PROTOCOL OF REAL LIFE

REAL LIFE is a randomized controlled clinical trial (RCT) on the efficacy and safety of incremental hemodialysis. REAL LIFE is the acronym of RandomizEd clinicAL triaL on the effIcacy and saFety of incremental haEmodialysis

RATIONALE

Most patients with kidney failure begin dialysis with a thrice a week hemodialysis (HD) regimen (3HD/week), ideally 4 hours per session, with little individualization of the prescription based on residual kidney function (RKF) or other factors of the patient (1,2). Although this is a consolidated practice and considered "standard of care", empirical evidence suggests that other therapeutic regimens, such as incremental HD, could be taken into consideration in the initial phase of HD treatment, favoring a progressive "adaptation" of the patient to the dialysis treatment. Then, the number of weekly dialysis sessions could be progressively increased, bearing in mind that a non-negligible number of patients retain RKF at the start of HD treatment (2). In particular, there is the scientific equipoise for the comparative evaluation, in the context of RCTs, of the benefits and risks of therapeutic regimes starting HD treatment with 1 or 2 HD sessions per week compared to the standard approach which involves 3 HD sessions a week (3). An RCT is necessary and requested by the clinical-scientific community to evaluate whether starting a HD treatment with a lower number of sessions in the presence of RKF is adequate, harmful or equivalent compared to starting a standard dialysis treatment with a thrice a week HD regimen (2,3).

The optimal dialysis regimen for incident patients on HD is unknown. It is plausible that the routine practice of 3HD/week regimen is due to purely organizational needs, and does not take into account RKF, and that direct initiation with a 3HD/week regimen could accelerate the loss of RKF (2-6). The incremental HD approach is based on the idea of adjusting the dialysis dose in the initial phase of dialysis treatment based on the metrics of RKF. Indeed, most patients who begin dialysis maintain some degree of RKF, with residual renal clearance of urea (Kru) > 3 ml/min and urinary output > 500 ml/day (1-3). In particular, in the latest report from the United States Dialysis Registry (2021 USRDS related to the year 2019), 13% of incident patients started dialysis with an estimated

glomerular filtration rate (eGFR) < 5 ml/min/1.73 m^2; 48% with eGFR between 5 and 10 ml/min/1.73 m^2; 28% with eGFR between 10 and 15 ml/min/1.73 m^2; and 11% with eGFR > 15 ml/min/1.73 m^2 (1).

Given the importance of preserving RKF in conservative therapy, and given that the initiation of a 3HD/week regimen represents a trauma for the patient, it is important to consider the possible contribution of RKF in incident patients on HD and evaluate if the paradigm of a 3HD/week regimen approach to treatment could not undergo a change: patients with residual diuresis could start treatment with a lower number of weekly dialysis sessions, and then move on to a higher number of weekly treatments based on the reduction of the same diuresis and Kru.

The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, based on scientific evidence from RCTs and prognostic studies, suggest that minimum objectives of adequacy of the dialysis dose (Kt/V) can be reduced in patients with Kru > 2 ml/ min/1.73 m^2 (7). The European Best Practice Guidelines recommend measurement of RKF in incident patients on HD, using the mean of urea and creatinine clearance, and suggest how to incorporate RKF into the HD prescription: this allows for individual adjustments of dialysis prescription to achieve minimum dialysis adequacy goals (8). Given this premise, there are solid scientific assumptions for the design and conduct of a randomized intervention study, aimed at evaluating the benefits and risks of incremental HD (starting with 1 or 2 HD sessions a week with progressive increase up to 3 HD sessions a week) compared to the standard clinical practice (3HD/week) (9). Some studies of this type have already been designed and conducted and others are underway (10-13).

Furthermore, chronic kidney disease (CKD) is characterized by the alteration of the hydro-electrolyte balance, acid-base balance, tendency to volume overload, alteration of the homeostasis of the hormonal systems and accumulation of uremic toxins with repercussions on the survival of the patients, determined mainly by fatal cardiovascular events (7). Among the uremic toxins of greatest interest, indoxyl sulfate (IS) and para-cresol sulfate (pCS) are associated with the progression of kidney damage and with uremic complications and cardiovascular damage, such as vascular calcification and arterial stiffness, which increase the risk of mortality in patients with CKD (14,15). To date, HD represents the most effective therapy for eliminating uremic toxins in patients with kidney failure; however, different approaches in HD regimens could have repercussions on serum IS and pCS levels, as well as on related cardiovascular events (14,15).

OBJECTIVES OF THE STUDY

The aim of this RCT is to compare the standard 3HD/week approach with an incremental HD approach (1 or 2 sessions a week with subsequent increase to 3 sessions a week).

METHODS

Design of the study

REAL LIFE is an RCT on the efficacy and safety of incremental HD. REAL LIFE is the acronym for RandomizEd clinicAL triaL on the effIcacy and saFety of incremental haemodialysis (NCT04360694). It is a randomized, prospective, multicenter, non-blinded, independent study comparing incremental dialysis (experimental group) with the standard 3HD/week regimen (control group). Incident patients will be randomized 1:1 centrally into one of the two treatment groups, after obtaining informed consent and within 2 weeks from the start of dialysis to prevent a potential irreparable impairment of RKF due to a previous intensive dialysis approach.

There are no differences between treatments for patients in the two groups, other than the frequency of treatment. The type of HD method envisaged is a high-flow HD with highly biocompatible membranes or hemodiafiltration.

Recruitment will be open for as long as is necessary to reach the expected sample size, while follow-up will be for 24 months.

Identification of the eligible population

Individuals of both sexes aged ≥18 years who meet the following characteristics are eligible for the REAL LIFE study:

INCLUSION CRITERIA

1. Adult patients (>18 years) with kidney failure who are starting HD
2. Patients who have already started HD since ≤ 2 weeks
3. Patients with eGFR < 10 ml/min/1.73 m^2 (CKD EPI), key criterion recommended for starting HD treatment
4. Patients with urine output ≥ 600 ml/day
5. Patients able to understand and sign the informed consent; who agree to carry out the monthly 24-hour urine collection until urine output is ≤ 200 ml/day; who agree to increase the dialysis frequency based on the Kru values foreseen by the protocol

EXCLUSION CRITERIA

1. Patients with acute kidney injury or acute kidney injury on CKD
2. Patients already treated with other replacement therapies (peritoneal dialysis or kidney transplant)
3. Patients with an active cancer, severe heart failure or ejection fraction ≤ 30%, or life expectancy < 6 months
4. Patients who are in the waiting list for a living kidney transplant or with a planned transfer to other dialysis modalities or to a dialysis center not participating in the REAL LIFE study

TREATMENTS

Experimental group

The experimental group will perform incremental HD. It adopts the so called variable target model (VTM), recently introduced by Casino and Basile (16). VTM allows to start dialysis treatment with just one HD session per week, if the Kru is between 3.0 and 4.5 ml/min/1.73 m^2. One HD session a week will be maintained, unless differently decided by the investigator, until the Kru drops below 2.5 – 3.0 ml/min/1.73 m^2 or the GFR is approximately 4 ml/min/1.73 m^2; then, patients in the experimental group will transition to 2 HD sessions a week until Kru drops below 1.5 ml/min/1.73 m^2, progressing to 3 HD sessions a week.

Where the investigator's judgment does not include the possibility of starting a once a week treatment or expressly requested by the patient, it will be possible to start with a twice a week treatment, with a subsequent transition to the standard dialysis treatment of 3HD/week in the presence of a Kru lower than 1.5 ml/min/1.73 m^2. All patients will receive the same dialysis dose of equilibrated Kt/V (eKt/V) = 1.05, corresponding to a single pool Kt/V (spKt/V) = 1.2 per session, which is the minimum value recommended by the KDOQI guidelines (7), with the frequency of sessions changing as a function of the Kru value for the patients in the experimental group.

In addition to the decline of Kru there are 3 other conditions that can lead to intensification of the dialysis treatment and in particular:

- Need for ultrafiltration rate > 13 ml/kg/hour, despite an adequate use of diuretics (17)
- Severe clinical problems of the patient requiring intensive treatment
- Patient decision

The progression pattern from once a week to thrice a week dialysis in the experimental group is shown in Figure 1.

Control group

The patients in the control group will undergo the standard 3HD/week regimen, with eKt/V = 1.05, corresponding to a spKt/V = 1.2 per session.

OUTCOMES

Primary outcome

Preservation of RKF (assessed as presence/absence of anuria and time to anuria). The event is defined by the achievement of a urinary output ≤ 200 ml/day (18), confirmed at the next monthly check-up, to exclude a contingent condition.

Secondary outcomes

Decreased Kru, all-cause mortality, loss/malfunction of the vascular access, fatal and non-fatal cardiovascular events, hospitalizations for any cause, alterations in uremic toxin levels (IS and pCS), and other parameters of CKD (anemia, calcium-phosphorus metabolism, etc.).

Patient's Questionnaire Survey: Patient's Satisfaction

A patient's questionnaire survey will be used to evaluate and compare the effects of incremental HD with that of standard HD on patient's compliance and satisfaction level. We will use the questionnaire adopted in the publication by Karkar et al (19). It is focused on 16 out of the 44 questions of the validated Kidney Disease Quality of Life Short Form (KDQOL-SF) version 1.3 (http://www.rand.org/health/surveys_tools/kdqol.html). The questionnaire is based on HD-associated complications that are usually of concern to dialysis patients. Each question has a score ranging from 0 to 100, where 0 indicates the lowest and 100 the highest grade of satisfaction (eCRF Form 3).

The answer to each question is based entirely on the patient's own subjective assessment within the score range. The form is distributed by the local study nurses who help the patients fill in the forms and show them the way to score their answers, if necessary.

Each patient, in both groups, is asked to answer a sheet of the questionnaire at the beginning of the study and every 6 months until the completion of the study.

All participants will be monitored until the study is completed, including patients who will not complete the study due to death, kidney transplant, interruption of dialysis (e.g., recovery of kidney function), transfer to another dialysis center or interruption of the study due to the patient's decision. The data will be analyzed according to the "intention to treat" principle.

DATA MANAGEMENT

Baseline data and subsequent clinical data (body weight, diuresis, arterial blood pressure), biochemical data (pre- and post-dialysis blood tests as routinely performed in the dialysis center, creatinine and urea clearance) and number and cause of hospitalizations will be recorded. Furthermore, every six months, starting from the beginning of the study, a pre-dialysis blood sample will be drawn to carry out serum uremic toxin measurements (IS and pCS).

Calculation of kinetic parameters and prescription of dialysis

The calculation of the main kinetic parameters and of dialysis prescription, aimed at obtaining an $eKt/V \geq 1.05$, corresponding to $spKt/V \geq 1.20$, for each session of each patient, will be carried out using SPEEDY, an extremely simplified software dedicated to the prescription of incremental HD, recently developed by Casino and Basile (20). It essentially uses the same equations used by Solute Solver (21), the software based on the double pool urea kinetic model recommended by the 2015 KDOQI guidelines (7).

Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) is established to monitor the progress of the study and ensure that the safety of participants enrolled in the study is not compromised. The DSMB consists of 3 members. The DSMB will meet at least once a year. In case of an efficacy or safety issue, the DSMB will meet *ad hoc* as soon as possible. The independent DSMB will review safety data and main outcomes at regular intervals. Reports and recommendations (continue, amend or stop the study based on findings) will be reported to the Project Coordinator.

Security checks

Adverse events of special interest (AESIs) and serious adverse events (SAEs) will be assessed from the signing of Informed Consent Form until end of the study for the

participant. If the participant drops out (e.g. due to kidney transplantation or switch to other dialysis modality) he/she will still be followed for mortality and morbidity until the date that he/she was intended to end study participation.

AESIs

The following pre-dialysis laboratory parameters as checked at the monthly blood tests are collected as AESIs:

Hyperkalemia: serum potassium $\geq$ 6 mmol/l

Hyperphosphatemia: serum phosphate $\geq$ 6 mg/dl

Acidosis: serum bicarbonates $\leq$ 18 mmol/l

Any supplemental dialysis session prescribed because of the occurrence of signs and/or symptoms of uremia, volume overload, hyperkalemia, etc., is collected as AESI.

SAEs

A SAE is defined as any adverse event that

• Led to death;

• Led to serious deterioration in the health of the participant, that either resulted in

o A life-threatening illness or injury, or

o A permanent impairment of a body structure or a body function, or

o Inpatient hospitalisation or prolonged hospitalisation, or

o Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

• Any important medical event and any event which, though not included in the above, may jeopardize the patient or may require intervention to prevent one of the outcomes listed above.

Planned hospitalisation for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a SAE.

Hospitalisation is defined as at least one night's stay (eCRF Form 9).

The REAL LIFE study will be conducted in full conformance with the principles of the "Declaration of Helsinki" (64th WMA General Assembly, Fortaleza, Brazil, October 2013) (22) and with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the participant.

STATISTICAL ANALYSIS

The study data will be reported in a descriptive and inferential manner using standard techniques. The study data will be analyzed according to the "intention-to-treat" principle.

Sample size calculation

The sample size calculation is based on the primary outcome "presence of anuria", defined as urine output $\leq$ 200 ml/day (18), confirmed at the next monthly check, in order to exclude conditions of temporary reduction in urine output due to concomitant pathologies. The assumptions for calculating the sample size, derived from data of Teruel Briones et al. (23), are the following:

- Percentage of subjects who developed anuria in the experimental group (incremental HD): 25%
- Percentage of subjects who developed anuria in the control group (standard 3HD/week regimen): 51%
- Power: 0.8
- Ratio: 1:1
- Non-compliance: 20%
- Total expected sample size: 190 (95 participants in each group)

CONCLUSIONS

The optimal dialysis regimen for incident patients on HD is unknown. It is plausible that the routine practice of 3HD/week regimen in incident patients with RKF may contribute to accelerating its loss and may not represent the optimal approach for initiating dialysis treatment.

Despite growing evidence from observational studies supporting the use of incremental HD, conclusive RCTs evaluating the benefits and risks of incremental HD are lacking. If the potential benefits of incremental HD will be confirmed by our REAL LIFE study, starting dialysis with a 3HD/week regimen will subject patients to unnecessarily long and/or more frequent treatments at higher costs (24).

Our study is particularly important because it aims to evaluate the adequacy of incremental HD starting with once a week session in patients with a relatively low Kru (around 3.0 ml/min/1.73 m^2) and with a moderately low protein intake, at variance with other studies that start incremental HD with a twice a week regimen with the same Kru values indicated above (10, 12, 13), or at variance with another study that starts dialysis with once a week session, but with a very strict low-protein diet and in selected patients (25).

It is also important to note that the adequacy of the proposed once a week HD treatment is based on the so-called VTM of equivalent renal urea clearance (EKR) of urea (16). Therefore, the REAL LIFE study could also be able to validate the VTM.

Project Coordinator
Carlo Basile

Principal Investigators
Francesco G Casino
Carlo Basile
Loreto Gesualdo

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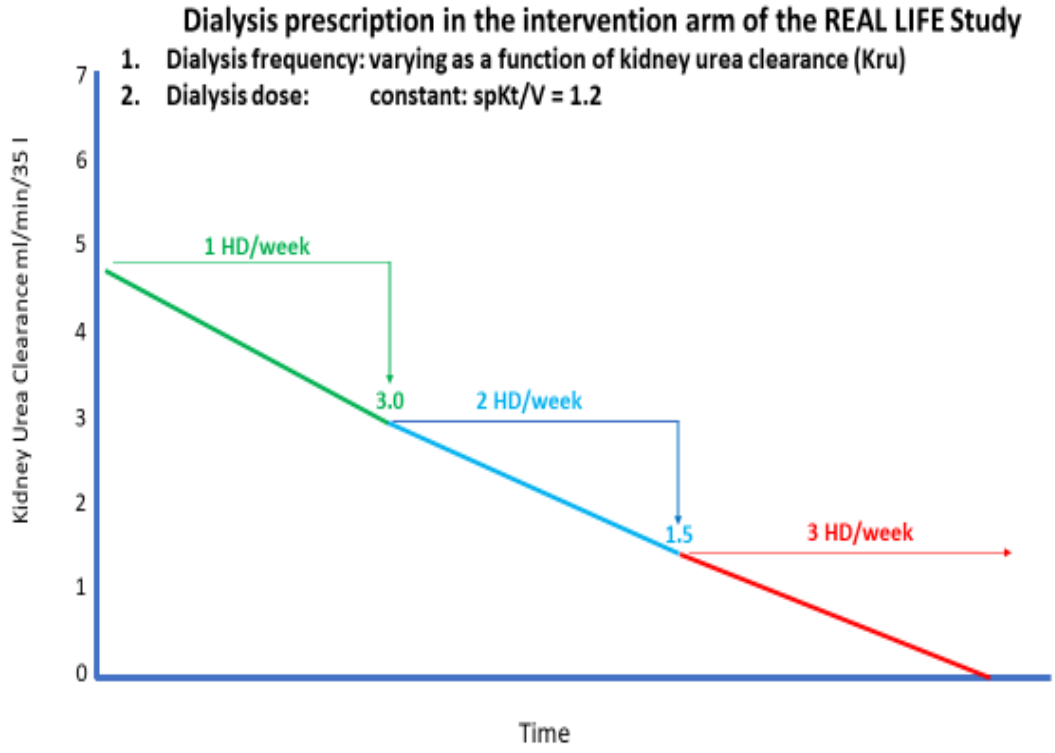
Figure 1


Dialysis prescription in the intervention arm of the REAL LIFE Study
1. Dialysis frequency: varying as a function of kidney urea clearance (Kru)
2. Dialysis dose: constant: spKt/V = 1.2
Kidney Urea Clearance ml/min/35 l
7
6
5
4
3
2
1
0
1 HD/week
3.0
2 HD/week
1.5
3 HD/week
Time