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Commentary

Treatment of anaemia in end-stage renal disease: A double-edged iron sword?

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Non-alcoholic fatty liver disease (NAFLD) is emerging as the most common cause of chronic liver disease worldwide [1] and it is likely to become a global public health problem [2]. Several observational studies have shown a strong association between NAFLD, chronic kidney disease (CKD) and cardiovascular disease (CVD). NAFLD was associated with an increased risk of cardiovascular events in two separate meta-analyses, one of which included 164,494 participants [3,4]. The link between NAFLD and CKD was demonstrated in another meta-analysis of 33 studies with 63,902 participants [5] and, in certain populations of CKD stage 3–4 patients, the prevalence of NAFLD has been reportedly as high as 85% [6]. We have shown that NAFLD is a strong independent risk factor for adverse cardiovascular events in advanced CKD patients not on dialysis [7] and this has also been seen in dialysis patients [8]. Several proinflammatory and oxidative stress mechanisms have been postulated to interlink the onset and progression of these three conditions [9].

In this study in *EBioMedicine* [10], Rostoker and colleagues have raised an issue that will be of interest to the nephrology and hepatology communities, as their study links intravenous iron therapy, used ubiquitously for anaemia management in end-stage renal disease (ESRD) patients, with NAFLD. They used magnetic resonance imaging (MRI) techniques to quantify liver iron concentration (LIC) and hepatic proton density fat fraction (PDFF), a marker of NAFLD, in a group of dialysis patients. In a small sample of ESRD patients they showed that greater hepatic PDFF was associated with greater LIC following intravenous iron treatment, and that withdrawal of iron treatment associated with a decrease in both LIC and PDFF. They speculated that excess hepcidin synthesis, generated due to iron overload, could be one of the factors involved in the development of cardiovascular complications which frequently occur in ESRD. They have also postulated a possible mechanism to explain how iron overload might predispose to the development of NAFLD. This is a new development as the group's previous work was cited by the KDIGO 'Iron Management in CKD' expert report in 2016 which concluded that there was then insufficient evidence to support the use of hepatic MRI in guiding iron therapy in dialysis patients [11]. There remains uncertainty as to whether the detection of hepatic iron by MRI can distinguish between iron within Kupffer cells (where it can be safely stored) or within the hepatocytes (where it is potentially toxic and may cause liver damage).

Iron therapy in the management of anaemia in non-dialysis CKD and ESRD patients has generated a great deal of interest amongst researchers in recent years. The optimum ferritin and transferrin saturation targets for intravenous iron dosing in ESRD patients is under active debate, with practice patterns varying in different countries. Studies have shown that iron therapy improves mortality in CKD patients [12]; however, one study showed that higher dose iron was associated with poor outcome [13]. Hepcidin, a hormone released by hepatocytes in a feedback mechanism sensing excess body iron, is a critical factor in the regulation of iron metabolism. Hepcidin retards iron absorption in the gut and the mobilisation of iron from the reticuloendothelial system to the circulation, and its release is stimulated by the inflammatory response. CKD itself is viewed as a chronic inflammatory state which results in increased production of hepcidin. This and decreased renal clearance in CKD results in greater hepcidin levels leading to functional iron deficiency which explains why oral iron therapy has not been effective in the management of anaemia in the ESRD population. It is well established that a greater hemoglobin response is seen with intravenous iron rather than oral iron in dialysis patients [14] who are usually also receiving erythropoiesis stimulating agents (ESA).

The study by Rostoker et al. has appeared at an important juncture in the management of anaemia with intravenous iron therapy in ESRD patients. The recently published PIVOTAL (Proactive IV iron therapy in haemodialysis patients) trial, which is a UK multicentre randomized controlled trial including almost 2200 patients, has shown that higher dose intravenous iron given proactively was superior to a reactive low-dose iron regimen, with fewer major cardiovascular events occurring in the higher dose arm which allowed serum ferritin concentrations of up to 700 μg/l [15]. There was also benefit in a reduction in the effective dose of ESA therapy and blood transfusion requirements. As a result of the PIVOTAL trial it is quite likely that nephrologists will be encouraged to use greater quantities of iron, perhaps targeting higher ferritin levels (above the current 450–500 μg/l average) in European dialysis populations; US practice already sees patients treated to ferritin targets of close to 1000 μg/l. Although no safety signals

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relating to liver dysfunction were noted in PIVOTAL, it is acknowledged that no additional bespoke imaging of the liver was undertaken in the study.

Given the changes in nephrological practice that may potentially result from PIVOTAL, it seems that nephrologists should be mindful to not overlook the possibility of liver disease in their dialysis population. Importantly, there is a need for Rostoker et al.'s findings to be validated or refuted with a larger scale study, and there is a need for more detailed mechanistic work to confirm any pathogenetic link between iron loading and NAFLD.

Conflicts of interest

IM was chief investigator of the PIVOTAL trial, and has also received honoraria for lecturing and advisory board attendance from Vifor and Pharmacosmos. PK was part of the steering committee of the PIVOTAL trial, and has also received honoraria for lecturing and advisory board attendance from Vifor and Pharmacosmos. RC has nothing to disclose.

Authors contributions

Rajkumar Chinnadurai- Drafted the article.

Iain Macdougall- Revised the draft critically for important intellectual content.

Philip Kalra- Conceptualisation, revision of the draft critically for important intellectual content and approval of the final version submitted.

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