In Focus

Is haemodialfiltration more favourable than haemodialysis for treatment of renal anaemia?

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The introduction of recombinant human erythropoietin (rHuEPO) into clinical practice in the 1980s and the later new modified erythropoiesis stimulating agents (ESAs) was a real breakthrough in the treatment of severe anaemia in patients with chronic kidney disease (CKD). Use of ESAs is primarily based on an assumption that failing kidneys produce less erythropoietin which is needed for adequate erythropoiesis. However, with the development of our knowledge, the pathogenesis of anaemia in CKD becomes more and more complex (insufficient iron storage, inflammation, vitamin B12 and folic acid depletion, bone marrow fibrosis due to severe secondary hyperparathyroidism, use of myelosuppressive agents, blood loss or haemolysis, etc.). Moreover, large clinical trials failed to provide evidence that trying to achieve higher haemoglobin (Hb) levels (as in subjects with normal kidney function) using ESAs is beneficial for these patients. In fact, there is a suggestion that it may be, in some cases, even harmful. Therefore current guidelines recommend haemoglobin target levels way below normal values [1]. It is reasonable to use ESA therapy in CKD patients generally to maintain Hb values ranging between 10 and 12 g/dL individualizing the value in this target range according to the possible comorbidities of the patients [2]. One of the problems we must face when treating CKD patients with ESAs is resistance to this class of medication. There are several reasons why the patient does not respond well to ESA therapy. Active blood loss, insufficient iron supply, inflammation, malnutrition and inadequate renal replacement therapy are all causes of insufficient ESA responsiveness. There is no universal definition of ESA hyporesponsiveness. According to Kidney Disease Improving Global Outcomes (KDIGO) guidelines, ESA hyporesponsiveness may be ‘initial’ (if there is no increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing) or ‘subsequent’ (if there is need for two increases in ESA doses up to 50% beyond the dose at which the patient had been stable in order to maintain a stable Hb level) [1]. Resistance to ESA therapy correlates with worse survival in CKD patients [3–5]. Some strategies have been proposed to improve ESA responsiveness. Some new methods of therapy like intestinal adsorption of uraemic toxins with AST-120 [6], pentoxifylline [7] and vitamin D [8] have been showing promising results.

Panichi et al. [9] show, in a small cross-over, randomized, multicentre study, that high-volume on-line hemodiafiltration (HV-OL-HDF) improves responsiveness to ESAs when compared with standard low-flux haemodialysis (BHD). Improved responsiveness to ESAs was accompanied by lower hepcidin concentration in a population of patients without increased inflammation markers.

Hepcidin is one of the main regulators of iron homeostasis [10]. It is eliminated by the kidneys and accumulates in patients with CKD. Hepcidin binds to ferroportin, the main cellular iron efflux channel, causing its internalization and degradation. Subsequently, iron is sequestrated in macrophages and prevented from being absorbed from the intestine. A strategy aimed to lower high hepcidin levels seems to be reasonable for anaemia treatment in CKD patients. High-volume OL-HDF certainly has the potential to lower hepcidin levels. Further studies are needed, however, to determine whether it is directly eliminated through the high-flux membranes. Hepcidin is a 25-aminoacid peptide most probably not removed by low-flux BHD but potentially removable by HV-OL-HDF.

ESA resistance is correlated with worse survival. It is not clear whether this association is due to some unfavourable effects of ESAs itself or rather if ESA resistance is a marker of
other underlying clinical problems. Nevertheless, HV-OL-HDF, potentially reducing ESA resistance, should also improve survival of CKD patients (Figure 1).

Chronic inflammation is common in haemodialysed patients and is, at least partially, responsible for ESA resistance [11]. HV-OL-HDF may potentially influence the degree of inflammation in different ways. Convective transport in HV-OL-HDF allows elimination of larger molecules, including proinflammatory cytokines. On the other hand, high permeability membranes and infusion of large volumes of supplemental fluid may increase the exposure to endotoxins and subsequently production of proinflammatory cytokines. Some recently published data suggest that HV-OL-HDF may reduce the systemic inflammation [12].

Studies comparing HV-OL-HDF with conventional BHD provide conflicting results. Several randomized controlled trials have been published comparing HV-OL-HDF with low-flux or high-flux BHD. Only some were able to show improvement in ESA resistance. The same is true for inflammatory markers, all-cause and cardiovascular mortality [13]. It is noteworthy that there is no study published yet, which documents that HV-OL-HDF is inferior to BHD in any relevant clinical parameters. Should we change then our routine treatment of patients with end-stage renal disease? This conclusion seems to be premature at the moment. However, HV-OL-HDF should be more frequently used in the dialysis population and further studies are needed.

Cost-effectiveness is important for health-care providers when deciding on new treatment modalities. The analysis of the CONTRAST trial showed that HV-OL-HDF is ~3% more expensive than standard BHD [14]. Other estimates put HV-OL-HDF at 34% more expensive than BHD [15]. The reasons for the difference are more expensive disposables and more frequent control of the dialysate and substitution fluid quality. Taking into account that high-flux BHD requires the same fluid quality as HV-OL-HDF, the cost of the two modalities become even more similar. Should the lower demand for ESAs in HDF treated patients be confirmed, the total cost of HV-OL-HDF would not be different from that of BHD. This would be another important argument for a wider use of HV-OL-HDF in the dialysis population.

Finally, it is important to stress that we still need more data before recommending HV-OL-HDF as a routine method of treatment of ESA resistance in all end-stage renal disease patients.

CONFLICTS OF INTEREST STATEMENT

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REFERENCES

A new chance to beat diabetic kidney disease: innate immunity and MCP-1: a matter of good and bad macrophages?

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As clinicians, we often feel disarmed in front of the relentless decline of renal function in patients with diabetes despite optimal medical treatment.

In the last decade, inflammation and ways to target it have become probably the most promising therapeutic approach to tackle diabetic nephropathy (DN).

Research studies in experimental animal model of diabetes have implicated the innate immunity as an important pathogenic mechanism driving the development and progression of DN [1]. The innate immunity is a non-specific defence mechanism characterized by up-regulation of monocyte chemoattractant protein-1 (MCP-1) paralleled by an increase in macrophage infiltration in the glomeruli and tubular interstitium.

MCP-1 is an inflammatory cytokine that binds to its receptor CCR2, expressed mainly on monocytes and macrophages. The chronic activation of the MCP-1/CCR2 system, driven by the metabolic and haemodynamic perturbations seen in diabetes, is an important player in the pathogenesis of diabetic chronic microvascular complications and, specifically in the kidney, drives renal inflammation (macrophage tissue infiltration), fibrosis and ultimately loss of renal function.

In this issue of NDT, Fufaa et al. describe, for the first time, in patients with type-1 diabetes without any clinical evidence of DN, an association between urinary MCP-1 concentrations and early renal lesions.

This work is a post hoc analysis of the renin–angiotensin system study (RASS) [2] where two renal biopsies were performed 5 years apart in patients with type-1 diabetes. The authors found a significant association between urinary MCP-1 at baseline and changes in renal structural parameters (specifically increased interstitial volume) at 5 years, an observation present only in women. No association was observed between urinary MCP-1 and early glomerular lesions.

The authors highlight the potential differences between sex and disease progression, and because of the study design (post hoc analysis), the absent potential association between urinary MCP-1 and the observed initial/mild glomerular lesions could relate to an insufficient statistical power of the study.

These data reinforce, in humans, the role of innate immunity in the very early stages of DN.

Along with the observations of Fufaa et al., others have described, in patients with type-2 diabetes with chronic kidney disease, a significant association between elevated urinary MCP-1 levels and advanced tubulointerstitial lesions and macrophage infiltration, an occurrence mainly observed in patients with macroproteinuria (>3.5 g/day) [3].

References