CLINICAL INVESTIGATION

Oral iron therapies in development for iron deficiency in chronic kidney disease

Iron supplementation remains a key component of anemia management in chronic kidney disease, which is associated with functional as well as absolute iron deficiency. There remains concern about the risks of intravenous iron, but oral iron supplements are poorly absorbed due to hepcidin-induced absorption block and are associated with gastrointestinal intolerance. Newer iron preparations with greater bioavailability and better tolerability than ferrous sulfate, or other agents which bypass the gastrointestinal block of iron absorption, offer the potential for normalizing iron stores without the need for intravenous iron. We review the current status of available iron supplements and summarize the recent clinical trial evidence for their use, with a particular focus on new oral supplements and those currently in development.

Keywords: chronic kidney disease • iron • supplement

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Background

Importance of iron supplementation in chronic kidney disease

It has long been known that iron is an important component of anemia management in chronic kidney disease [1] and is frequently required in patients on dialysis in addition to erythropoietin. Although shortened red blood cell survival, reduced erythropoietin concentration and factors inhibiting erythropoiesis, such as inflammation, all play a part in the high rate of anemia in chronic kidney disease (CKD), iron deficiency has increasingly been recognized as an important contributing factor. For example, in a large, multicenter, cross-sectional observational cohort study of more than 5000 subjects in 237 US sites during the period 2000–2001, the prevalence of anemia, defined as a hemoglobin level below 12 g/dl, rose steeply from 26% in patients with early-stage disease (stage 1 and 2, estimated glomerular filtration rate [eGFR] >60 ml/min/1.73 m^2 body surface area) to 42% of patients with a moderate degree of CKD (eGFR 30–60 ml/min/1.73 m^2) to more than 75% of patients with an eGFR below 15 ml/min/1.73 m^2 [2]. After adjusting for potentially confounding variables, the odds of anemia decreased by 32% (95% CI: 28–35%) for every 10 ml/min/1.73 m^2 increase in eGFR. More importantly, the investigators found that for patients with CKD who had anemia, 56% had a transferrin saturation less than 20%, and 47% had a serum ferritin concentration of less than 100 ng/ml [2]. In other words, approximately half of the patients with varying stages of CKD were iron deficient as a key component of their anemia based on these standard criteria. As well as this significant prevalence of absolute iron deficiency in CKD patients, there is also the problem of functional iron deficiency. This is in part due to the elevated levels of hepcidin seen in patients with CKD, which has the twofold effects of the block of intestinal absorption of iron, as well as the reticuloendothelial block in iron availability which can, in part, be overcome by iron supplementation to supraphysiological levels. Indeed, the current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend iron replacement in patients with stage 3 CKD [3].

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Recently, it has become clear that CKD patients, especially those on dialysis, require iron supplementation in addition to erythropoietin to maintain their hemoglobin level [4]. This article will examine iron supplementation in patients in CKD, particularly focusing on clinical trial evidence for the safety and efficacy of existing oral supplements compared with intravenous (iv.) preparations, as well as that of promising new therapies.

Oral versus iv. iron supplementation in CKD

A variety of studies have evaluated the comparative efficacy of different preparations of iron in patients with CKD, both on dialysis and in those not on dialysis. In the case of nondialysis patients, an earlier meta-analysis of six trials in CKD (rather than dialysis) patients found improved hemoglobin levels with iv. iron, although the benefit was small (weighted mean difference 0.31 g/dl; 95% CI: 0.09–0.53) (Figure 1) [5]. Two similar reviews of iv. versus oral iron for nondialysis-dependent CKD patients reached similar conclusions that iv. iron was probably superior [6], but that concerns remained as to the safety of rapid iv. infusions [7]. For patients with earlier stages of CKD not yet requiring dialysis or erythropoiesis-stimulatory agents, there are sparse specific data on the efficacy of oral iron. A recent observational study of 182 patients, most of whom had an eGFR in the 30–60 ml/min/1.73 m^2 range (stage 3 CKD), found that hemoglobin levels did not change significantly in patients treated with oral iron over the 12-month period of the study, but decreased significantly in those who were not treated with oral iron [8]. This suggests that oral iron therapy may be appropriate for patients with milder or earlier stage CKD who do not require additional anemia treatments, such as erythropoiesis-stimulatory agents.

A more recently published *Cochrane* Review of parenteral versus oral iron therapy for adults and children with CKD [9] identified 28 studies with over 2000 participants who were randomized to either oral or iv. iron preparations. Compared with patients receiving treatment with oral iron, those receiving iv. iron demonstrated significantly higher levels of hemoglobin (mean difference 0.9 g/dl; 95% CI: 0.44–1.37 g/dl; 22 studies, 1862 patients), serum ferritin (mean difference 243 µg/l; 95% CI: 189–298 µg/l; 24 studies, 1751 patients) and transferrin saturation (mean difference 10.2%; 95% CI: 5.6–14.9%; 18 studies, 1457 patients). These differences were both statistically significant and clinically important. Indeed, the authors of this review also noted that for dialysis patients treated with iv., as opposed to oral iron, there was also a significant reduction in erythropoiesis-stimulating agent dose (standardized mean difference -0.76; 95% CI: -1.22 to -0.30; nine studies, 487 patients) [9]. In terms of potential harms, no significant differences were observed between the iv. and oral iron groups with respect to all-cause mortality, cardiovascular mortality or need for commencement of dialysis, although there was considerable trial heterogeneity and the analysis was underpowered for these outcomes. Only 12 (43%) of the 28 studies provided some information on

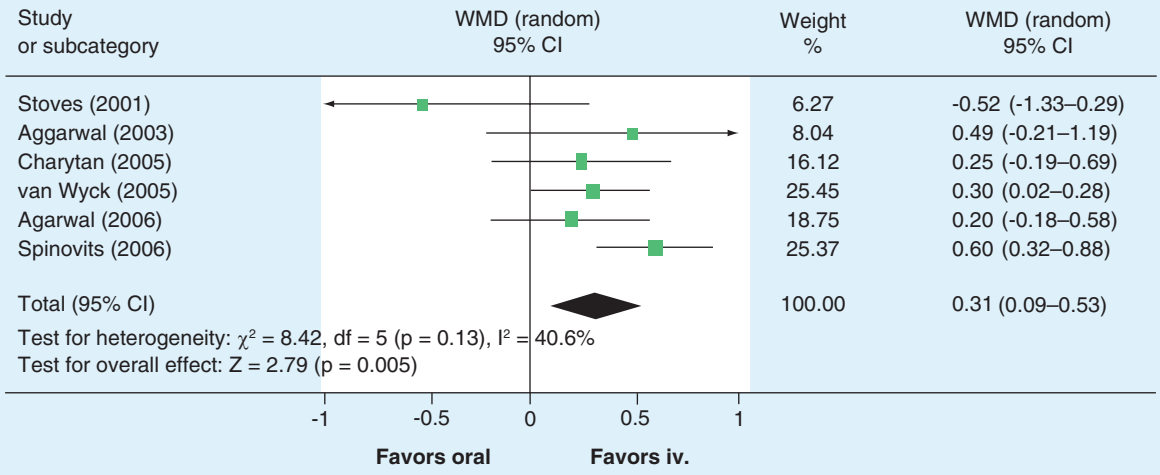

Figure 1. Hemoglobin level or change from baseline for trials comparing intravenous iron versus oral iron in patients with chronic kidney disease not on dialysis therapy. Studies are identified by name of first author and year of publication and sorted by their weight. WMDs are pooled using the random-effect model and shown on a scale of -1 to 1 g/dl. The iv. iron arm included 421 patients and the oral iron arm included 281 patients. Serum hemoglobin may be converted from g/dl to g/l by multiplying by 10.
iv.: Intravenous; WMD: Weighted mean difference.
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adverse events. Nevertheless, iv. iron therapy was associated with significantly increased risks of both allergic reactions and hypotension (risk difference 0.02; 95% CI: -0.00 to 0.04; eight studies, 1199 patients), but lower risks of total gastrointestinal adverse events (risk difference -0.17; 95% CI: -0.27 to -0.06; eight studies, 925 patients), constipation (risk difference -0.07; 95% CI: -0.14–0.00) and diarrhea (risk difference -0.07; 95% CI: -0.14–0.00). Numerical data for patient medication adherence were only reported in two studies and found to be 95–97% with iv. iron and 85–88% with oral iron. The authors concluded that "further studies that focus on patient-centered outcomes are needed."

In peritoneal dialysis, although there are fewer trials of oral versus iv. iron for maintenance of erythropoiesis compared with hemodialysis, both a single-center prospective study [10] and a recent systematic review concluded that the evidence similarly suggests iv. iron is efficacious whereas oral iron is not [11], again because of poor absorption and high frequency of gastrointestinal side effects.

Current oral iron therapies

Ferrous sulfate

Ferrous sulfate has been the mainstay of oral iron replacement for iron deficiency or maintenance of erythropoiesis in CKD, as well as iron deficiency in general, for many years. Its use in CKD has also been known to be associated with significant rates of gastrointestinal intolerance (e.g., nausea, bloating and constipation) for some time. Some older studies specific to patients with CKD report rates of such side effects of 46% [10] when self-reported by patients, although a recent meta-analysis of 104 studies (of which 82 were randomized) yielded data on gastrointestinal tolerability of various oral iron preparations in over 10,000 patients enrolled in prospective trials. This review found that the rate of gastrointestinal adverse events for ferrous sulfate was 30.2% [12]. It should be noted that the studies in this review were of patients with iron deficiency in general, not just patients with CKD, who may be more prone to the side effects of oral iron.

Ferrous fumarate

Ferrous fumarate has been studied in only one trial specifically involving patients with CKD. A prospective single-center trial from Nepal of hemodialysis patients on erythropoietin-stimulating agents were allocated in an alternating fashion to receive either iv. iron sucrose or oral ferrous fumarate. A total of 60% of patients in the iv. iron sucrose group met the hemoglobin rise target of 1 g/dl, compared with only 20% of the oral iron fumarate group [13]. The study was only of 30 days duration and did not report gastrointestinal adverse effects of the oral ferrous fumarate in detail. In a systematic review of gastrointestinal tolerability of various oral iron supplements in other populations with iron deficiency anemia, the reported rate of gastrointestinal side effects for ferrous fumarate was the worst of all agents at 47.0% (Figure 2) [12], compared with a reported rate of 32.3% for ferrous sulfate in that review.

Ferrous gluconate

Ferrous gluconate is another oral iron preparation that has not been well studied in patients with CKD. A single study reported serum iron levels after high doses of either ferrous sulfate or ferrous gluconate in 29 peritoneal dialysis patients [14], in which approximately 400 mg of elemental iron was administered. Adverse effects were more common in the ferrous sulfate group. In the aforementioned systematic review of studies of tolerability of oral iron supplements, ferrous gluconate use was associated with gastrointestinal adverse effects in 30.9% of patients studied, as compared with 32.3% of patients taking ferrous sulfate (Figure 2) [12].

Iron–polymaltose complex

Oral iron(III)–hydroxide polymaltose complex has been used for treatment of iron deficiency in Europe, particularly in the setting of pregnancy, for more than two decades. It has not, as yet, been subjected to a clinical trial in CKD patients, but is worthy of some discussion because in other populations it does appear to have clear advantages to ferrous sulfate. Indeed, a recent review [15] of the safety and efficacy of oral iron–polymaltose complex found evidence of superiority to ferrous sulfate in adults and children with iron-deficiency anemia, although most of the studies were comparative in nature and from single centers rather than being robustly conducted randomized controlled trials. None of the published studies were specifically in CKD patients. Despite some other single-center studies suggesting that iron–polymaltose complex is not effective in some patients with iron-deficiency anemia [16], several recent well-conducted randomized controlled trials in pregnant women [17] and in a pediatric population [18] clearly demonstrated that iron–polymaltose complex was equally efficacious but better tolerated than oral iron sulfate in patients with iron-deficiency anemia. Indeed, the incidence of gastrointestinal adverse events rates in the iron–polymaltose complex group was approximately half that of the ferrous sulfate group in both of these two studies (29.3% for iron–polymaltose complex compared with 56.4% for ferrous sulfate, and 26.9 vs 50.9%, respectively). However, whether iron–polymaltose complex is effective in patients with milder or early-stage CKD remains to be proven. The

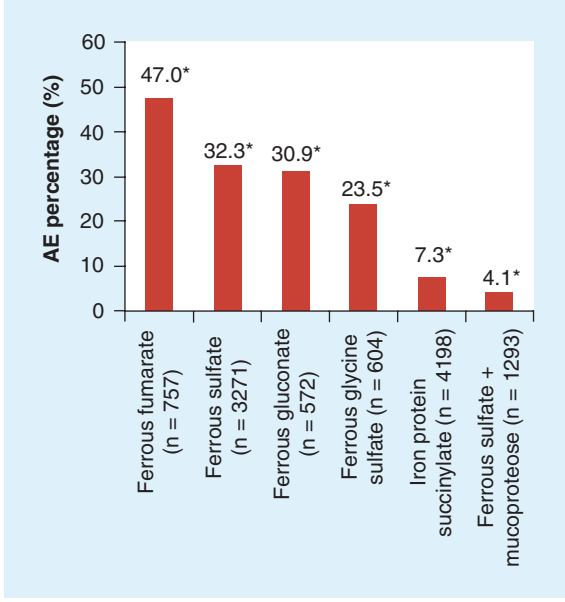

Figure 2. Overall tolerability: tolerability of the iron supplements studied. The 'n' shows the sample size of each iron supplement in which frequency has been calculated.
*p < 0.001 compared with the iron supplement of reference (ferrous sulfate plus mucoproteose).
AE: Adverse effect.
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currently published literature suggests that it is a therapy that could be a good target for future research in such patients, particularly given the known problem of gastrointestinal intolerance in this group. If iron–polymaltose complex were to be as well tolerated in CKD patients as it was in the trials of pregnant women and children as described above, then it could well be a useful therapy.

Problems with currently available iron therapies

Current oral iron treatments are limited by high rates of gastrointestinal adverse effects, such as constipation and dyspepsia, and by poor efficacy, primarily related to suboptimal absorption [7]. One large UK-based cross-sectional study, comprising over a million primary care patients from the QICKD trial, recently reported that from the patients in the study with anemia and CKD, two thirds were taking oral iron supplements. However, the mean hemoglobin level of patients receiving oral iron (10.0 g/dl; n = 582) was lower than that of those not taking oral iron (10.3 g/dl; n = 1214) [19]. The authors of this study found that three quarters of subjects with microcytic anemia, and more than half of patients with normocytic anemia (including many patients with CKD), had been prescribed oral iron, but had uncorrected anemia despite this. The reason for the poor response to oral iron supplements seen in patients with CKD is partly due to elevated levels of the peptide hepcidin, now known to be the key regulator of iron in the body [20]. Elevated levels of hepcidin lead directly to reduced absorption of iron from the gastrointestinal tract as well as suppressed iron release from the reticuloendothelial system, and as discussed later, may be a target for anemia treatment in CKD patients.

Although current oral iron treatments are problematic, iv. iron supplements are similarly limited by relatively high cost, inconvenience [10] and significant adverse reactions, such as allergic reactions, infections and iron overload. Concerns pertaining to anaphylaxis or anaphylactoid reactions, particularly with older preparations, such as iron dextran [21], mean that most iv. iron preparations must be administered slowly and under medical supervision. Less severe infusion reactions, such as rash, flushing, chest pain and nausea, have also been seen with various iv. iron preparations with rates approximately 1% [22]. There has also been concern for some time, largely based on animal and *in vitro* studies, that iv. iron might be associated with infections due to impairment of neutrophil activity [23]. However, in a recent mouse model of critical care anemia where animals were given the iv. iron preparation ferric carboxymaltose (FCM), no increase in mortality was seen in the animals treated with iv. iron despite having active septicemia [24]. Further to this, although some observational studies in dialysis patients have linked high-dose iv. iron to infectious outcomes [25], there are very little prospective data in dialysis patients receiving iv. iron. One single-center study after kidney transplantation [26] showed no significant increase in infections after a single iv. iron dose.

The other significant concern for dialysis patients receiving repeated iv. iron doses is of liver accumulation of iron. A recent study [27] reported that current serum markers of iron status, such as ferritin, did not adequately predict liver iron concentration as measured by magnetic resonance R2 relaxometry. Moreover, two patients in this study who had received more than 6 g of parenteral iron were observed to have liver iron concentrations similar to those seen in patients with hemochromatosis. Cumulative iron doses are not something that nephrologists routinely measure. Further prospective studies of iv. iron with infections and perhaps some measure of liver iron content as major safety outcomes are needed before clinicians can be reassured that iv. iron is completely safe from an infection risk point of view.

Newer oral iron therapies

In view of the significant issues pertaining to the safety and efficacy of current oral iron therapies and the

safety of iv. iron therapies, new strategies for oral iron supplementation are being actively pursued.

Heme iron polypeptide

Heme iron polypeptide is a product manufactured from bovine hemoglobin, resulting in a soluble, iron-rich form of heme iron. It is absorbed from the GI tract directly through the intestinal mucosa by a specific transporter [28], which is different to ionic (ferrous) iron, the absorption of which is regulated by the divalent metal transporter (DMT-1) and subject to interference by elevated hepcidin levels [29]. It has, therefore, been of considerable interest to nephrologists for potential use in patients with CKD where iv. iron compounds are either contraindicated, inconvenient or disliked by patients. In a recent small trial of 40 nondialysis-dependent CKD patients randomly allocated to receive either heme iron polypeptide (11 mg orally three times a day) or iv. iron sucrose (200 mg monthly) for 6 months, heme iron polypeptide resulted in similar hemoglobin levels (117 vs 113 g/l, respectively; p = 0.37) and overall adverse events [30]. Interestingly, although transferrin saturation values were comparable in both groups (21.5 vs 21.5%; p = 0.82), serum ferritin concentrations were significantly lower in the group of patients receiving oral heme iron polypeptide (85.5 vs 244 µg/l; p = 0.004). Similar findings were also reported in a randomized controlled trial of 62 darbepoetin-treated peritoneal dialysis patients randomized to oral heme iron polypeptide (one capsule twice daily equivalent to 210 mg elemental iron daily; n = 32) or oral ferrous sulfate (one capsule twice daily equivalent to 240 mg elemental iron daily; n = 30) for 6 months, whereby the two groups exhibited comparable median values for hemoglobin (111 vs 113 g/l, respectively; p = 0.59), transferrin saturation (22 vs 20%; p = 0.65), darbepoetin dose (20 vs 20 µg/week; p = 0.61) and overall adverse events (23 vs 24), but lower serum ferritin concentrations were observed in the heme iron polypeptide group (124 vs 292 µg/l; p = 0.003) [29]. The cost of heme iron polypeptide was also found to be seven-times higher than that of ferrous sulfate during the course of the study. Another 6-month, open-label, nonrandomized trial of heme iron polypeptide following discontinuation of maintenance iv. iron therapy in 37 hemodialysis patients reported preserved transferrin saturation and hematocrit levels, but significantly reduced serum ferritin levels [31]. In summary, the limited available evidence for the use of heme iron polypeptide in CKD patients suggests that heme iron polypeptide is capable of maintaining hemoglobin levels over a 6-month period, although serum ferritin concentrations fall significantly compared with either oral or iv. iron supplementation. The clinical significance of the lower serum ferritin values remains unclear but is cause for concern, as it may reflect lower iron availability in the longer term.

Ferrous glycine sulfate & ferrous sulfate with mucoproteose

These two variants of iron sulfate have an extra moiety added in order to try to reduce gastrointestinal erosions and therefore symptoms. They have been used in various forms of iron deficiency, but there are no randomized or even prospective trials of either agent in patients with CKD. However, in the previously mentioned systematic review of observational studies of oral iron supplements [12], gastrointestinal adverse events occurred with a frequency of 18.5% for ferrous glycine sulfate and 30.2% for ferrous sulfate with mucoproteose, which compared favorably with the frequencies reported for ferrous gluconate (29.9%) and ferrous fumarate (43.4%).

Other oral agents that may also supplement iron

SBR759

SBR759 is a novel iron(III)-based phosphate binder that was developed as an alternative to calcium-based binders for dialysis patients because of the concern about vascular calcification associated with the use of these agents. The amount of available iron in this compound, which is administered with food in order to prevent absorption of inorganic phosphate and correct the hyperphosphatemia of CKD, is minimal, only approaching a similar amount to that in oral iron supplements at doses higher than would be required as a phosphate binder. In a Phase I study of 44 hemodialysis patients given varying doses of the agent for a period of 4 weeks, there was a significant lowering of phosphate but no change in the measured iron parameters (ferritin, iron saturation) [32]. Some gastrointestinal adverse events were seen in this study, which included diarrhea and discolored feces, the former of which was dose-related. In a second, similar study of 63 Japanese hemodialysis patients where SBR759 was given over 4 weeks at varying doses, mild gastrointestinal adverse events were seen in 16.7–53.8% of patients, depending on the dose, compared with 25% in the placebo group [33], although the side effects were not dose-related. For moderate gastrointestinal adverse events, the numbers were too small to ascertain a difference (only one patient with moderate diarrhea in two of the four treatment groups versus none in the placebo group). As the numbers of patients were small in both of these studies, and the duration of treatment only 4 weeks long, it is not surprising that there were no differences in iron parameters noted in either study. It remains to be seen whether patients treated with

SBR759 will have some gastrointestinal absorption of iron and therefore less requirement for other iron supplements. This will require much larger studies of longer duration to adequately assess.

PA21

PA21, similar to SBR759, is a novel, iron-based phosphate binder developed for use in dialysis patients. It was studied in a Phase I trial to assess the possibility of causing iron overload in a small number of both dialysis and nondialysis CKD patients [34]. The results of this study demonstrated that PA21 was an effective phosphate binder in both groups of patients. Median iron uptake, as measured by radiolabeled PA21, was low in both dialysis patients (0.06%) and nondialysis-dependent CKD patients (0.02%) compared with healthy subjects (0.43%). Side effects, similar to what was seen in the studies of SBR759, included diarrhea in nine (53%) of 17 patients, although all cases were only reported as mild-to-moderate. It should be noted that even though iron absorption was observed to be minimal, the results were obtained from a single dose of drug, such that it remains to be determined whether or not a clinically significant quantity of iron would be absorbed in patients treated with this agent over a much longer period of time. This would be likely to be an end point in future trials of longer duration.

A more definitive (although again, short-term) multicenter randomized controlled trial of hemodialysis patients has been recently published [35], which compared PA21 to the noncalcium phosphate binder, sevelamer hydrochloride, in 154 patients from 50 clinical sites in Europe and the USA. In terms of efficacy, the phosphate-lowering effect of PA21 was equal to that of a similar dose of sevelamer, and in terms of adverse events, the most frequent in PA21-treated patients were hypophosphatemia and discolored feces (11.7% of patients). Actual discontinuation rates for PA21 versus sevelamer were similar at 21.1 and 23.1%, respectively. No changes were observed in either serum ferritin or transferrin saturation over 4 weeks.

Roxadustat

Roxadustat, also known as FG-4592, is one of several newly developed molecules which are inhibitors of hypoxia-inducible factor prolyl hydroxylase (HIF-PH), which, in turn, inhibits the degradation of HIF thereby stimulating erythropoiesis. In addition, it has effects on iron metabolism, including improved iron mobilization and utilization from the reticuloendothelial system [36] such that iron supplementation may not be required when used as an alternative to other erythropoiesis-stimulatory agents. As yet, there are no published data from the clinical program.

Conclusion

There are several new classes of orally available iron supplements in development or in early clinical trials, which may be useful for patients with CKD, given the poor efficacy and significant rates of side effects of the currently available supplements. In addition, several other new agents such as iron-based phosphate binders and HIF-stabilizing agents may also have a positive effect on iron status such that the requirement for iron supplementation is either reduced or alleviated completely.

Executive summary

Background

- Iron deficiency is a common problem in chronic kidney disease (CKD), and iron supplementation is required in most patients.
- Most oral iron supplements are poorly absorbed and cause gastrointestinal side effects in a high proportion of CKD patients.

Newer oral iron supplements

- Despite their proven efficacy, there is on-going concern regarding the safety of intravenous iron preparations (infusion reactions, infections, liver accumulation, oxidative stress); therefore, alternative oral iron preparations are actively being sought.
- Heme iron polypeptide has shown efficacy in non-dialysis-dependent CKD patients and in both peritoneal dialysis and hemodialysis patients in short term studies, although serum ferritin concentrations have consistently been lower with this therapy.
- Iron–polymaltose complex is better tolerated than ferrous sulfate but has not been trialed in CKD patients.

Conclusion & future perspective

- Several newer classes of iron or iron-modifying compounds hold promise for kidney disease patients.
- The oral phosphate binders, SBR759 and PA21, are iron-based and may prove to also supplement iron to some degree in the longer term.
- Oral HIF-stabilizing agents, such as roxadustat, also improve iron availability in dialysis patients when used as an alternative to erythropoiesis-stimulating agents, thereby mitigating the need for additional iron supplementation.

Future perspective

The future of iron supplementation in CKD appears very promising, especially from the point of view of the HIF-stabilizing agents. This novel class of drugs may result in a big change in the treatment of anemia in patients on dialysis or with CKD from the current requirement for the combination of injectable iron and injectable erythropoiesis-stimulating agents to a single oral medication given perhaps once or twice per week, which will achieve the same results without the requirement for injections. This would be a major advance for kidney patients. In combination with the newer iron-based phosphate binders, this may reduce the need for parenteral iron therapy and the potential for iron toxicity in CKD patients by improving iron availability.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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