Effect of oral liposomal iron versus intravenous iron for treatment of iron deficiency anaemia in CKD patients: a randomized trial

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ABSTRACT

Introduction. Iron deficiency is a common cause of anaemia in non-dialysis chronic kidney disease (ND-CKD). Controversies exist about the optimal route of administration for iron therapy. Liposomal iron, a new generation oral iron with high gastrointestinal absorption and bioavailability and a low incidence of side effects, seems to be a promising new strategy of iron replacement. Therefore, we conducted a study to determine whether liposomal iron, compared with intravenous (IV) iron, improves anaemia in ND-CKD patients.

Methods. In this randomized, open-label trial, 99 patients with CKD (stage 3–5, not on dialysis) and iron deficiency anaemia [haemoglobin (Hb) ≤12 g/dL, ferritin ≤100 ng/mL, transferrin saturation ≤25%] were assigned (2:1) to receive oral liposomal iron (30 mg/day, Group OS) or a total dose of 1000 mg of IV iron gluconate (125 mg infused weekly) (Group IV) for 3 months. The patients were followed-up for the treatment period and 1 month after drug withdrawal. The primary end point was to evaluate the effects of the two treatments on Hb levels; the iron status, compliance and adverse effects were also evaluated.

Results. The short-term therapy with IV iron produced a more rapid Hb increase compared with liposomal iron, although the final increase in Hb was similar with either treatment; the difference between the groups was statistically significant at the first month and such difference disappeared at the end of treatment. After iron withdrawal, Hb concentrations remained stable in Group IV, while recovered to baseline in the OS group. The replenishment of iron stores was greater in the IV group. The incidence of adverse event was significantly lower in the oral group (P < 0.001), and the adherence was similar in the two groups.

Conclusions. Our study shows that oral liposomal iron is a safe and efficacious alternative to IV iron gluconate to correct anaemia in ND-CKD patients, although its effects on repletion of iron stores and on stability of Hb after drug discontinuation are lower.

Keywords: anaemia, erythropoiesis, inflammation, iron-deficiency

INTRODUCTION

Anaemia is a common complication of chronic kidney disease (CKD) and is associated with increased cardiovascular (CV) morbidity and mortality and decreased quality of life [1–3]. The main cause of anaemia in CKD is the relative deficit of renal production of erythropoietin (EPO); however, iron deficiency plays a crucial role in the genesis of CKD-related anaemia [4]. Erythropoiesis, in fact, is limited by a low iron availability [5], either for an absolute or functional deficiency and for an iron block, largely due to an underlying inflammatory status, a common condition in CKD patients [6]. Iron deficiency and inflammatory block, indeed, represent the main causes of hyporesponsiveness to erythropoiesis-stimulating agents (ESA) [7, 8].

The use of ESA and iron therapy have been the cornerstones in the management of CKD anaemia for the last two
decades. However, on the basis of the results of CREATE [9], CHOIR [10] and TREAT [11] studies, the management of anaemia with ESA aiming at a complete correction or at high values of haemoglobin (Hb) levels has been questioned and the interest in the role of iron treatment has been heightened. In fact, the latest anaemia guidelines from the Kidney Disease Improving Outcomes (KDIGO) initiative recommends that iron deficiency should be corrected before initiating ESA and that iron treatment may be performed also in patients with a normal iron balance to increase Hb level [12].

The optimum route of administration of iron in CKD patients is still controversial. While in haemodialysis intravenous (IV) iron has been shown to correct anaemia and replete iron stores more effectively than oral treatment, in non-dialysis chronic kidney disease (ND-CKD) there is no widely accepted consensus on whether IV or oral iron should be used as first-line therapy in CKD-related anaemia. A contribution to this issue is expected from the FIND trial, a randomized study that has evaluated the response to both i.v. ferric carboxymaltose and oral ferrous sulphate in 626 patients with CKD during 1 year, whose results will be available in the near future [13]. Despite the potential benefits of oral iron that include the low cost and easy administration, its use is limited by poor gastrointestinal absorption and high rate of adverse events [14–17]. On the other hand, there are concerns that IV iron may accelerate kidney damage, promote infections by supplying iron to pathogenic bacteria, enhance atherosclerosis by generating oxidative stress and cause endothelial damage and anaphylaxis [18–25]; a recent report by Europena Medicines Agency (EMA) (September 2013) clearly points out that IV iron should be prescribed when oral iron cannot be given or does not work, and that should be administered in environments in which resuscitation facilities are present by personnel specifically trained to treat allergic reactions (EMA/579491/2013).

Most CKD patients need a minimum dose of 1000 mg of elemental iron to replete iron stores and to raise Hb [24], which can require from two IV injections of ferric carboxymaltose (up to 500 mg/visit) to eight to sixteen infusions of ferric gluconate (125 or 62.5 mg/visit, respectively), depending on drug availability [6, 26–28]. Liposomal iron (Sideral® Forte), a preparation of ferric pyrophosphate conveyed within a phospholipid membrane associated with ascorbic acid, is a new-generation oral iron which shows a high gastrointestinal absorption and high bioavailability with a low incidence of side effects, due to lack of any direct contact with intestinal mucosa. In comparison with the other oral iron formulations, liposomal iron seems to be a promising new strategy of iron replacement in ND-CKD patients.

For this reason, we performed a randomized, open-label controlled trial to determine if liposomal iron is as effective as IV iron in the treatment of iron deficiency anaemia for patients with ND-CKD.

MATERIALS AND METHODS

Patients

This randomized trial was conducted in the CKD Clinic of the University Federico II of Naples, Italy, where 188 consecutive patients (stage 3–5) were screened from October 2011 to September 2013.

Inclusion criteria for the study were age >18 years, estimated glomerular filtration rate (eGFR, Modification of Diet in Renal Disease equation) ≤60 mL/min/1.73 m², Hb levels ≤12 g/dL, plasma ferritin levels ≤100 ng/mL, transferrin saturation (TSAT) ≤25%, parathormone (PTH) serum levels between 30 and 300 pg/mL, according to the suggested values for kidney disease stage and calcium and phosphate plasma levels within their normal values (i.e. <10.5 and <4.5 mg/dL, respectively).

Exclusion criteria included high-sensitivity C-reactive protein (hsCRP) levels ≥5 mg/L, presence of inflammatory, infectious disease or surgical interventions in the last 3 months, haematological disorders, bleeding or blood transfusions in the last 6 months, malignancies, treatment with immunosuppressive drugs, severe malnutrition, concomitant severe liver or CV disease, chronic alcohol or drug abuse within the past 6 months, known hepatitis B or C infection, pregnant or lactating women.

Withdrawal from the study occurred in the case of malnutrition, need to start dialysis (eGFR ≤60 mL/min, K⁺>6.0 mEq/L and intractable hypertension), need of blood transfusion, non-adherence and withdrawal of consent. Protein-caloric malnutrition was defined by a loss of body weight >5% in 1 month (or 7.5% in 3 months) or body mass index <20 kg/m² with serum albumin levels <3.2 g/dL and normal values of C-reactive protein (CRP). Pharmacological and non-pharmacological therapies were prescribed to each patient to achieve the therapeutic targets in keeping with the current practice guidelines suggested by K/DOQI CKD for Stages 3–5.

The trial was approved by our local Medical Ethics Committee and was in adherence with the Declaration of Helsinki. Informed written consent was obtained from each patient.

Study design and procedures

According to our inclusion/exclusion criteria, 106 patients were enrolled in the study and entered the screening phase, during which they underwent history and clinical evaluation and discontinued any non-study oral iron for the next 2 months. Subjects were randomized into the treatment phase at baseline (T0) in a 1:2 ratio of IV iron to oral iron. The randomization list was generated by a computer and kept concealed with the use of numbered, sealed envelopes opened in sequence by staff personnel not involved in patient care. The first arm received IV iron gluconate, divided into eight administrations of 125 mg diluted in 250 mL normal saline, infused weekly for 3 months (Group IV); the second arm received one oral capsule/day containing 30 mg of pyrophosphate liposomal iron and 70 mg of ascorbic acid (Sideral® Forte, Pharmanutra Spa) for 3 months (Group OS) (Figure 1). Subjects were clinically evaluated prior to drug administration, immediately after and 30 and 60 min after iron infusion. Laboratory tests were obtained at T0 and all follow-up visits at months 1 (T1), 2 (T2) and 3 (T3), at least 1 week after the last IV infusion and 1 month after drug withdrawal (T4). Standard laboratory procedures were used for blood and urinary measurements.

A specific effort was devoted to maintaining patients at the same pharmacological therapies throughout the study. In particular, the doses of angiotensin-converting enzyme inhibitors
(ACE-I)/angiotensin receptor blockers (ARBs), and of ESA were never changed during the experimental period; if Hb values resulted in >13 g/dL, ESA dosage was reduced by 25%; similarly, if Hb values resulted <10 g/dL, ESA dosage was increased by 25%. If TSAT resulted >50% or ferritin >800 ng/mL, iron therapy was suspended. Any patient with an Hb below 8 g/dL during the follow-up was excluded from the study. Patients of both groups were followed monthly for compliance (pill counts) and possible adverse effects (standardized questionnaire). The questionnaire specifically asked patients to quantify (none, somewhat/occasionally, a lot/often) if they experienced constipation (<1 bowel movement per 2 days), diarrhoea (>3 bowel movements per day), bloating, nausea, cramps, indigestion, muscle cramps, episodes of low blood pressure and skin rash.

**Statistical analyses**

The primary efficacy end points of the study included the change in Hb values from baseline to end of treatment (T3) in each group, the difference in the per cent of patients achieving an increase in Hb of ≥0.6 g/dL at any study point between baseline and T3. The major predefined secondary efficacy end points included change in TSAT and ferritin from baseline to end of treatment and from T3 to completion of the study (T4).

Adverse effects and compliance data were reported from the day of initial treatment to the end of treatment (T3). The sample size was calculated under the assumption that 85% of participants randomized to receive IV iron gluconate would achieve an increase in Hb of ≥0.6 g/dL at any study point between baseline and T3. The prespecified non-inferiority margin was −40%. Assuming a difference in proportions between randomized treatments of −15% under the null hypothesis and a one-sided 5% significance level, to have 90% power to demonstrate non-inferiority with a 2:1 allocation rate required 57 participants in the OS group and 29 participants in the IV group.

Variables with normal distribution are reported as mean and SD and those with non-normal distribution as median and interquartile range (IQR); categorical data are expressed as percentage and frequency. Between groups comparisons of independent variables were performed by Student’s t-test for normally distributed variables and the Mann–Whitney U-test for those not normally distributed. Differences of categorical variables between two groups were investigated by the χ² test. A P value <0.05 was considered statistically significant.

The independent relationship between the treatments (IV and oral iron) and Hb data over time (i.e. Hb values at the second, third and fourth visit) (dependent variable) was investigated by a multiple linear mixed model (LMM) by adjusting
for the Hb value at baseline as well as for a series of other potential confounders (i.e. for ferritin levels at baseline). In multiple LMM analysis, data were expressed as regression coefficient, 95% confidence interval and P-value. Data were analysed using the Statistical Package for Social Sciences (SPSS) for Windows, version 20.0 software (SPSS Inc., IL, USA).

RESULTS

Baseline data

As shown in Figure 1, 106 out of 188 patients assessed for eligibility were randomized to the two different treatments: 37 to IV iron (IV group) and 69 to oral iron (OS group). Seven patients were excluded from the study; three patients (one in the IV group, two in the OS group) lacked post-baseline Hb levels and four patients (three in the IV group and one in the OS group) withdrew consent. Accordingly, the statistical analysis was performed on 99 patients (n = 33 in the IV Group and n = 66 in the OS Group) (Figure 1 and Tables 1 and 2).

The characteristics of these patients are summarized in Table 1. At baseline, the two groups were comparable for age, sex, body weight, eGFR (and distribution of CKD stages) and use of ESA. Baseline laboratory data are reported in Table 2. No difference was detected in main laboratory data between the two groups, including the anaemia-related laboratory characteristics.

Follow-up data

Both iron treatments were associated with a progressive and significant increase in Hb levels (T3 versus respective T0), although to a different extent. At the end of the treatment period, in fact, the mean increases in Hb levels (T3 versus T0) were 9.3 and 5.6% in the IV and OS group, respectively (Table 3).

The patients of the IV group showed a rise in Hb levels compared with baseline, statistically significant since the first month of study (T1), which progressively increased until the end of the follow-up (P = 0.01). In patients of the OS group, conversely, a significant rise in Hb concentration was observed at T3 (P = 0.05). Starting from the first month of treatment (T1), the differences in Hb levels between the groups under study became statistically significant (P < 0.05) and such difference persisted at T2 and disappeared at T3 (Table 3 and Figure 2a). The proportion of patients who achieved the end point of an increase in Hb of ≥0.6 g/dL at any study point between the baseline and the end of treatment was significantly greater with IV iron than with oral iron (33.3 versus 8.7% at T1, 52.2 versus 27.3% at T2, 56.2 versus 43.5% at T3, P < 0.05).

Ferritin serum levels showed a divergent pattern in the two groups (Figure 2b); in fact, patients of the IV group showed a rise in ferritin levels compared with baseline, statistically significant since the first month of study (T1), which progressively increased until T3 (P < 0.01, T3 versus T0). In the OS group, conversely, serum ferritin levels remained stable throughout the treatment. Starting from the first month of treatment (T1), the differences in ferritin concentrations between the groups under study became statistically significant (P < 0.05) and such difference persisted at T3 (Table 3 and Figure 2b).

A marginal, although significant difference, was also detected in TSAT that remained stable in patients of Group OS, but resulted in an increase in Group IV (P = 0.05, T3 versus baseline; Table 3 and Figure 2c).

No modification was observed throughout the observation period in main laboratory data, including serum albumin, hsCRP and PTH, nor in eGFR in both groups (Table 3). Finally, BP remained stable and sufficiently well controlled in both groups during the whole study period. These results persisted when patients who needed ESA were excluded (data not shown).

The multiple LMM analysis indicated that the effect of iron treatment on Hb values over time was independent from potential confounders (including Hb at baseline; Table 4).

According to the protocol, patients were maintained at the same pharmacological therapies throughout the follow-up period.
Thus, while non-liposomal oral iron is an effective strategy to increase Hb levels in iron-deficiency anaemia, its efficacy in replenishing iron stores may be limited by its ineffective absorption, potential gastrointestinal events, non-compliance [15, 16, 33] and inflammation, a common condition in ND-CKD patients, often associated with increased hepcidin levels, which lead to impaired absorption of iron from the gastrointestinal tract and retention of iron in the reticuloendothelial system [5]. However, liposomal iron, a preparation of ferric pyrophosphate conveyed (carried) within a phospholipid and sucrose esters of fatty acid membrane, is a new generation of oral iron, which shows a high gastrointestinal absorption and high bioavailability with a low incidence of side effects. Due to the sophisticated technology that uses liposomes as a carrier, the iron never comes into contact with gastrointestinal mucosa, and it is directly absorbed in the intestine. In the intestinal lumen, the liposome is directly absorbed by the M cells of the small intestine, which originate from the lymphatic system. Subsequently, the liposome is incorporated by endocytosis, by macrophages and through the lymphatic system that reaches, intact, the hepatocytes [34], where the liposome is ‘opened’ by lysosomal enzymes, making the iron available.

Hence, our working hypothesis was to compare, in a randomized trial, the effects of both IV and liposomal oral iron on Hb levels in patients with moderate–severe CKD. Our effort was to enrol patients with normal levels of PTH (according to their CKD stage), with a particularly well-controlled calcium-phosphate homeostasis and no clinical or laboratory sign of inflammation, potentially able to hide the positive effects of both drugs on Hb concentration. Our results showed that liposomal iron was non-inferior to a typical dosing strategy of iron gluconate with regard to the primary efficacy end point of mean change from baseline Hb to the end of treatment. The short-term therapy with IV iron produced a more rapid Hb increase compared with liposomal iron, although the final increase in Hb was similar with either treatment. However, after iron withdrawal, Hb concentrations remained stable in the IV group, while recovered to baseline in the OS group. Achievement of the end point of replenishing iron stores was greater in the IV group. The mean increase in ferritin levels indicated greater repletion of body iron stores with IV iron than with oral iron. Similarly, the mean level of

### Table 3. Main clinical and laboratory data in the two groups under study throughout the follow-up period (Group OS, patients treated with oral iron, n = 66; Group IV, patients treated with IV iron, n = 33)

<table>
<thead>
<tr>
<th></th>
<th>Group OS</th>
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<th>Group IV</th>
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<td></td>
<td>T0</td>
<td>T1</td>
<td>T2</td>
<td>T3</td>
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<tr>
<td>Hb (g/dL)</td>
<td>10.8 ± 0.6</td>
<td>10.8 ± 0.5a</td>
<td>11.2 ± 0.8a</td>
<td>11.4 ± 0.8a</td>
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<tr>
<td>T0</td>
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<tr>
<td>Hb (g/dL)</td>
<td>10.7 ± 0.8</td>
<td>11.3 ± 0.9a</td>
<td>11.7 ± 1.1a</td>
<td>11.7 ± 1.0a</td>
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<tr>
<td>Ferritin (ng/mL)</td>
<td>71.4 ± 23.7</td>
<td>79.5 ± 26.4a</td>
<td>84 ± 25.4a</td>
<td>85.5 ± 31.3a</td>
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<tr>
<td>T0</td>
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<tr>
<td>Ferritin (ng/mL)</td>
<td>67.7 ± 31.6</td>
<td>145 ± 47.8a</td>
<td>195 ± 51.2a</td>
<td>238.5 ± 49.7a</td>
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<tr>
<td>TSAT (%)</td>
<td>16.5 ± 2.2</td>
<td>17.0 ± 3.1</td>
<td>18.1 ± 2.4</td>
<td>18.3 ± 4.3</td>
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<tr>
<td>T0</td>
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<tr>
<td>TSAT (%)</td>
<td>17.0 ± 2.1</td>
<td>19.3 ± 4.2</td>
<td>20.1 ± 5.6</td>
<td>21.3 ± 5.2</td>
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<tr>
<td>PTH (pg/mL)</td>
<td>116 (44–146)</td>
<td>110 (40–102)</td>
<td>108 (33–101)</td>
<td>103 (27–98)</td>
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<td></td>
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<tr>
<td>T0</td>
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</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>114 (38–137)</td>
<td>112 (39–121)</td>
<td>108 (21–118)</td>
<td>104 (34–120)</td>
</tr>
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<tr>
<td>T0</td>
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<tr>
<td>hsCRP (mg/L)</td>
<td>1.2 (0.8–1.7)</td>
<td>1.2 (0.9–2.0)</td>
<td>1.2 (0.8–1.7)</td>
<td>1.0 (0.8–1.5)</td>
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<tr>
<td>T0</td>
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<tr>
<td>hsCRP (mg/L)</td>
<td>1.3 (0.9–1.9)</td>
<td>1.0 (0.9–2.0)</td>
<td>0.9 (0.8–1.5)</td>
<td>1.0 (0.8–1.9)</td>
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Data are expressed as means ± SD or as median and IQR.

Hb, haemoglobin; eGFR, glomerular filtration rate; TSAT, saturation of transferrin; PTH, parathormone; hsCRP, high sensitivity C-reactive protein.

**Table 3.** Main clinical and laboratory data in the two groups under study throughout the follow-up period (Group OS, patients treated with oral iron, n = 66; Group IV, patients treated with IV iron, n = 33).

**Figure 2.** A typical dosing strategy of iron gluconate with regard to the primary effi- ciency end point of mean change from baseline Hb to the end of treatment. The short-term therapy with IV iron produced a more rapid Hb increase compared with liposomal iron, although the final increase in Hb was similar with either treatment. However, after iron withdrawal, Hb concentrations remained stable in the IV group, while recovered to baseline in the OS group. Achievement of the end point of replenishing iron stores was greater in the IV group. The mean increase in ferritin levels indicated greater repletion of body iron stores with IV iron than with oral iron. Similarly, the mean level of

## Discussion

The effectiveness of IV iron therapy in replenishing iron stores and correcting anaemia has been demonstrated in the ND-CKD population [15, 16, 29–31]. However, only few studies have compared the effectiveness of IV versus oral iron therapy [15, 17, 29, 30], showing that treatment with IV iron is superior to oral iron with regard to replenishing iron stores, and has shown a small but significant superiority to oral iron with regard to increasing Hb [32]. However, these studies yielded contradictory results and differed in several important ways including baseline Hb levels, study duration, iron status of the patients, sample size and type of IV iron preparations.
TSAT, another indicator of iron supply for erythropoiesis, increased significantly more with IV iron than with oral iron. In addition, iron repletion was significantly faster with IV iron, and the difference could be clearly identified since the first month of therapy. There is to consider, however, that we used an association of liposomal iron and ascorbic acid, which was likely responsible for the poor repletion of iron stores with the oral iron; it is possible that vitamin C, while enhancing the synthesis of heme, may lessen iron uptake by its storage sites [35].

It is interesting to note that at the multiple LMM analysis, iron therapy represented the first independent effector of Hb changes, excluding any role for confounding factors potentially depressing erythropoiesis, like ACE-I, diabetes, hyperparathyroidism and inflammation. In particular, we did not measure more accurate markers of inflammation, but several studies have clearly demonstrated that CRP levels positively correlate with the severity of anaemia and EPO resistance in CKD patients, and that CRP concentrations closely reflect interleukin-6 levels [36–39].

Administration of large doses of IV iron was associated with significantly higher rates of adverse events. Besides its efficacy, oral liposomal iron was well tolerated and the compliance was very good if compared with other oral iron salts. In fact, it is reported in the literature that over 30% of patients may experience adverse events with the non-liposomal oral iron that can result in dose reduction and/or non-adherence to the prescribed treatment [16], while adverse events occurred only in 3.1% of our subjects taking oral liposomal iron. Moreover, the use of oral iron consents to preserve the veins, a very important issue in conservative CKD patients. Finally, although the price of ferric gluconate is low and affordable, the costs related to its administration (like patient admission in the hospital and the necessity of dedicated personnel) and those related to the patient (necessity to move to the hospital, travel expenses, loss of working hours) make this option more expensive than oral iron administration.

This study has some limitations. First, patients of both groups were highly selected and therefore are not representative of the general CKD population; indeed, this selection was necessary to minimize potential determinants of renal anaemia, like inflammation; this did not allow the examine of the efficacy of liposomal iron in the presence of an inflammatory state, a relevant issue because inflammation is a common feature in CKD patients and impairs iron absorption and

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Units of increase</th>
<th>P</th>
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<tbody>
<tr>
<td>Treatment arm</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>1 g/dL</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0 = no; 1 = yes</td>
<td>0.57</td>
</tr>
<tr>
<td>Use of ACE inhibitors</td>
<td>0 = no; 1 = yes</td>
<td>0.62</td>
</tr>
<tr>
<td>PTH</td>
<td>10 pg/mL</td>
<td>0.53</td>
</tr>
<tr>
<td>lnCRP</td>
<td>0.1 mg/L</td>
<td>0.68</td>
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</tbody>
</table>

Table 4. Multiple LMM with longitudinal values of haemoglobin (at the second, third and fourth visit) as dependent variable

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Group OS</th>
<th>Group IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>3 (4.5)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3 (4.5)</td>
<td>3 (9.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (3)</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>Infusion site reaction</td>
<td>0 (0)</td>
<td>4 (12.1)</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>0 (0)</td>
<td>2 (6.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3)</td>
<td>6 (18.2)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0 (0)</td>
<td>4 (12.1)</td>
</tr>
</tbody>
</table>

Table 5. Adverse events experienced by subjects of either treatment group
utilization. Second, we also did not examine the potential effects on oxidative stress between the two different types of iron and their effects on eGFR. Indeed, several studies have shown conflicting results regarding the impact of iron on renal function; some small clinical studies, in fact, have suggested that IV iron therapy may adversely affect renal tubular function and increase proteinuria [20, 40, 41]. Third, given the short follow-up period, we cannot predict whether the beneficial effects of liposomal iron may persist in the long term and may affect the outcome of CKD; this, obviously, requires longer trials and a significantly greater number of patients. Finally, we did not compare liposomal iron to other oral iron formulations.

The strength of the study, conversely, resides in the optimal clinical and metabolic control of our CKD patients, which was carefully maintained throughout the study.

In conclusion, our study shows that oral liposomal iron is not inferior to IV iron gluconate to correct anaemia in NDCD patients, although its ability to replete iron storage sites and to maintain raised Hb values after drug withdrawal remains lower than the IV administration. However, the low rate of adverse events with liposomal iron, its practicality and the globally lower cost of oral therapy suggest that this formulation may represent the first step to correct anaemia in uncomplicated CKD patients.

CONFLICT OF INTEREST STATEMENT
The authors declare no disclosure.

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