The reasons for a clinical trial on incremental haemodialysis

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INTRODUCTION

There is growing interest in an incremental approach to haemodialysis (HD) for incident end-stage kidney disease (ESKD) patients, starting with one or two sessions per week [1–5]. Such an approach not only seems to preserve residual kidney function (RKF) and improve health-related quality of life with similar or higher survival rates than those observed in patients receiving the standard thrice-weekly HD regimen, but also allows saving economic resources [6–10].

The term ‘incremental HD’ means that, in the presence of substantial RKF, both dialysis dose and frequency can be low at dialysis inception but should be progressively increased to compensate for any subsequent reduction in RKF [11–13]. The current principle for calculating the amount of dialysis required to compensate for RKF reduction is based on the constancy of the value of total (renal + dialytic) weekly clearance as expressed by the equivalent continuous clearance (ECC) of urea [11–13]. Two versions of ECC exist, the standard $Kt/V$ [14] and the equivalent renal urea clearance (EKR) [15]. For the sake of simplification, only EKR will be used. The assumption of a constancy of the total EKR (renal + dialytic), the so-called fixed target model of EKR, implies the attribution of a clinical equivalence to dialytic urea clearance [15]. The mistake of attributing a clinical equivalence to dialytic urea clearance and Kru is not trivial, because it leads to overestimates of dialysis needs in the presence of substantial RKF, requiring such high values for both RKF and dialysis dose ($Kt/V$) that it would be difficult to prescribe less frequent treatments [1, 16]. Moreover, delivering more dialysis than really needed could accelerate the decline of RKF [17], likely due to many factors, such as more blood–membrane and blood–dialysate interactions, intradialytic arterial hypotension with cardiac and renal ischaemia, as well as disruption of the compensating mechanisms set in motion by intact nephrons in response to nephron loss [17–19].

The above concept [16, 20] can be applied to both versions of ECC. In fact, the concept of an increased clinical weight of Kru introduced by the VTM [16, 20] is in line with the new version of standard $Kt/V$, which uses Kru at 100%, instead of a ‘compressed’ Kru used with the original standard $Kt/V$ [13, 21].

Table 1 shows a simulation study using Solute-Solver software [22] based on the double-pool urea kinetic model recommended by the 2015 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines [13]. It allows drawing two trajectories for the variable target as Kru approaches zero [20]: a low-level one with EKR increasing from 4 mL/min/35 L,
corresponding to a glomerular filtration rate (GFR) of 6 mL/min/1.73 m², in agreement with the European Renal Best Practice position statement [23], to 10 mL/min/35 L, corresponding to an eKt/V of 1.05 for anuric patients on a 3 HD/week schedule, which is the adequate dialysis dose established by the Hemodialysis (HEMO) Study [24]; and a high-level one, with EKR increasing from 6 mL/min/35 L, corresponding to a GFR of 9 mL/min/1.73 m², to 12 mL/min/35 L, corresponding to an eKt/V of 1.29 on a 3 HD/week schedule (Table 1) [16].

The availability of two prescription lines, instead of a single one, allows defining a 'prescription zone' between the two lines. This can avoid both delivering unnecessarily high doses of dialysis, which could accelerate Kru decline, and maintaining a stable prescription in front of reductions in Kru. In particular, Table 1 shows that an eKt/V of 0.79 is adequate for a 1 HD/week schedule in the presence of Kru ≥3.0 mL/min/35 L, so that an eKt/V of 1.05 (+31%) should be largely adequate. Analogously, an eKt/V of 0.97 suffices on a 2 HD/week schedule, and even more, an eKt/V of 1.05 will be adequate because it corresponds to a single-pool Kt/V (spKt/V) of 1.2 [24]. On this basis, one could safely use a constant eKt/V of 1.05 on a 1 HD/week schedule until Kru is ≥3.0 mL/min/35 L and on a 2 HD/week schedule for Kru ≥1.5–<3.0 mL/min/35 L [20, 25]. Moreover, relying on a prescription zone with a constant Kt/V largely above the minimum value required reduces the need for a frequent Kru measurement.

Table 1. A simulation study using Solute-Solver software [22] based on the double-pool urea kinetic model recommended by the 2015 KDOQI guidelines [13]

<table>
<thead>
<tr>
<th>Kru (mL/min/35 L)</th>
<th>EKR = 10–1.5</th>
<th>eKt/V 1 HD/week</th>
<th>eKt/V 2 HD/week</th>
<th>eKt/V 3 HD/week</th>
<th>EKR = 12</th>
<th>eKt/V 1 HD/week</th>
<th>eKt/V 2 HD/week</th>
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<td>0.0</td>
<td>10.00</td>
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The eKt/V values required to reach two different levels of target EKR (in bold) as a function of Kru and treatment schedule. The simulation was made for a patient with a urea distribution volume of 35 L and ultrafiltration volume per session of 1, 2 and 3 L, for 1, 2 and 3 HD/week regimens, respectively. The values in columns 3–5 refer to the lowest target in column 2; the values in columns 7–9 refer to the highest target in column 6.
The above construct is apparently sound but, obviously, it should be confirmed by a randomized clinical trial (RCT) before its clinical implementation.

**THE REAL LIFE PROJECT**

To this end, the European Dialysis (EUDIAL) Working Group of the ERA-EDTA is ready to start the ‘RandomizEd clinicAL trial on the efficacy and saFety of incremental haEmodialysis’ (REAL LIFE), using VTM on incident HD patients [25]. Keystones of this study are the following concepts: (i) Incremental dialysis represents a continuum and integration of pre-dialysis care [11], with a smooth transition from conservative management of chronic kidney disease (CKD) to the full 3 HD/week regimen [2, 19, 25, 26]. Interestingly, such a smooth transition has been advocated in opposition to the ‘abrupt’ start with a full thrice-weekly schedule, which could be responsible for the exceptionally high annualized mortality rate of ~40% for the first few months after HD inception [2]. Accordingly, the patient on transition to the full HD therapy should be seen as a patient essentially on conservative therapy, with dialysis being added on top of all dietary and/or pharmacologic measures well established for conservative treatment. On this basis, it is of paramount importance to focus on RKF preservation, both by avoiding any substances or manoeuvres that can damage it and implementing any intervention that could preserve it [2, 18]. (ii) To prescribe and deliver the adequate dose of dialysis as a function of Kru is mandatory. Actually, the VTM has been devised for this aim. An important corollary is that any clinical problem, such as high levels of serum potassium and/or phosphate, as well as metabolic acidosis, arterial hypertension, volume overload, etc., should be primarily treated with dietary and/or pharmacological interventions, if possible, without increasing the dose and/or frequency of dialysis.

In conclusion, the basic hypothesis of the study is that just by delivering the needed dialysis dose, as predicted by VTM, one could preserve RKF, which in turn should reduce the occurrence of cardiovascular diseases and improve the survival of patients.

**THE REAL LIFE PROTOCOL**

REAL LIFE is a pragmatic, prospective, multicentre, open-label, investigator-led RCT comparing the intervention arm (incremental HD) with the control arm (standard 3 HD/week). The full study protocol is available as Supplementary Data. Here the key points of the RCT are summarized.

**Enrolment and allocation (see Supplementary Data)**

Both planned and unplanned incident adult ESKD patients, with GFR [preferably assessed by the mean of urea and creatinine clearances or by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation] between 5 and 10 mL/min/1.73 m², will be randomized 1:1 by means of a computer-generated code after written informed consent has been obtained before the third HD session (to avoid possible irreversible RKF damage from prior intensive dialysis treatment). The patients randomized to the control arm should receive the conventional treatment as usual from the local centre. The patients randomized to the intervention arm should be treated the same as the patients in the control arm, the only difference being the frequency of treatment (Figure 2).

**Eligibility criteria**

Inclusion and exclusion criteria are detailed in Figure 2 and in Supplementary Data.

**Prescription of the dialysis dose**

For the sake of simplification, all patients will receive the same dialysis dose (i.e. an \( eKt/V \) of 1.05, corresponding to an \( spKt/V \) of 1.2 per session), with the frequency of sessions changing as a function of the actual Kru, only for the patients in the intervention arm (Figure 2). The frequency should be once a week until the Kru falls to <3.0 mL/min/35 L, followed by a twice-weekly schedule until the Kru falls to <1.5 mL/min/35 L and then by a thrice-weekly HD schedule. If required, the patient could start directly on a twice-weekly HD schedule and keep on it until the Kru falls to <1.5 mL/min/35 L (Figure 2). The \( Kt/V \) should be assessed on a monthly basis with the Daugirdas formula [27]. The assessment of key kinetic parameters as well as the selection of operative parameters will be done using the Spreadsheet for the Prescription of incrEmental haEmoDialYsis (SPEEDY) [28], a prescription tool that uses essentially the same equations used by Solute-Solver software [22]. SPEEDY is freely available at www.era-edta.org/en/eudial. Kru should be normalized, as already reported, to 35 L [16, 28], and measured on a monthly basis, but not less than quarterly [13].

**Progression criteria**

Progression criteria are detailed in Figure 2 and in Supplementary Data.

**Sample size**

The sample size was derived from a prospective observational study by Teruel-Briones et al. [29] enrolling patients with an RKF in the range of the selection criteria of this study: 15 of 61 patients starting with the 2 HD/week regimen (25%) and 25 of 49 patients starting with the 3 HD/week regimen (51%) had lost RKF after a 2-year follow-up (see Supplementary Data). Thus a rate of 0.169 to reach the event, i.e. RKF loss, was estimated for the intervention arm and a relative hazard of 2.5 was estimated for the control arm.

**Outcomes**

**Primary outcome.** Survival of kidney function, with the event ‘loss of RKF’ defined as urine output ≤200 mL/day [30], is confirmed by a further collection after 2 weeks to exclude temporary illness.

**Secondary outcomes.** Details are given as Supplementary Data.
**Data collection and statistical analysis**

Data at baseline and at the subsequent time intervals will be collected on web-based electronic case report forms at the specified time intervals (see Supplementary Data). Specifically, Kru must be computed from a timed urine collection, for instance, over the 24 h preceding the monthly HD session associated with the kinetic studies.

**Monitoring of adverse events**

Details are given as Supplementary Data.

**Participant timeline and recruitment**

The recruitment will start in September 2020. Participants will be recruited over an 18-month period at HD centres throughout Europe. The recruitment period will start from the enrolment of the first patient, with a follow-up of 24 months (see Supplementary Data).

**Safety controls**

Details are given as Supplementary Data.

A website functional to the operational activities of the RCT is being built-up at www.incrementaldialysis.eu (under construction).

**SUPPLEMENTARY DATA**

Supplementary data are available at ndt online.
CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

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