High-volume online haemodiafiltration improves erythropoiesis-stimulating agent (ESA) resistance in comparison with low-flux bicarbonate dialysis: results of the REDERT study

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ABSTRACT

Background. In haemodialysis (HD) patients, anaemia is associated with reduced survival. Despite treatment with erythropoiesis-stimulating agents (ESAs), a large number of patients with chronic kidney disease show resistance to this therapy and require much higher than usual doses of ESAs in order to maintain the recommended haemoglobin (Hb) target, and recent studies suggest that hepcidin (HEP) may mediate the ESA resistance index (ERI). High-volume online haemodiafiltration (HV-OL-HDF) has been shown to improve anaemia and to reduce the need for ESAs in HD patients; this effect is associated with a reduced inflammatory state in these patients. The aim of the REDERT study (role of haemodiafiltration on ERI) was to investigate the effect of different dialysis techniques on ERI and HEP levels in chronic dialysis patients.

Methods. A single cross-over, randomized, multicentre study (A–B or B–A) was designed. Forty stable HD patients from seven different dialysis units (male 65%, mean age 67.6 ± 14.7 years and mean dialytic age 48 ± 10 months) were enrolled. Patients were randomized to the standard bicarbonate dialysis (BHD) with low-flux polysulfone (PS) membrane group or to the HV-OL-HDF group with high-flux PS membranes and exchange volume of >20 L/session. After 6 months, patients were shifted to the other dialytic group for a further 6 months. Clinical data, Hb, ESA doses and iron metabolism were recorded every month. HEP, beta2-microglobulin (b2MG) and C-reactive protein (CRP) were determined every 3 months, and ERI was calculated monthly as the weekly ESA dose per kilogram of body weight divided by Hb level. Data were analysed using paired-samples t-test, Wilcoxon signed-rank test and Spearman’s correlation coefficient.

Results. Dialysis efficiency for small molecules assessed as Kt/V was significantly increased in HV-OL-HDF from 1.47 ± 0.24 to 1.49 ± 0.16; P < 0.01. A significant reduction of b2MG was obtained in HV-OL-HDF from month 3 whereas CRP values were not significantly changed during the study period either in BHD or HV-OL-HDF. ERI was significantly reduced in HV-OL-HDF at month 3 and 6 (from 9.1 ± 6.4 UI/weekly/Kg/Hb to 6.7 ± 5.3 UI/weekly/Kg/Hb; P < 0.05) due to a higher ESA consumption in BHD in spite of similar Hb levels. HEP levels were reduced in HV-OL-HDF with respect to BHD after 3 and 6 months. Iron consumption was not significantly different during BHD or HV-OL-HDF treatment as well as transferrin, ferritin and TSAT levels. A significant positive linear correlation between HEP and ERI (r² = 0.258, P < 0.001) was observed.

Conclusions. In a uraemic patient population with low-grade inflammation treated with HV-OL-HDF, we observed a significant reduction of ERI values as well as HEP levels. The positive correlation between these two parameters supports a role for HEP in the development of ERI in the dialytic population. Moreover, the lower b2MG and the higher Kt/V achieved
INTRODUCTION

Anaemia is a common complication of chronic kidney disease (CKD). It results primarily from inadequate production of erthropoetin to support erthropoiesis, with inflammation and oxidative stress also playing a relevant role [1]. As a matter of fact, a consistent subgroup of CKD patients may require much higher than usual doses of erthropoiesis-stimulating agents (ESAs) in order to maintain the recommended haemoglobin (Hb) target of 11 g/dL [2–4]. In many instances, these patients will have either an obvious or a clinically unapparent ESA resistance, and demonstrated as a strong predictor of all-cause and fatal/non-fatal cardiovascular events in the uraemic population [5, 6]. In this setting, the term ‘ESA resistance’ has been introduced to define patients who fail to reach the target despite a higher than usual dose of ESAs or who continuously need these higher doses in order to maintain it. Furthermore, ESA resistance was inversely correlated to Hb levels and demonstrated as a strong predictor of all-cause and fatal/non-fatal cardiovascular events in the uraemic population [7].

Recent studies demonstrated that hepcidin (HEP) may mediate the inflammatory-driven ERI; this peptide is produced by the inflammatory cells and has a major role in the anaemia of inflammatory chronic disease. HEP levels also increase in response to iron sufficiency, decreasing intestinal iron absorption and inhibiting release of iron from stores and macrophages [8–10].

New dialysis modalities improving the clearance of uraemic toxins have been developed; high-volume online HDF (HV-OL-HDF), using high biocompatible membranes and ultra-pure dialysate, is suggested to provide higher clearances both for small and middle-molecule solutes and superior reduction in inflammation and oxidative stress than in high-flux HD [11–14]. Regarding mortality, previous observational [15] and the more consistent randomized controlled trial showed conflicting results [16, 17]; however, very recently, in the ESHOL study, a mortality risk reduction was observed in patients receiving convection volume >23 L/session [18].

The present randomized cross-over multicentre study was designed to compare the effects of HV-OL-HDF and BHD on inflammatory markers, ERI and HEP levels in a population of chronic HD patients followed up for 13 months.

MATERIALS AND METHODS

Patients

This study was conducted in 7 HD centres in Tuscany (Italy) from February 2011 to May 2013, and 40 chronic dialysis patients were recruited and followed prospectively for 13 months. The mean age was 66.7 ± 15.4 years, male 67.5% with a dialysis vintage of 56 ± 40 months and a BMI of 25.6 ± 5.5 kg/m². Fifteen patients (37.5%) were affected by cardiovascular disease, 9 by diabetes (22.5%) and 19 (47.5%) by hypertension.

Mean systolic blood pressure was 139.9 ± 19 mmHg and diastolic blood pressure resulted 69.3 ± 14 mmHg.

Routine patient care including iron and ESA doses was performed according to the opinion of the attending nephrologist and based on European Best Practice Guidelines for the management of anaemia, ESAs and iron utilization [2]. ESAs and iron supplementation were administered via the venous line at the end of a dialysis session.

Written informed consent was obtained from each participating patient, and the study protocol was approved by the local ethics committee. Patients were selected on the basis of the following inclusion criteria: older than 18 years, with CKD stage V and having undergone HD for at least 6 months, stable ESA therapy for at least 3 months, adequate iron stores (ferritin levels 200–400 ng/mL and transferrin saturation 20–40%), Hb levels ranging between 9 and 13 g/dL, arteriovenous fistula or prosthesis as vascular access. Patients with a central vascular catheter, with conditions that could influence cytokine production or ESA requirements, such as acute infection or blood transfusion in the past month, haemoglobinopathies, chronic infection, active immunological disease, immunosuppressive therapy or a history of malignancy, were excluded from the study.

During the study periods, patients were carefully checked for comorbidities and infections, in particular regarding dialysis access.

Study design

This was a 13-month, randomized, two-arm, cross-over study (A–B or B–A); after a 1-month run-in period of BHD, patients were centrally randomized into 2 groups according to the type of treatment. The study flow-chart is depicted in Figure 1. The dialysis technique was randomly assigned with a 1:1 ratio at the beginning of the study by means of a computer-generated random list. Group 1 patients were treated with BHD (Treatment A) for 6 months, and afterwards, they were transferred to HV-OL-HDF for a further 6 months (Treatment B). Group 2 patients were treated with Treatment B for 6 months, and afterwards, they were transferred to Treatment A for a further 6 months. All administered drugs during each dialysis session along with all prescribed interdialytic therapies were recorded. Pre- and post-dialysis body weight, blood pressure and heart rate were recorded at baseline and at every dialysis. All intradialytic symptoms and signs were registered.

The study was conducted according to the Principles of Good Clinical Practice and the Declaration of Helsinki and registered at https://eudract.ema.europa.eu under the unique identifier number 2010-018718-57.

Dialysis modalities

The dialysis modality before inclusion was BHD for all patients since at least 6 months. All treatments were carried out on 5008 dialysis machines (Fresenius Medical Care, Bad Homburg, Germany). BHD was performed with low-flux polysulphone (PS) membranes (F8-F10 HPS Fresenius Medical Care, Bad Homburg, Germany) with a surface area ranging from 1.8 to 2.2 m² with a blood flow of 320 ± 41 mL/min and a dialysate
flow of 550 ± 100 mL/min, dialysis time 240 ± 15 min. The composition of the dialysate was the same in both groups, as was the reinfusate in HV-OL-HDF: sodium 140 mmol/L, potassium 2.0 mmol/L, bicarbonate 32 mmol/L, calcium 1.5 mmol/L, magnesium 0.5 mmol/L, chloride 111 mmol/L, acetate 3 mmol/L and glucose 1 g/L, and the dialysate was purified by sterile filtration before entering the dialyser. Patients were weighed before each treatment to determine the volume of ultrafiltration. Net fluid removal was set on an individual basis according to the patient’s clinical needs. All dialytic treatments were carried out with a volumetric control machine allowing for a precise rate of fluid removal. In all centres, analyses of the dialysis water were performed monthly, ascertaining the absence of bacteria (<100 colony forming units/mL) or bacteriological contaminant products (endotoxin levels of <0.025 endotoxin units).

In HV-OL-HDF, the replacement volume was standardized to 25–30% of the total blood volume treated, and a high-flux polysulfone membrane (HF80S) with a surface area ranging from 1.8 to 2.2 m² was used.

Anticoagulation was performed with sodium dalteparin (Pfizer®, Puurs, Belgium). For each patient, the dialysis prescription was kept constant throughout the study (total dialysis time, dialysate flow, dialysate temperature and dialysate composition), and the blood flow was kept as stable as possible. Arteriovenous fistula recirculation was measured after 4 weeks of treatment with either BHD or HV-OL-HDF.

Clinical monitoring included intradialytic symptoms (symptomatic hypotension, episodes of arrhythmia and thoracic pain), hospital admissions for any reasons and withdrawal from the study and its causes.

**Biochemistry**

Pre-dialysis serum urea, creatinine, albumin, sodium, potassium, total calcium, phosphate and bicarbonate were measured at the start of the study and at monthly intervals. Serum albumin was measured by means of a nephelometric technique (Dade Behring GmbH, Marburg, Germany) with an intra- and inter-assay variability of 4.3 and 4.4%, respectively. Haemoglobin, white cells, lymphocytes, platelet counts and reticulocytes were also assessed monthly. Iron status was evaluated monthly by transferrin saturation and plasma ferritin levels. Equilibrated \( \text{Kt/V} \) was performed monthly in a midweek session according to the methods suggested by Daugirdas [19]. Post-dialysis urea samples were obtained 10 min after the end of the dialysis session. Pre- and post-dialysis beta-2 microglobulin (b2MG) levels were measured every 3 months.

**Inflammation parameters and hepcidin**

Inflammation parameters were determined centrally every 3 months in blood samples obtained from patients starting a midweek dialysis, after 20–30 min of quiet resting in a semirecumbent position at baseline.

Whole blood was collected into tubes containing gel and clot activator. Serum samples were prepared by centrifugation at room temperature after complete clotting had occurred and stored at −80°C until the measurements were made. The serum was later thawed and used to measure C-reactive protein (CRP), interleukin-6 (IL-6) and HEP.

CRP was measured by a high-sensitivity modified laser nephelometry technique (Behring Diagnostics GmbH, Marburg,
Hepcidin clearance measurements

Serum HEP measurements were obtained immediately before a midweek HD and then at 120-min time points from both the arterial and the venous access points during the dialysis treatment in 10 patients. A final sample was obtained immediately after dialysis was completed. The average blood flow (Qb) was 320 ± 41 mL/min, and clearance was then calculated as Qb × (arterial HEP – venous HEP)/arterial HEP [20]. The HEP reduction ratio was calculated as (HEP at start of dialysis – HEP at end of dialysis)/HEP at start of dialysis.

Statistics

Continuous data are presented as means ± standard deviation or medians (interquartile ranges) and quartiles, and nominal data are presented as percentages. The difference between mean values was evaluated by the paired-samples t-test or by the Wilcoxon signed-rank test for non-normally distributed data; analysis of variance for multiple comparisons was used to analyse differences between the two groups. Spearman’s correlation coefficient was calculated for correlation assessments between variables. Linear regression coefficients for ERI and HEP were calculated. P < 0.05 was taken to be statistically significant.

End points

ESA resistance. In order to normalize the amount of ESAs required depending on the severity of anaemia, we calculated ERI defined as the weekly ESA dose per kilogram of body weight divided by Hb level (grams per decilitre) [7]. ERI was calculated at the start of the study and every month. Thirty-two patients received EPO alfa (Eprex, Jansen) and eight patients darbopoietin (Nespo, Dompe Biotech). A ratio of 1:200 was used to convert darbopoetin alpha to the ESA equivalent dose (1 microgram of darbopoetin alpha = 200 IU of epoetin alpha). The ESA molecules were not changed throughout the study period.

The primary end points were the changes in h2MG, HEP, and ERI after BHD or HV-OL-HDF.

RESULTS

Thirty-six of 40 enrolled patients completed the study; of the 4 dropouts, 2 patients died (1 patient during Phase A and 1 patient during Phase B), 1 patient was transplanted during Phase A and 1 patient withdrew consent to the study.

No differences in terms of days of hospitalization, treatment-related or treatment-unrelated adverse events were observed.

As shown in Table 1, the mean dry weight did not change significantly during the two phases of the study.

Dialysis efficiency for small molecules assessed as Kt/V was significantly increased in HV-OL-HDF (from 1.47 ± 0.24 to 1.49 ± 0.16; P < 0.01) and was reduced in BHD (from 1.51 ± 0.2 to 1.36 ± 0.21; P < 0.001).

During the OL-HDF period, the mean infusion volume was 20.9 ± 2.1 L/session with a mean total convective volume of 23.8 ± 2.3 L/session; a significant removal of b2MG was obtained in HV-OL-HDF at Months 3 and 6 as shown in Table 1.

A slight decrease of serum albumin was observed at 3 months in patients treated with HV-OL-HDF whereas CRP values were not significantly changed during the study period either in BHD or in HV-OL-HDF (Table 1).

ERI was significantly reduced in HV-OL-HDF at Months 3 and 6 (Figure 2) whereas ERI increased in BHD; since Hb levels were similar in both treatments, the divergent ERI behaviour was due to a reduced weekly ESA consumption in HV-OL-HDF (Table 1). Moreover, the total amount of ESAs administered in the study period was 192 444 ± 131 341 IU/6 months in BHD versus 135 955 ± 96 070 IU/6 months in HV-OL-HDF; P < 0.001.

In order to avoid a carry-over effect, data from the two study periods are presented in Figure 3. Group 1 consisted of 18 patients starting in BHD and shifted to HV-OL-HDF, and Group 2 consisted of 18 patients starting in HV-OL-HDF and shifted to BHD.

Iron consumption assessed as weekly iron dose was not significantly different during BHD or HV-OL-HDF treatment as similar levels were demonstrable for transferrin, ferritin and transferrin saturation index (Table 1). A positive correlation was found between ferritin and ERI (R² 0.246; P < 0.001).

Finally, significantly lower HEP levels were observed in HV-OL-HDF (Table 1) with respect to BHD, and we were able to demonstrate a positive linear relationship between ERI and HEP, pooling all values collected during both HV-OL-HDF and BHD (Figure 4).

HEP reduction ratio resulted 25 ± 17% in HV-OL-HDF and 9 ± 10% in BHD (P < 0.05) with an HEP clearance of 103.9 ± 20.3 versus 53.3 ± 30.3 mL/min (P < 0.05), respectively.

Neither pre-dialysis nor post-dialysis systolic and diastolic blood pressure were significantly modified by treatments as well as days of hospitalization.

DISCUSSION

The main result of the present randomized cross-over study is that, at variance with low-flux BHD, HV-OL-HDF significantly
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD) M0</th>
<th>Median (IQR) M0</th>
<th>Mean (SD) M3</th>
<th>Median (IQR) M3</th>
<th>Mean (SD) M6</th>
<th>Median (IQR) M6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry weight (kg)</td>
<td>77.7 (20.1)</td>
<td>71.0 (20.3)</td>
<td>78.8 (21.5)</td>
<td>77.3 (27.5)</td>
<td>79.1 (21.2)</td>
<td>77.6 (32.8)</td>
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<tr>
<td>Albumin (g/L)</td>
<td>3.7 (0.4)</td>
<td>3.8 (0.4)</td>
<td>3.8 (0.4)</td>
<td>3.6 (0.7)</td>
<td>3.6 (0.9)</td>
<td>3.9 (0.5)</td>
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<tr>
<td>b2MG (mg/L)</td>
<td>33.3 (8.2)</td>
<td>34.1 (11.0)</td>
<td>31.8 (8.6)</td>
<td>31.9 (12.0)</td>
<td>28.2 (8.4)</td>
<td>29.3 (14.0)</td>
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<tr>
<td>CRP (mg/L)</td>
<td>4.12 (4.43)</td>
<td>2.35 (4.48)</td>
<td>5.57 (6.38)</td>
<td>2.90 (8.15)</td>
<td>5.16 (7.09)</td>
<td>4.20 (5.90)</td>
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<tr>
<td>Hb (g/dL)</td>
<td>11.5 (0.9)</td>
<td>11.4 (1.0)</td>
<td>11.6 (0.9)</td>
<td>11.6 (1.2)</td>
<td>11.6 (0.9)</td>
<td>11.6 (1.2)</td>
</tr>
<tr>
<td>ERI (UI/weekly/kg/g Hb)</td>
<td>9.0 (6.9)</td>
<td>7.4 (8.0)</td>
<td>9.1 (6.4)</td>
<td>6.3 (6.7)</td>
<td>6.7 (5.1)</td>
<td>6.1 (4.4)</td>
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<td>ESA dose (UI/weekly)</td>
<td>5625 (3597)</td>
<td>4500 (5750)</td>
<td>5600 (4051)</td>
<td>6000 (5200)</td>
<td>5083 (3623)</td>
<td>4000 (4000)</td>
</tr>
<tr>
<td>HEP (ng/mL)</td>
<td>48.3 (27.6)</td>
<td>45.1 (37.2)</td>
<td>44.3 (33.3)</td>
<td>37.8 (37.1)</td>
<td>43.2 (31.3)</td>
<td>34.3 (13.2)</td>
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<tr>
<td>Ferritin (ng/mL)</td>
<td>412.6 (365.2)</td>
<td>301.0 (386.3)</td>
<td>386.0 (209.4)</td>
<td>319.0 (298.3)</td>
<td>49.5 (29.9)</td>
<td>43.2 (32.8)</td>
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<td>TSAT (%)</td>
<td>29.5 (7.94)</td>
<td>29.0 (17.0)</td>
<td>25.0 (7.5)</td>
<td>24.9 (15.2)</td>
<td>30.1 (10.0)</td>
<td>27.9 (14.5)</td>
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<tr>
<td>Week iron dose (mg)</td>
<td>43.1 (46.8)</td>
<td>31.3 (62.5)</td>
<td>43.1 (49.0)</td>
<td>31.3 (62.5)</td>
<td>46.9 (47.7)</td>
<td>46.9 (62.5)</td>
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</tbody>
</table>

Number of patients = 36. The difference between mean values was evaluated by the paired-samples t-test or by the Wilcoxon signed-rank test for non-normally distributed data; analysis of variance for multiple comparisons was used to analyse differences between the two groups. TSAT, transferrin saturation. *P < 0.05.
reduced ERI, HEP and b2MG plasma levels in a low-inflamed dialysis population. To maintain the same Hb values, ESA dosages were increased in BHD and reduced in HV-OL-HDF. Even if severe ESA resistance accounts only for a small number of patients, a mild form of ESA resistance is, however, common in the dialytic population. On the basis of this observation, our results may have relevant clinical fall-out since ERI is a strong independent predictor of morbidity and mortality in HD patients [7].

Studies on the effect of HDF on ESA resistance have been conflicting. The recent negative results of a secondary analysis of the randomized controlled convective transport study (CONTRAST) [21], of the Italian [22] and the ESHOL studies [18], are not in agreement with the results of previous cross-over, observational and randomized controlled trials in which ESA resistance decreased in patients treated with HV-OL-HDF [23–25].

In the uraemic population, ESA resistance and chronic inflammation are tightly related. Inhibition of erythropoiesis by cytokines, such as tumour necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ), plays a pivotal role in erythropoietin resistance. In CKD patients, elevated levels of IL-1, IL-6, TNF-α and CRP (suggestive of a chronic inflammatory status) have been frequently described [26–33]. Del Vecchio et al. [34] reported that cytokine-induced inflammation suppresses bone marrow erythropoiesis in HD patients and is a possible cause of anaemia. Shinzato et al. [35] found higher levels of ferritin, hs-CRP and IL-6 in 19 HD patients with rHuEPO-resistant anaemia, compared with control HD patients without anaemia and iron deficiency. In a randomized study of Costa et al. [36] on 50 HD patients, non-responders to ESA treatment had higher CRP, lower serum albumin levels as well as a lower number of total and CD4+ lymphocytes, in comparison with responders. This suggested a relationship between resistance to rHuEPO therapy and the magnitude of the inflammatory response.

In the last decade, the hepatic hormone HEP has been progressively recognized as the master regulator of the erythroid response to the inflammatory stimulus [37, 38].

25-HEP, a middle-molecular-weight-substance with a molecular weight of 2791 Daltons, is a key regulator of iron homeostasis. It binds to and induces internalization of ferroportin, a transmembrane iron channel present in enterocytes, macrophages and hepatocytes. Thereby, iron transport is hindered, and increased HEP levels can cause true iron deficiency by blocking iron release from iron stores.

HEP is upregulated by both increased iron stores and inflammation.

In a cross-sectional study of a cohort of the CONTRAST study [39], 25-HEP levels were shown to be independently and positively associated with ferritin levels and inversely with residual renal function; of note, no relations between ESA dose and iron supplementation were observed.

Thus, HEP represents a common effector of the homeostatic regulation of the intracellular iron fluxes in response to iron stores, erythroid and inflammatory regulators such as cytokines [9, 10, 40].

25-Hepcidin is cleared by the kidneys, and progression of renal disease has been associated with increased HEP levels [41]. The removal of HEP via dialysis has been demonstrated in adult patients with varying degrees of efficacy [20]. It has been recently suggested that the use of new dialysis techniques and more efficient membranes allows the removal of larger quantities of HEP [42]. Recently, Stefansson and colleagues [43], in a short-term study and in a small population of 20 patients, suggested that HEP levels were significantly reduced after 60 days of HV-OL-HDF with respect to BHD.

In this paper, we confirmed these preliminary data in a longer follow-up and in a larger population; in fact, significantly lower 25-HEP levels were observed at 3 and 6 months after HV-OL-HDF treatment. Moreover, in a small subset of our population, we were able to demonstrate higher reduction rates and higher HEP clearances in HV-OL-HDF; and this can contribute to the higher observed ERI reduction, HEP levels being significantly related to ERI.

Finally, clearance of middle-to-large molecules depends on the type of dialysis membrane, and the amount of convection volume and that of course are increased with HV-OL-HDF treatment. So, the observed decrease of b2MG values in HV-OL-HDF in this study is an expected result as previous data showed a positive correlation between infusion volume and the b2MG reduction rate. Moreover, several studies have shown that the pre-dialysis b2MG levels were reduced after patients were switched from bicarbonate dialysis to HV-OL-HDF [44, 45].

We account for several limitations: first, the relatively small number and the low comorbidity state of the enrolled patients. As a further limitation, HDF was compared with flow flux HD and not to high-flux HD; however, this study reflects usual care in Italy where the vast majority of patients are treated with low-flux HD; moreover, several other remarkable RCTs such as the CONTRAST trial compared HDF with low-flux HD [16].

We underline that we have studied a cohort of patients with a low degree of chronic inflammation, based on the normal values of CRP, and this may explain the lack of correlation between ERI and the other conventional markers of inflammation. However, even in these patients, ERI was significantly further reduced by HV-OL-HDF. Remarkably, the ERI reduction occurred as early as the third month and was confirmed.
at 6 months. In agreement with recent RCTs showing that only high convective volumes are associated with good clinical results [18], in our study, the favourable effects observed have occurred by applying a convection of almost 22 L/session, on average.

To the best of our knowledge, this is the first study comparing HEP clearances in HDF and HD, and this can be considered as a strength of our study.

Further studies in larger cohorts of low inflamed patients or even un-inflamed patients should confirm our results and should prospectively ascertain the impact of ERI reduction on morbidity and mortality.

FIGURE 3: ERI values change in BHD and HV-OL-HDF. In Group 1, patients starting in BHD and shifted to HV-OL-HDF, and in Group 2, patients starting in HV-OL-HDF and shifted to BHD. Number of patients = 36.

FIGURE 4: Positive linear relationship between ERI and HEP ($r^2 = 0.258; P < 0.001$). Spearman’s correlation coefficient was calculated for correlation assessments between variables.

CONFLICT OF INTEREST STATEMENT

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