither FDA nor EMA recognizes NBCD as a different category of drugs, but in the scientific community the lack of an appropriate regulatory evaluation system is progressively expressed. For highlighting the significant discrepancy with generics, the follow-on version of a nanomedicine was termed "nanosimilar" (8). However, some progress has been made and reflection papers from EMA regarding data requirements for nanosimilars of IV iron originator formulations was released in 2011, 2013 and 2015, recognizing that the generic pathway for approval of a nanosimilar was inappropriate (100).

Regarding IV iron products, some follow-on versions were approved over the time – for example, iron sucrose similars (ISS) were approved but following the same framework as small molecule generic products (101). Still, NBCD are different from classical small molecules, consisting of multiple structures maintained in a close relation, which cannot be entirely isolated, nor characterized based on the chemical structure alone (102). Moreover, the quality, composition and clinical profile of these formulations are highly dependent on complicated and not easy to control proprietary manufacturing processes (8). On the other hand, standard assays, test protocols and laboratory instrumentation have limitations when trying to fully characterize this products since their biological behavior is extremely variable (103). Furthermore, it has been problematic to evaluate the biodistribution of these complex IV iron nanomedicines in human target tissue. For this reason, some authorities suggested that animal models would be more appropriate to assess bioequivalence for nanosimilars approval (104). In this regard, recent experimental data from a study that comparatively assessed iron tissue biodistribution for different IV iron formulations in anemic rats (FCM, IS, iron isomaltoside, iron dextran) showed that, despite similar pharmacokinetic profiles, the tissue biodistribution pattern was not the same (105). Thus, demonstrating therapeutic equivalence (pharmaceutical equivalence and bioequivalence) between nanomedicines and their follow-on products is challenging, if not impossible (Table 3).

Iron sucrose and iron sucrose similars (ISS). Approval and clinical experience

Approval of ISS

Older IV iron products as IS or sodium ferric gluconate have already lost their patent, and follow-on products are available on the market. For newer IV nanomedicines as for FCM, the patent will soon expire.

There are two distinct pathways established in the European Union for obtaining marketing

authorization of *intended copies* of an originator drug. They are classified as either generics (small classical molecules, *e.g.*, acetaminophen) or biosimilars (therapeutic proteins, *e.g.*, erythropoietin) (91). The issue is that the regulatory requirements for these two categories are considerably different. While generics approval needs only proof of bioequivalence with the reference product (studies of bioavailability in healthy volunteers), a biosimilar is approved after an exhaustive documentation of therapeutic equivalence, different for each biologic product (non-clinical and clinical studies) (107). Thus, a nanosimilar seems to be inappropriately regulated as a generic, since nanomedicines are highly complex structures. Given that EMA classifies these follow-on products as generics or biosimilars, despite that they act differently as compared to the originator, one would consider that there is an equal therapeutic equivalence (91). Therefore, it is not unusual that these formulations are substituted at the pharmacy level (108).

Several follow-on iron sucrose formulations (*e.g.*, FerMylan®, Ferijet®, Ferosoft-S®, Encifer®, Iron sucrose AZAD®, Generis®) were approved as intended copies of iron sucrose originator (Venofer®), but the regulatory pathway for approval was the same as for generics. Still, Venofer® is not a simple small molecule, but a NBCD, with properties that cannot be completely characterized only by physicochemical analysis. Nonetheless, both non-clinical and clinical studies showed that there was no interchangeability between iron sucrose similars (ISS) and the reference product (109). Moreover, there are potentially differences in efficacy, adverse effects and also costs (110, 111) (Table 4).

Iron sucrose similars' experience

Non-clinical data

Experimental data showed significant differences between IS and ISS regarding oxidative stress and inflammation (catalase, thiobarbituric reactive species, Cu,Zn-superoxide dismutase, glutathione peroxidase activity, level of glutathione) in the liver, heart and kidney of normal rats. Moreover, kidney function was impaired in ISS groups (109). Other data from non-anemic rats revealed vasodilatory effects, kidney and liver injury only in ISS groups. Furthermore, serum iron and transferrin saturation levels were higher in ISS groups, which could reflect an increased level of labile iron and could explain the elevated markers of oxidative stress and inflammation. Additionally, not only physicochemical analyses of ISS and originator showed different molecular structures, but there were differences even between different lots of a single ISS formulation (110). Assessing the potential to induce nitrosative stress and apoptosis between IS originator and ISS also in non-anemic rats, more elevated levels of tyrosine nitration and a higher expression of caspase 3 were found in all ISSs, even if the physicochemical properties of all ISS were in agreement with the United States Pharmacopeia for IS injection. These results sustain that physicochemical methods alone were not suitable to fully characterize such a complex molecule as IV iron-carbohydrates (112).

Clinical data

Differences in efficacy – Efficacy was comparatively assessed between Venofer® and an ISS in an observational study in CKD dialysis patients with well controlled levels of hemoglobin. It was

TABLE 4. Potential disadvantages of iron sucrose nanosimilars

Physicochemical properties	• Different from IS (110) • Vary from one lot to another (110)
Experimental studies	• Enhanced oxidative stress (109) • Higher serum iron, transferrin saturation and labile iron (110) • Nitrosamine stress and apoptosis (112)
Clinical studies	• Activation and damage of mononuclear cells in dialysis patients (114) • Lower efficacy in anemia correction in dialysis patients (increased iron and ESA doses to stabilize hemoglobin level) (111) • Higher incidence of adverse effects (injection site reaction, phlebitis) in obstetric surgery (115)

found that they were not interchangeable. After switching to the ISS, destabilization of hemoglobin levels, and an increase in iron (32%) and ESA requirements (20%) were seen. This induced a higher total exposure to drugs and also a higher total cost for anemia management (111).

Differences in adverse effects – In terms of adverse effects, observations from clinical cases, highlighted that IS originator and ISS were not interchangeable (medical prescription) or substitutable (pharmaceutical dispensation) (113). Additionally, a more pronounced activation and damage of mononuclear cells in CKD patients on hemodialysis was noted after they received ISS as compared to IS originator (114). Other data from an obstetrics and gynecology surgery, which replaced Venofer® with an ISS for economic reasons, revealed a higher incidence of adverse events (reaction at injection site, phlebitis) in ISS groups when these formulations were compared (115).

Economical differences – From the minimization-of-costs point of view, it was supposed that the follow-on product and the originator were therapeutically equivalent and substituting the originator would lead to identical outcomes at lower costs. It is not the case with nanomedicines and nanosimilars, at least regarding IV iron NBCD. Data from a CKD an observational cohort study in hemodialysis patients showed that, after switching from an ISS to Venofer® (56 weeks for both treatment periods), lower doses of IV iron and ESA were needed to maintain hemoglobin levels (108). These data did not withstand for any economic advantage in switching from the originator to a similar.

Nonetheless, it is also worthy to point out that some published data can use the term "iron sucrose" without a clearly differentiation between IS originator and ISS, thus generating confusion (116). ❑

CONCLUSIONS

Iron therapy is frequently needed because ID and IDA are present worldwide. Moreover, there is a high occurrence of ID and IDA in chronic conditions that are also globally highly prevalent. Intravenous iron therapy seems to be preferred not only for a better and a more rapid hematologic response but also for the non-hematologic benefits.

Intravenous iron products are non-biological complex molecules with a biological behavior that depends not only on the core composition and size as well as characteristics of the shell, but also on the manufacturing process. Thus, intravenous iron products are significantly different from small molecular common drugs. Any subtle change variation in the manufacturing process affects the physicochemical properties, with impact on stability, iron release rate, cellular uptake and tissue distribution, therefore safety and efficacy of the final formulation.

Various follow-on versions of IV iron originators were approved by a regulated pathway that seemed inadequate since these NBCD were essentially different from small molecules as their structure and properties could not be fully and precisely characterized. These intended copies are similar but unquestionably not identical. Moreover, plenty of non-clinical and clinical data point to the fact that IV iron originators and their similars are not therapeutically equivalent, thus neither interchangeable, nor substitutable. The clinical impact regarding efficacy and safety could be different between them and the originator. Additionally, a similar does not mandatory imply lower costs as it has been described.

Hence, our choice as clinicians should be based solely on evidence. ❑

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