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Ideas, Conjectures and Refutations

Defining end-stage renal disease in clinical trials: a framework for adjudication

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ABSTRACT

Unlike definition of stroke and myocardial infarction, there is no uniformly agreed upon definition to adjudicate end-stage renal disease (ESRD). ESRD remains the most unambiguous and clinically relevant end point for clinical trialists, regulators, payers and patients with chronic kidney disease. The prescription of dialysis to patients with advanced chronic kidney disease is subjective and great variations exist among physicians and countries. Given the difficulties in diagnosing ESRD, the presence of estimated GFR <15 mL/min/1.7 $3m^2$ itself has been suggested as an end point. However, this definition is still a surrogate since many patients may live years without being symptomatic or needing dialysis. The purpose of this report is to describe a framework to define when the kidney function ends and when ESRD can be adjudicated. Discussed in this report are (i) the importance of diagnosing symptomatic uremia or advanced asymptomatic uremia thus establishing the need for dialysis; (ii) establishing the chronicity of dialysis so as to distinguish it from acute dialysis; (iii) establishing ESRD when dialysis is unavailable, refused or considered futile and (iv) the adjudication process. Several challenges and ambiguities that emerge in clinical trials and their possible solutions are provided. The criteria proposed herein may help to standardize the definition of ESRD and reduce the variability in adjudicating the most important renal end point in clinical trials of chronic kidney disease.

Keywords: adjudication, clinical trials, death, end point, end-stage renal disease

INTRODUCTION

Worldwide, end-stage renal disease (ESRD) has produced a burden that is both social and economic. However, until now, the number of large successful clinical trials that have shown to delay the onset of ESRD has been three [1–3]. And all three conducted among patients with diabetic nephropathy have found that blockade of the renin angiotensin system mitigates the progression to ESRD [1–3]. Although each of these three trials used a composite end point of doubling of serum creatinine, ESRD or death to seek regulatory approval for delaying kidney failure, the only firm and unambiguous end point that represents irreversible kidney failure is ESRD; this end point was met in only two of the three trials [1, 2]. ESRD is a clinically meaningful end point that affects both well-being and lifespan. However, compared with end points such as stroke, myocardial infarction or death, ESRD is an end point that is more subjective in nature. Unlike, the clear guidelines that exist which define myocardial infarction [4] and stroke [5], at this time there are no universally accepted definitions of ESRD. The lack of a universal definition poses a challenge in developing effective therapies.

Drawing from personal experience in adjudicating ESRD in multicenter, randomized trials, the purpose of this report is to describe a framework to define when the kidney function ends and when ESRD can be adjudicated.

THE NEED FOR DEFINING ESRD

Although several trials have defined ESRD, the definitions are limited. The published definitions from prior trials each of which had progression of CKD to ESRD as a primary or secondary end point are as follows:

(i) The reduction of end points in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study defined ESRD as the need for long-term dialysis or transplantation [2].

(ii) Irbesartan diabetic nephropathy trial (IDNT) defined ESRD as the initiation of dialysis, renal transplantation

or a serum creatinine concentration of at least 6.0 mg/dL (530 μmol/L) [3].

(iii) Study of Heart and Renal Protection (SHARP) trial defined it as the need for long-term dialysis or transplantation [6].

(iv) The Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) defined ESRD as decrement in the subject's kidney function to a level at which either dialysis or kidney transplantation is required to sustain life meeting one of the following: (i) underwent >30 days of dialysis therapy, (ii) received a kidney transplant, (iii) a physician recommended renal replacement therapy (RRT) (dialysis and/or transplant) and the subject refused therapy or (iv) began dialysis and expired <30 days later [7].

A FRAMEWORK FOR DEFINING ESRD

To define ESRD, two criteria must be fulfilled: establishing the presence of uremia and the need for RRT which is chronic. Although there are many controversies on what may constitute ESRD (Table 1), discussed further below is what constitutes uremia that may be either symptomatic or asymptomatic and what may be reasonably and practically defined as chronic RRT.

Symptomatic uremia

As CKD progresses to ESRD, patients frequently present with characteristic signs and symptoms, due to worsening uremia. Once these signs and symptoms develop, RRT whether it be renal transplantation, peritoneal dialysis or hemodialysis is necessary to reverse the symptoms of uremia and prolong life. The challenge is that in the vast majority of the patients, the signs and symptoms of uremia are nonspecific and variable. The interpretation of these signs and symptoms being attributable to uremia, at least in the early stages, is subjective. For example, signs and symptoms of nausea, vomiting, deterioration in nutritional status, recent significant weight loss and fatigue could be due to diabetic gastroparesis or could be attributed to uremia. Similarly, neurologic dysfunction (e.g. neuropathy, encephalopathy, psychiatric disturbances, seizures), bleeding diathesis, pleuritis, pericarditis, intractable sleep disturbance, anhedonia or diuretic refractory volume overload (manifested as shortness of breath, effort intolerance, severe edema) may be attributed to uremia or other causes.

Some patients may be asymptomatic, nonetheless may have indications for initiation of chronic dialysis such as due to hypertension poorly controlled with multiple drugs or hyperkalemia unresponsive to reasonable medical management.

It is important to note that no diagnostic criteria exist to establish the presence of symptomatic uremia. Often, but not always, worsening of symptoms together with deterioration of kidney function is used to establish that uremia is symptomatic. Ultimately, it is the experienced physician who can best establish the presence of the uremic syndrome at the bedside. Thus, documented reasoning of the physician, who makes the diagnosis of the uremic syndrome, can provide invaluable support when ascertaining the presence of symptomatic uremia. This is particularly important in multicenter trials where despite access to raw data it may be difficult to establish the presence of symptomatic uremia for the adjudicators.

Table 1. Examples of uncertainties in the diagnosis of ESRD

1	Is it rational to distinguish symptomatic from asymptomatic uremia?
2	In an asymptomatic patient what should be the threshold of eGFR that may be considered acceptable to initiate dialysis in the absence of symptoms?
3	For how many days should the patient receive dialysis before it is considered chronic?
4	Should the patient with CKD who requires dialysis for AKI who then dies be counted as ESRD?
5	Should an eGFR of <15 mL/min/1.73 m^2 be used as a hard end point in clinical trials?
6	If the dialysis is deemed futile, should the date on which such a discussion occurred or when death occurred be taken as the date of event?

Advanced asymptomatic uremia

The above definitions may not diagnose all ESRD. Some patients may remain asymptomatic and without hyperkalemia or poorly controlled hypertension despite a very low eGFR. Although it is possible that patients with extremely low eGFR may be asymptomatic, it is to be noted that many require dialysis initiation. For example, the initiating dialysis early and late study tested the effect of wait-and-watch approach (delayed start) prior to initiating dialysis compared with an early start [8]. The intent was to initiate RRT early when estimated GFR was between 10 and 14 mL/min and to test this strategy against a late-start when GFR was between 5 and 7 mL/min for hard outcomes on follow-up. In the usual group, only 18.6% of the patients started dialysis when eGFR was <10 mL/min/1.73 m^2. On the other hand, in the late-start group, 75.9% of the patients were dialyzed at estimated GFR of >7 mL/min/1.73 m^2. This provides the rationale for a threshold of <8 mL/min/1.73 m^2 to be a permissible estimated GFR at which an experienced clinician may weigh the benefits of initiating dialysis to outweigh its risks. Accordingly, when the physician believes that the benefit of RRT exceeds the risks of waiting for symptoms to develop when eGFR has dropped to <8 mL/min/1.73 m^2 and patient undergoes chronic dialysis such cases can be adjudicated as ESRD.

Considerations for establishing chronicity

Patients may have a transient acute decline in kidney function that may recover with a few dialysis treatments. Thus, to diagnose ESRD unambiguously, chronicity needs to be established. The duration of RRT can be useful to establish chronicity. Whether 30, 60 or 90 days is sufficient to establish ESRD can be debated. Shortening the duration requirement will trade specificity for sensitivity. Prolonging the duration to say 90 days may cause needless delay in time to adjudicating ESRD events. Accordingly, to provide a compromise, I suggest that the patient should undergo regular course of dialysis over at least 30 days. Furthermore, there should be absence of evidence that the patient recovered from dialysis over 3 months.

When a regular course of dialysis has not been documented for 30 days or more, questions may arise regarding whether the event was chronic in nature. If a patient is unable to continue for 30 or more days after initiating chronic dialysis due to receiving a renal transplant or the patient dying, the event can be classified as ESRD, and the date when dialysis was initiated considered the date of the ESRD event. The cause of death (cardiovascular or not) should also be adjudicated.

Establishing ESRD when dialysis is not delivered

Patients may refuse RRT because they believe that their current quality of life, with their expected lifespan, outweighs the quality and quantity of life following RRT. It may also occur when the clinician withholds RRT and the patient consents because both the clinician and the patient consider RRT futile and they believe that the patient's current quality of life, with their expected lifespan, outweighs the quality and quantity of life following RRT. In some instances, the clinician may withhold RRT without the patients consent. Occasionally, RRT is planned and the specific start date is documented but the patient dies prior to starting dialysis. Rarely, RRT may not be available or be affordable by the patient. In such instances, the date they need for dialysis is established and it is considered the date of ESRD. If such a patient dies, the cause of death would be separately adjudicated.

Acute kidney injury in CKD precipitating the need for dialysis

The progression to ESRD may not be an inexorable chronic decline in kidney function. An acute illness (e.g. pneumonia) or surgery may trigger an acute deterioration in kidney function warranting dialysis. The physician may decide in the context of advanced kidney failure and severity of injury that there is little possibility that the patient will recover substantial kidney function to sustain life without RRT. If RRT is initiated and the patient dies within 30 days of initiation of dialysis, such a patient should be counted as ESRD. The context is important; adjudication committees can sometimes need to weigh in if the patient had ESRD or not. For example, if the patient has septic shock and AKI requiring dialysis and dies within a few days of initiating RRT, should this be considered ESRD? If the patient had little or no evidence of CKD, the committee may decide it is not ESRD. On the other hand, if Stage 4 CKD was present, superimposed AKI needing dialysis may be considered ESRD. This is because few people with advanced CKD and AKI will recover completely to come off dialysis. After an AKI event which leads to dialysis, it is difficult to predict renal recovery had the patient survived. AKI events accelerate the progression to ESRD and had the patient survived, it is possible that the length of time to dialysis would have been shortened. Thus, in a trial where all participants have CKD, it is my view that AKI events leading to dialysis and death while being on dialysis be counted as an ESRD event.

Renal transplantation

Renal transplantation may occur at any time due to the availability of a transplant and the health of the patient. Therefore, the date of transplantation even if the patient does not survive the surgical procedure should be considered confirmation of the onset of ESRD.

Identification of events

Large clinical trials often have physicians other than nephrologists who participate as investigators. For example, internists and endocrinologists may participate in a diabetic nephropathy trial. Often the principal investigator is not the physician treating the patient who may be hospitalized. Thus, the detection of ESRD events is not trivial. Education of the investigator regarding the need for detecting symptomatic uremia, the concept of eGFR and RRT is therefore important. Especially important is the need to identify the need for RRT in the hospital. To err on the side of safety, any dialysis treatment should trigger the need for committee review. The ESRD events are ideally identified by the investigators and reported as such. However, ESRD events may be identified by sponsors by reviewing the adverse event forms and discharge summaries, and by standardized medical queries of the database. Especially important may be reports by the pharmacovigilance group of the sponsoring company.

The adjudication process

In a blinded way, and without the knowledge of drug group assignment, at least two experienced nephrologists should review and vote on a case with ESRD. In instances when the two nephrologists disagree, a third nephrologist, without knowledge of the first two votes, should evaluate the case as well. If all three members disagree (say on the date of event) a panel meeting with help of a chairperson can resolve the differences.

DISCUSSION

Progressive symptoms of uremia together with decline in kidney function often trigger the onset of dialysis and thus herald the onset of ESRD. The syndrome of symptomatic uremia is difficult to define but easy to recognize at the bedside. No single sign or symptom or even a cluster of symptoms listed can firmly establish the diagnosis of uremia. Thus, a narrative by the treating physician outlining the rationale why the patient has symptomatic uremia and needs initiation of RRT may be invaluable in adjudicating the presence of symptomatic uremia. By requiring the need for dialysis for at least 30 days, not known to subsequently recover (for at least 90 days), the question of reversibility of decline in kidney function is mitigated and the diagnosis of ESRD is established. However, as noted above, there are several situations where ESRD may be diagnosed without the patient having symptomatic uremia or needing chronic dialysis. Examples of such situations are extremely low GFR, renal transplantation, or death shortly after initiating dialysis. In the latter case, dialysis is required to be initiated for the intent of treating chronic uremia; those who had no prior CKD may not qualify for the diagnosis of ESRD.

Should Stage 5 CKD be called ESRD?

Given the difficulties in diagnosing ESRD, one may propose that the presence of estimated GFR <15 mL/min/1.73 m^2 itself

should constitute an end point. Despite being simple to adjudicate, there are several reasons against this definition. First, many patients remain asymptomatic of uremia for long periods of time despite having this arbitrarily low estimated GFR; thus, this end point is not clinically meaningful to these patients. Second, drugs (e.g. cimetidine) may alter serum creatinine concentration independent of GFR, and influence this end point. Third, the economic impact of such an end point instead of provision of dialysis is difficult to measure; the economic impact would be important for payers. Thus, this end point remains a surrogate of ESRD.

Should provision of RRT alone serve as an end point?

Since the provision of dialysis itself is such a clinically meaningful end point, the requirement to establish the need for RRT may be questioned. Despite the subjective nature of decision to initiate dialysis, the provision of dialysis is a landmark event and changes the quality of life of the patient and costs to the society. In this context, the provision of long-term dialysis itself may be considered as an appropriate end point. Past experience suggests that substantial differences exist among physicians and countries on what is considered appropriate symptoms for establishing uremia. Waiting to initiate dialysis before symptoms of uremia are manifest is associated with a survival that is similar to an earlier start of dialysis. In a clinical trial, to ensure that the ESRD outcomes in the treated and control groups were directionally similar regardless of reason why dialysis was initiated due to symptomatic and asymptomatic uremia would be important to the scientific community, the regulators and the payers.

Challenges in establishing chronicity

Establishing chronicity may seem trivial but can pose to be challenging in clinical trials. Once the trial participant initiates dialysis, he or she may stop study medication and have less interaction with the trial site. Many trials follow patients for at least 30 days after stopping the study drug. Since study drug is often stopped with the onset of dialysis, establishing whether the patient is on regular RRT and remains on dialysis 30 days after initiation is less burdensome. Communication such as through a phone call or a letter with the study participant establishing that the kidney function has not recovered at 90 days is important because it will further establish chronicity.

Acute kidney injury and dialysis

All dialysis is not ESRD. For example, acute kidney injury may result in sudden, large and potentially reversible declines in renal function. The treating physician may initiate dialysis to treat drug overdose. Dialysis may be performed to treat volume overload, severe hyperkalemia or severe acidosis with an intention to relieve that acute complication of sudden decline in kidney function. This may be the case when the baseline level of kidney function is excellent and decline in kidney function is large. The physician may reasonably believe that such a decline in kidney function is reversible. If the intention of the dialyzing physician is to provide relief to the acute manifestation of uremia and not provide chronic RRT, then the date of initiation of RRT cannot be considered the date of onset of ESRD. However, if such a patient dies of cardiovascular causes he would contribute to the composite end point on the date of cardiovascular death. On the other hand, if at baseline the level of kidney function is severely impaired and the acute injury is severe, the physician may reasonably believe that dialysis may be needed for the long term. The intention of the physician is to initiate chronic dialysis. If the patient does not recover sufficient renal function and remains on chronic dialysis for at least 30 days then chronicity is established and the date of initiation of dialysis is considered to be the date of ESRD. This is despite dialysis being initiated for an acute decline in kidney function.

In conclusion, a framework for definition for adjudicating ESRD events primarily for use in clinical trials for regulatory purposes is provided. Careful adjudication of this end point is superior to accepting a surrogate definition of ESRD as eGFR <15 mL/min/1.73 m^2. Several challenges to the diagnosis of ESRD such as establishing the presence of symptomatic uremia, variations in the practice of initiating dialysis, and ascertaining ESRD in the absence of dialysis are noted. However, the criteria proposed herein may help to standardize the definition of ESRD and reduce the variability in adjudicating the most important renal end point which is of great relevance to patients, their providers, regulators and payers.

CONFLICT OF INTEREST STATEMENT

R.A. chaired the event adjudication committee of the BEACON trial (sponsor Reata). He currently cochairs the event adjudication committees of the CREDENCE trial (sponsor: Johnson and Johnson) chairs the event adjudication committee of the SONAR trial (sponsor: Abbvie) and is a member of the event adjudication committee of the CARMELINA trial (sponsor: Boehringer Ingelheim).

REFERENCES

1. Lewis EJ, Hunsicker LG, Bain RP *et al.* The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med 1993; 329: 1456–1462
2. Brenner BM, Cooper ME, de Zeeuw D *et al.* Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; 345: 861–869
3. Lewis EJ, Hunsicker LG, Clarke WR *et al.* Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001; 345: 851–860
4. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. J Am Coll Cardiol 2007; 50: 2173–2195
5. Sacco RL, Kasner SE, Broderick JP *et al.* An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013; 44: 2064–2089
6. Baigent C, Landray MJ, Reith C *et al.* The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011; 377: 2181–2192
7. Pfeffer MA, Burdmann EA, Chen CY *et al.* A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009; 361: 2019–2032
8. Cooper BA, Branley P, Bulfone L *et al.* A randomized, controlled trial of early versus late initiation of dialysis. N Engl J Med 2010; 363: 609–619

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