In Focus

Intravenous iron therapy in non-dialysis CKD patients

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Iron deficiency anaemia in non-dialysis-dependent chronic kidney disease patients is common, with a study (admittedly from more than 10 years ago) suggesting that >800 000 such patients in the USA are affected [1]. This may significantly impact on quality of life and exercise capacity, and it is also associated with significant morbidity and mortality. Correction of the anaemia will require iron replacement therapy, with or without erythropoiesis-stimulating agents (ESAs). The optimum route of administration of iron is controversial, with a wide variability in clinical practice among different countries, different renal units and indeed among different nephrologists within the same unit. The use of oral versus intravenous iron as the first-line management of this condition varies, partly because of the individual nephrologist’s beliefs and also partly due to a paucity of scientific evidence in this clinical setting, but is also influenced by the accessibility to a service that is readily able to provide intravenous iron supplementation. Thus, in primary care, general practitioners are likely to start with oral iron, whereas renal units that support an intravenous iron clinic (usually nurse-led) are more likely to start with intravenous iron. Reimbursement policies for intravenous iron in the non-dialysis CKD setting are also variable throughout the world, and this too may impact on the relative use of IV versus oral iron.

Until recently, with the exception of iron dextran-containing preparations (which themselves have generated concerns about anaphylactic or hypersensitivity reactions), the available intravenous iron compounds were unable to provide high doses of iron as a single administration. Thus, for iron gluconate (used in the USA, Italy and Germany), doses of 62.5–125 mg of iron were the maximum recommended at a single sitting [2], whereas for iron sucrose (IS) - used widely in the USA, Europe, and Australia, bolus doses of up to only 200 mg were recommended [3]. Thus, many patients were required to attend for repeated boluses of IV iron, e.g. three or more injections of IS, 200 mg at a time, to replenish their iron deficits.

Within the last few years, three new intravenous iron preparations have been licensed [4]. These include ferumoxytol (Feraheme® in the USA; Rienso® in Europe), ferric carboxymaltose (FCM, Ferinject® in Europe; Injectafer® in the USA) and iron isomaltoside-1000 (Monofer® in Europe). Data comparing these new preparations to the more traditional IV iron compounds are sparse, with small numbers of patients included in the clinical trials, most of which were not randomized, and with short follow-up. Qunibi et al. [5] performed a randomized controlled trial comparing intravenous FCM with oral iron for the treatment of iron deficiency anaemia in non-dialysis-dependent chronic kidney disease patients, and showed that the response to intravenous iron was slightly greater with intravenous iron compared with oral iron, with an acceptable safety profile. However, the total number of patients exposed to intravenous FCM was 152 and the period of follow-up was only 8 weeks. In another recent randomized controlled trial, Charytan et al. [6] administered 15 mg/kg of FCM intravenously up to a maximum of 1000 mg in 204 non-dialysis CKD patients and compared the haemoglobin responses with a group of patients treated with standard medical care (IV, oral or no iron, as determined by the investigator). Otherwise, head-to-head comparisons of IV iron preparations in the non-dialysis CKD population have been lacking. Onken et al. [7], in this issue of *Nephrology Dialysis Transplantation*, however, have gone some way to correcting this deficit in the evidence base, by reporting the results of the REPAIR-IDA trial. This was a large randomized controlled trial involving 2584 non-dialysis CKD patients with iron...
deficiency anaemia (iron deficiency being defined as a serum ferritin ≤100 μg/L, or ≤300 μg/L plus transferrin saturation ≤30%, whilst anaemia was defined as Hb ≤11.5 g/dL), who were randomized to receive two doses of FCM 750 mg 1 week apart, or IS 200 mg administered in up to five infusions over 14 days. The primary efficacy end point was the mean change to the highest haemoglobin level from baseline, and the primary composite safety end point included all-cause mortality, non-fatal myocardial infarction, non-fatal stroke, unstable angina, congestive heart failure, arrhythmias, and both hypertensive and hypotensive events.

As with all randomized controlled trials, new and useful information is generated, but the limitations of the trial (as well as residual unanswered questions) are apparent.

The aim of this commentary is to discuss what the REPAIR-IDA trial tells us, and what it does not tell us, as well as what the future of iron management in non-dialysis CKD patients might look like.

The main message from the REPAIR-IDA trial is that (within the limitations discussed below), it is possible to obtain at least as good a haemoglobin with two ‘high’ doses of intravenous FCM as it is with five smaller doses of IV IS [7] in non-dialysis CKD patients with iron deficiency anaemia. The mean increase in haemoglobin was 1.13 (0.04) g/dL in the FCM group and 0.92 (0.92) g/dL in the IS group (95% CI, 0.13–0.28 g/dL), thus demonstrating not only the pre-specified non-inferiority (lower limit of two-sided 95% CI of treatment comparison was ≥−0.2) of FCM to IS, but also supporting the hypothesis that FCM was significantly superior to IS at the 5% level, given that the lower limit of the two-sided 95% CI was greater than zero. Using the same superiority threshold, FCM also demonstrated superiority over IS with respect to mean haemoglobin increases for participants with baseline haemoglobin ≥10.1 g/dL, CKD stages 3–4, and any or no ESA use. The majority of patients recruited to the study were not receiving ESAs, but a significant proportion (around 18%, equally distributed between the two groups) was on a stable dose of ESA. The lower the haemoglobin value, the greater the increase in haemoglobin from baseline to highest value for both patient groups. Higher and earlier increases in serum ferritin and transferrin saturation were obtained with IV FCM compared with IV IS [7].

Regarding safety, again the primary composite safety end point was achieved, demonstrating no obvious safety concern with the use of IV FCM. Interestingly, protocol-defined hypertensive events were significantly more common in the FCM group compared with the IS group (7.5 versus 4.4%; 95% CI 1.19–4.99%), whereas more subjects in the IS group experienced protocol-defined hypotensive events than the subjects in the FCM group. Of the drug-related treatment-emergent adverse events, nausea, hypertension, flushing, dizziness and dysgeusia were slightly more common in the FCM group, as was transient hypophosphataemia [7].

Thus, in brief, IV FCM represents a viable treatment option for iron deficiency anaemia in non-dialysis CKD patients. The most obvious benefit for both the patient and the healthcare team is the need for fewer IV iron administrations, and this may have considerable impact on patients who live some distance from the treatment centre. Although no formal health economic assessment was performed, it is likely that this would be positive, particularly for patients requiring to travel considerable distances. Other advantages not discussed in the paper include the need for less intravenous cannulations, which may be beneficial in terms of future arteriovenous fistula creation and survival.

The major strength of this randomized controlled trial (RCT) is its sample size, which exceeds any other published RCT of IV iron. There are, however, some limitations. The most obvious of these is the short study duration, being only 8 weeks for the efficacy end points and 120 days for the safety evaluation. While this may be long enough to show a difference in haemoglobin response, it is hard to argue that two doses of study drug and 4 months of follow-up is sufficient to fully evaluate safety, particularly the hard clinical end point used for the primary composite. Secondly, the total dose of IV FCM given was 1500 mg compared with 1000 mg for IS (the latter is the current FDA-approved dose for this comparator). This may well account for the slightly greater haemoglobin increases seen with the FCM group [7], and in my personal view, it would have been more interesting to compare like with like (i.e. two 500 mg administrations of FCM and 5 × 200 mg administrations of IS). There are also implications for extrapolation into clinical practice with the 750-mg dose. In Europe, FCM is packaged as 100- and 500-mg vials, and in routine clinical practice, doses of 500 or 1000 mg are often administered. The concept of discarding the unused contents of a vial of intravenous iron appears foolhardy and is not accepted by most clinicians in this clinical scenario where fine tuning of IV iron dosing is far from critical (as it is with, e.g. chemotherapy). Of course, physicians may choose to administer 1000 mg followed by 500 mg to circumvent this problem, rather than two doses of 750 mg.

Since this was a randomized controlled trial comparing two different intravenous iron preparations, no information is available on the haemoglobin response and adverse events seen with oral iron supplementation in this patient population. The study also does not tell us whether this treatment strategy of administering 1000–1500 mg of IV iron is optimal, nor whether repeated doses of IV iron are beneficial or advisable in this patient group. There is also no information on how long the haemoglobin response was sustained for, nor how rapidly the anaemia or iron deficiency recurred. Thankfully, these issues have been largely addressed in the FIND-CKD study, the study design of which is reported elsewhere in this issue of NDT [8], which is expected to report by the end of 2013. This too is a randomized controlled trial of >600 patients, randomly allocated to one of three arms: (i) Group 1: IV FCM, aiming for a serum ferritin target range of between 400 and 600 μg/L; (ii) Group 2: IV FCM, aiming for a serum ferritin target range of between 100 and 200 μg/L; (iii) Group 3: oral ferrous sulphate 200 mg per day, with no defined ferritin target range (oral iron was withheld if the serum ferritin exceeded 200 μg/L). The primary objective of the study was to evaluate the long-term efficacy and safety of IV FCM (using targeted ferritin levels to determine dosing) or oral iron to delay and/or reduce ESA use and/or other anaemia.
management options in non-dialysis CKD patients with iron deficiency anaemia. Patients in the two IV iron arms received further FCM as required to maintain their allocated ferritin target ranges, with monthly dosing up to 1 year of follow-up. This study therefore represents the longest follow-up of any randomized controlled trial of IV iron in the CKD population.

REPAIR-IDA is a noteworthy and commendable study that has contributed significantly to the literature on the use of IV iron in CKD patients. The investigators should be congratulated on achieving both their primary efficacy and safety end points, and for the not inconsiderable task of recruiting this large number of patients. The study provides data that supports a practice that is already being implemented in the non-dialysis CKD population, namely that fewer administrations of higher doses of IV iron are preferable to repeated boluses of small doses. Although it was reassuring to see that there is no obvious safety signal with this new strategy, it is prudent to recognize that an administration of two doses of study drug and a follow-up of only 4 months is insufficient to be confident about long-term safety.

Finally, in the current healthcare environment, not only are the clinical benefits of different treatments considered important, but so too are their costs. For the two intravenous iron preparations assessed in the REPAIR-IDA study, milligram for milligram there are significant differences in the acquisition costs of each product. However, in this instance it is important to consider not only the relative drug acquisition costs of the two products but also the complete cost of each treatment. In the case of IV iron preparations, the following also need to be considered: infusion times, intravenous tubing, nursing time, travel time and costs, and number of hospital/clinic visits. The more visits needed often translate into higher ‘in-hospital’ costs and lower compliance with the treatment regimen. In the REPAIR-IDA study, one group received two IV injections of FCM, and the other received five IV infusions of IS. This difference in the number of IV administrations was associated with an increased number of hospital or clinic visits, increased equipment costs, and increased patient and nursing time. All of these factors can be translated into different costs to the healthcare system and the patient.

This issue has been investigated in two separate nurse-led outpatient clinic settings in the UK where previously IS was the IV iron of choice for treating iron-deficient ND-CKD patients. In the study by Pugh-Clarke et al. [9], following a change in the iron protocol to use FCM instead of IS, the authors reported a reduction in waiting times for iron administration, as well as a reduction in both material and hospital transport costs. A similar study by Wilson et al. [10], evaluated data from 365 patients who had received multiple doses of IS and, using a decision analytical model, determined that the ferric carboxymaltose protocol saved each patient two hospital visits and 2.66 h of time (equating to a saving of approximately £36.21 in loss of earnings) and £19 in travel costs. Direct attributable costs for iron administration (which included drug, disposables, nursing staff and hospital-provided patient transport costs) were £58 646 for IS versus £46 473 for ferric carboxymaltose. Direct overhead costs (which included nursing preparation time, administration staff, clinic space and consultant time costs) were £40 172 for the IS service versus £15 174 for the FCM service. Similar findings have been reported in Danish patients with inflammatory bowel disease treated with FCM [11].

Thus, in conclusion, the advent of the new IV iron preparations such as FCM has allowed greater flexibility for clinical staff, allowing larger amounts of iron to be administered intravenously at a single sitting. The REPAIR-IDA trial shows that this is at least as effective in correcting iron deficiency as IS, appears to be relatively safe (at least in the short term), and may indeed prove cost-effective in settings where nursing time is stretched and the patient’s travel costs are significant. The data from the FIND-CKD study, which is due to report shortly, and which has a study duration of more than a year, will go some way towards filling other gaps in our evidence base, but even longer duration clinical trials may be required before we truly know where we are with the safety of intravenous iron.

CONFLICT OF INTEREST STATEMENT

The author has received consultancy fees and lecture honoraria from the three manufacturers of intravenous iron preparations mentioned in this review (Vifor Pharma, Takeda and Pharmacosmos); however, no assistance or input from any pharmaceutical company was obtained, and no medical writer was involved.


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New renal guidelines; is more better?

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Guidelines for optimal diagnosis and treatment are a standard in current health care. They guide practitioner and patient decisions about appropriate health care in defined disease areas. Given the rapid developments in renal disease diagnosis and the multiplicity of available interventions, guidelines become an important tool in this area not only for optimal health care, but also to satisfy rules of accountability and transparency. Thus, to the question ‘do we need guidelines in nephrology?’ the answer is clearly, YES. However, the mere existence of a guideline does not guarantee that we are actually improving health care. In fact, although designing a guideline is a major effort, the biggest challenge appears to be its implementation [1, 2]. Many studies indicate that guideline recommendations are insufficiently followed in practice [3, 4]. For example, regarding risk factor management in patients with diabetes or chronic kidney disease, it was found that up to 59% of patients received less care than recommended according to the guidelines [5, 6]. Especially, guideline implementation for the management of albuminuria appears to be poor [5–7]. Additional efforts are needed to implement chronic kidney disease guidelines in practice [8]. Much of the research has been conducted in primary care, but studies suggest that specialists perceive even less need and are less inclined to adopt guidelines when compared with primary care or less experienced physicians [2, 9].

Nagler et al. [10] report in this Journal about the ‘European Renal Best Practice (ERBP) Guideline development methodology: towards the best possible guidelines’. Clearly, the authors recognize the problem and are actually not only focusing their efforts on an accurate guideline development process, but also try to tackle the relative lack of success of implementation by introducing dedicated experts in this field to the guideline team, optimizing the wording of recommendations, as well as taking specific measures involving the opinion of a panel of ‘users’.

We question, however, whether these measures will actually help in daily practice, since they do not solve several important obstacles to guideline adherence [11], such as (i) the vast number of different guideline bodies, (ii) the diversity of their guideline advice, (iii) the diversity of health-care providers and patients and (iv) the limited applicability of single-disease guidelines to patients with co-morbid conditions. The renal community counts at least six guideline bodies according to Nagler et al.: global KDIGO (Kidney Diseases Improving Global Outcomes), Latin-American SLANH (Sociedad Latino-Americana de Nefrologia e Hipertension), Australian/New Zealand KHA-CARI (Kidney Health Australia—Caring for Australasians with Renal Impairment), American KDOQI (Kidney Disease Outcomes Quality Initiative), Canadian CSN (Canadian Society of Nephrology) and English UK-RA (United Kingdom Renal Association). If that is not enough, we believe that there are more, such as the Renal Physicians Association Clinical Practice guidelines or the European Association of Urology guidelines, as well as hypertension or diabetes guidelines drafted by non-renal guideline bodies, which often include ‘renal diagnosis or therapies’. In addition, many countries have guideline organizations like the English National Institute for Clinical Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN) or the Dutch Institute for Healthcare Improvement (CBO), which develop a broad range of either multidisciplinary guidelines or guidelines for specific target users [12]. The mere fact that we have so many guideline bodies may, and most likely does, confuse the end users. In addition, these different bodies issue guidelines on the same topic, with partly diverging advice [13]. This definitely is not helping smooth implementation, it is in fact counterproductive, given the competing demands and time limitations perceived in practice. The suggestion that the ERBP will deal with this by searching for guideline...