Expanded Hemodialysis Therapy: Prescription and Delivery

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Abstract

Expanded hemodialysis (HDx) therapy is a novel treatment concept in hemodialysis patients, using innovative membrane technology with a high retention onset for improved solute clearance in the upper middle molecular range. HDx therapy thereby resolves a key limitation of current hemodialysis techniques and targets an important pathophysiologic link to many of the sequelae of end-stage renal disease. The present chapter reviews the current evidence and discusses considerations for prescription and delivery of HDx therapy upon implementation in clinical practice.

Introduction

Incorporating innovations and novel therapeutic strategies into routine clinical practice is key to improve patient outcome. It implies an understanding of the underlying concept, adoption of the idea and implementation in clinical routine, as well as monitoring the effect size and related outcomes.

Expanded hemodialysis (HDx) therapy [1] targets one of the major shortcomings of current extracorporeal dialysis techniques, that is, the inability to adequately remove large middle molecules, associated with many of the long-term consequences of end-stage renal disease (ESRD). Attempts to improve middle molecule elimination have included prolongation of dialysis time (nocturnal hemodialysis) and the use of standard high-flux filters in convective techniques (hemodiafiltration). Both have proven effective, but impose additional time constraints on patients or result in increasing cost and a more complex infrastructure.
HDx therapy follows a different approach. Innovative membrane technology for the first time allows superior and unprecedented middle molecule clearance using a standard hemodialysis setting [2, 3]. In adopting and implementing this novel therapeutic concept, two aspects are central for the clinician and to be discussed in the present chapter: Patient selection and conduct of therapy, or – in other words – whom to prescribe and how to deliver.

**Whom to Prescribe HDx Therapy**

By concept, HDx targets the disease burden of chronic kidney disease (CKD) requiring renal replacement therapy and, ultimately, excess mortality in ESRD. This holds true for all CKD 5 patients, irrespective of ethnicity, age, gender or underlying disease and thereby renders most chronic hemodialysis patients potential candidates for HDx therapy. As per our current knowledge, there are no contraindications specific to the use of high retention onset (HRO) membranes in chronic hemodialysis patients.

Nonetheless, in the early phase of adoption, a number of considerations may help the clinician to decide which patients to start with and gain experience in HDx therapy.

One is residual renal function. With non-protein bound middle molecules physiologically cleared by glomerular filtration and proximal tubular degradation, retention of middle molecules starts in the pre-dialysis state and aggravates with progressive decline in renal function [4]. Even after the initiation of hemodialysis, the residual renal function will – to a certain extent – contribute to middle molecule clearance and may be preserved for a reasonable period of time with prudent patient management. With increasing dialysis vintage, loss of residual renal function is inevitable, aggravating not only fluid management but also retention of uremic toxins. The impact of HDx and individual patient benefit may hence be more pronounced in patients without residual renal function.

A second aspect is the patient’s anticipated time on dialysis. After the first year, clinical disease burden, complications and annual mortality increase with time on renal replacement therapy [5], and patients with a long expected lifespan and without the option of a timely transplant are likely to benefit most from HDx therapy over time. Whereas clinical trials have uniformly reported measurable and sustained reductions in middle molecule concentrations within weeks after treatment initiation [2, 3], an impact on CKD-associated complications and end-points clearly is only to be expected after continuous treatment over long periods of time. Patient well-being and self-reported quality of life may actually be one of the earliest, albeit highly relevant clinical readouts available.
A third criterion is a detoxification deficit, that is, patients with persistent hyperphosphatemia under their current dialysis regime, despite adherence to dietary recommendations and medication intake. Although phosphorus has a low-molecular weight, mass transfer across the dialysis membrane is hindered by water particles tightly bound to the molecule, increasing the hydrated radius and limiting membrane transfer, especially in diffusive mode [6]. In many patients, a switch to hemodiafiltration may not be an option due to either regulatory or local settings (dialysis center infrastructure, treatment in a limited- or self-care center) or to patient-related factors, such as access flow rate, volume issues or others [7]. In these patients, HDx therapy allowing for a significant amount of convection inside the filter is a simple and viable option to substantially improve dialysis quality without leaving a standard hemodialysis setting.

Other considerations include patients with comorbidities, that is, diabetes mellitus, which by themselves contribute to microinflammation and cardiovascular complications, as well as patients carrying a high cardiovascular risk from other cause. And lastly, additional aspects may emerge from ongoing clinical trials.

A repeatedly discussed aspect and a theoretical limitation to HDx therapy in individual patients is albumin loss. Owing to tailing characteristics, the use of HRO membranes will result in some albumin removal. For the first-in-class HRO membrane, the Theranova dialyzer, albumin losses between 1.2 and 3.9 g per dialysis session have been described. This is an amount in a range also seen in high-volume hemodiafiltration with high-flux dialyzers [8, 9] and significantly below what has been observed with high cut-off filters [10]. These albumin losses can largely be reconstituted in between sessions by hepatic albumin synthesis, as underlined by an increase in cholinesterase activity observed under such conditions. In a 12-week clinical trial addressing inflammation under HDx therapy [3], a moderate and transient drop in serum albumin concentration (around 0.2 mg/dL) was seen after 4 weeks of treatment, which largely recovered thereafter. No patient developed clinical symptoms related to hypoproteinemia. Nonetheless, a small caveat remains in patients starting HDx therapy with substantially low serum albumin levels and a closer monitoring appears prudent from a clinical standpoint.

**How to Deliver HDx Therapy**

Delivery of HDx therapy is simple, as the relevant technology is in the dialyzer and not part of a complex technical setup. HDx therapy can be delivered with any standard hemodialysis monitor. A blood flow of $Q_b$ 300 mL/min and a dialysate flow rate of $Q_d$ 500 mL/min or higher will be adequate [11]. Under these conditions, an average internal filtration 40–45 mL/min can be obtained at zero
net filtration, resulting in a solute clearance superior to high-flux hemodialysis and comparable to or even exceeding hemodiafiltration, including larger middle molecules whose clearance otherwise is marginal [2, 11].

The handling of HRO filters in clinical routine does not differ from standard high flux-filters and no specific technical or nursing skills are required regarding setup, conduct, and discontinuation of treatment. The largest body of evidence regarding the handling of HRO filters outside clinical trials is derived from a limited controlled distribution trial of the Theranova dialyzer [12], covering more than 5,000 treatments in 18 centers over 5 European countries. With a focus on handling and usability under real-world conditions and in a broad spectrum of patients, hemodialysis monitors and clinical settings, the dialyzer proved as easy to use as high-flux membranes, and compatibility was verified over a wide range of competitive hemodialysis monitors. Following clinical practice guidelines for priming and rinseback, no specific aspects arose from the use of HRO membranes.

HDx therapy requires no specific or intensified clinical monitoring. As with all changes in dialysis prescription, a somewhat closer look at the patient is advisable after initiation and during the first few treatment sessions. A need to adapt anticoagulant dose may occur if the patient is shifted to a larger membrane surface area (currently available dialyzers offer an effective membrane surface area of 1.7 or 2.0 m²), a feature not specific to HRO membranes. Regarding laboratory parameters, it is sufficient to continue routine monthly controls in the vast majority of patients. With respect to the standard parameters relevant for quality assessment and reporting as well as for reimbursement in certain markets, a switch to HDx therapy is not critical, even for patients previously on hemodiafiltration, as underlined by data from clinical trials and from personal experience.

In clinical routine, middle molecule concentrations need not be monitored. If by interest, a readout is desired, λ free light chain levels are a suitable maker for higher molecular weight middle molecules, which is inexpensive and readily available in laboratories throughout the world. A number of clinical trials are under way addressing the identification of molecules that may serve as surrogate parameters for specific aspects targeted by HDx therapy, among them are microinflammation, vascular calcification or iron metabolism.

Finally, two practical aspects deserve attention in delivering HDx therapy: First, HRO filters are certified to be used in diffusive mode only. Dialyzers are labeled accordingly, but especially in patients previously on hemodiafiltration or when using dialysis monitors capable of hemodiafiltration the correct setting to hemodialysis mode should be verified prior to treatment initiation. This is a relevant aspect in clinical routine. Second, as with all filters with internal back filtration, dialysis fluid quality is an issue to avoid back transport of contaminants and water purity needs to be assured.
Conclusion

HDx treatment has the potential to change the current hemodialysis practice. Unlike other innovations, implementation of the novel treatment concept into clinical practice is simple and requires no additional skills or infrastructure. With middle molecules involved in most of the sequelae of ESRD, a broad range of dialysis patients have the potential to benefit from HDx therapy with a focus on those without residual renal function and a long expected time on hemodialysis. HDx therapy is likely to modulate disease burden and quality of life in hemodialysis patients. Whether this translates to less complications and, essentially, improved survival remains to be determined.

References

1 Ronco C: The rise of expanded hemodialysis. Blood Purif 2017;44:I–VIII.