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Scholarly Review

# Impact of iatrogenic iron overload on the course of hepatitis C in the dialysis population: A plea for caution

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**Abstract**

About 2.5% of the world population, corresponding to about 177 million individuals, are infected by hepatitis C virus (HCV), a small, single-stranded RNA virus. The prevalence of HCV infection among dialysis patients in Japan, Europe, and North America during the 2012 to 2015 period was found to be 8.7% in the DOPPS study. Nosocomial HCV spread in hemodialysis facilities still occurs. Increased hepatic tissue iron has been shown to play a deleterious role in the course of hepatitis C, favor development of fibrosis and cirrhosis and possibly increase the risk of liver cancer in the general population. Regular loss of blood in the hemodialysis circuit, in routine blood sampling for laboratory tests (for uremia monitoring), and in gut due to uremic enteropathy, invariably results in iron deficiency for which patients are commonly treated with intravenous (IV) iron preparations. Data on the effects of IV iron in hemodialysis patients with hepatitis C are limited (2 studies) and strongly suggest that parenteral iron may contribute to hepatocellular injury.

Iatrogenic iron overload is extremely prevalent among hemodialysis population worldwide. Iron overload and toxicity has emerged as one of the most controversial topic in the management of anemia in dialysis patients. Given the known impact of iron in promoting growth and virulence of HCV and the associated liver disease, it is necessary to use iron therapy cautiously and closely monitor plasma markers of iron metabolism and liver iron stores non-invasively by means of MRI to avoid iron overload in this vulnerable population.

**Key words:** HCV, hemodialysis, hepatopathy, IV iron, ferrotoxicity

## INTRODUCTION

Hepatitis C virus (HCV) is a small, single-stranded RNA virus which belongs to the genus *Hepacivirus* (Flaviviridae family). An estimated 177 million people are infected with HCV worldwide, representing about 2.5% of the world population. Two-thirds of these individuals are viraemic.[1] Once infected with HCV, 80% of viraemic patients progress to chronic hepatitis, of whom 20% will

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develop cirrhosis. HCV is one of the most common causes of progressive liver disease and is a major indication for liver transplantation in developed countries.[1] Moreover, HCV is responsible for a large number of significant health problems in up to 74% of the patients, including endocrine, renal, lymphoproliferative, cardiovascular, metabolic, and central nervous system comorbidities, which contribute significantly to HCV-related mortality.[1,2] HCV infection can induce cryoglobulinemic membranoproliferative glomerulopathy, and non-cryoglobulinemic nephropathy. In addition, patients with chronic kidney disease (CKD) are at high risk of HCV infection, which can adversely affect the outcome of dialysis and transplantation.[2] The prevalence of HCV infection in dialysis patients in Japan, Europe, and North America was 14.3% in the 1996 to 2001 period and had declined to 8.7% in the 2012 to 2015 period according to the DOPPS study.[2] Unfortunately, nosocomial HCV spread continues to occur in hemodialysis facilities. Adjusted HCV seroconversions per 100 hemodialysis patient-years ranged from 1.2 (0.7–2.0) in the United Kingdom to 3.9 (2.9–5.2) in Italy.[2]

Liver iron deposits are associated with worse outcomes in hepatitis C; moreover, iron may increase the risk of liver cancer in patients with HCV-related chronic hepatitis.[3]

Iron overload is an increasingly recognized clinical situation among hemodialysis patients. Recent studies using quantitative MRI to estimate liver iron stores have suggested a strong link between the IV iron dose and the risk of iron overload in dialysis patients, and have challenged the reliability of currently accepted iron biomarker cutoff values and clinical guidelines, especially regarding recommended iron doses.[4,5] Iron-overload toxicity is now one of the most controversial topics in the management of anemia in dialysis patients.[6]

The KDIGO Controversies Conference on iron management in chronic kidney disease, which was held in San Francisco on 27 to 30 March 2014, recognized "iron overload" among hemodialysis patients as an entity in its consensus statement, and called for an agenda of research on this topic. Among the research recommendations, the KDIGO conference underlined the possibility of potential aggravation of viral hepatitis by therapeutic iron in CKD and end-stage renal disease (ESRD) patients.[7] Finally, the Dialysis Advisory Group of the American Society of Nephrology recently published an *aggiornamento* on the policy of high "blind" usage of iron in hemodialysis patients.[8] Thus, a narrative review of the complex relationship between iron and HCV might help to build a safe, largely evidence-based approach to iron therapy in HCV-infected ESRD population.

## ABNORMAL LEVELS OF IRON BIOMARKERS ARE FREQUENTLY ENCOUNTERED IN HCV-INFECTED PATIENTS

Analysis of data from the third US national health and examination survey (NHANES III) in 2005, which included 14,462 participants, revealed that HCV-infected patients had higher ferritin levels than healthy participants (229 ng/mL; 95% CI: 195–263 ng/mL vs. 101 ng/mL; 95% CI: 99–104 ng/mL), and that ferritin levels correlated with the serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gammaglutamyl transpeptidase.[9] HCV-infected patients with high ferritin levels (above the sex-specific median: 85 ng/mL in females and 203 ng/mL in males) were shown to be poorly responsive to the combined therapy with interferon and ribavirin in the Swiss cohort of 876 patients.[10] Ferritin levels were a strong predictor of severe liver fibrosis and steatosis in this Swiss cohort, and a good predictor of severe liver fibrosis and severe necroinflammatory activity in Roumanian patients.[10,11] Finally, oscillations of serum ferritin levels have also been linked to combined antiviral therapy with interferon and ribavirin.[12]

## DELETERIOUS EFFECTS OF LIVER IRON DEPOSITS ON THE NATURAL HISTORY OF HEPATITIS C

Mild or moderate liver iron deposits are seen on liver biopsy (spectophotometry and/or Perls stain) in 7% to 61% of patients with chronic hepatitis C.[13–15] These liver iron deposits are associated with the severity of liver disease (higher histological inflammatory activity score) and decrease significantly with interferon therapy.[14] Mesenchymal iron accumulation within Kupffer cells and endothelial cells is more common than hepatocellular iron in HCV-related liver disease, but both compartments can be affected, especially in advanced chronic hepatitis C.[14,15] In the HALT-C study, higher baseline levels of iron in hepatocytes and in portal triads increased the risk of poor clinical outcome (ascites, hepatic encephalopathy, variceal bleeding, spontaneous bacterial peritonitis, hepatocellular carcinoma, and death) and were associated with a high Child-Turcotte-Pugh score (>7). In contrast, the likelihood of the adverse clinical outcomes was not significantly related to the presence of stainable iron in reticulo-endothelial cells or portal stromal cells.[15] Iron deposition predominantly within Kupffer cells and portal macrophages, together with the correlation between hepatic necroinflammatory activity and

iron accumulation, strongly suggest that mesenchymal hepatic iron overload results from hepatocyte necrosis leading to release of ferritin from hepatocytes and its uptake by macrophages and Kupffer cells. These events can contribute to cytokine release triggering inflammation and fibrosis.[3]

The reduction of excess liver and body iron stores by phlebotomy has been shown to ameliorate the course of hepatitis C among patients who cannot receive interferon. In addition, phlebotomy improves histologic lesions and potentiates the salutary effects of interferon. In fact phlebotomy was an accepted therapy for hepatitis C infection in the United States and Japan before the advent of direct-acting antiviral agents.[16–18] In a systematic review, Fanchini et al. reported that patients treated with phlebotomy followed by interferon therapy (in 7 studies with 373 patients) had an odds ratio of 2.32 (95% CI: 0.96–6.24) for achieving a sustained virologic response as compared to patients receiving interferon alone[19]; of note, in that meta-analysis CIs crossed 1, thus weakening the demonstration. Similarly, in a second meta-analysis of 6 randomized controlled trials including 367 patients, Desai and co-workers compared interferon therapy alone to interferon plus concomitant phlebotomy.[20] The authors concluded that phlebotomy significantly improved the virologic response to interferon (odds ratio: 2.69: 95% CI: 1.60–4.52).[20]

## DELETERIOUS ROLE OF LIVER IRON DEPOSITS IN NON-HCV HEPATOPATHIES

Elevated liver tissue iron (usually mild or moderate) is encountered in about 40% of patients with chronic hepatitis B and has been linked to the severity of liver disease (higher activity scores and fibrosis).[21] Similarly, mild to moderate increase in liver tissue iron is encountered in about half of patients with non-alcoholic steatohepatitis (NASH). Mesenchymal iron deposition is more common than hepatocellular iron accumulation in NASH, but both compartments are usually affected. Hepatic iron accumulation is linked to the severity of hepatic fibrosis in NASH patients.[22,23] Iron was shown to induce liver fibrosis in gerbils by increasing collagen and TGF beta expression, which were reduced by vitamin E used as an antioxidant.[24]

## THE HEMOCHROMATOSIS GENE (*HFE*) MODULATES LIVER IRON OVERLOAD IN HEPATITIS C

*HFE* is located in the HLA region of chromosome 6 and HFE protein regulates iron absorption. Homozygous mutation of C282Y is associated with hereditary hemochromatosis in 64% of Italian patients and 100% of Australian patients.[25]

The homozygous or heterozygous mutation of HFE C282Y causes hepatic iron overload which promotes steatosis and liver fibrosis in HCV-infected patients.[26–29] Similarly deleterious influence of HFE C282Y and H63D mutations has been shown in chronic hepatitis B[26] and in NASH.[22,23] HFE mutation is also associated in NASH with ethnicity.[30] Interestingly, a recent meta-analysis (605 patients, 7 studies) concluded that contrary to C282Y and S65C mutations, the common H63D mutation (homozygous or heterozygous), was associated with a sustained virological response in chronic hepatitis C patients treated with interferon-based therapy.[31]

## HCV INFECTION ALTERS HEPCIDIN SYNTHESIS

Hepcidin-25 is the master regulator of iron metabolism.[32,33] Deficient hepcidin synthesis plays a central role in genetic hemochromatosis,[25,34] whereas unregulated hepcidin synthesis is responsible for a new genetic form of iron-deficiency anemia (IRIDA: Iron-Refractory Iron-Deficiency Anemia).[35]

Serum hepcidin has been shown to be lower in the cohorts of Italian and Greek patients with hepatitis C and liver hepcidin production has been shown to be lower in Japanese patients with hepatitis C than in patients with other liver diseases.[36–38] Due to the suppression of hepcidin, ferroportin is upregulated in the duodenum of HCV-infected patients, leading to unregulated intestinal iron absorption, as seen in genetic hemochromatosis and thalassemia.[39] Thus, decreased hepcidin-mediated degradation of ferroportin constitutes one of the main pathophysiological mechanism responsible for superimposed hepatic iron overload in HCV-infected patients.[40]

## MOLECULAR AND CELLULAR MECHANISMS OF IRON TOXICITY IN HCV-INFECTED PATIENTS

Iron, at concentrations of 50 and 100 $\mu$mol of FeSO4, has been shown to enhance HCV replication about 10-fold in cultured human hepatocytes (non-neoplastic PH5CH8 cells) within 48 hours.[41] Conversely, supra-physiologic doses of iron induced by haemin were shown to downregulate HCV replication by inactivating NS5B RNA polymerase in the neoplastic cell line Huh7.[42,43]

Excessive iron load in the liver induces oxidative stress by catalyzing generation of hydroxyl radical which promotes formation of lipid peroxides, oxidation of amino acid side-chains, disruption of DNA strains, and fragmentation of proteins. These events cause damage and dysfunction in hepatocyte and their organelles (lysosomes, mitochondria, endosomes, and micropinocytotic vesicles) and deposition of scar tissue in the liver.[3]

## INTERPLAY OF IRON AND HCV AT THE CELLULAR LEVEL

Uptake of transferrin-bound iron ($Fe_2$-Tf) at physiological concentrations is mediated by 3 pathways involving transferrin receptor 1 (TfR1, the "classical" pathway), TfR2, and a TfR-independent pathway. TfR1 is highly expressed on erythroblasts and, to a lesser degree, on hepatocytes. After binding to TfR1, the $Fe_2$Tf-TfR1 complex is internalized by endocytosis, and iron is released within the endosome.[44] Interestingly, transferrin receptor 1 (TfR1) was recently identified as an HCV entry port in hepatocytes, during HCV glycoprotein-mediated entry.[45] Moreover, in the hepatoma cell line Huh 7, HCV infection was shown to cause cellular iron depletion by increasing iron regulatory protein (IRP) activity (via the accumulation of IRP 2) and suppressing transferrin receptor 1 (TfR1) and divalent metal transporter 1 on these cells.[46]

The HCV genome contains an RNA structure mimicking an iron-responsive element (IRE) on its internal ribosome entry site (IRES) suggesting that HCV itself can modulate iron metabolism at cellular level; nevertheless it seems that the HCV IRES domain IV RNA structure is not an authentic IRE, as shown by electrophoretic mobility shift assays.[47]

## IRON AND THE RISK OF LIVER CANCER IN PATIENTS WITH CHRONIC HEPATITIS C

Hepatocellular carcinoma is the third leading cause of cancer death in the world, accounting for about half a million of deaths per year.[48] Chronic liver infection with hepatitis B virus and HCV have been recognized as human liver carcinogens; these 2 viruses cause about 75% of all cases of hepatocellular carcinoma worldwide.[48] In southern Italy, an epidemiologic study recently showed a prevalence of hepatocellular carcinoma of 63.3 cases/$10^5$, with a hazard ratio (HR) of 61.8 (95% CI: 13.3–286) for HCV-infected patients and of 75 (95% CI: 12.3–456.5) for HBV antigen carriers.[49] Of note, in HCV infection, hepatocellular carcinoma develops almost exclusively in a liver with established fibrosis or cirrhosis, and dual HBV and HCV infection in cirrhotic patients markedly increases the risk of hepatocellular carcinoma (odds ratio of 165, as compared to 17 for HCV alone and 23 for HBV alone).[50]

Besides iron overload (genetic hemochromatosis and secondary hemosiderosis), non-viral factors have been linked to hepatocellular carcinoma, including alcohol and tobacco consumption, aflatoxin, schistosomiasis, diabetes and obesity, and some liver diseases.[48] Alcohol synergizes with HCV, increasing the risk of hepatocellular carcinoma 1.7- to 2.9-fold as compared to HCV alone.[50]

The relative risk of hepatocellular carcinoma in patients with genetic hemochromatosis and cirrhosis was initially thought to be as high as 200-fold, but more recent estimates suggest a 20-fold increase. Hepatocellular carcinoma has even been reported in cirrhosis-free patients with genetic hemochromatosis.[48] Patients with thalassemia and those with African iron overload (10-fold increased risk) are also at a greater risk of hepatocellular carcinoma.[48]

In patients with chronic hepatitis C, the incidence of hepatocellular carcinoma follows a J shape pattern with respect to serum ferritin levels, i.e., the incidence being highest when the ferritin is lower than 80 ng/mL or higher than 323 ng/mL, with a HR of 2.19 (95% CI: 1.02–4.70).[51]

Of note, exposure to iron in groundwater was also recently shown to be a strong risk factor for hepatocellular carcinoma in an ecological study conducted in Taiwan.[52]

Transgenic C57BL/6 male mice expressing HCV polyprotein and fed an iron-rich diet had an increased liver iron content, marked hepatic steatosis, ultrastructural alterations of mitochondria, and increased hepatocyte proliferation.[53] At 12 months, 45% of transgenic mice fed high iron, but in none of those fed a normal-iron diet developed hepatic tumors including hepatocellular carcinoma.[53] Of note, iron compounds have also been shown to cause lung cancer, pleural and peritoneal mesothelioma and renal carcinoma in experimental animals.[54]

The beneficial impact of phlebotomy on the risk of hepatocellular carcinoma in HCV infection also supports the deleterious role of iron in liver carcinogenesis. Indeed, in 2 Japanese studies, the incidence of liver cancer in HCV-infected patients not responsive to interferon-ribavirin therapy was dramatically reduced by phlebotomy (which decreases body iron stores) from 43.7% to 10.3% after 8 years of observation in 102 patients[55] and from 39% to 8.6% after 10 years in 75 patients.[56] The reduction in the risk of hepatocellular carcinoma after

phlebotomy is predicted by the decrease in serum alpha-fetoprotein.[57]

At the molecular level, iron has been shown to induce liver carcinogenesis by promoting cyclin D1 gene expression in hepatocytes.[58] Cyclin D1 is a protein involved in the G1 phase of the cell cycle; it is overexpressed in iron-overloaded liver and correlates with early abnormalities of hepatocyte cell cycle progression.[58] It was also recently shown that activation of Fenton reaction by iron overload can be cancerogenic by altering the p15 $^{INK4B}$ and p16 $^{NK4A}$ tumor suppressor genes (homozygous deletion or methylation of the promoter region[59]) and microRNA physiology. MicroRNAs are endogenous single-strand regulatory RNAs that modulate protein synthesis: they are non-coding, but regulate gene expression post-transcriptionally.[60] MicroRNAs are involved in the development and progression of hepatocellular carcinoma by regulating oncogenes and tumor suppressor genes. The 2 mediators of cell cycle arrest, Cyclin D2 and E2, are directly targeted by *miR-26a,* and are frequently low in hepatocellular carcinoma. Expression of miR-195, which regulates the expression of cyclin D1, CDK6, and EnF3, is also reduced, leading to a failure to induce cell cycle arrest at the G1-S checkpoint.[60] MicroRNAs might thus represent important new therapeutic targets in hepatocellular carcinoma.[60]

## EFFECT OF HCV ON IRON AND ERYTHROPOIETIN REQUIREMENTS IN ANEMIC HEMODIALYSIS PATIENTS

Although several studies have shown that HCV-infected hemodialysis patients may have higher hemoglobin, transferrin saturation and ferritin levels, and lower iron and erythropoiesis-stimulating agent (ASE) requirements than dialysis patients without HCV infection,[61–68] the recent DOPPS study showed that HCV infected dialysis patients have higher incidence of hemoglobin decline below 8.5 g/dL (HR: 1.12; 95% CI: 1.03 to 1.21), blood transfusion (HR: 1.36; 95% CI: 1.20 to 1.55) and of gastrointestinal bleeding (HR: 1.32; 95% CI: 1.13 to 1.54) as compared to non-HCV dialysis patients, pointing to the deleterious effect of their liver disease on anemia.[2]

## INFLUENCE OF PARENTERAL IRON THERAPY ON THE COURSE OF LIVER DISEASE IN HCV-INFECTED HEMODIALYSIS PATIENTS

Data on the use of IV iron in hemodialysis patients with HCV infection are scarce. Two studies from Turkey (one with 89 HCV-infected patients, the other with 66 patients; these patients were defined by a positive serology associated with abnormalities of liver enzymes) showed that IV iron, given according to current guidelines, significantly increased transaminase levels (ALT and AST) after the third month of therapy, leading the authors to conclude that parenteral iron therapy might contribute to hepatocellular injury in these patients; of note, effect of IV iron on viremia and liver histology were not assessed in these 2 studies.[69,70]

## THE RESIDUAL RISK OF LIVER CANCER IN HCV-INFECTED PATIENTS TREATED WITH ANTIVIRAL DRUGS

Introduction of the novel highly effective and safe direct-acting antiviral (DAA) has revolutionized the treatment of HCV-infected patients. Total cure, defined as a sustained undetectable HCV RNA in serum, is expected in more than 90% of chronically HCV-infected patients after 2 or 3 months of therapy.[71] DAA is highly effective in the treatment of HCV infection in both CKD patients and general population.[71] Of note, the recent DOPPS study has shown an increased risk of mortality from liver disease (HR: 4.4; 95% CI: 3.14–6.15) in HCV-infected dialysis patients and a dramatically low percentage of patients (1.5%) treated by antiviral drugs even in the DAA era.[2]

Among these DAA agents, a combination of elbasvir (a second-generation NS5A inhibitor) with grazoprevir (a NS2/A4 protease inhibitor) was recently shown to be highly effective and devoid of adverse effects in the C-SURFER study of 235 CKD patients, including some with ESRD.[71]

A recent meta-analysis of 30 retrospective observational studies that included 31,528 patients followed for 2.5 to 14.4 years showed a significant reduction in the risk of hepatocellular carcinoma in HCV-infected patients with a sustained response to interferon-based therapy (HR = 0.24 (95% CI: 0.18–0.31)); a similar reduction was observed in HCV-infected patients with advanced liver disease (HR = 0.23 (95% CI: 0.16–0.35); n = 2649 patients in 8 studies).[72]

Given the ability of DAA to cure HCV infection and their good tolerance, they are likely to be more effective than interferon-based therapy in lowering the residual risk of hepatocellular carcinoma in HCV infected patients.[71,73] Routine life-long screening for hepatocellular carcinoma with twice-yearly ultrasonography is warranted in healed HCV-infected cirrhotic patients who

should also reduce exposure to other avoidable risk factors.[48,50]

## IATROGENIC HEPATIC IRON OVERLOAD AS A REDISCOVERED RISK FOR DIALYSIS PATIENTS IN THE ESA ERA

Most ESA-treated dialysis patients receive parenteral iron to ensure sufficient available iron before and during ESA therapy. A 12-year-old study based on hepatic susceptometry (SQUID)[74] and more recent use of quantitative MRI to estimate liver iron concentration (LIC) in hemodialysis patients have underlined the risk of hepatic iron overload in this setting.[4,75,76] A study conducted in 2012 with the Rennes University MRI protocol (signal intensity ratio method) showed hepatic iron overload (LIC > 50 μmol/g dry weight) in 84% of 119 French stable hemodialysis patients treated according to current guidelines (target ferritin between 200 and 500 μg/L). Hepatic iron overload was even severe (LIC > 200 μmol/g dry weight) in 30% of the patients at levels usually observed in genetic hemochromatosis.[4] Of note, signal-intensity-ratio MRI was very recently shown in a pilot study to accurately estimate hepatic iron load in hemodialysis patients by comparison with histology.[77] Moreover, 3 long-term prospective epidemiological studies recently showed that higher IV iron administration may adversely affect the prognosis of hemodialysis patients by increasing cardiovascular events and mortality; of note some other studies have not found difference in outcomes and observational studies can mislead.[78–80]

It is therefore tempting to postulate that hepatic iron overload may act by disrupting hepcidin homeostasis and by increasing the burden of cardiovascular diseases in ESRD patients.[6] Indeed, high hepcidin-25 levels correlated strongly with the frequency of cardiovascular events in hemodialysis patients in the Dutch CONTRAST study, irrespective of C-reactive protein levels, cardiovascular risk factors, and comorbidities.[81] Hemodialysis patients with liver iron overload have been shown to have increased hepcidin levels,[4,76] which normalize within 1 year when IV iron products are stopped, in parallel with iron stores.[4] High hepcidin levels are suspected of activating and trapping iron in macrophages inside the atherosclerotic plaques, thereby leading to plaque instability and clinical vascular events.[7]

The conception of iron therapy in hemodialysis patients has evolved markedly over the past 2 decades. When erythropoietin replacement therapy became possible in the late 1980s, the goal of iron therapy was to maintain iron stores and prevent iron deficiency, mainly with oral iron supplements, usually in patients with serum ferritin levels below 50 μg/L.[6] Based solely on bone marrow studies and short-term tolerability in controlled trials of IV iron products, the United State Kidney Disease Outcomes Quality Initiative (KDOQI) issued a new guideline in 2006[82] and endorsed by the European Renal Best Practice (ERBP) of the European Renal Association EDTA-ERA,[83] which redefined iron deficiency (ferritin < 100 μg/L instead of 50 μg/L) and adopted higher iron repletion criteria (ferritin target >250 μg/L and <500 μg/L).[6] The 2012 KDIGO guideline set the upper ferritin limit at 500 μg/L for hemodialysis patients, underlined the risk of functional iron deficiency during ESA treatment, and emphasized the ability of IV iron to limit the use of expensive ESA products.[84]

It is also very likely that iatrogenic iron overload in hemodialysis patients has been favored by reimbursement policies in the United States and many other industrialized countries, which have led to a dramatic increase in the use of IV iron by dialysis stakeholders seeking to minimize the high costs of ESA products.[5,6,8] The situation has been compounded by the fear of the adverse effects of ESA.[6,84,85]

## PROPOSALS FOR SAFE USE OF IRON IN DIALYSIS PATIENTS WITH HEPATITIS C

To avoid the rise in viral replication, aggravation of histological lesions, and development of hepatocellular carcinoma most hepatologists avoid use of oral and IV iron products in HCV-infected patients without kidney disease.[3] However, it is not possible to withhold iron supplementation in ESRD patients in whom recurrent losses of blood in the hemodialysis circuit, in sampling for laboratory tests (especially for uremia monitoring), and in gut due to uremic enteropathy invariably result in depletion of iron stores.[7] Thus iron replacement should be used with careful monitoring and extreme caution in HCV-infected ESRD patients. The cautious Japanese strategy applying to iron therapy, aimed at maintaining an optimal hemoglobin level with minimal use of IV iron products and low ferritin levels, is of great interest in this setting.[86,87] Indeed, the Japanese Society for Dialysis recently proposed that a minimal amount of IV iron (up to 650 mg in the induction phase) should be given to dialysis patients only in case of true iron deficiency (ferritin <100 μg/L) and warned against maintenance intravenous

iron therapy.[86] Of note, taking into account the lower body surface area of Japanese patients, the proposed dose would be around 800 mg in European patients and 1000 mg in US patients.

Quantitative MRI, has recently been advocated by French and Japanese authors for routine monitoring of liver iron store in dialysis patients.[4,88–90] Of note, the KDIGO controversies conference did not advocate at that time MRI monitoring of liver iron stores in dialysis patients.[7] Nevertheless, this approach may be crucial for the monitoring of HCV-infected dialysis patients who are exposed to a high risk of liver damage from iatrogenic iron overload.[88–90]

Finally, based on the in vitro and in vivo evidence that iron contributes to HCV proliferation, and cellular damage, and given the new availability of safe and effective DAA, we strongly recommend to physicians to screen all HCV antibody dialysis patients for viral load; in case of viremia to plan on curing with DAA. Until HCV disease is cured, we advocate to limit IV iron to the minimum required to compensate blood losses and to achieve an hemoglobin target of 10 g/dL.

In an attempt to improve the safe use of parenteral iron products and determine the accuracy of biomarkers of iron metabolism, 2 cohort studies were recently conducted employing French dialysis patients as a whole, and a subset of HCV-infected patients. These studies combined quantitative MRI with data-mining and classical statistical analysis, to determine the safe dosage of IV iron and identify the accurate target values for biological markers of iron metabolism.[91,92]

Together, these results strongly suggest that ferritin targets for iron therapy management should be lowered to avoid iron overload and minimize its potential harmful effects on the liver in HCV-infected hemodialysis patients.

Moreover, a specific research agenda is urgently needed for this frail dialysis population, including proof-of-concept studies to determine a potential detrimental effect of IV iron infusions and iatrogenic increase in LIC on HCV replication. Retrospective analyses of data from prospective cohorts such as USRDS, DOPPS, and CONTRAST could help to determine the possible impact of oral and IV iron therapy on the course of liver disease in HCV-infected dialysis patients, including the risk and degree of fibrosis, cirrhosis, and liver cancer.

## CONCLUSION

Excessive use of IV iron products despite compliance with accepted guidelines has led to the pandemic of iron overload in ESRD population. Elevated liver tissue iron content has been shown to adversely affect natural history of hepatitis C in the general population. Given the adverse effects of iron overload on the course of hepatitis C and the high prevalence of iatrogenic iron overload in hemodialysis population, caution should be exercised in the use of iron compounds in HCV-infected dialysis patients with careful monitoring of biomarkers of iron metabolism and non-invasive measurements of liver tissue iron contents with MRI.

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