Iron therapy for managing anaemia in chronic kidney disease

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Purpose of review
Iron deficiency is a major contributory cause to the development of anaemia in chronic kidney disease (CKD), and thus, iron replacement therapy plays a critical role in the management of this condition. The two main routes for administering iron are oral and intravenous, and there have been a number of new publications relevant to both routes of administration.

Recent findings
Recent developments on the topic of iron management in CKD include the introduction of new oral iron preparations, as well as two recent meta-analyses on iron therapy in CKD (one on oral *versus* intravenous iron, and one on high- *versus* low-dose intravenous iron in haemodialysis patients). There is also increasing interest in other strategies to improve iron availability, such as intradialytic iron, hypoxia-inducible factor stabilization and antihepcidin strategies.

Summary
Even despite the latest publications in this field, we are still left with serious gaps in our evidence base on how best to provide supplemental iron to CKD patients. Most of the evidence suggests that intravenous iron is superior to oral iron in increasing haemoglobin and minimizing the use of erythropoiesis-stimulating agents, but the safety of intravenous iron remains a controversy. The PIVOTAL study will hopefully provide informative data to fill some of the gap in the evidence-base and inform best clinical practice.

Keywords
anaemia, chronic kidney disease, intravenous, iron, oral

INTRODUCTION

Iron deficiency is a major contributory cause to the development of anaemia in chronic kidney disease (CKD) [1]. This arises due to both an inadequate supply of iron, as well as increased losses. Inadequate intake is due to poor appetite in uraemia, as well as poor absorption from the gastrointestinal tract caused by increased hepcidin activity, and exacerbated by concomitant medications such as phosphate binders, proton pump inhibitors and certain antibiotics. Increased iron losses occur due to frequent blood sampling, trapping of red cells in the dialyzer and occult gastrointestinal blood loss, the latter of which may be exacerbated by antiplatelet drugs and anticoagulation on dialysis [1].

Iron supplementation has therefore become a front-line therapy in the management of CKD anaemia, and the majority of patients with this condition are likely to receive additional iron at some stage. How this iron is administered will depend on a number of factors, including the stage of CKD or modality of renal replacement therapy, as well as physician preference.

For more than three centuries, orally administered iron has been available, and is still used widely today [2]. In the mid-1900s, the concept of giving iron parenterally was introduced to the therapeutic armamentarium [3], and several new intravenous iron preparations have become available for use over the last few years. More recently, several novel strategies for improving iron availability have evolved, including administration of ferric pyrophosphate citrate (FPC) in the dialysate for haemodialysis patients, and newer oral iron preparations (such as ferric citrate), as well as hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitors and antihepdidin agents [4].

This review will focus largely on what is new regarding both oral and intravenous iron supplementation, as the use of prolyl hydroxylase

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KEY POINTS

- Recent interest in oral iron supplementation has focused on nonferrous preparations, such as ferric citrate, ferric maltol, heme iron polypeptide and liposomal iron.
- Of these, only ferric citrate has so far been shown to have any possible role in the management of CKD anaemia.
- A recent meta-analysis (an update on a previous one) confirmed the superior efficacy of intravenous iron compared with oral iron in improving haemoglobin and minimizing the use of ESAs.
- Two recent randomized controlled trials in nondialysis CKD anaemia (FIND-CKD and REVOKE) yielded conflicting results on the safety of intravenous iron, further confusing the evidence base.
- A further meta-analysis from February 2018 suggested that there was no obvious safety signal with administration of high doses of intravenous iron versus low-dose intravenous iron.

inhibitors and antihepcidin strategies remains largely experimental.

Oral iron supplementation: what is new?

By far, the most commonly used oral iron preparation in clinical practice remains ferrous sulphate. Other older iron compounds include ferric gluconate, ferric succinate and iron polymaltose. In recent times, however, there have been a number of new oral iron compounds developed and marketed, such as ferric citrate, ferric maltol, heme iron polypeptide (HIP) and oral liposomal (sucrosomial) iron.

The major concerns about oral iron supplementation are largely two-fold: inadequate absorption in many chronic disease states, and gastrointestinal side effects. Preliminary attempts to use serum hepcidin as a new biomarker to predict the likelihood of adequate iron absorption have unfortunately failed to show any potential role in iron management in CKD.

In the two latest trials of oral iron versus intravenous iron in CKD (FIND-CKD [5] and REVOKE [6]), oral iron did show some efficacy in relation to correction of anaemia and replacement of iron stores. In a secondary analysis of FIND-CKD, hepcidin levels were measured in a subgroup of patients [7▪], and were generally low at baseline, a consequence of the inclusion criteria that mandated that CRP levels had to be low at screening. This likely contributed to the reasonable efficacy of oral iron in the study. A secondary analysis of FIND-CKD, however, suggested that 4 weeks after starting oral iron therapy, only 21.6% of nondialysis-CKD patients with anaemia and iron deficiency showed an increase of at least 1 g/dl. Among early nonresponders, less than 30% responded at any subsequent time point over the 12 months of follow-up [8▪].

In recent times, there has been a new concern about the potential for oral iron to alter the gut microbiome adversely [9▪]. The evidence for this comes from both in-vitro and in-vivo studies investigating the effects of oral iron supplementation on the gut microbiota composition, got metabolome and intestinal health, which in turn may result in an increased production of uremic toxins. It may also affect the circulating levels of other microbe-derived molecules, which can act as mediators of immune regulation.

Ferric citrate was initially developed as a non-calcium containing oral phosphate binder, but in phase 2 trials, it became apparent that much of the iron was being absorbed from the gut, even in haemodialysis patients, as indicated by an increase in ferritin and transferrin saturation levels [10]. This was in contrast to another iron-based phosphate binder, sucroferric oxyhydroxide (Velphoro), which was designed specifically to avoid or minimize iron absorption, and to simply bind phosphate in the gut [11]. Enhanced oral iron absorption from the gastrointestinal tract in haemodialysis patients was an unexpected finding, and this was systematically assessed in several randomized controlled trials, both in nondialysis CKD [12▪] and haemodialysis patients [13].

Ferric maltol was initially assessed in patients with inflammatory bowel disease, with favourable results in improving anaemia and iron status compared with intravenous iron [14]. However, preliminary data from patients with CKD have been disappointing, and at present, there are no data to support any role for this drug in CKD.

HIP is absorbed from the gut via a different mechanism, which is believed to be hepcidin-independent. This latter characteristic was felt to be of benefit in patients with chronic inflammatory disease, such as occurs in CKD, and was the impetus for a number of randomized controlled trials in this patient cohort. Dull and Davis [15] conducted a review of this iron compound in patients with anaemia and CKD, and found that in general the effect of HIP on haemoglobin (Hb), transferrin saturation and EPO dose was, rather disappointingly, similar to intravenous and oral nonheme iron supplementation. HIP was also associated with lower ferritin levels compared with traditional iron supplementation. Finally, the cost of HIP is substantially more than nonheme iron preparations [15].

Finally, liposomal (sucrosomial) iron has been the subject of several randomized controlled trials. Pisani *et al.* [16] compared this oral iron preparation with intravenous iron gluconate in 99 patients with nondialysis CKD and iron deficiency anaemia for 3 months. Intravenous iron produced a more rapid Hb increase than liposomal iron, although the final increase in Hb was similar with both treatments. After iron withdrawal, Hb concentrations remain stable in the intravenous iron-treated group but recovered to baseline in the microsomal iron group. Replenishment of iron stores was greater in the intravenous iron group, but adverse events were significantly lower in the oral liposomal iron group.

Intravenous iron supplementation: what is new?

Most of the scientific evidence regarding iron supplementation in CKD suggests that intravenous iron is superior to oral iron in raising the Hb and markers of iron status. This is particularly true in haemodialysis patients, in whom upregulation of hepcidin activity potently inhibits iron absorption from the gut [17]. There are two meta-analyses/systematic reviews of this topic, both from the same Israeli group. The first of these was published in 2008 [18] and showed that Hb responses and repletion of iron stores were greater with intravenous iron than oral iron. However, the authors commented that most of the studies were of short duration, and with small numbers of patients.

An updated meta-analysis/systematic review was published in 2016 [19▪▪], this time including 24 trials (13 including 2369 patients with CKD stages 3–5, and 11 including 818 patients on haemodialysis). Patients treated with intravenous iron were more likely to reach a Hb response greater than 1 g/dl (risk ratios of 1.61 for CKD stages 3–5, and 2.14 for haemodialysis patients). Safety analysis showed similar rates of mortality and adverse effects. Intravenous iron replacement was associated with a higher risk of hypotension (risk ratio 3.71) and fewer gastrointestinal adverse events (risk ratio 0.43). Again, a major limitation of this meta-analysis was that follow-up was often limited to a maximum of 3 months. It did, however, include two more recent larger studies with longer follow-ups (1 year, FIND-CKD [5]; and 2 years, REVOKE [6]).

The FIND-CKD study [5] randomized 626 nondialysis patients with CKD, anaemia and iron deficiency into three arms: high-ferritin (400–600 μg/l) target ferric carboxymaltose, low-ferritin (100–200 μg/l) target ferric carboxymaltose and oral iron. The study met its primary endpoint of showing that the high-ferritin intravenous iron group delayed the need for alternative anaemia management, including further iron therapy, erythropoiesis-stimulating agent (ESA) therapy and blood transfusions. There were also no obvious safety concerns, and particular attention was paid to progression of renal impairment [20▪] and incidence of infections [21▪] in separate secondary analyses.

In contrast, the REVOKE study [6] was terminated early because of a safety signal in relation to excess cardiovascular and infection-related SAEs. This latter study was primarily focused on determining the rate of progression of renal failure, as assessed by measured GFR. At the time the study was terminated, there was no difference in the rate of GFR progression between intravenous iron and oral iron. However, there was a significantly higher rate of cardiovascular events (adjusted incidence ratio 2.51) and infections resulting in hospitalisations (adjusted incidence rate ratio 2.12) in the intravenous iron-treated group [6].

The disparity between these two studies has been the subject of much discussion. There were indeed significant differences between the two studies: FIND-CKD used ferric carboxymaltose, while REVOKE used iron sucrose. FIND-CKD was a global multicentre study, while REVOKE was a single-centre US study.

In haemodialysis patients, there is less debate about whether to use intravenous iron or oral iron, but instead the focus has been on how much intravenous iron is optimal, and how best to administer this [22▪]. It is well recognized from DOPPS [23] and other observational data that there is a high usage of intravenous iron in the US, a low usage of intravenous iron in Japan, with the rest of the world somewhere in between. Although there is little doubt that intravenous iron is more efficacious than oral iron in this patient cohort, the concern has been, and still is, the potential for intravenous iron to exacerbate oxidative stress, cardiovascular risk, infections and mortality [24]. Observational data on this issue are conflicting, and randomized controlled trial data are sparse. This was the subject of a KDIGO Controversies Conference held in San Francisco in March 2014 [25▪]. Since then, a meta-analysis/systematic review of intravenous iron dosing has been published [26▪▪], and a large randomized controlled trial (PIVOTAL) is near-complete [27▪].

The meta-analysis located 2231 eligible studies, although only seven randomized controlled trials and 15 observational studies met the inclusion criteria [26▪▪]. The randomized controlled trials showed no association between higher-dose intravenous iron (>400 mg/month for most studies) and mortality (six studies; $n = 970$; pooled relative risk, 0.93; 95% confidence interval, 0.47–1.84; follow-up

ranging from 35 days to 26 months) or infection (four studies; $n = 743$; relative risk, 1.02; 95% confidence interval, 0.74–1.41). The observational studies showed no association between higher-dose intravenous iron (>200 mg/month for most studies) and mortality (8 studies; $n = 241{,}408$; hazard ratio, 1.09; 95% confidence interval, 0.98–1.21; follow-up ranging from 3 to 24 months), infection (eight studies; $n = 135\,532$; pooled hazard ratio, 1.13; 95% confidence interval, 0.99 to 1.28), cardiovascular events (seven studies; n = 135 675; hazard ratio, 1.18; 95% confidence interval, 0.90 –1.56) or hospitalizations (five studies; $n = 134\,324$; hazard ratio, 1.08; 95% confidence interval, 0.97–1.19). Despite this comprehensive analysis, the accompanying editorial highlighted its limitations and the need for further study of the safety and effectiveness of intravenous iron among patients on haemodialysis. The PIVOTAL study, which is near completion, has randomized 2141 patients across 50 sites in the UK to a high-dose versus a low-dose intravenous iron regimen, looking at hard endpoints such as all-cause mortality, heart attack, stroke and heart failure, as well as infections [27▪].

Future strategies for enhancing iron availability

FPC was developed to provide small amounts of supplemental iron (around 7 mg) across each dialysis session, on the basis that this is the average loss of iron in haemodialysis patients [28]. FPC donates iron directly to transferrin, bypassing the reticuloendothelial system. Two large phase 3 randomized controlled trials have been published [29,30]. The first of these reported data from the PRIME study, in which 103 patients were randomized to receive either regular intradialytic iron with FPC or placebo. Patients randomized to FPC had a 35% reduction in prescribed ESA dose compared with placebo, and also used 51% less intravenous iron [29]. Two identical phase 3 randomized placebo-controlled trials (CRUISE 1 and 2) were conducted in 599 haemodialysis patients, with a follow-up of up to 48 weeks.

Table 1. Newer oral iron preparations

Ferric citrate	Approved in the US and Japan, not available in Europe
Ferric maltol	Approved for use in patients with inflammatory bowel disease only
Heme iron polypeptide	Limited data in CKD
Liposomal (sucrosomial) iron	Limited data in CKD

CKD, chronic kidney disease.

Table 2. Newer IV iron preparations

Ferumoxytol	Approved in the US as Feraheme, not available in Europe
Ferric carboxymaltose	Approved in Europe as Ferinject and in the US as Injectafer
Iron isomaltoside-1000	Approved in Europe as Monofer

In both trials, haemoglobin concentration was maintained in the FPC group, but decreased by 0.4 g/dl in the placebo group ($P < 0.001$) [30].

Hypoxia-inducible factor prolyl hydroxylase inhibitors

This new class of drugs for treating anaemia in CKD was based on their ability to upregulate erythropoietin gene expression and allow patients to increase their own EPO levels without the need for exogenous ESA administration [31]. It became clear from phase 2 randomized controlled trials, however, that they also reduced the need for iron supplementation, and this is believed to be due to their ability to also upregulate a number of iron regulatory genes, thus enhancing iron availability to the bone marrow. HIF PHIs have also been shown to reduce hepcidin levels (probably as an indirect effect), which allow these drugs to be effective in patients with anaemia and inflammation, with an associated functional iron deficiency. This effect on hepcidin has been shown for both roxadustat [32▪,33▪] and vadadustat [34▪].

Antihepcidin strategies

Ever since the discovery of hepcidin as the major iron regulatory peptide at the turn of the millennium, several molecules for inhibiting hepcidin activity have been developed as a possible treatment for the anaemia of inflammation and CKD. These molecules have been shown to be effective in animal models of inflammatory anaemia, and several of them have now been translated into clinical trials.

Table 3. New strategies for delivering iron in chronic kidney disease

Ferric pyrophosphate citrate (Triferric)	Approximately 7 mg of iron administered via the dialysate to haemodialysis patients; approved in the US only
HIF prolyl hydroxylase inhibitors	e.g. roxadustat; daprodustat, vadadustat, molidustat. None approved; in phase 3 clinical trials
Antihepcidin strategies	Not approved; in clinical trials

These molecules inhibit hepcidin activity either directly (mAb, spiegelmer, anticalin and so on) or indirectly via its signalling mechanism (e.g. BMP-6 antagonist), and have been the subject of several in-depth reviews. Given the current lack of clinical efficacy for treating CKD anaemia, they will not be discussed further in this article, but the interested reader may find useful information in one or other of the comprehensive reviews (Tables 1–3) [35,36].

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Gotloib L, Silverberg D, Fudin R, Shostak A. Iron deficiency is a common cause of anemia in chronic kidney disease and can often be corrected with intravenous iron. J Nephrol 2006; 19:161–167.
2. Auerbach M, Macdougall IC. Oral iron therapy: a three centuries, it is time for a change. Am J Kidney Dis 2016; 68:665–666.
3. Heath CW, Strauss MB, Castle WB. Quantitative aspects of iron deficiency in hypochromic anemia; the parenteral administration of iron. J Clin Invest 1932; 11:1293–1312.
4. Macdougall IC. Supplemental iron via dialysate: a novel mode of delivery for hemodialysis patients. Kidney Int 2015; 88:946–949.
5. Macdougall IC, Bock AH, Carrera F, *et al.* FIND-CKD Study Investigators. FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia. Nephrol Dial Transplant 2014; 29:2075–2084.
6. Agarwal R, Kusek JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. Kidney Int 2015; 88:905–914.
7. ■ Gaillard CA, Bock AH, Carrera F, *et al.* Hepcidin response to iron therapy in patients with nondialysis dependent CKD: an analysis of the FIND-CKD trial. PLoS One 2016; 11:e0157063.

One of the four secondary analyses of the FIND-CKD study published within the last couple of years, this one examining the hepcidin response to iron therapy in the three groups of patients in the study. Hepcidin levels increased in all three groups, but the speed and extent of the rise was greatest in the group receiving intravenous iron targeting a high ferritin level.

8. ■ Macdougall IC, Bock AH, Carrera F, *et al.* Erythropoietic response to oral iron in patients with nondialysis-dependent chronic kidney disease in the FIND-CKD trial. Clin Nephrol 2017; 88:301–310.

Another secondary analysis of the FIND-CKD study, suggesting that less than 30% of patients who failed to show an early response to oral iron responded at a later time point.

9. ■ Kortman GAM, Reijnders D, Swinkels DW. Oral iron supplementation: potential implications for the gut microbiome and metabolome in patients with CKD. Hemodial Int 2017; 21(Suppl 1):S28–S36.

A recent review discussing the effects of iron on the gut microbiome in CKD patients, revealing another potential concern for giving oral iron to this patient population.

10. Yokoyama K, Akiba T, Fukagawa M, *et al.* Long-term safety and efficacy of a novel iron-containing phosphate binder, JTT-751, in patients receiving hemodialysis. J Ren Nutr 2014; 24:261–267.
11. Covic AC, Floege J, Ketteler M, *et al.* Iron-related parameters in dialysis patients treated with sucroferric oxyhydroxide. Nephrol Dial Transplant 2017; 32:1330–1338.
12. ■ Fishbane S, Block GA, Loram L, *et al.* Effects of ferric citrate in patients with nondialysis-dependent CKD and iron deficiency anemia. J Am Soc Nephrol 2017; 28:1851–1858.

One of the several recent articles describing the efficacy of ferric citrate in increasing markers of iron status in CKD patients, thereby suggesting a possible role for this new drug as an iron supplement, beyond its original role as a noncalcium-containing phosphate binder.

13. Lewis JB, Sika M, Koury MJ, *et al.* Collaborative Study Group. Ferric citrate controls phosphorus and delivers iron in patients on dialysis. J Am Soc Nephrol 2015; 26:493–503.
14. Gasche C, Ahmad T, Tulassay Z, *et al.* AEGIS Study Group. Ferric maltol is effective in correcting iron deficiency anemia in patients with inflammatory bowel disease: results from a phase-3 clinical trial program. Inflamm Bowel Dis 2015; 21:579–588.
15. Dull RB, Davis E. Heme iron polypeptide for the management of anaemia of chronic kidney disease. J Clin Pharm Ther 2015; 40:386–390.
16. Pisani A, Riccio E, Sabbatini M, *et al.* Effect of oral liposomal iron versus intravenous iron for treatment of iron deficiency anaemia in CKD patients: a randomized trial. Nephrol Dial Transplant 2015; 30:645–652.
17. Babitt JL, Lin HY. Mechanisms of anemia in CKD. J Am Soc Nephrol 2012; 23:1631–1634.
18. Rozen-Zvi B, Gafter-Gvili A, Paul M, *et al.* Intravenous versus oral iron supplementation for the treatment of anemia in CKD: systematic review and meta-analysis. Am J Kidney Dis 2008; 52:897–906.
19. ■■ Shepshelovich D, Rozen-Zvi B, Avni T, *et al.* Intravenous versus oral iron supplementation for the treatment of anemia in CKD: an updated systematic review and meta-analysis. Am J Kidney Dis 2016; 68:677–690.

An update of the 2008 systematic review and meta-analysis comparing intravenous versus oral iron supplementation in the treatment of CKD anaemia, this time encompassing data from the FIND-CKD and REVOKE studies.

20. ■ Macdougall IC, Bock AH, Carrera F, *et al.* FIND-CKD Study investigators. Renal function in patients with nondialysis chronic kidney disease receiving intravenous ferric carboxymaltose: an analysis of the randomized FIND-CKD trial. BMC Nephrol 2017; 18:24.

Another secondary analysis of the FIND-CKD study, showing that there was no obvious adverse effect of iron on renal function throughout the 12 months of follow-up in the study.

21. ■ Roger SD, Gaillard CA, Bock AH, *et al.* FIND-CKD Study Investigators. Safety of intravenous ferric carboxymaltose versus oral iron in patients with non-dialysis-dependent CKD: an analysis of the 1-year FIND-CKD trial. Nephrol Dial Transplant 2017; 32:1530–1539.

The last of the four secondary analyses of the FIND-CKD study, reporting a more detailed analysis of safety than was published in the primary manuscript.

22. ■ Wish JB, Aronoff GR, Bacon BR, *et al.* Positive iron balance in chronic kidney disease: how much is too much and how to tell? Am J Nephrol 2018; 47:72–83.

A thought-provoking perspective on how much iron replacement is required in patients with chronic kidney disease, and how to detect and monitor this.

23. Bailie GR, Larkina M, Goodkin DA, *et al.* Variation in intravenous iron use internationally and over time: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Nephrol Dial Transplant 2013; 28:2570–2579.
24. Del Vecchio L, Longhi S, Locatelli F. Safety concerns about intravenous iron therapy in patients with chronic kidney disease. Clin Kidney J 2016; 9:260–267.
25. ■ Macdougall IC, Bircher AJ, Eckardt KU, *et al.* Conference Participants. Iron management in chronic kidney disease: conclusions from a 'Kidney Disease: Improving Global Outcomes' (KDIGO) Controversies Conference. Kidney Int 2016; 89:28–39.

Conclusions from an expert consensus group convened for a KDIGO Controversies conference examining the key issues related to iron management in CKD.

26. ■■ Hougen I, Collister D, Bourrier M, *et al.* Safety of intravenous iron in dialysis: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2018; 13:457–467.

A systematic review and meta-analysis of iron dosing in dialysis patients, revealing how poor the evidence base is in this area of clinical practice.

27. ■ Macdougall IC. Intravenous iron therapy in patients with chronic kidney disease: recent evidence and future directions. Clin Kidney J 2017; 10(Suppl 1):i16–i24.

A description of the near-completed PIVOTAL randomized controlled trial of high-dose versus low-dose intravenous iron in haemodialysis patients, in which 2141 individuals were randomized from 50 centres in the UK.

28. Gupta A, Amin NB, Besarab A, *et al.* Dialysate iron therapy: infusion of soluble ferric pyrophosphate via the dialysate during hemodialysis. Kidney Int 1999; 55:1891–1898.
29. Gupta A, Lin V, Guss C, *et al.* Ferric pyrophosphate citrate administered via dialysate reduces erythropoiesis-stimulating agent use and maintains hemoglobin in hemodialysis patients. Kidney Int 2015; 88:1187–1194.
30. Fishbane SN, Singh AK, Cournoyer SH, *et al.* Ferric pyrophosphate citrate (Triferic™) administration via the dialysate maintains hemoglobin and iron balance in chronic hemodialysis patients. Nephrol Dial Transplant 2015; 30:2019–2026.
31. Locatelli F, Fishbane S, Block GA, Macdougall IC. Targeting hypoxia-inducible factors for the treatment of anemia in chronic kidney disease patients. Am J Nephrol 2017; 45:187–199.

32. Provenzano R, Besarab A, Wright S, *et al.* Roxadustat (FG-4592) versus epoetin ■ alfa for anemia in patients receiving maintenance hemodialysis: a phase 2, randomized, 6- to 19-week, open-label, active-comparator, dose-ranging, safety and exploratory efficacy study. Am J Kidney Dis 2016; 67:912–924.
One of the several studies showing a reduction of hepcidin levels in patients receiving a HIF prolyl hydroxylase inhibitor.
33. Provenzano R, Besarab A, Sun CH, *et al.* Oral hypoxia-inducible factor prolyl ■ hydroxylase inhibitor roxadustat (FG-4592) for the treatment of anemia in patients with CKD. Clin J Am Soc Nephrol 2016; 11:982–991.
Another study showing a reduction of hepcidin levels in patients receiving a HIF prolyl hydroxylase inhibitor.
34. Pergola PE, Spinowitz BS, Hartman CS, *et al.* Vadadustat, a novel oral HIF ■ stabilizer, provides effective anemia treatment in nondialysis-dependent chronic kidney disease. Kidney Int 2016; 90:1115–1122.
And yet another study showing a reduction of hepcidin levels in patients receiving a HIF prolyl hydroxylase inhibitor, this time with vadadustat.
35. Sun CC, Vaja V, Babitt JL, Lin HY. Targeting the hepcidin-ferroportin axis to develop new treatment strategies for anemia of chronic disease and anemia of inflammation. Am J Hematol 2012; 87:392–400.
36. Malyszko J, Malyszko JS. Emerging drugs for the treatment of kidney disease-induced anemia. Expert Opin Emerg Drugs 2016; 21:315–330.