Expanded Hemodialysis as Effective Alternative to On-Line Hemodiafiltration: A Randomized Mid-Term Clinical Trial

Fernando Hadad-Arrascue

Hospital Universitario Reina Sofía

Lars-Göran Nilsson (✉ lars_goran_nilsson@baxter.com)

Baxter (Sweden)

Angela S Rivera

Baxter (United States)

Angelito A Bernardo

Baxter (United States)

Juan B Cabezuelo Romero

Hospital Universitario Reina Sofía

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Abstract

BACKGROUND.

Hemodiafiltration (HDF) enhances middle molecule (MM) removal by convection and shows survival benefit compared to high-flux hemodialysis. Expanded hemodialysis (HDx), a novel therapy that effectively clears MM, uses medium cut-off (MCO) membrane without need for replacement fluid. We aimed to compare HDx to HDF prospectively in an open randomized controlled clinical study.

METHODS.

In a 24-week prospective study, HDF patients (age 18–80 yrs; on HDF > 3 months) were randomized to switch to HDx (N = 21) or continue HDF (N = 22). Pre- to post-dialysis reduction ratios (RR) and changes in pre-dialysis levels over time were evaluated for MMs and other clinical biomarkers. Use of erythropoiesis-stimulating agents (ESAs) were evaluated.

RESULTS.

HDx showed greater RR for YKL-40 while RR appeared similar between groups for beta₂-microglobulin, FGF-23, and free light chains. Intra-dialytic changes in inflammatory biomarkers (IL-6, CRP, PTX3) did not differ between therapies. Changes from baseline to 12 and 24 weeks did not differ between groups for MMs, inflammatory markers, albumin, fibrinogen, hemoglobin, PTH, and phosphorus. Usage of erythropoiesis-stimulating agents tended to decrease in HDx arm while remaining stable in HDF arm.

CONCLUSIONS.

HDx showed equivalent removal of MMs versus high volume HDF. Greater RR of YKL-40, predictor of cardiovascular mortality in HD, was noted in HDx group. HDx appeared safe with similar clinical effectiveness as HDF. With fewer requirements and resource needs, HDx provides an attractive alternative to HDF. Further clinical studies are needed to confirm our results.

TRIAL REGISTRATION.

The study was registered as NCT03499691

Background

The efficacy of blood purification by hemodialysis depends on the vascular access condition, type of dialysis membrane, treatment time, and blood flow rate. The choice of membrane becomes particularly

important for effective clearance of middle molecular uremic toxins (MMs), for which the membrane's permeability properties are essential [1]. The most well-studied MM is beta₂-microglobulin (β₂m) having a molecular weight of 11.8 kDa; its role in dialysis-related amyloidosis is well established and its plasma level is associated with mortality risk in dialysis patients [2]. Furthermore, recent research points at a significant role of large MMs, larger than 25 kDa, in the progression of comorbidities and poor outcome in dialysis patients [3, 4]. A chronic state of inflammation appears an important link between large MMs and long-term dialysis complications [5].

HDF enhances the removal of conventional and large MMs, as increased convection across the membrane helps to overcome limits in membrane permeability [6]. Analysis of pooled data from randomized controlled studies pointed at a survival benefit of HDF versus HD when HDF was applied in postdilution mode with high convective volume [7]. Although the mechanism of superior outcome has not been firmly established, it is commonly hypothesized that enhanced MM removal by HDF plays a key role.

Recent innovation in membrane design resulted in the MCO membranes with higher retention onset than conventional high-flux membranes and effective selectivity to limit permeability for albumin [1, 8]. MCO membranes are designed for HDx, a new therapy option to enhance the clearance of large MMs without the need for external replacement fluid as in HDF [9]. Short-term performance studies have shown the HDx therapy to deliver similar clearance of β₂m and large middle molecules as HDF [10–13] with potential to outperform HDF for some large MMs [10]. So far only one observational study presented data on mid-term clinical effectiveness of HDx therapy in comparison to HDF, indicating non-inferiority over a 6-month period [14]. Here we report a randomized trial over 24 weeks comparing HDx to HDF under typical treatment conditions in Spain.

Materials And Methods

Study design

Patients with chronic kidney disease receiving hemodialysis in the Renal Therapy Services dialysis center, Murcia, Spain, were included in an open-label, prospective, 1:1 randomized, parallel-group study with a 24-weeks follow-up.

Patients aged 18–80 years were eligible if clinically stable, as demonstrated by pertinent medical history, physical examination, and laboratory testing, and on postdilution on-line HDF three times per week for at least 3 months prior to study enrollment. Exclusion criteria included, but was not limited to, conditions that could interfere with the patient's ability to provide informed consent, unstable vascular access with risk of low and variable extracorporeal blood flow rate, chronic liver disease, bleeding disorder or red blood cell transfusion within 12 weeks prior to enrollment, acute infection within 4 weeks prior to enrollment, or scheduled for interventions requiring hospitalization for more than one week.

After informed consent was obtained, patients were stratified by residual renal function (anuric [< 100 mL/24h] or non-anuric) and randomized to either transfer to HDx therapy or to stay on previous HDF therapy. HDx treatments were delivered using the TheraNova 500 dialyzer (polyarylethersulfone/polyvinylpyrrolidone membrane, 2.0 m^2 surface area; Baxter, Hechingen, Germany). HDF treatments were delivered in postdilution mode using the Polyflux 170H dialyzer (polyarylethersulfone/polyamide/polyvinylpyrrolidone membrane, 1.7 m^2 surface area; Baxter, Hechingen, Germany) with a target convective volume of at least 23 liters. Patients and staff were unblinded to the applied therapy. All treatments were delivered with Artis Physio dialysis systems (Baxter, Medolla, Italy). Treatment duration, blood flow rate (targeted for at least 350 mL/min), dialysis fluid composition and temperature were to be maintained as before study initiation. Anticoagulation with low molecular weight heparin was provided.

The study protocol was approved by the ethics committee of Reina Sofia General University Hospital, Murcia; the study was conducted in accordance with the Declaration of Helsinki, the ethical and quality standards of good clinical practice, and all applicable regulatory requirements and laws, local, national and European.

Data collection

Primary outcome assessment included blood sampling pre- and post-dialysis after 12 weeks of treatment and calculation of the reduction ratios (RRs) for a range of MMs: beta₂-microglobulin ($\beta_2\text{m}$, 11.8 kDa), fibroblast growth factor 23 (FGF-23, 32 kDa), chitinase-3-like protein 1 (YKL-40, 40 kDa), kappa free light chain (FLC, monomers 22.5 kDa), and lambda FLC (dimers 45 kDa).

Secondary outcome assessments were i) change from pre- to post-dialysis in plasma levels of inflammatory markers – interleukin-6 (IL-6), C-reactive protein (CRP), and pentraxin-3 (PTX3) – at 12 weeks of treatment, ii) change from baseline to 12 and 24 weeks of study treatments in mid-week pre-dialysis plasma levels of MMs and inflammatory markers, iii) change from baseline in pre-dialysis plasma levels of albumin, fibrinogen, hemoglobin, parathyroid hormone (PTH), and phosphorous, iv) delivered single pool Kt/Vurea, and v) weekly dose of erythropoiesis-stimulating agents (ESA) and intravenous iron to manage anemia.

Biomarker analysis was performed by an external laboratory that was blinded to how the samples related to the study subjects. Assay details are listed in Supplement Table 1.

Calculations

For calculations of pre- to post-dialysis reduction ratios or percent changes, the post-dialysis concentrations were corrected for hemoconcentration using the formula by Bergström and Wehle [15].

ESA doses were assessed every 4 week and given as the mean weekly dose in the preceding 4 weeks. Darbepoetin alpha doses were converted from mg to IU using a factor of 200. Erythropoietin resistance

index (ERI) for a certain week was calculated using the weekly ESA dose divided by the hemoglobin level in that week.

Statistical analysis

A feasibility analysis indicated that a sample size of approximately 40 patients was possible in the study site, which was deemed to give enough power to evaluate the primary objectives of the study based on previous study results (10). Given the exploratory nature of most other outcomes of the study, this sample size was also seen as enough to establish data for future and more focused studies.

Descriptive data are reported as mean $\pm$ standard deviation (SD) unless otherwise stated. Differences between study arms in reduction ratio or change during session were analyzed using ANCOVA model. Differences between therapies in change over time were analyzed using mixed-effect repeated measurement (MMRM) models for most biomarkers. Both models used baseline pre-dialysis concentration and baseline urine output as covariates. The Wilcoxon rank-sum test was used to analyze change over time for FGF-23 and CRP due to the non-normal distribution of data.

Results

Forty-three patients were enrolled in April 2018, fulfilling the inclusion/exclusion criteria and providing informed consent. Twenty-one patients were assigned to start HDx therapy and 22 to stay on HDF therapy. Baseline demographics were similar between the two study arms (table 1).

Table 1: Patient demographics at study baseline

	HDx study arm (N = 21)	HDF study arm (N=22)
Age (y)	60.7 $\pm$ 14.3	61.8 $\pm$ 9.4
Gender (% males)	57%	73%
Body weight (kg)	76.6 $\pm$ 13.1	75.9 $\pm$ 16.0
Dialysis vintage (months)	58 $\pm$ 59	60 $\pm$ 78
Urine production		
Anuric (<100 ml/24h)	48%	45%
Oliguric (100-500 ml/24h)	29%	32%
Non-oliguric (>500 ml/24h)	23%	23%
ESRD comorbidity index	2.5 $\pm$ 1.7	1.9 $\pm$ 1.8
Malnutrition Inflammation Score	3.4 $\pm$ 2.1	3.5 $\pm$ 1.4

Acceptance to the HDx therapy was high in those patients who switched from HDF to HDx. One patient in the HDF arm died during the study. Two patients were excluded due to severe adverse events not related to dialysis, one in each study arm. In addition, nine patients were discontinued from the study as they left the study unit going on vacation for more than two weeks. Most of these left after the week 12 assessment and, by chance, most were in the HDF study arm. The patient flow is summarized in Supplementary figure 1.

Treatment characteristics are reported in table 2. Mean blood flow rate during the study was close to 400 mL/min in both groups over time. Treatment duration was 4 hours. HDF treatments showed a substitution volume that averaged 24 liters. With 2.4 liters of mean UF volume the mean total convective volume was close to 26 liters.

Table 2: Study treatment characteristics at week 12

	HDx (N = 21)	HDF (N=19)
Treatment duration (min)	241 ± 4	239 ± 7
Blood flow rate (mL/min)	400 ± 12	396 ± 8
Dialysis fluid flow rate (mL/min)	500	600
Ultrafiltration volume (L)	2.5 ± 0.8	2.1 ± 0.8
Substitution fluid volume (L)	n.a.	24.4 ± 3.2

n.a. = not applicable

Intra-dialytic changes in biomarker levels

Pre- to post-dialysis RR for MMs was greater in the HDx study arm for YKL-40 (58.1 ± 9.5 vs 42.4 ± 12.5 %; $p < 0.0001$) while it appeared similar between HDx and HDF for β_2m (76.6 ± 5.6 vs 77.2 ± 5.6 %; $p = 0.47$) and FGF-23 (48.1 ± 21.3 vs 45.1 ± 20.8 %; $p = 0.63$). For FLC, measured by the N Latex assay, the RRs were also similar between therapies for kappa FLC (67.0 ± 5.9 vs 64.9 ± 6.9 %; $p = 0.40$) and lambda FLC (67.7 ± 6.2 vs 65.9 ± 8.2 %; $p = 0.31$) – see figure 1.

The HDx and HDF study arms showed similar percent change from pre- to post-dialysis for inflammatory biomarkers: IL-6 (-13.7 ± 13.2 vs -16.9 ± 14.7 %; $p = 0.29$), CRP (-7.2 ± 12.1 vs -8.8 ± 10.6 %; $p = 0.62$), and PTX3 ($+5.2 \pm 24.9$ vs $+8.6 \pm 30.5$ %; $p = 0.45$).

Both study arms showed a mean delivered spKt/V of 1.8, ranging between subjects from 1.3 to 2.6.

Biomarker changes over time

Pre-dialysis levels of β_2 m, FGF-23, FLCs, and YKL-40 were similar between study arms at baseline and their changes to 12 and 24 weeks did not differ between arms except for borderline differences at week 24 for β_2 m ($p=0.045$) and FGF-23 ($p=0.039$); see table 3. Inflammatory markers CRP, IL-6, and PTX3 were also similar between groups at baseline, and changes over the 24-week study period appeared insignificant and similar between study arms. Likewise, changes over time in plasma levels of albumin, fibrinogen, hemoglobin, PTH, and phosphate did not differ between study arms (table 3).

Table 3
Baseline pre-dialysis levels and changes from baseline for the studied biomarkers

		baseline	Change to week 12	Change to week 24
B2m (mg/L)	HDx	25.4 ± 7.6	-0.6 ± 3.6	-0.6 ± 3.9
	HDF	24.3 ± 7.5	-1.0 ± 4.5	+ 3.3 ± 6.1
	<i>p-value</i>	<i>0.62</i>	<i>0.55</i>	<i>0.046</i>
FGF-23 (pg/mL)	HDx	1153 (402, 1979)	-20 (-597, + 512)	-24 (-623, + 202)
	HDF	825 (277, 1438)	+ 208 (-537, + 494)	+ 343 (+ 44, + 1152)
	<i>p-value</i>	<i>0.28</i>	<i>0.45</i>	<i>0.039</i>
YKL-40 (ng/mL)	HDx	432 ± 325	+ 2 ± 114	0 ± 132
	HDF	507 ± 491	-3 ± 234	+ 103 ± 432
	<i>p-value</i>	<i>0.56</i>	<i>0.94</i>	<i>0.16</i>
Kappa FLC (mg/L)	HDx	143 ± 41	-5 ± 17	+ 7 ± 35
	HDF	151 ± 45	-4 ± 30	+ 20 ± 46
	<i>p-value</i>	<i>0.52</i>	<i>0.75</i>	<i>0.56</i>
Lambda FLC (mg/L)	HDx	129 ± 37	-3 ± 28	+ 19 ± 37
	HDF	173 ± 141	8 ± 43	+ 44 ± 58
	<i>p-value</i>	<i>0.17</i>	<i>0.65</i>	<i>0.28</i>
IL-6 (pg/mL)	HDx	8.6 ± 5.3	-0.3 ± 2.6	-0.5 ± 2.2
	HDF	7.2 ± 3.2	-0.1 ± 3.1	-0.1 ± 2.3
	<i>p-value</i>	<i>0.32</i>	<i>0.83</i>	<i>0.49</i>
CRP (mg/L)	HDx	2.4 (1.3, 4.7)	-0.3 (-1.0, + 0.3)	0.0 (-0.7, + 1.1)
	HDF	5.6 (2.6, 8.4)	-0.7 (-4.0, + 0.1)	-0.4 (-1.6, + 4.2)
	<i>p-value</i>	<i>0.18</i>	<i>0.34</i>	<i>0.68</i>
PTX-3 (pg/mL)	HDx	4.8 ± 2.7	+ 0.6 ± 2.1	0.0 ± 1.8
	HDF	6.8 ± 4.8	-0.9 ± 2.4	-1.0 ± 3.9
	<i>p-value</i>	<i>0.10</i>	<i>0.39</i>	<i>0.75</i>
Albumin (g/dL)	HDx	3.67 ± 0.38	+ 0.06 ± 0.46	-0.02 ± 0.25
Data presented as mean ± SD or as median (25th, 75th percentile)				

		baseline	Change to week 12	Change to week 24
	HDF	3.78 ± 0.32	-0.01 ± 0.26	-0.02 ± 0.34
	<i>p-value</i>	<i>0.33</i>	<i>0.89</i>	<i>0.59</i>
Fibrinogen (mg/dL)	HDx	352 ± 95	-45 ± 75	-22 ± 74
	HDF	376 ± 126	-72 ± 117	-94 ± 103
	<i>p-value</i>	<i>0.49</i>	<i>0.78</i>	<i>0.13</i>
Hemoglobin (g/dL)	HDx	11.3 ± 0.8	+ 0.3 ± 1.2	-0.2 ± 1.0
	HDF	11.4 ± 0.8	-0.3 ± 1.1	+ 0.1 ± 1.0
	<i>p-value</i>	<i>0.69</i>	<i>0.19</i>	<i>0.16</i>
PTH (pg/mL)	HDx	413 ± 214	+ 36 ± 328	+ 51 ± 330
	HDF	309 ± 181	+ 34 ± 191	+ 210 ± 293
	<i>p-value</i>	<i>0.09</i>	<i>0.66</i>	<i>0.30</i>
Phosphorous (mg/dL)	HDx	4.25 ± 1.11	+ 0.04 ± 1.54	+ 0.17 ± 1.16
	HDF	3.79 ± 0.68	+ 0.36 ± 0.96	+ 0.67 ± 0.76
	<i>p-value</i>	<i>0.11</i>	<i>0.87</i>	<i>0.67</i>
Data presented as mean ± SD or as median (25th, 75th percentile)				

Exploratory – anemia management

All subjects in the HDF study arm and 20 out of 21 subjects in the HDx study arm received ESA during the study. Thirty-one subjects received erythropoietin (HDF: 17; HDx:14) while 9 received darbepoetin alpha (HDF: 3; HDx:6); in addition, 2 patients in the HDF arm were on darbepoetin alpha at the start of the study but shifted to erythropoietin during the study. When evaluating subjects who completed the 24-week study period, those in the HDF study arm (N=12) showed stable mean weekly dose of ESA over time (baseline: 99 ± 74 IU/kg, week 12: 113 ± 75 IU/kg, week 24: 102 ± 74 IU/kg) while the HDx study arm subjects (N=19) showed a trend towards a decrease in weekly ESA dose from week 8 (baseline: 106 ± 87 IU/kg, week 12: 98 ± 102 IU/kg, week 24: 77 ± 103 IU/kg) (figure 2A). ERI in ESA-treated patients showed a similar trend without significant difference between groups (figure 2B) while hemoglobin level appeared stable over time in both groups (figure 2C). The use of intravenous iron did not differ significantly between treatment arms, although with a trend of reduced need over time in the HDx arm. Transferrin saturation and ferritin levels were comparable at baseline (23.1 ± 7.8 % and 297 ± 275 ng/mL for HDx arm vs. 20.8 ± 7.4 % and 231 ± 201 ng/mL for HDF arm) and changes during the study period were similar between groups.

Adverse events

Overall, a total of 37 subjects (86%) were reported to experience 134 adverse events (AEs, serious or nonserious) during the study; 18 subjects with 79 AEs in the HDx group and 19 subjects with 55 AEs in the HDF group. Hypotension, muscle cramps, and hypertension were the most reported AEs. Intradialytic hypotension episodes were not seen in any patient during the study period. Eight AEs were rated as serious (3 in HDx, 5 in HDF); none of these were judged to be related to the dialysis procedure.

Discussion

The clinical effectiveness of expanded hemodialysis (HDx), using the recently introduced MCO membrane, is not yet fully characterized in comparison to on-line HDF. We here report what we believe to be the first randomized controlled study comparing HDx to HDF with a 24-week follow-up. The key finding is that the HDx therapy provided similar reduction ratios as high-efficiency HDF for a wide range of MMs, with greater reduction ratio for YKL-40. Compared to patients who were continued on HDF, patients assigned to HDx exhibited no change over time in biomarker levels, indicating that HDx is non-inferior to HDF in clinical effectiveness.

Effective removal of a wide spectrum of uremic toxins is a key objective of the dialysis treatment. While β_2 m has long been the marker of conventional MMs, there is currently no consensus of what is appropriate as marker for the large middle molecule class of uremic toxins. A global removal score was recently proposed [13], calculated from reduction ratios of urea, several middle molecules, and albumin; α 1-microglobulin and α 1-acid glycoprotein were included as large middle molecules. In our study, we measured the removal of four other large middle molecules—FGF-23, kappa FLC, lambda FLC, and YKL-40—for which a high plasma level has been found to be predictive of poor outcome in CKD patients [16-19]. We suggest these are appropriate markers for a global removal score when assessing therapy performance.

In terms of blood purification performance for middle molecules our results are comparable to the single-treatment data reported by Kirsch et al for the Theranova MCO membrane (initially reported as MCO AA dialyzer) [10], except for lambda FLC. While Kirsch et al found increased removal of lambda FLC with the MCO dialyzer in comparison to HDF, we did not. Importantly, Kirsch et al found for both therapies a lower RR for lambda FLC than for kappa FLC, consistent with the fact that lambda circulates mostly as dimers while kappa circulates as monomers. In our analysis the RRs for kappa and lambda were high and of a similar magnitude, which indicates that the dialytic removal of lambda dimers was not accurately captured. We believe these differences are explained by the assay used, being a Siemens N Latex assay in our study and the Binding Site Freelite assay in the Kirsch study. Recent comparisons of these two immunochemical methods have revealed significant differences in their ability to discriminate between monomers and dimers of lambda FLC [20, 21]. Based on these data we would recommend the use of the Freelite assay when evaluating the removal of lambda FLC by dialysis.

We did not find a change over time in pre-dialysis plasma levels of MMs in study patients transferring from HDF to HDx but observed a trend for increased levels in those patients who stayed on HDF. The apparent difference between groups in these changes for β_2m and FGF-23 at week 24 (p-values 0.048 and 0.039 respectively) should be interpreted with caution, considering the multiple testing and the risk of attrition bias in the week 24 data.

Interestingly, we saw a trend for reduced ESA dose over time in the HDx study arm without a concomitant reduction in hemoglobin level, indicating an improved response to the ESA administered in comparison to HDF. HDF has been found superior to conventional HD in reducing ESA resistance in some [22] but not all studies [23]. A positive effect on anemia management is possibly limited to patients receiving intravenous erythropoietin [24]. ESA hyporesponsiveness in iron-replete dialysis patients is considered linked to a state of inflammation. We did not find evidence of a difference between HDx and HDF in inflammatory biomarkers; it should be noted, though, that the variability in the data and the small sample size gave us low power to detect such a difference. When Lim et al. in a randomized controlled trial found reduced ESA dose and ERI with HDx in comparison to high-flux HD they also found with HDx a significantly lower serum TNF- α level at 12 weeks [25].

This study has several limitations. It was not designed for a formal non-inferiority analysis of HDx therapy in comparison to HDF but was merely exploratory. Although our sample size appears appropriate to evaluate differences in reduction ratios for middle molecules, it was too low to draw firm conclusions on the impact of therapy over time. The fact that we lost several patients in the HDF arm after the week 12 visit translates into an increased risk of attrition bias for the week 24 comparison. All study patients were on HDF treatments at study enrollment; our results may not reflect a situation where patients are on HD for transfer to HDF or HDx.

Conclusion

In a randomized controlled study, we found that HDx therapy using MCO membrane delivers large middle molecule removal at least at level with high-efficiency HDF. We found for HDx therapy a trend for reduced need of erythropoiesis-stimulating agents without indication that HDx is inferior to HDF in other parameters of clinical effectiveness, results that should be viewed as preliminary while awaiting additional and larger studies in this field. Being easy to implement and not dependent on on-line HDF equipment, the HDx therapy appears an attractive option to manage long-term dialysis.

List Of Abbreviations

HDx: Expanded hemodialysis

HDF: Hemodiafiltration

MM: Middle molecules

MCO: Medium cut-off membrane

RR: Pre- to post-dialysis reduction ratio

FLC: Free light chains

YKL-40: Chitinase-3-like protein 1

FGF-23: Fibroblast growth factor 23

IL-6: Interleukin-6

CRP: C-reactive protein

PTX3: Pentraxin-3

β 2m: β_2 -Microglobulin

PTH: Parathyroid hormone

ESA: Erythropoiesis-stimulating agents

ERI: Erythropoietin resistance index

AEs: Adverse events

Declarations

Ethics approval and consent to participate: This study was approved by the Clinical Research Ethics Committee of the Reina Sofía University General Hospital, Murcia. It was conducted in accordance with the ethical principles of the Declaration of Helsinki, the ethical and quality standards of good clinical practice and all applicable regulatory requirements and laws. Patients were appropriately informed of the study concept and enrolled only after signing an informed consent document.

Consent for publication: Not applicable

Availability of data and materials: The data that support the findings of this study are available from Baxter Healthcare, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Baxter Healthcare.

Competing interests: FHA was an employee of Renal Therapy Services (RTS), an independent entity owned by Baxter International, Inc, at the time the study was conducted. LGN, AR and AAB are employees of Baxter Healthcare.

Funding: Baxter Healthcare Corporation acted as sponsor of the study

Authors' contributions: All authors provided intellectual content of critical importance to the work described. Individual contributions of each co-author are: LGN and AAB provided significant input to the study protocol that was further discussed and revised by FHA, AR, and JBCR; FHA provided the clinical implementation of the study; LGN supported the data analyses that were performed by a statistician from Baxter Healthcare; LGN drafted the manuscript, which was revised and approved by all authors.

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Figures

Figure 1

Middle molecule pre- to post-dialysis reduction ratios. Pre- to post-dialysis reduction ratios measured at week 12 (* p<0.0001). Note that as FLC concentrations were measured by the N Latex assay the lambda FLC reduction ratios likely reflect only the removal of lambda monomers.

A.

B.

C.

Figure 2

Anemia parameters over time in subjects who completed the 24-week study period. A: Weekly ESA dose per kg body weight. B: Erythropoietin Resistance Index (ERI). C: Blood hemoglobin level. Filled squares show means for patients switching to HDx, open squares show means for patients maintained on HDF. Error bars indicate standard errors of the means. Lines and R2 values refer to linear regressions.

Supplementary Files

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