Ferric pyrophosphate: good things come to those who wait?

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Most patients with moderate-to-severe impairment in kidney function develop anaemia of chronic kidney disease (CKD). In these patients, anaemia has been associated with a plethora of adverse consequences, which comprise—but are not limited to—increased cardiac output with subsequent left ventricular hypertrophy, reduced cognition and concentration, reduced libido and reduced immune responsiveness [1]. Therefore, anaemia treatment has been a focus of clinical care since the early days of nephrology.

Our traditional conception of anaemia of CKD centres on the inability of the failing kidneys to produce erythropoietin, which is the major driver of erythropoiesis in bone marrow cells. Once recombinant DNA technology allowed producing proteins for medical uses >30 years ago, anaemia treatment with erythropoietin was welcomed with great excitement by nephrologists, who for two decades became partly ignorant of other pathophysiological contributors to anaemia of CKD.

The sobering results from randomized clinical trials on erythropoietin and darbepoietin in the last decade [2–4] substantially helped us to overcome this ignorance, and non-erythropoietin contributors to anaemia regained scientific and clinical interests.

Exemplarily, an analysis within the United States Renal Data System revealed that prescription rates for erythropoiesis-stimulating agents (ESAs) among senior CKD patients approaching end-stage renal disease have substantially decreased since 2007, which was paralleled by a drop in haemoglobin levels in these patients [5].

A more comprehensive approach to anaemia treatment comprises definition of novel pharmacological pathways—including hypoxia-inducible factor stabilizers—and re-appreciation of conventional treatment strategies, particularly of iron substitution.

Conventionally, two different approaches exist for iron therapy, namely oral administration of ionic iron as ferrous salts, or intravenous (i.v.) injection of colloidal iron compounds, most of which are spheroid particles with an iron oxyhydroxide core and a carbohydrate shell. Oral iron substitution is generally considered of limited effectiveness in advanced CKD, where high levels of hepcidin inhibit intestinal iron uptake (although this may be less a case with novel compounds as ferric citrate [6]). Moreover, oral iron preparations further increase the substantial pill burden for CKD patients and may cause constipation and other intestinal side effects. In contrast, i.v. iron substitution has gained substantial popularity in recent years [5], and several new compounds were approved by regulatory authorities recently.

The effectiveness of these products to alleviate iron deficiency and anaemia of CKD is undisputed, as i.v. iron preparations bypass the intestinal barrier that limits uptake of oral iron products. This intestinal barrier may, however, not only be considered as an obstacle impeding our therapeutic efforts to replace iron deficiency but also as a protective barrier against fast, untoward changes in plasma iron levels. Thus, with increasing popularity of i.v. iron preparations, we must re-sharpen our understanding of potential safety concerns of these compounds, which may exert immunological, cardiovascular and renal side effects [7–9].

Against this background, a novel strategy for iron replacement in CKD patients is eagerly awaited. Gupta et al. [10] proposed 16 years ago to add a soluble, non-colloidal iron salt (ferric pyrophosphate), which is not conjugated with a sugar moiety, to the bicarbonate concentrate during haemodialysis. With a molecular weight of ~745 Da, ferric pyrophosphate crosses the dialyser and enters the circulating blood. Conceptually, such substitution during each dialysis session shall match iron losses that inevitable occur during each single dialysis session—via trapping of blood in the dialysis circuit, vascular access bleeding and diagnostic blood draws—which may amount to 5–7 mg per treatment. Thereby, the intermittent application of high dosages of i.v. iron preparations may be avoided.

In this issue of NDT, Fishbane, Singh and colleagues now report their results from the eagerly awaited Continuous Replacement Using Iron Soluble Equivalents (CRUISE) trials that studied delivery of iron via dialysate as such a novel strategy. The study has been funded by the producer of ferric pyrophosphate citrate (FPC), Rockwell Medical, and several authors are employees of this company.

In these two randomized and placebo-controlled trials, 599 iron-replete haemodialysis patients (almost all on ESA therapy)
were treated either with FPC or placebo. Patients received no additional iron supplementation. The efficacy of FPC administration to maintain iron stores and erythropoiesis at stable levels was evaluated by measuring changes in haemoglobin levels, which was predefined as primary end point, and other laboratory parameters of iron homeostasis and erythropoiesis, predefined as secondary end points. After 48 weeks of therapy, more patients who received FPC than patients on placebo maintained haemoglobin levels within the predefined target ranges. In these patients, FPC was apparently capable of replacing ongoing dialysis and uremia-related iron losses. Moreover, FPC induced neither overt iron overload nor other apparent severe side effects.

The CRUISE studies follow an early report published in 1999, in which first clinical data on ferric pyrophosphate were reported in a small cohort of 10 patients, providing first feasibility data. At that time, Gupta et al. [10] assessed efficacy and safety of ferric pyrophosphate in comparison to i.v. iron dextran administration and proposed ferric pyrophosphate as a promising alternative to i.v. iron. In this preliminary report, ferric pyrophosphate maintained stable iron balance without inducing iron overload and without affecting phosphate levels.

Surprisingly, despite the rising popularity of i.v. iron treatment in CKD [5], it took another 16 years before the idea of ferric pyrophosphate regained interest.

It is intriguing to speculate to what extent soluble ferric pyrophosphates may have beneficial effects on vascular calcification in CKD patients, as pyrophosphate is considered a strong calcification inhibitor [11]. Thereby, soluble ferrous pyrophosphate becomes the second novel iron product which may connect treatment of anaemia and CKD-mineral and bone disorder, after a novel oral compound—ferric citrate—has been shown to combine phosphate lowering and iron replacement [6].

The authors of the CRUISE studies hypothesize that FPC may have further potential advantages in clinical practice. They state that FPC, unlike colloidal iron compounds, bypasses the reticuloendothelial system. It is assumed that FPC enters the blood and donates its iron directly to transferrin, which is rapidly cleared from the circulation via transferrin-receptor-1 expressed on erythroblasts. However, macrophages express the same transferrin-receptor-1 [12], which questions to some degree the selective uptake by erythrocytes, and supplemental ferrokinetic studies are strongly recommended.

The authors further suggest that FPC may reduce the need for intermittent i.v. iron substitution in haemodialysis. This looks attractive at first glance, since intermittent application of i.v. iron at higher doses has been associated with poorer patient outcome than regular low-dose administration [13]. Adverse cardiovascular implications of higher i.v. iron dosages have been confirmed in some [14], but not all [15], subsequent cohort studies, and it is fully unclear whether different colloidal iron compounds differ in their safety, as suggested in in vitro studies from our group on substance-specific toxicity of i.v. iron preparations [16].

Against this background, neither the two CRUISE studies nor the earlier preliminary data presented by Gupta et al. [10] suggest that FPC may beneficently affect the cardiovascular event rate or infectious complication rate in comparison to conventional treatment. Instead, mortality was numerically higher among patients randomized to FPC, even though death was not considered drug related in any of those patients. Admittedly, the study size was too small to analyse the prognostic implications of FPC compared with standard care.

In the same vein, even though it is exciting to speculate that FPC may reduce healthcare costs due to its lower prices, and its ease of application, a direct economic comparison is difficult. Particularly, the individual amount of iron administered during a single dialysis session with FPC cannot be precisely quantified, given differences in treatment duration, dialyser size, dialysate bicarbonate as well as dialysate and blood flow.

Finally, a vast majority of patients did not complete 48 weeks of randomized therapy, which was the scheduled maximal treatment period. These patients either discontinued the study for diverse reasons (107 patients on FPC and 79 patients on placebo) or had mandatory changes in anaemia treatment, which per protocol led to termination of the randomized treatment. In those patients who remained in the randomized trial until week 48, a trend towards lower ferritin levels was seen not only in the placebo arm but also in the FPC arm. This is particularly notable, as haemodialysis patients with high baseline dosages of ESAs or i.v. iron were excluded from CRUISE. Similar results have been shown in the preliminary report 16 years ago, in which a slight but continuous decrease in ferritin levels occurred in FPC-treated patients, but not with standard medical care (e.g. iron dextran supplementation) [10]. Thus, it remains questionable whether patients on FPC will in the long term escape the need for conventional i.v. iron treatment, and some may argue that the introduction of another iron product will cause undesirable complexity to anaemia treatment.

Thus, the CRUISE trails cannot prove superiority of FPC administration over conventional anaemia treatment for the time being and FPC will not be able to fully replace conventional i.v. iron treatment.

In summary, Fishbane, Singh and colleagues should be commended for their efforts to define a novel pathway for i.v. iron substitution, and we are looking forward to receiving more clinical and experimental data on the efficacy and safety of this approach. As a word of caution, we have to keep in mind that we generally lack data from adequately powered clinical trials on the benefits and risks of i.v. iron supplementation in CKD. The rise and fall of ESAs has taught us that any treatment strategy for anaemia of CKD must be tested in adequately designed clinical trials that do not merely focus on surrogates such as changes in haemoglobin levels, but on clinical end points. Against this background, we are eagerly awaiting results from the ongoing PIVOTAL trial, which analyses among 2080 haemodialysis patients the impact of restrictive versus liberal i.v. iron substitution on cardiovascular event rate and survival.

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Parathyroidectomy and patient survival in CKD patients

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Secondary hyperparathyroidism (SHP) in patients with chronic kidney disease (CKD) is recognized as a key player in most of the adverse outcomes observed in this clinical setting [1, 2]. Until not much later than a decade ago, the therapy available for SHP control was limited and of relatively low efficacy, so that the indication to parathyroidectomy (PTX) remained high up to the beginning of the present century [3, 4]. More recently, an astonishing increase in new medical tools available to control SHP has translated into an improved control of biochemical parameters, with a progressive reduction in the use of PTX [5]. Despite a better biochemical control of SHP, no evidence has been produced of a positive impact of any of these new treatments on mortality [6, 7]. In view of the fact that the cost of these new medical therapies is far higher than PTX [8, 9], the critical question of which of the two strategies, the medical or the surgical therapeutic approach, is more cost effective remains of critical relevance. That being said, any new scientifically appropriate data that could add information in this field are welcome.

In this issue of NDT, Ivarsson et al. [10] analysed the Swedish Renal Registry to explore the impact of PTX on


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