



## Review Article

# Risk of iron overload with chronic indiscriminate use of intravenous iron products in ESRD and IBD populations

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## ABSTRACT

The routine use of recombinant erythropoiesis-stimulating agents (ESA) over the past three decades has enabled the partial correction of anaemia in most patients with end-stage renal disease (ESRD). Since ESA use frequently leads to iron deficiency, almost all ESA-treated haemodialysis patients worldwide receive intravenous iron (IV) to ensure sufficient available iron during ESA therapy. Patients with inflammatory bowel disease (IBD) are also often treated with IV iron preparations, as anaemia is common in IBD. Over the past few years, liver magnetic resonance imaging (MRI) has become the gold standard method for non-invasive diagnosis and follow-up of iron overload diseases. Studies using MRI to quantify liver iron concentration in ESRD have shown a link between high infused iron dose and risk of haemosiderosis in dialysis patients. In September 2017, the Pharmacovigilance Committee (PRAC) of the European Medicines Agency (EMA) considered convergent publications over the last few years on iatrogenic haemosiderosis in dialysis patients and requested that companies holding marketing authorization for iron products should investigate the risk of iron overload, particularly in patients with end-stage renal disease on dialysis and, by analogy, patients with IBD. We present a narrative review of data supporting the views and decision of the EMA, and then give our expert opinion on this controversial field of anaemia therapeutics.

## 1. Introduction

The discovery of epoetin (EPO) in the 1980s represented a therapeutic revolution and the routine use of recombinant erythropoiesis-stimulating agents (ESA) over the past three decades has enabled the partial correction of anaemia in most patients with end-stage renal disease (ESRD) [1]. These patients have a better quality of life, reduced need for blood transfusions and fewer anaemia-related diseases [1]. Most ESRD patients on dialysis commonly have a negative iron balance owing to: a-dietary restrictions, b-increased hepcidin levels which blocks physiological iron transport channels in duodenal epithelial cells and decreased intestinal absorption due to the interaction of multiple drugs such as phosphate chelators and proton pump inhibitors, and c-losses of blood related to the haemodialysis procedure, uremic platelet dysfunction, and ESRD enteropathy aggravated by antiplatelet and anticoagulant drugs frequently used in this population and blood samples routinely drawn for laboratory testing [2]. This true iron deficiency is worsened by the use of ESA, which frequently leads to superimposed functional iron deficiency, due to massive transfer of stored iron to erythroid progenitor cells and also inadequate iron mobilization from the storage sites induced

by increased hepcidin levels caused by the ESRD-associated inflammatory state [2].

Almost all ESA-treated haemodialysis patients worldwide (approximately 2 million) receive intravenous iron (IV) to ensure sufficient available iron during ESA therapy [3, 4, 5, 6]. Therefore, the two risks of iron deficiency and iron overload must be closely controlled in dialysis patients receiving iron therapy [7]. Iron overload among dialysis patients was widely considered to be more prevalent during the pre-ESA era, when blood transfusions were routinely used to treat anaemia and parenteral iron was given without concomitant ESA; as a result, iron overload was considered rare or even exceptional in the post-ESA era, but is now an increasingly recognized controversial clinical situation [7].

In addition to ESRD, patients with inflammatory bowel disease (IBD) are commonly treated with IV iron preparations, as IBD is often associated with anaemia, mainly due to a combination of iron deficiency and systemic inflammation [8]. Anaemia is considered to be one of the most common comorbid conditions in patients with IBD. A negative iron balance is frequently encountered in IBD patients which is due to: a-blood loss from the bowel lesions, b-restricted diet to mitigate diarrhoea and intestinal discomfort, and c-decreased ferroportin expression

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on enterocytes due to high hepcidin levels triggered by inflammation (mainly IL6) leading to poor iron duodenal absorption of iron [8].

The liver is the main site of iron storage in humans and the liver iron concentration (LIC) closely correlates with total body iron stores in patients with secondary haemosiderosis and genetic haemochromatosis [9]. Over the past decade, major progress has been made in the non-invasive measurement of LIC using radiological techniques to replace liver biopsy for the diagnosis and monitoring of iron overload disorders [10]. Magnetic resonance imaging (MRI) of the liver has now become the gold standard method for non-invasive diagnosis and follow-up of iron overload diseases [11]. Studies using MRI to quantify LIC, in recent years have shown a link between high infused iron dose and risk of haemosiderosis in dialysis patients [12, 13, 14].

In September 2017, the pharmacovigilance committee (PRAC) of the European Medicines Agency (EMA) considered convergent publications over the last few years on iatrogenic haemosiderosis in dialysis patients and requested that companies holding marketing authorization for iron products should investigate the risk of iron overload, particularly in patients with chronic kidney diseases (CKDs), especially those with end-stage renal disease maintained on dialysis and, by analogy, patients with IBD [15].

We present a review of the data supporting the views and decision of the EMA and then give our expert opinion on this controversial field of anaemia therapeutics.

## 2. Main text

### 2.1. Iron metabolism

Iron is an essential metal for the body; iron deficiency leads to anaemia while excess iron accumulation can cause organ failure through production of reactive oxygen species [16]. Total iron stores average 2–3.5 g in healthy women and 3–4 g in men [16]. Approximately two-thirds of iron stores are sequestered in the haemoglobin molecules of circulating erythrocytes and, to a lesser degree, in medullary erythrocytes. Another 20% is held in the liver (in hepatocytes and Kupffer cells) or in the reticulo-endothelial system (mainly in splenic macrophages), predominantly in the form of the physiological iron-storage protein ferritin (marginally as haemosiderin), while muscle myoglobin accounts for a further 10% [16]. Iron-containing enzymes contain only 1% of iron stores, while circulating transferrin-bound iron represents only 0.2% (3 mg) of iron stores [16]. Each day, reticulo-endothelial macrophages recycle about 30 mg of iron originating from senescent erythrocytes, covering the 20–30 mg of iron required for normal erythropoiesis [16]. Physiological iron losses are estimated to be about 1 mg/day and comprise excretion in urine (0.1 mg/day), enterocyte desquamation (0.6 mg/day) and skin loss (0.3 mg/day) [17]. In women, these losses are increased by menstruation (which is the leading cause of iron-deficiency anaemia worldwide) [17]. Recommended dietary iron intake is about 10 mg/day (as only about 10% of dietary iron is absorbed) [17].

Storage and transport of body iron are tightly regulated by several factors, including hepcidin-25, which is the main hormone of iron metabolism [16]. The liver synthesizes hepcidin which inhibits both intestinal iron absorption and iron release from reticulo-endothelial macrophages and hepatocytes; hepcidin reduces the expression of ferroportin, a protein which regulates cellular iron export [16]. Hepcidin-25 synthesis is enhanced by iron itself and by inflammation, and is down-regulated by anaemia, hypoxia, blood loss, iron deficiency, erythropoietin and increased medullary erythropoiesis [16].

Erythropoietic stimulation after blood loss down-regulates hepcidin synthesis via a newly discovered peptide hormone, erythroferrone, which is secreted by erythroblasts and acts directly on the liver [18]. Deficient hepcidin-25 synthesis plays a central role in genetic haemochromatosis, whereas unregulated hepcidin synthesis is responsible for a genetic form of iron-deficiency anaemia known as iron refractory iron deficiency anaemia (acronym IRIDA) [16, 19].

Most importantly, iron metabolism is a closed system, critically regulated by hepcidin (and also erythroferrone), but with no active or passive excretory mechanisms of iron excess from the body; thus iron progressively accumulates when exogenous iron is loaded by hereditary factors such as genetic haemochromatosis or repeated transfusions in patients with anaemia due to genetic disorders such as thalassemia and sickle-cell disease, and in cases of acquired bone-marrow failure such as myelodysplastic syndrome [20, 21, 22]. Similarly, in ESRD and IBD patients treated long-term with IV iron products, IV iron doses exceeding ongoing blood losses may be associated with an increased risk of a positive iron balance [23, 24].

### 2.2. Intravenous iron products

Iron deficiency is an important clinical problem in patients with CKDs, especially those on haemodialysis, and in IBD patients, as it gives rise to superimposed iron-deficiency anaemia and ESA resistance, events which may impair various cellular functions and aggravate cardiac insufficiency [25, 26]. Oral supplementation, in particular with ferrous salts, is associated with a high rate of gastrointestinal side-effects in ESRD and may even be deleterious in cases of IBD flare-up by increasing oxidative stress [8, 23, 27]. Finally, oral iron is poorly absorbed, a problem that is overcome by administration of IV iron products [23, 27].

Seven different IV iron pharmaceuticals are currently available in the USA, Europe and other industrialized countries. The main physico-chemical and pharmacokinetic characteristics of these products are summarized in Table 1 [23, 27, 28]. With the exception of iron gluconate and ferumoxytol, which are particularly indicated in CKD patients with iron deficiency, IV iron pharmaceuticals are only indicated for use in general cases of iron deficiency anaemia (whatever the underlying disease) when oral iron is unavailable, ineffective or poorly tolerated, or as first-line treatment when there is a clinical need to rapidly replenish iron stores (drug label indications for iron sucrose and low molecular weight iron dextran) [29]. It is also noteworthy that iron overload is a contraindication to beginning or pursuing therapy with these IV iron products, as stressed in the *Contraindications* or *Precautions* section of the summaries of product characteristics [29]. The most recent and stable IV iron complexes (low molecular weight iron dextran, ferric carboxymaltose, iron isomaltoside 1000 and ferumoxytol) can be given at higher single doses and more rapidly than older preparations such as iron sucrose (Table 1) [23, 27, 28].

Iron supplementation is recommended in current clinical guidelines for all CKD patients with iron-deficiency anaemia and in those who receive ESA, irrespective of whether they require dialysis or not [3, 4, 5, 6]. Randomized trials in haemodialysis patients have demonstrated significantly greater increases in haemoglobin levels with IV iron when compared to oral iron, and a low rate of treatment-related adverse events during these short trials [1, 4]. In addition, IV iron products are associated with cost savings of about 30% by reducing ESA dose requirements [23, 27]. Of note, the meta-analysis performed by the Cochrane network comparing parenteral versus oral iron in ESRD concluded that the 28 studies included (2098 participants) provided strong evidence for large increases in ferritin (mean difference: 243 µg/L [95% Confidence Intervals (CI): 188–297 µg/L]) and transferrin saturation (mean difference: 10.2% [95%CI: 5.5–14.8%]), together with a moderate increase in haemoglobin (mean difference: 0.9 g/dl [95%CI: 0.44–1.37 g/dl]) in the IV iron-treated groups when compared to patients treated with oral iron [30].

Interestingly, the recently published PIVOTAL study confirms the efficacy and safety of IV iron plus ESA for the treatment of anaemia in ESRD patients maintained on dialysis [31]; This was based on a multi-centre open-label non-inferiority trial with blinded end-point evaluation, which randomized 2141 UK haemodialysis patients either to high-dose IV iron-sucrose originator (Venofer®) (n = 1093 patients) or to low-dose IV iron-sucrose originator (Venofer®) (n = 1048) for a median follow-up of 2.1 years [31]. In the group with high-dose iron,

**Table 1**  
Intravenous iron products: main physicochemical and pharmacokinetic characteristics (according to [23]).

Commercial name	Venofer®	Ferlecit®	Cosmofer®/ Ferrisat® (Europe) and INFeD® (USA)	Ferinject® (Europe) and Injectafer® (USA)	Monofer® (and Diafer®/ Monover® in some European countries)	Rienso® (Europe) and Feraheme® (USA)
Carbohydrate composition	Iron sucrose	Iron gluconate	Iron dextran (low molecular weight)	Iron carboxymaltose	Iron isomaltoside	Ferumoxylol (polyglucose sorbitol carboxymethyl-ether iron)
Molecular weight measured by manufacturer (Daltons) (kDa according to USP method of Geisser)	34 000–60 000 (44 kDa)	289 000–440 000 (37 kDa)	165 000 (165 kDa)	150 000 (150 kDa)	150 000 (69 kDa)	750 000 (185 kDa)
Reactivity	Moderate	High	Low	Low	Low	Low
Plasma half-life (h)	5.3	1.4	27–30	7.9–9.4	23.2	14.7
Cmax (mg Fe/L)	35.3	20.6	120	37	37.3	130
AUC (mg Fe/L x h)	83.3	35	1371	333	1010	922
Clearance (L/h)	1.23	2.99	-	0.26	0.10	0.11
Maximum infused dose	300 mg	125 mg	20 mg/kg	20 mg/kg	20 mg/kg	510 mg
Minimum time of infusion (min)	90	60	240	15	60	15

C: concentration; AUC: area under the curve

Venofer® was given in a proactive fashion: patients were scheduled to receive 400 mg/month of iron-sucrose originator, up to a ferritin level of 700 ng/ml or a transferrin saturation  $\geq 40\%$ , whereas patients in the low-dose iron group were administered Venofer® (0–400 mg monthly) in a reactive fashion aimed at maintaining ferritin  $>200$  ng/ml or a transferrin saturation  $>20\%$  [31].

The primary end-point was a composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure or death, whereas secondary end-points included death, infection rate and ESA dose [31]. In the PIVOTAL trial, non-inferiority was demonstrated ( $p < 0.001$ ) with a slight superiority ( $p = 0.04$ ) related to fewer cardiovascular events (fatal and nonfatal myocardial infarction; HR = 0.69 (0.52–0.93)) or hospitalizations for cardiac failure (HR = 0.66 (0.46–0.94)) [31]. Finally, the PIVOTAL trial also confirmed that maintenance iron therapy is better than an iron loading strategy for sparing ESA requirements (–19.4%) [31].

In addition to ESRD populations, patients with IBD commonly receive long-term treatment with IV iron preparations [32]. In 2007, the European guidelines for the “Management of anaemia in patients with IBD” strongly advocated the use of the IV route of iron administration [8]. This was based on the fact that IV iron is more effective and better tolerated than oral iron supplements and improves quality of life in this population (Grade A recommendation) [8].

### 2.3. Modern radiological tools for non-invasive study of in vivo liver iron content

Liver is the main iron storage site in healthy humans and in patients with iron overload disorders. LIC reflects total body iron stores in patients with secondary haemosideroses such as transfusion-dependant thalassemia (TDT) and non-transfusion-dependant thalassemia (NTDT), sickle-cell disease and in patients suffering from genetic haemochromatosis [9, 11]. Non-invasive radiological techniques for estimating liver iron stores have appeared over the past 2 decades with the aim of avoiding liver biopsy, including the superconducting quantum interference device (SQUID), quantitative computed tomography (qCT) and MRI [9, 11]. Hepatic MRI has become the gold standard method for estimating and monitoring iron stores, providing “iterative radiological biopsy” in the setting of iron overload diseases [10, 11].

MRI is based on the paramagnetic properties of iron: the magnetic signal falls when LIC increases. Like SQUID, MRI does not distinguish ferritin from haemosiderin iron [11]. The advantages of MRI include its low cost (about 300 euros per test in Europe), non-irradiating nature and availability. In addition, it does not require gadolinium, avoiding the risk of gadolinium-associated nephrogenic fibrosis in CKD patients (a severe clinical situation mimicking scleroderma). The three MRI modalities for

liver iron quantification are the signal-intensity ratio (SIR), R2 relaxometry and R2\* relaxometry [33, 34, 35].

The SIR method was first published in the *Lancet* in 2004 and was developed at Rennes University, France, on a 1.5-Tesla apparatus [33]. It was validated in a cohort of 174 patients (139 in the study group and 35 in a validation group) with genetic haemochromatosis, hepatic disorders and secondary haemosiderosis requiring liver biopsy for biochemical iron assay [33]. SIR-MRI is based on a comparison of liver and muscle intensities in various sequences (T1, PD, T2, T2+, T2++) and the results are analysed using an algorithm that chooses the most sensitive and specific sequence depending on iron overload severity [33]. Free analytical software is available on the Rennes University website. This method has a sensitivity of 89% and a specificity of 80% for iron overload diseases, and is linear up to 350  $\mu\text{mol/g}$  of dry liver tissue [33]. An additional sequence with a modified algorithm as established by the Rose group in Lille, France (called high LIC technique), is requested for LIC values  $> 350$   $\mu\text{mol/g}$  of dry liver tissue [36].

A recent pilot study in ESRD compared Scheuer's histological classification and Deugnier and Turlin's histological classification of iron overload by Perls staining with SIR-MRI values obtained with the Rennes University algorithm in 11 haemodialysis patients in whom liver biopsy was indicated in their medical follow-up; of note only two of these patients had hepatitis C [37,38]. Taking into account the fact that the semi-quantitative histological scoring of Deugnier and Turlin has been validated in both haemochromatotic and non-haemochromatotic iron overload disorders, this pilot study strongly suggests that liver iron determination based on SIR-MRI with the Rennes algorithm accurately identifies iron load in haemodialysis patients [37,38].

The second MRI method, based on R2 relaxometry, was developed on a 1.5-Tesla apparatus in Australia in 2005 [34]. It was validated in a cohort of 105 patients with thalassemia, genetic haemochromatosis or hepatic disorders who had liver biopsy and biochemical iron assay [34]. R2 relaxometry was also favourably compared to SQUID in 23 patients [39], and these results were recently replicated in comparison to biochemical iron assay on hepatic biopsies in an international study called ESCALATOR in 233 patients with beta-thalassemia living in the Middle East and treated with the iron chelator deferasirox [40]. This method, based on R2/T2 sequences, is commercially available as Ferriscan® and has been approved in the USA by the Food and Drug Administration (FDA); it has a sensitivity of 86% and a specificity of 88% for iron overload disease [34]. It is linear up to 700  $\mu\text{mol/g}$  of dry liver, but the apparatus must be specifically configured and calibrated with phantoms [34].

The third MRI technique for iron-store quantification is based on R2\* relaxometry and uses a 1.5 T apparatus with specific software [35]. R2\* relaxometry quantifies liver iron and can in the same session detect iron

overload in other target organs (e.g. the heart, spleen and pancreas) [35]. Its main limitation relates to the fact that it has been validated against a smaller number of liver biopsies than SIR with the Rennes algorithm and R2/T2 relaxometry (in 22, 30, 43, 25 and 17 patients, respectively, in the five studies available in this setting) [35, 41, 42, 43, 44]. Equations have also been proposed by Wood, Pennell and Garbowsky to transform the results into mg of liver iron [35, 43].

Using multi-peak fat spectral modelling, MRI-R2\*, has been recently shown to allow simultaneous and reliable quantifications of liver fat and iron for which the main MRI manufacturers have developed specific software (General Electric: IDEAL-IQ; Phillips: M Dixon Quant; Siemens: Liver Lab; Toshiba: MR Body Expert) [45, 46, 47].

Therapeutic proposals for clinically relevant thresholds of MRI-determined LIC are now included in hepatology and haematology guidelines for iron overload diseases; examples include chelation therapy for secondary haemosiderosis and phlebotomy for genetic haemochromatosis, and also specific follow-up of target organs, especially the heart [9, 11, 48, 49]. Of note, these MRI-thresholds, like those for ferritin, have been deeply reconsidered by haematologists for NTD and lowered to 5 mg/g of dry weight (e.g. 96  $\mu\text{mol/g}$ ). This was in light of the findings in thalassemia intermedia where morbidities were demonstrated to be highly associated with liver iron load [50]; moreover, in the case of unavailability of MRI, a lower safe threshold for ferritin of 300 ng/ml has been proposed in this setting [51]. Finally, in NTD, specific softwares for R2\* Relaxometry for concomitant accurate measurement of both liver iron and fat fraction may be particularly useful to overcome the high frequency of liver steatosis recently reported in this setting and its misleading influence with artefacts on ferritin levels [45, 46, 47, 52].

Use of R2\* MRI for early detection and use of chelation in iron-induced cardiomyopathy has translated into improved survival of thalassemia patients [22, 53, 54, 55, 56].

#### 2.4. Iron overload induced experimentally by IV iron products and in healthy individuals by oral and IV iron products

In 1971, Goldberg et al. analysed the effects of chronic administration of intramuscular iron dextran to albino rats and rabbits and discovered that it induced renal lesions [57]. In the same year, Lisboa was the first to reproduce cirrhosis with massive siderosis mimicking advanced haemochromatosis in dogs-administered IV dextran [58]. Following these studies, numerous experimental models have been developed mainly with subcutaneous iron dextran administered chronically to various animal species (rats, gerbils and baboons) to analyse the pathophysiology, histological findings, natural history and effect of chelators on induced iron overload disorders simulating either genetic haemochromatosis or secondary haemosiderosis [59, 60, 61, 62, 63]. A mouse model of haemosiderosis induced by IV iron dextran recently analysed the differential effect on splenic and hepatic iron load by MRI [64]. More recently, a mouse model using chronic iron sucrose administered intraperitoneally was shown to mimic thalassemia with hepatic and cardiac iron overload [65], whereas others models with IV iron sucrose in infant mice assessed the occurrence, kinetics and effects of chronic iron overload in a vulnerable animal population with the aim of preventing its appearance and consequences in paediatric patients [66].

Excessive intake or IV infusions of iron compounds were reported anecdotally as causes of iron overload 2 decades ago [67]. These are now increasingly recognized as a potential clinical problem among athletes [68, 69]. Iron overload in road cyclists caused by the illicit use of iron and EPO was first reported in detail in 2002 [69]. Among 83 cyclists participating in the "Tour de France", 30% had serum ferritin concentrations  $>300 \mu\text{g/L}$  and 37% had elevated transferrin saturation. All were asymptomatic and had normal clinical examinations; seven admitted having used EPO [69]. All received oral, and sometimes IV, iron supplementation, either as self-medication or prescribed for low serum iron [69]. LIC measured by SIR-MRI with the Rennes algorithm was elevated in 24/27 road cyclists who underwent this examination, with LICs up to

187  $\mu\text{mol/g}$  [69]. Of note, the usefulness of iron supplementation in high-level athletes has never been documented in the scientific literature [69].

#### 2.5. End-stage renal disease

##### 2.5.1. Blood loss in ESRD

Blood loss is the main factor responsible for iron deficiency in haemodialysis patients [2, 70]. There are three cumulative sources of blood loss in dialysis patients: (i) via the haemodialysis technique itself; (ii) regular blood sampling (for laboratory tests aimed at follow-up of the uremic state); and (iii) occult intestinal bleeding due to uremic enteropathy (favoured by platelet dysfunction and anticoagulation of the extracorporeal circuit during dialysis sessions with either unfractionated or low molecular weight heparin); this latter loss is increased by the use of antiplatelet drugs and vitamin K antagonists in dialysis patients with cardiovascular diseases [2, 70].

Two studies have estimated the blood loss with the modern haemodialysis technique as 0.3 ml/session [71] and 0.9 ml/session [72], whereas blood-line loss was quantified at 0.2 ml/session [71]. Thus, annual blood loss due to the classical haemodialysis technique (assuming losses of 1.1 ml per session and 3 sessions/week or 150 sessions/year) represents approximately 165 ml [23]. Residual blood in the tubing and dialyser (measured by atomic spectrometry) was recently measured in 238 patients in Japan and represented an average loss of 1245  $\mu\text{g}$  of iron per dialysis session [73]. Nevertheless, another important source of blood loss in dialysis centres is related to the care of haemodialysis catheters by nurses applying a universal purge protocol (10 ml of blood in each catheter branch at the session outset), leading to an annual blood loss of 2.4 L [23]. Of note, sudden accidental bleeding due to insufficient compression or high internal pressure of a native fistula can cause additional, severe blood loss in haemodialysis patients [23].

Regular blood sampling is the second major source of blood loss in the setting of haemodialysis; this was quantified as 368 ml at the University of Tennessee in Memphis in 2004 [70] and between 350 and 450 ml/year in a survey in 10 dialysis centres in France published in 2015 [23]; it was recently estimated as 600 ml/year in Japan [73].

Occult gut bleeding is the third source of blood loss [23]; using chromium 51-labelled erythrocytes, Rosenblatt et al. quantified faecal blood loss as 0.83 ml/day in healthy controls, 3.15 ml/day in non-dialysed CKD patients and 6.27 ml/day (or 2.2 L/year) in haemodialysis patients [74]. These latter blood losses are increased by antiplatelet drugs and vitamin K antagonists, which are frequently used in dialysis patients; the additional loss related to antiplatelet drugs and vitamin K antagonists requires 703–961 mg of additional IV iron per year to compensatory replenish iron stores [75, 76].

##### 2.5.2. Epidemiology of IV iron products use in ESRD patients

An epidemiological study in American haemodialysis patients (based on the United States Renal Data System (USRDS) register) showed that the use of IV iron increased from 64% of patients in 2002 to 76% in 2008, whereas the monthly infused dose increased over the same period from 166 to 216 mg [77]. The average monthly dose of IV iron during the first year after dialysis initiation was much higher, ranging from 270 to 305 mg/month [77].

In June 2010, the FDA modified the ESA product label resulting in a significant increase in proportion of USA dialysis patients receiving IV iron from 57% in August 2010 to 71% in August 2011, together with a significant decrease in ESA dosages [78]. During the same period, median ferritin level increased from 556 to 650  $\mu\text{g/L}$ , while 34% of patients had ferritin values  $>800 \mu\text{g/L}$  [78]. Approximately 20% of USA dialysis patients received  $>500 \text{ mg/month}$  IV iron during this period [78].

Similar trends in the use of IV iron were also observed in ESRD in other industrialised countries (with the exception of Japan): between 1999 and 2010, the percentage of dialysis patients treated with IV iron increased from 65% to 80% in Canada, from 55% to 70% in France, from



65% to 80% in Germany and from 60% to 80% in the UK [79]. Between 1999 and 2010, mean ferritin level increased from 380 to 450  $\mu\text{g/L}$  in Canada, from 420 to 580  $\mu\text{g/L}$  in Germany and from 400 to 500  $\mu\text{g/L}$  in the UK, but remained stable in France (around 400  $\mu\text{g/L}$ ) [79]. Overall, in industrialized countries outside the USA, the average monthly dose of IV iron infused during dialysis sessions increased by 21%, from 232 mg/month in 1999 to 281 mg/month in 2010 [79]. Conversely, in Japan, during the period 1999–2010, the proportion of patients receiving IV iron increased only slightly from 25% to 36% and the mean ferritin level also increased slightly from 280 to 320  $\mu\text{g/L}$  [79].

### 2.5.3. Avoidance of blood transfusions in ESRD

The main benefit of the introduction of epoetin in the 1990s, beside its dramatic improvement of quality of life of ESRD patients, was the dramatic decrease in blood transfusions, leading to the disappearance of transfusion-induced haemosiderosis and HLA sensitization in the setting of dialysis [80]. As shown by the National Kidney Foundation, the change of ESA label by the FDA and EMA in 2010 and the bundling policy in the USA in 2011 (and in most Western countries in subsequent years) has led to a decrease in dosage of ESA (-28%), an increase in use of IV iron (in 77% of patients instead of 57%), reduction of haemoglobin levels of about 0.4 g/dl and a slight but real reappearance of blood transfusions (from 2.2% in September 2010 to 4.9% in September 2011) to maintain haematocrit stability [80].

Data on blood transfusions in pre-dialysis patients are scarce. In a retrospective study of a cohort of 374 adult ESRD patients not on dialysis (at the Henri Ford health centre, USA, between 2004 to 2008), showed that 20% received at least one transfusion (mean of 2 blood units) during a mean follow-up of 459 days. The transfusion rate was 182.2/100 patient-years; the mean haemoglobin level prior transfusion was 8.8 g/dl and patients who were hospitalized in the 6 months prior to anaemia diagnosis were 6.3-times more likely to be transfused as those with peripheral arterial disease; surprisingly, a prior nephrologist visit did not influence the rate of transfusions [81].

A recent prospective epidemiological study performed from 2012 to 2014 in Canada analysed the rate of blood transfusions in 314 incident haemodialysis patients in their first year of dialysis [82]. Nearly one-third (29.9%) of these patients received at least 1 blood unit; during the first 3 months of dialysis and the rate of blood transfusion was 148.4/100 patient-years as compared to 62.6/100 patient-years after the first 90 days of dialysis. Low haemoglobin level was the indication in 92% of cases (mean haemoglobin values of 7.5–7.8 g/dl). Blood transfusion was associated in Cox regression analysis with the initiation of dialysis as an inpatient (37.5% of the cohort); most importantly, these latter patients had less pre-dialysis care and a higher degree of inflammation [82].

### 2.5.4. Iron overload revealed by modern imaging techniques in dialysis patients

Recent quantitative MRI studies of LIC in haemodialysis patients, as well as a SQUID study (performed 13 years ago), have demonstrated a high risk of iron overload in dialysis patients treated with high doses of IV iron products; of note, these doses are currently advocated by anaemia management guidelines for dialysis patients [2, 12, 13, 14, 83].

Two MRI studies have focused on iron overload in haemodialysis patients with serum ferritin levels  $>500 \mu\text{g/L}$ , which is the upper limit advocated by the Kidney Disease Outcomes Quality Initiative (KDOQI)-2006 guidelines [3] and European Dialysis and Transplant Association - European Renal Best Practice (EDTA-ERBP)-2009 statement [5]. Using R2 relaxometry to study 15 Australian patients with a median serum ferritin of 782  $\mu\text{g/L}$ , Ferrari et al. found hepatic iron overload in two-thirds of cases (Table 2) [12]. Ghoti and Rachmilewitz used T2\* MRI to measure liver and spleen iron content and pancreatic and cardiac iron deposits in 21 Israeli haemodialysis patients with serum ferritin levels  $>1000 \mu\text{g/L}$  [13]. They found hepatic siderosis in 19/21 patients (90%) and spleen involvement in 20/21 patients (95%) (Table 2) [13].

Pancreatic involvement was investigated in the eight most motivated patients and was found in three cases (37%) [13]. None of the Israeli dialysis patients had abnormal cardiac R2\* relaxometry, but only a small number of patients was studied and thus no definitive conclusions could be drawn on the risk of cardiac iron deposits in haemodialysis patients with very high ferritin levels ( $>1000 \mu\text{g/L}$ ) [13].

Two other studies have analysed liver iron stores in cohorts of haemodialysis patients with optimal ferritin levels (between 200 and 500  $\mu\text{g/L}$ ) treated according to the KDOQI-2006 guidelines [3] and EDTA-ERBP-2009 statement [5] using SQUID in 2004 in Italy [83] and MRI in France in 2012 (Table 2) [14]. Canavese et al. used SQUID to study liver iron stores in 40 Italian haemodialysis patients and found normal LIC values in only 30% of cases, mild iron overload in 32.5% and moderate iron overload in 37.5% [83]. At that time, it was claimed that these findings could not be extrapolated to the general haemodialysis population because of possibly biased selection of an iron-overloaded population in the study [84]. Using the Rennes University SIR-MRI protocol, the French study published in 2012 showed hepatic iron overload ( $>50 \mu\text{mol/g}$  dry weight) in 84% of 119 stable haemodialysis patients treated according to the accepted guidelines [3,5]; iron overload was mild in 42 patients (35.3%), moderate in 22 (18.5%) and severe ( $>200 \mu\text{mol/g}$  dry weight) in 36 patients (30.2%), at levels usually observed in genetic haemochromatosis [14]. MRI also showed splenic abnormalities (a feature of secondary haemosiderosis) in several patients [14]. Moreover, in 11 patients who were monitored closely during parenteral iron therapy, the iron dose infused per month correlated strongly with both the overall increase and monthly increase in LIC; in 33 patients with iron overload on MRI, iron stores fell significantly after iron withdrawal or after a major reduction in iron dose [14].

Five recent studies have confirmed this high incidence of iron overload in haemodialysis patients. Two studies performed in the USA and Australia enrolled a small number of haemodialysis patients: using R2\* relaxometry, Tolouian et al. found liver iron overload in 50% of 17 American patients with a mean ferritin level of 596  $\mu\text{g/L}$  [85] (Table 2). Likewise, using Ferriscan® R2 relaxometry, Holman et al. found liver iron overload in 80% of 10 Australian haemodialysis patients with a median serum ferritin level of 371  $\mu\text{g/L}$  [86] and Turkmen et al. using T2\* MRI found liver and (mild) cardiac iron overload in 25% of 36 Turkish haemodialysis patients (with a mean ferritin of 472  $\mu\text{g/L}$ ) [87] (Table 2).

Finally, three other studies performed in Europe have analysed larger cohorts of haemodialysis patients, both with SIR-MRI according to the Rennes algorithm; patients were treated according to the EDTA-ERBP-2013 statement [6], which is more conservative and cautious for iron therapy than the Kidney Disease Improving Global Outcomes (KDIGO)-2012 [4] and EDTA-ERBP-2009 statement [5]. The French study included 80 haemodialysis patients and found liver iron overload in 65% (mild iron overload in 41.25%, moderate iron overload in 12.5% and severe iron overload in 11.25%) (Table 2) [88]. The Spanish study focused on 47 haemodialysis patients with serum ferritin  $>500 \mu\text{g/L}$  and found liver iron overload by MRI in 91% of patients (mild iron overload in 53%, moderate and severe iron overload in 38%) (Table 2) [89].

The latest study (published this year), conducted in 68 French dialysis patients (62 on haemodialysis and six on peritoneal dialysis), analysed the hypothetical relationship between LIC and hepatic fat fraction (PDFF) using simultaneous SIR-MRI and T2\* relaxometry with a specific algorithm (IDEAL-IQ, aimed at measuring both LIC and PDFF) [90]. In this cohort, 57% (39/68) of the patients had hepatic siderosis (mild,  $n = 23$ ; moderate,  $n = 9$ ; severe,  $n = 7$ ) [90] (Table 2). The data from this study on liver fat fraction are analysed in detail in section 2.8.3.2. (Are liver fibrosis and cirrhosis relevant endpoints for iron toxicity?).

Finally, a recent medical thesis in Egypt focused on hepatitis C carriers: LIC was analysed in 50 haemodialysis patients, 25 of whom suffered from hepatitis C [91]. Liver iron overload identified by MRI was present in 44% of their dialysis patients and was more frequent in the HCV group (60%) compared to patients without HCV (28%); moreover,

**Table 2**

Non-invasive radiological studies analysing liver iron concentration in haemodialysis patients treated with intravenous iron products.

Author (Ref.)	Year	Country	Radiological method	No of patients	Main characteristics of the patients	Main results
Canavese et al. [83]	2004	Italy	SQUID	40	Patients treated according to KDOQI 2006 and ERBP 2009 Ferritin target 200–500 µg/L	<ul style="list-style-type: none"> <li>- Normal LIC = 25% (n = 12) (median ferritin 245 µg/L)</li> <li>- Mild iron overload = 32.5% (median ferritin 329 µg/L)</li> <li>- Moderate iron overload = 37.5% (median ferritin 482 µg/L)</li> </ul>
Ferrari et al. [12]	2011	Australia	MRI-T2 Relaxometry (Ferriscan®) for liver	15	Ferritin >500 µg/L Median Ferritin = 782 µg/L	Hepatic siderosis in 9/15 patients (60%)
Ghoti et al. [13]	2012	Israel	MRI-T2* relaxometry	21	Ferritin >1000 µg/L	<ul style="list-style-type: none"> <li>- Hepatic siderosis in 19/21 patients (90%)</li> <li>- Spleen siderosis in 20/21 patients (95%)</li> <li>- Pancreatic siderosis in 3/8 patients tested (37%)</li> <li>- No cardiac involvement in 21 patients tested</li> </ul>
Rostoker et al. [14]	2012	France	SIR-MRI	119	Patients treated according to KDOQI 2006 and ERBP 2009 Ferritin target 200–500 µg/L	<ul style="list-style-type: none"> <li>- Normal LIC = 16% (<math>\leq 50</math> µmol/g dry weight)</li> <li>- Mild iron overload = 35.3% (<math>50 &lt; LIC \leq 100</math> µmol/g dry weight)</li> <li>- Moderate iron overload = 18.5% (<math>100 &lt; LIC \leq 200</math> µmol/g dry weight)</li> <li>- Severe iron overload = 30.2% (<math>LIC &gt; 200</math> µmol/g dry weight)</li> </ul>
Rostoker et al. [88]	2014	France	SIR-MRI	80	Patients treated according to ERBP Statement 2013 Ferritin target up to 300 µg/L	<ul style="list-style-type: none"> <li>Iron overload in 65 % of patients</li> <li>- Normal LIC = 35% (<math>\leq 50</math> µmol/g dry weight)</li> <li>- Mild iron overload = 41.25% (<math>50 &lt; LIC \leq 100</math> µmol/g dry weight)</li> <li>- Moderate iron overload = 12.5% (<math>100 &lt; LIC \leq 200</math> µmol/g dry weight)</li> <li>- Severe iron overload = 11.25% (<math>LIC &gt; 200</math> µmol/g dry weight)</li> </ul>
Tolouian et al. [85]	2016	USA	MRI-T2* relaxometry	17	Mean Ferritin 596 µg/L	Hepatic siderosis in 50% of patients of the 14 patients tested for LIC No cardiac involvement in the 17 patients tested
Castillo et al. [89]	2016	Spain	SIR-MRI	47	Patients with Ferritin >500 µg/L	<ul style="list-style-type: none"> <li>Hepatic siderosis in 43/47 (91%) patients</li> <li>- Mild iron overload = 53%</li> <li>- Moderate and severe iron overload = 38%</li> </ul>
Holman et al. [86]	2017	Australia	MRI-T2 relaxometry (Ferriscan®) for liver MRI-T2* relaxometry for cardiac analysis	10	Median ferritin 371 µg/L [95% CI: 175–1025]	Hepatic siderosis in 80% of patients No cardiac involvement in the 10 patients tested
Turkmen et al. [87]	2017	Turkey	MRI-T2* relaxometry	36	Mean Ferritin 472 µg/L (70% of patients had Ferritin between 200–500 µg/L)	<ul style="list-style-type: none"> <li>- Liver iron overload in 3 patients (8%)</li> <li>- Mild cardiac iron overload in 6 patients (16%)</li> </ul>
Ali et al. [91]	2018	Egypt	MRI-T2* relaxometry	50	25 patients suffering from hepatitis C	<ul style="list-style-type: none"> <li>Hepatic siderosis in 22/50 (44 %) patients</li> <li>- Mild iron overload = 14%</li> <li>- Moderate iron overload = 16%</li> <li>- Severe iron overload = 14%</li> </ul>
Rostoker et al. [90]	2019	France	SIR-MRI for liver iron MRI-T2* relaxometry for fat fraction	68 (62 on HD and 6 on PD)	Patients treated according to ERBP Statement 2013 Ferritin target up to 300 µg/L	Hepatic siderosis in 39/68 patients (57%): mild in 23, moderate in 9 and severe in 7

SQUID: superconducting quantum interference device; MRI: magnetic resonance imaging; LIC: liver iron concentration; SIR: signal intensity ratio; KDOQI: kidney disease outcomes quality initiative; ERBP: European renal best practice

iron overload was more severe in HCV patients (Table 2) [91].

No relationship was found in Europe between liver iron overload detected radiologically in the setting of dialysis and the major C282Y mutation of the HFE gene (implicated in genetic haemochromatosis), either homozygous or heterozygous in 40 Italian patients [83] and initially 119 French patients [14] with an extended analysis to 169 patients [92]. Likewise, no relationship was found between homozygosity and heterozygosity for the HFE gene variants H63D and S65C in haemodialysis-associated haemosiderosis in 75 French patients [92], whereas an association was found in Turkey between H63D heterozygosity and dialysis iron overload [87].

These findings reveal true liver iron thesaurosis; this differs markedly from the rapid, transient increase in exchangeable compartment of iron, with rapid efflux by the liver in a few days described in humans and minipigs by Beshara et al. using PET scan technology after infusion of iron sucrose and iron carboxymaltose [93, 94, 95], as opposed to slow efflux of iron from the overloaded liver continuing for several months, as

observed in dialysis patients after iron withdrawal [13, 14, 83].

While most haemodialysis patients receive parenteral iron supplementation, only a small number of peritoneal dialysis (PD) patients are treated with IV iron, usually as second-line therapy. Moreover, the ferritin target is far lower and more physiological in PD than in haemodialysis populations. A prospective, observational study recently measured LIC using SIR-MRI with the Rennes algorithm in a cohort of 32 PD patients in the Greater Paris area (France). The study showed that in contrast to haemodialysis patients, LIC is normal in most PD patients demonstrating that ESRD *per se* is not the culprit for iron overload in this setting [96] (Table 2).

In addition, a recent MRI-SIR study of LIC (with the Rennes algorithm) performed on 23 Portuguese ESRD patients not yet on dialysis showed the presence of iron overload in 74% of these patients who either exhibited dysmetabolic iron overload syndrome or had previously received iron products or blood transfusions [79]. Interestingly, their iron overload worsened during dialysis with anaemia treatment and iron

therapy as advocated by current guidelines [97].

Thus, the prevalence of iron overload may be vastly underestimated in haemodialysis patients receiving both ESA and IV iron [12, 13, 14, 83, 85, 86, 87, 88, 89, 90, 91]. These recent LIC imaging studies using SQUID (one study) or MRI (either SIR or T2\* relaxometry or T2/Ferriscan®) (10 studies) performed in various countries around the world have all documented hepatic iron overload in a very high percentage of haemodialysis patients receiving ESA and IV iron supplementation in compliance with current guidelines: the percentage of patients was found to be 66% (330/500) [99%CI according to Wald method: 0.60–0.71] in a pool analysis of the 11 radiological studies published on LIC in haemodialysis (Table 2) [12, 13, 14, 83, 85, 86, 87, 88, 89, 90, 91]. This iatrogenic side-effect may also affect ESRD patients not yet receiving dialysis [97].

From a pathophysiological point of view, haemodialysis-associated haemosiderosis observed in the modern ESA era seems to mimic that observed in transfusional siderosis with a tendency to deposit both in the liver and extrahepatic tissues (especially the spleen) [9]. Moreover, taking into consideration the achievements of iron biomarkers and MRI in secondary haemosiderosis and genetic haemochromatosis in recent years, neither levels of serum ferritin nor LIC are able to precisely stratify morbidity risk in ESRD patients on dialysis [9].

#### 2.5.5. Epidemiological studies analysing morbidity and mortality related to high IV iron doses

Short-term epidemiological studies have not demonstrated a detrimental impact of high-dose IV iron on morbidity or mortality in dialysis patients [98, 99, 100]. This was confirmed by a recent meta-analysis including seven clinical trials, mostly of short-term duration (median time of the studies: 16 weeks (range: 5–104)) with a small number of participants (n = 970), and also mostly short-term epidemiological studies [101]. Moreover, as stressed in the editorial accompanying this recent meta-analysis, concerns also arose due to important clinical heterogeneity between the studies, which span more than 20 years with changing use of ESA and lower haemoglobin targets differing significantly from the end-points of these trials [101, 102].

Conversely, four prospective, epidemiological studies with long-term follow-up (including the DOPPS study including 32435 haemodialysis patients followed for a median of 1.7 years in 12 industrialized countries) have all shown an association between excessive IV iron doses and an increased risk of cardiovascular morbidity and mortality among haemodialysis patients [103, 104, 105, 106]. Of note, despite their large sample sizes, these four observational studies could not establish causality and all remain susceptible to the possibility of residual confounding factors.

A prospective cohort study conducted in Taiwan in 2004 and 2005, included 1239 haemodialysis patients followed for 1 year: 583 patients were not receiving any iron therapy while 656 patients were treated with IV ferric chloride hexahydrate; those receiving IV iron were divided into three subgroups according to the cumulative dose received over 6 months: 40–800 mg, 840–1600 mg or 1640–2400 mg [103]. Patients in the two subgroups with the highest cumulative iron doses had the highest adjusted mortality with hazard ratios (HRs) of 3.1 and of 3.7, respectively, and more cardiovascular events (respective HRs = 3.5 and 5.1) than patients not receiving IV iron and those who had received <820 mg/6 months (equivalent dose of 136 mg/month) [103].

The main limitations of this study relate to the fact that the available data did not allow the analysis of the influence of the type of vascular access (e.g. native fistula, graft or catheter) and that the study relates to a unique homogenous Asian population in Taiwan [103].

In Japan in 2007, Kuragano et al. monitored 1086 haemodialysis patients prospectively for 2 years and compared oral iron versus IV iron therapy; patients treated with IV iron were divided into three groups: oral iron + very low-dose IV iron, low-dose IV iron (<200 mg/month) and high-dose IV iron (>200 mg/month) [104]. These authors observed more acute cardiovascular events and stroke (HR = 6.02) and hospitalization (HR = 2.77) in the high-dose IV iron group as compared to the low-dose

IV iron and very low-dose IV iron groups; moreover both the low (HR = 1.78) and high (HR = 5.22) IV iron regimens had an increased risk of infections [104]. The main limitations of this study relate to the fact that the available data did not allow the determination of the cause of infection and the study relates to a unique homogenous population in Japan where serum levels of iron biomarkers are remarkably lower than those found in other countries and where iron strategy is highly cautious [104].

The DOPPS study analysed the association between IV iron and clinical outcome in 32435 haemodialysis patients followed for a median of 1.7 years (range: 1–2.4) from 2002 to 2011 in 12 industrialized countries allowing the transposition of its results to most parts of the world; analysis was performed using Cox regression models with multiple adjustments [105]. This study found higher adjusted mortality in haemodialysis patients receiving either 300–399 mg/month (HR = 1.13) or ≥400 mg/month (HR = 1.18) compared to those receiving no iron, 1–99 mg/month, 100–199 mg/month or 200–299 mg IV iron/month [105]. In addition, the risk of hospitalization was higher (HR = 1.12) in dialysis patients receiving ≥300 mg/month of IV iron as compared to those receiving less [105]. This DOPPS study did not address the impact of cumulative doses of IV iron over many years and the effect of long dialysis vintage [105]. Of note, the detrimental monthly iron doses found in the DOPPS study are lower than that reported in 2005 by Kalantar-Zadeh et al. (400 mg/month) to be associated with higher mortality among USA haemodialysis patients treated in DaVita centres [107].

At the annual American Society of Nephrology meeting held in New Orleans in November 2017, Menoyo et al. presented the results of a prospective study of 1370 incident dialysis patients included between 2005 and 2015 in 49 French haemodialysis centres of the ECHO non-profit dialysis provider [106]. The average follow-up time was 41.5 months and 481 deaths occurred during the study period with a strong relationship between mortality and iron sucrose dose >200 mg/month [106]. The main limitation of this last study relates to the fact that it has not yet been published as a full article, notably with detailed methods and results [106].

Finally, a recent epidemiological study analysed the influence of five commonly used strategies of iron utilization (a set of decision rules with levels of iron status tests and corresponding iron dosing approaches) in a cohort of 18 697 USRD patients who started haemodialysis between 2009 and 2012 [108]. The authors analysed mortality and infection-related hospitalization in a dynamic Cox marginal structural model, after multiple adjustments for factors contributing to strategy initiation and deviation [108]. When compared to the strategy that recommended less intensive treatment at lower ferritin levels, strategies using a large amount of iron at high levels of ferritin and transferrin saturation inspired by the DRIVE trial [109], demonstrated an increased risk of all-cause mortality (60-day risk difference: 1.3% (0.8–2.1%); 120-day risk difference: 3.1% (1.0–5.6%)). These strategies with high IV iron use, inspired by the DRIVE trial [109] were also associated with an elevated risk of infection-related morbidity and mortality [108].

Interestingly, the recently published PIVOTAL trial confirms the lack of toxicity in dialysis patients of IV iron dosages <300 mg/month, as shown by DOPPS [31, 105].

Patients enrolled in the proactive high-dose arm received an average monthly dose of 264 mg (interquartile range, IQR 25<sup>th</sup> to 75<sup>th</sup> percentile: 200–336 mg) whereas patients in the low-dose reactive arm received 145 mg monthly during the trial (IQR: 100–190 mg) [31]. Thus, we do consider that via the PIVOTAL trial UK nephrologists have elegantly and firmly confirmed the validity of the epidemiological findings of the DOPPS study (published in 2015), which showed that IV iron dosages >300 mg/month are associated with increased mortality, especially of cardiovascular origin (cf supra) [105]. Of note, another recent DOPPS survey showed that about one-third of haemodialysis patients in Western countries still continue to receive an average IV iron dose of 400 mg/month and as such are exposed to the potential risk of iron toxicity

[110, 111].

Iron overload in haemodialysis patients (defined by high LIC on quantitative MRI) was shown to result in increased production and elevation of plasma hepcidin levels [13, 14], whereas a decrease in LIC (on MRI) after IV iron product withdrawal was associated with a parallel reduction in hepcidin-25 levels [14]. By activating macrophages, elevated hepcidin can cause atherosclerotic plaque instability and increase the risk of ischemic cardiovascular complications [2, 25]. High hepcidin-25 levels have recently been linked cardiovascular events (both fatal and nonfatal events) in dialysis patients, pointing to the increase in hepcidin as an additional culprit mediator of cardiovascular morbidity in dialysis patients with iatrogenic iron overload [112].

Moreover, liver iron load has recently been shown to influence hepatic fat fraction and moderate or severe iron overload in dialysis patients may trigger or aggravate NAFLD in this setting [90] (see infra section: 3.3.2. Are liver fibrosis and cirrhosis relevant endpoints for iron toxicity?).

## 2.6. Inflammatory bowel disease

Patients with IBD are commonly treated with IV iron preparations as IBD is often associated with anaemia, which is caused by a combination of iron deficiency and systemic inflammation [32]. IV iron preparations were strongly advocated in 2007, in the European guidelines for the “Management of anaemia in patients with IBD” on the basis of their better efficacy and tolerance [8]. In compliance with the 2007 European guidelines, after initial correction of iron deficiency, patients usually remain on maintenance IV iron treatment [8].

The increasing use of IV iron preparations for the treatment of anaemia in patients with IBD over the past decade has increased the potential risk of iatrogenic iron overload in this population [24], although in contrast to haemodialysis patients, there are no published studies devoted to the radiological analysis of LIC in IBD patients treated long-term with IV iron products.

The 2015-European “Consensus on the diagnosis and management of deficiency anaemia in inflammatory bowel diseases” has taken a more conservative approach by recommending oral iron supplementation in patients with inactive IBD and IV iron therapy once ferritin falls below 100 µg/L [113]. Moreover, to reduce the risk of iatrogenic haemosiderosis, quantitative MRI was advocated in 2013 by French gastroenterologists for the follow-up of liver iron stores in clinical practice in IBD patients treated long-term with IV iron products [24], in the light of the findings in dialysis patients [14].

## 2.7. Evaluation of the pharmacovigilance committee of the EMA on the risk of iron overload associated with intravenous iron products

In February 2013, after analysing the report and publication of Rostoker et al. in the *American Journal of Medicine* [14], the French Drug Agency (ANSM) published a letter of information to prescribers stipulating that although dialysis patients in the study were treated according to current clinical guidelines [3], the strategy of iron therapy was off-label, explaining the appearance of iron overload [114]. The ANSM then called for French nephrologists to strictly follow the label for IV iron products [114].

In 2015, the Committee for Medicinal Products for Human Use of the EMA (abbreviated as CHMP) published a reflection paper on “The data requirements for intravenous iron-based nano-colloidal products” and stated that the risk of iron overload leading to organ damage was inherent to all IV iron products [115]. The CHMP considered that this risk can be mitigated substantially by strict adherence to therapeutic indications/contraindications and by avoiding off-label use as medication errors [115].

Recently, in September 2017, the Pharmacovigilance Committee of the EMA (abbreviated as PRAC) considered recent publications on the risk of iatrogenic iron overload with its potential consequences in dialysis

patients and the potential analogy in IBD patients [15]; the PRAC requested that pharmaceutical companies with marketing authorization (MAHs) for iron products should “investigate the risk of iron overload, particularly in chronic kidney disease (CKD) patients and in patients with inflammatory bowel disease (IBD) and provide a cumulative review of all cases of iron overload reported with iron-containing products” [15]. The PRAC also stipulated that “MAHs should discuss the need to update the product information accordingly and develop appropriate communications to remind prescribers of the measures to minimize this risk” [15].

Of note, the EMA has not established guidelines on the management of anaemia and iron deficiency in ESRD and IBD, but has specifically focused on avoidance of the potential risk of iron overload favoured by the actual modalities of IV iron therapy in these settings and the need to monitor this issue in current clinical practice.

## 2.8. Expert opinion

### 2.8.1. Evolving conceptions of iron therapy in ESRD over the past 3 decades

Conceptions of iron therapy in CKD patients have dramatically changed over the past 3 decades, from the initial aim of avoiding iron deficiency in the late 1980s to overcoming functional iron deficiency and sparing costly ESA treatment today, leading to an increase in use of iron products worldwide [4,116]. When EPO replacement therapy first appeared on the market and was available for use in dialysis patients in daily practice in the late 1980s, the aim of iron therapy was to maintain iron stores repleted minimally (with serum ferritin levels >50 µg/L), allowing true iron deficiency to be prevented, with oral iron supplements used as first-line therapy. IV iron products were then considered only as a second-line therapeutic option in cases of poor tolerance or ineffectiveness of oral iron drugs or when severe iron deficiency was present [116, 117, 118]. The European Best Practice Guidelines (EBPG) of the European Renal Association (ERA-EDTA) published in 2004 and the KDOQI in the USA, published in 2006, both changed the definition of iron deficiency (ferritin <100 µg/L instead of 50 µg/L) and advocated even higher iron-store repletion criteria (ferritin target >200 µg/L and <500 µg/L) based only on short-term trials of IV iron products and bone marrow studies [3,119].

More recently, the international KDIGO 2012 guidelines highlighted the risk of functional iron deficiency (now called iron-restricted anaemia) during ESA treatment (despite the fact that the haemoglobin target has been lowered in the most recent product label of ESA), and put forward the capacity of IV iron products to either obviate the need for ESA or to reduce the dosage of ESA, by advocating a trial of IV iron up to 500 µg/L of serum ferritin [4]. These clinical guidelines and the older ERA-EDTA position statement, which are closely followed by nephrologists worldwide, have clearly contributed to the extensive use of IV iron in haemodialysis patients over the past decade [7,120]. The fear of nephrologists of severe cardiovascular and oncological side-effects of ESA has also deeply amplified this phenomenon [7,120,121]. Finally, it is very likely that the chronic indiscriminate use of IV iron products in haemodialysis patients in developed countries has also been promoted by new reimbursement policies (bundling in the USA and its equivalent in Europe, leading to ESA that is not chargeable and is now included in the price of the dialysis session package) in order to reduce the high costs of anaemia therapy for dialysis stakeholders [7,120,121].

### 2.8.2. Ongoing debate in the nephrology community on anaemia management

Some recent radiological and epidemiological findings have led to editorials and position papers highlighting the potential dangers of the excessive use of IV iron products in CKD patients and the inadequacy of guidelines proposed in 2012 by the KDIGO, the iron biomarker targets set by the KDOQI in 2006 and the EDTA-ERA statement in 2009 for their ability to protect ESRD patients from iron overload [120,122,123]. Moreover recent reviews on anaemia and iron therapy in CKD have also presented a more balanced view, emphasizing the benefits and also



describing the potential risks, including iron overload [124,125,126,127].

Recent changes in the approach to iron therapy have also occurred among nephrology societies. In 2013, the ERBP position (of the EDTA-ERA) on anaemia management clearly warned against the excessive and indiscriminate use of IV iron products in ESRD, owing to the potential risk of iatrogenic iron overload [6]; this statement was based on an analysis of studies of LIC by MRI in dialysis patients treated with IV iron products (published in 2011 and 2012) and a SQUID study published in 2004 [6, 13, 14, 83].

The KDIGO Controversies Conference on iron management in chronic kidney disease took place on March 2014 in San Francisco and was attended by an international panel of nephrologists, haematologists, hepatologists and specialists in iron metabolism [25]. The conference stated in its consensus paper that “*measurements in unselected haemodialysis 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. At present, there is insufficient evidence to support the use of hepatic magnetic resonance imaging in guiding iron therapy in clinical practice*” [25]. The conference also called for specific research agenda on the subject of iron overload [25].

Finally, in June 2015, the ASN (American Society of Nephrology) Dialysis Advisory Group analysed in a critical review the uncertainties of IV iron therapy in dialysis and put forward a detailed list of controlled trials, translational research and prospective epidemiological studies to overcome these uncertainties [121].

### 2.8.3. Main questions debated among nephrologists about iron toxicity

Publications on the potential risk of iatrogenic iron overload in haemodialysis patients and the recent decision of the EMA PRAC have led to increased debate among nephrologists on the safety of iron products. They also reveal an important gap in conception and practice between most American nephrologists compared to Japanese and European nephrologists. Most nephrologists in the USA use very large doses of IV iron to spare costly ESA [77, 78] and consider this practice safe [128,129]. In contrast Japanese physicians have for decades minimized exposure of their patients to IV iron products to prevent iron overload [79,130], and European nephrologists use more moderate doses of iron to maintain their haemodialysis patients in an iron replenished state [79]. This difference in conception of iron therapy between continents was obvious in the discussions of the KDIGO controversies conference, held in San Francisco in 2014 [25,129]. At least three topics in this field remain controversial among the nephrology community.

**2.8.3.1. Does exposure to supra-physiological doses of iron really matter in dialysis patients?** Taking into account that the average life-expectancy of dialysis patients in industrialized countries is around 4 years, some nephrologists have raised the relevant question as to whether or not patients exposed to high IV iron doses will live long enough to develop organ failure (especially liver and heart) due to iron overload [25]. Nevertheless, there is good evidence that iron overload with high LIC may act by disrupting homeostasis of hepcidin, rendering atherosclerotic plaques unstable and in this way increase the burden and accelerate the progression of cardiovascular diseases, which are extremely high in dialysis patients when compared to non-renal patients and healthy populations [7]. Moreover, high hepatic iron load in dialysis patients can adversely influence liver fat fraction (see infra: chapter 3.3.2) [90].

Finally, long-term exposure to excess iron may also apply to this subset of young highly sensitized dialysis patients who have repeated graft failure and therefore a relatively short time free from dialysis; these young patients consequently have a very long cumulative dialysis duration of 1–2 decades or even longer. In these patients a long-term positive iron balance can thus be detrimental [2].

This controversy in dialysis patients has some similarities with a

recent debate in the thalassemia field which arose due to the observation of a benefit of chelation up to normal ferritin and LIC levels, with the disappearance of morbidities [131]. This debate on the management of thalassemia has led the haematology community to reconsider the previously admitted comfort zones in this setting and to advocate physiological levels by intensive MRI monitoring and chelation therapy [132].

Thus, by analogy with the new strategy management for TDT and NTDT, it seems that ESRD patients on dialysis would also benefit from more physiological parameters of iron metabolism (e.g. ferritin and LIC) to prevent potential morbidities and lessen the disturbances of uraemia.

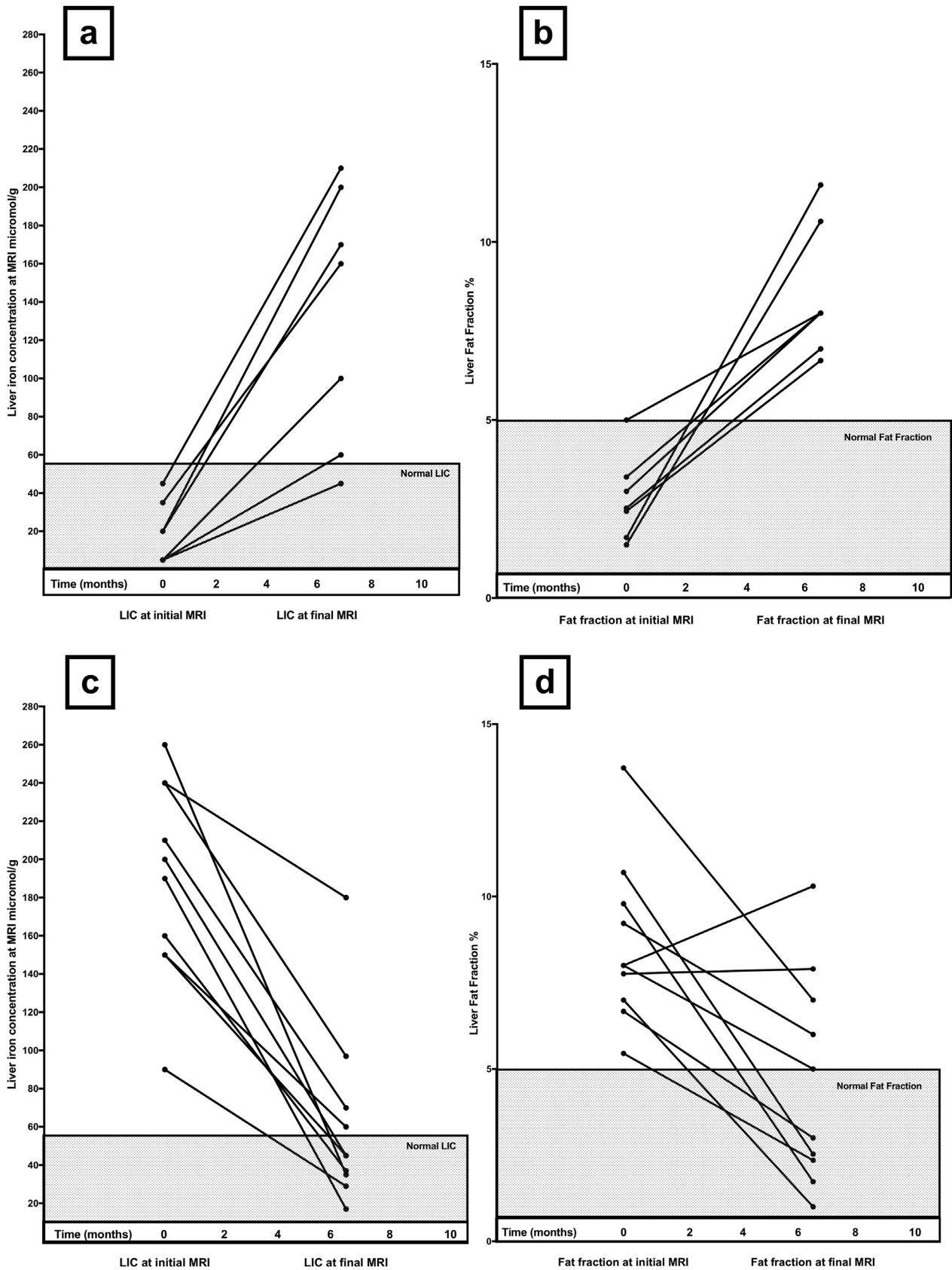
**2.8.3.2. Are liver fibrosis and cirrhosis relevant endpoints for iron toxicity?** Some nephrologists consider that abnormally high LIC has no clinical relevance and require either disturbance of hepatic enzymes or histological evidence of liver damage as a proof of iron toxicity [25,128,129,133].

In post-mortem studies of dialysis patients with severe hepatosplenic siderosis in the pre-ESA era, massive hepatic siderosis was seldom associated with cell damage whereas trichrome and reticulin stains showed a more abundant fibroconnective framework and a loss of liver cells; cirrhosis was rare [134,135,136]. Liver biopsy showed focal portal fibrosis in most patients with marked haemosiderosis [137]. All together, these studies showed that the risk of hepatic cirrhosis in historical iron-overloaded dialysis patients before EPO discovery was low in the absence of viral hepatitis [2,134,135,136].

These data, observed in the pre-ESA era, strongly suggest that hepatic fibrosis and cirrhosis are very late events in iron overload observed in ESRD dialysis patients and cannot be considered as adequate markers of hepatic iron toxicity in dialysis patients.

Of note, in pre-ESA studies of dialysis patients with iron overload, disturbance of liver enzymes was seldom encountered [135,136,137].

Very recently, a study analysed the hypothetical triggering and aggravating role of IV iron on non-alcoholic fatty liver disease (NAFLD) in dialysis patients [90]. NAFLD is a spectrum of diseases including isolated steatosis, non-alcoholic steatohepatitis (NASH), cirrhosis and end-stage liver failure. In NASH and NAFLD, hepatic iron accumulation has been linked to hepatic fibrosis [90]. In a cross-sectional prospective study, LIC and hepatic proton density fat fraction (PDFF) were analysed simultaneously in a cohort of 68 ESRD patients maintained on dialysis (receiving parenteral iron and ESA, in keeping with current guidelines) by MRI using SIR according Rennes University (LIC measurement) and R2\* with IDEAL-IQ (an algorithm devoted to measurement of both liver fat fraction and iron content) [90]. Close follow-up of LIC and PDFF by MRI was also performed in 17 dialysis patients during iron therapy [90]. In this cross-sectional study, 57.4% of dialysis patients had hepatic iron overload (of differing degrees of severity) (Table 2) and abnormal liver fat fraction was mainly observed in patients with moderate and severe iron overload. Indeed, PDFF (normal value < 5%) differed significantly among dialysis patients classified according to non-heme iron stores. The subgroup of patients with moderate and severe iron overload had increased fat fraction (PDFF: 7.9% [95%CI: 0.5–14.8]) when compared to those either with normal (PDFF: 5% [95%CI: 0.27–11]) or mild iron overload (PDFF: 5% [95%CI: 0.30–11.6]); (p = 0.0049, Kruskal-Wallis test) [90]. PDFF correlated with LIC and ferritin and body mass index. In a longitudinal study, seven patients were closely monitored during IV iron therapy: both their LIC and PDFF increased concomitantly (PDFF: initial 2.5%, final 8%, p = 0.0156; LIC: initial 20 µmol/g, final 160 µmol/g; p = 0.0156), whereas in 10 patients with iron overload closely monitored by MRI, PDFF decreased after IV iron withdrawal or major dose reduction (initial: 8%, final: 4%; p = 0.0098) in parallel with LIC (initial: 195 µmol/g, final: 45 µmol/g; p = 0.002) (Fig. 1) [90]. Thus, the similar evolution of LIC and PDFF, with increasing values observed on IV iron therapy, as well as their simultaneous decrease after iron withdrawal or a major reduction in iron dosage, supports the causal link between



**Fig. 1.** Time-course of hepatic iron stores and liver fat fraction studied by magnetic resonance imaging in 17 dialysis patients. (a) Initial and final liver iron concentrations (LIC) by magnetic resonance imaging (MRI) in 7 patients during iron therapy. (b) Initial and final liver fat fraction by MRI in 7 patients during iron therapy. (c) Initial and final liver iron concentrations by MRI in 10 patients after iron withdrawal (n=6) or a major iron dose reduction (n=4). (d) Initial and final liver fat fraction by MRI in 10 patients after iron withdrawal (n=6) or a major iron dose reduction (n=4).

liver iron load and hepatic fat fraction in dialysis patients [90]. This study also strongly suggests that iron overload induced by iron therapy may aggravate or trigger NAFLD in dialysis patients and that PDFF may represent a new early surrogate marker of iron liver toxicity in this setting.

**2.8.3.3. Do iron generics have a specific role in the occurrence of haemodialysis-associated haemosiderosis?** Taking into account publications highlighting a lesser clinical effect of iron sucrose generics in dialysis patients [138,139], Rottembourg in his recent review on Non Biologic Complex Drugs (which are complex classical drugs, including iron-carbohydrate drugs, liposomal drugs and glatiramoids), raised the question about the potential influence of generics on the occurrence of haemodialysis-associated haemosiderosis [140].

An analysis of published articles in this setting strongly suggests that radiological iron overload by MRI or SQUID is encountered equally with either original iron sucrose (Venofer®) [13, 14] or its generics [88], as with iron polymaltose [12, 86]. Moreover, a comparative study of two cohorts of French dialysis patients (treated with different ferritin targets) provided insight on the relationship between the infused dose of iron sucrose (either original Venofer® [14] or generic iron sucrose from Actavis) and LIC [88]. Both the cumulative dose of iron infused in the year before MRI (first cohort treated with Venofer®:  $\rho = 0.31$  (0.07–0.52),  $p = 0.01$ ; second cohort treated with iron sucrose-Actavis:  $\rho = 0.37$  (0.03–0.63),  $p = 0.03$ ; Spearman correlation test) and the iron dose infused per month in the year before MRI (first cohort treated with Venofer®:  $\rho = 0.31$  (0.07–0.52),  $p = 0.01$ ; second cohort treated with iron sucrose-Actavis:  $\rho = 0.37$  (0.04–0.63),  $p = 0.03$ ; Spearman's correlation test) correlated closely with LIC on MRI, within the same range, strongly suggesting a similar risk of liver accumulation with the two iron sucrose products [14, 88].

Thus, despite the fact that iron sucrose generics may have lower clinical efficacy (probably related to -15% of the pharmaceutical product authorized by the EMA), they cannot be seen as intrinsic culprits of iron overload in dialysis patients. The occurrence of cases of haemodialysis-associated haemosiderosis with generic IV iron product is more likely related to their long-term indiscriminate use (as with original IV iron products).

### 3. Conclusions

Given the strong of evidence of benefit of IV iron in the treatment of anaemia in ESRD [31] and IBD [8], there is a need to take into account its double-edged sword [141] effect highlighted in recent studies using new non-invasive liver imaging techniques. These studies showed that iatrogenic hepatic iron accumulation is associated with increased hepcidin production raising the risk of destabilizing atheromatous plaques (by activating their macrophages) [13, 14, 112] and triggering or worsening of fatty liver disease [90], as also shown by the epidemiological findings of DOPPS on association of toxic doses of iron with mortality [105].

The decision of the EMA to prevent or minimize the risk of liver iron overload in this setting, is aimed at favouring the emergence of new pharmacometric paradigms of iron therapy and anaemia management in ESRD and IBD with a therapeutic balance of efficacy versus safety. It is also likely to have important implications for the well-being of the 2 million haemodialysis patients and thousands of IBD patients worldwide.

### Declarations

#### Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

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#### Additional information

No additional information is available for this paper.

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