Rethinking End Points in Clinical Trials of Renoprotective Medication

Aliza Thompson


CKD is associated with significant morbidity and mortality and there is urgent need for therapies that can improve outcomes in patients with CKD. The development of such therapies will require, among other things, an adequate understanding of key pathways that are common to the myriad causes of CKD as well as those that are unique to specific causes of CKD, compounds that target these pathways, and an infrastructure for efficiently conducting clinical trials to test these therapies. Success in this endeavor will also require careful attention to trial design and, specifically, the primary efficacy variables (or end points) that are used in these trials to provide evidence of effectiveness and establish a benefit that outweighs the risks of the therapy.

To date, clinical trials in diabetic kidney disease have often used a renal composite end point to provide evidence of a product’s efficacy in slowing the loss of renal function and delaying progression to ESRD. Typically, this end point has included an increase in serum creatinine concentration of a prespecified magnitude (typically a doubling of serum creatinine) or, alternatively, an eGFR decline of a prespecified percentage (e.g., 40%); sustained kidney failure (eGFR<15 ml/min per 1.73 m² or serum creatinine above some threshold); and progression to ESRD, defined as receiving chronic dialysis or kidney transplantation (1). This composite end point has also sometimes included “renal death” as a component, a term that, to this day, lacks a standard definition. Although receipt of chronic dialysis and renal transplantation are widely regarded as important clinical outcomes, multiple factors influence when dialysis is initiated and when renal transplantation occurs. In this issue of the Clinical Journal of the American Society of Nephrology, Weldegiorgis et al. explore the time to initiation of chronic dialysis or kidney transplantation as a measure of a treatment’s effect on the filtration capacity of the kidney, and ask whether chronic dialysis is “the right” renal end point to evaluate the renoprotective effects of drugs (2).

To address this issue, the authors compare the time to initiation of RRT (defined as the decision to initiate chronic dialysis [≥4 weeks] or kidney transplantation) with the time to reach a fixed eGFR threshold of 11 ml/min per 1.73 m² in two randomized, controlled trials of angiotensin receptor blockers in patients with type 2 diabetes and nephropathy: the Irbesartan Diabetic Nephropathy Trial (IDNT) and the Reduction of End points in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan trial (3,4). According to the authors, an eGFR threshold of 11 ml/min per 1.73 m² was used for the analysis because it reflects the average threshold that was used in clinical practice to initiate dialysis at the time the trials were conducted.

In the analysis population, which included approximately 3000 subjects with at least three eGFR measurements during follow-up, a difference was observed in the time to initiation of RRT and time to reach the specified eGFR threshold; although the median time to initiation of RRT was 779 days, the median time to reaching an eGFR threshold of 11 was 678 days (P=0.01). Sensitivity analyses using an eGFR threshold of 15 ml/min per 1.73 m², reflecting both the current Kidney Disease Improving Global Outcomes guidelines’ definition of stage 5 disease as well as the eGFR threshold commonly used in clinical trials, produced similar results. The authors further note that in IDNT, which included reaching a serum creatinine threshold of 6 mg/dl as a component of the composite end point, the point estimate of the hazard ratio of the treatment effect was more favorable for this component than for the RRT component (0.60 and 0.78, respectively), with only the former reaching nominal statistical significance (95% confidence interval, 0.58 to 1.07; P=0.12), versus 95% confidence interval, 0.58 to 1.07; P=0.01, despite a greater number of RRT than serum creatinine end point events (5).

So, what of the provocative question that serves as the title of the article: Is chronic dialysis the right hard renal endpoint to evaluate renoprotective drug effects? The authors’ discussion of the findings offers a measured response. The authors conclude that their study shows that the effect of an angiotensin receptor blocker on a filtration-based end point differs from that of an RRT end point and that a combined RRT and eGFR end point may be testing more than the renoprotective effects of a drug. The authors note their findings require validation by others. The authors also make the point that it is possible that some therapies may not affect the decline in renal function, but rather improve “the tolerance of the patient to withstand the sequelae of reduced kidney function,” thereby allowing patients to postpone the start of dialysis. The authors acknowledge that this would be an important benefit, but also

Correspondence: Dr. Aliza Thompson, Center for Drug Evaluation and Research, Food and Drug Administration, White Oak Campus, Building 22, Room 4116, 10903 New Hampshire Avenue, Silver Spring, MD 20993. Email: Aliza.Thompson@fda.hhs.gov

Editorial
emphasize that this is different from a renoprotective benefit. Finally, the authors recommend that future trials systematically collect information on symptoms associated with uremia that drive the decision to initiate dialysis.

The subjective nature of the decision to initiate dialysis has long been recognized and is one of the reasons why the Food and Drug Administration’s Division of Cardiovascular and Renal Products has, with rare exception, encouraged sponsors to include a confirmed eGFR <15 ml/min per 1.73 m² in renal composite end points. The exception has been therapies that cause reversible pharmacodynamic increases in eGFR. Although some have argued that an eGFR <15 ml/min per 1.73 m² should be viewed as a surrogate for reaching dialysis, reaching such a low level of organ function (kidney failure) could also be viewed as a surrogate for the burden of other complications seen in patients who progress to this stage of disease. Admittedly, the threshold is somewhat arbitrary and some have proposed lower thresholds, citing current clinical practice to initiate dialysis at a lower level of eGFR, as well as higher thresholds. Of note, including such a component in a renal composite end point also addresses concerns about access to dialysis in some regions, and helps account for patients who decide not to initiate dialysis (and perhaps makes renal death unnecessary as a component of a renal composite).

The authors emphasize that an RRT end point (or combined RRT end point) may be testing more than the renoprotective effect of the drug; specifically, the end point may be capturing a treatment’s effect on other factors associated with the decision to start dialysis. Although this may be true, another potential interpretation of the authors’ analyses is that the RRT end point is a “noisy” end point because the timing of initiation of dialysis is influenced by factors that a drug would not be expected to affect. This “noise” would make the end point a less sensitive measure of a treatment’s effect. Specifically, a drug would not be expected to affect a number of factors cited by the authors as influencing the timing of initiation of dialysis, such as the lack of dialysis facilities, ability to dialyze during the day or evening rather than during the day only, availability of subsidized transportation, and possibly the patient’s mental state. This point aside, given the impact of dialysis on a patient’s quality of life, I agree with the authors that a therapy that forestalls the need for dialysis by helping to manage the sequelae of kidney failure (even if the therapy does not slow the loss of renal function) also provides an important benefit. However, the design of a trial intended to provide evidence of such a benefit is likely to be quite different from the design of a trial intended to show a treatment effect on the loss of renal function.

In the Materials and Methods section of the paper, Weldegiorgis et al. (1) highlight that all RRT events were adjudicated by an independent adjudication committee using “rigorous definitions.” One issue, however, that has not received sufficient attention is what is gained by adjudicating these or other components of renal composite end points in clinical trials. With perhaps the exception of renal death, do such end points need to be adjudicated? Given the cost of trials and widespread recognition of the need to limit unnecessary costs, it is an important issue for the larger nephrology community to consider. Arguably, laboratory-based components of the end point and whether dialysis reflects chronic dialysis could be determined on the basis of prespecified rules. Alternatively, adjudication could be limited to the small subset of cases that fall into a gray area, for example, for determining whether a subject who dies shortly after initiating dialysis before the definition of chronic dialysis has been met should be counted as having progressed to ESRD. If an adjudication committee is to be used to review this small subset of cases, then the protocol would need to prespecify criteria that would trigger review of a case by the adjudication committee.

In closing, I applaud the authors’ efforts to understand the time to initiation of chronic dialysis or kidney transplantation as a measure of a treatment’s effect on the filtration capacity of the kidney. These and other efforts to identify optimal end points for evaluating the efficacy of therapies for CKD, as well as efforts to standardize the collection and reporting of these data, will be critical for expediting the development of therapies for kidney diseases.

Acknowledgments

This article reflects the views of the author and should not be construed to represent Food and Drug Administration’s views or policies.

Disclosures

None.

References


Published online ahead of print. Publication date available at www.cjasn.org.

See related article, “Is Chronic Dialysis the Right Hard Renal End Point To Evaluate Renoprotective Drug Effects?,” on pages 1595–1600.