Exploring Novel Endpoints for Clinical Trials in Kidney Disease: Challenges and Opportunities

Prabir Roy-Chaudhury

1Division of Nephrology, Banner University Medical Center-Tucson, Banner-University Medical Center South, Tucson, Arizona, USA; 2Southern Arizona VA Health Care System, Tucson, Arizona, USA; and 3Division of Nephrology, University of Arizona Health Sciences, Tucson, Arizona, USA.

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Currently, 1 in 9 people have kidney disease. Perhaps more importantly, the presence of chronic kidney disease (CKD), especially advanced CKD and end-stage kidney disease, confers a significant comorbidity and mortality burden on these patients (with a subsequent reduction in quality of life). At the same time, we spend large amounts of money ($34 billion for dialysis, $50 billion for end-stage kidney disease, and between $80 and $100 billion for kidney disease as a whole) in order to achieve these extremely poor survival and quality-of-life indices.

Despite these sobering statistics, very few new kidney-specific therapies have been approved during the past 2 decades. Not surprisingly, the number of randomized clinical trials in nephrology (a prerequisite in most cases for novel safe and effective therapies) continues to languish at the bottom of the pile compared with other subspecialties of internal medicine.1

There are several possible reasons for this conundrum whereby such a disease state results in significant morbidity and mortality at a huge cost, but for which there are minimal available therapies.

An important, albeit often overlooked, reason for the lack of innovation, randomized clinical trials, and new therapies in kidney disease is the lack of qualified biomarkers and kidney-specific drug development tools that could serve as either validated or reasonably likely surrogate endpoints in clinical studies. These qualified biomarkers could also be used to enrich patient populations for inclusion in clinical trials. For example, a pivotal clinical trial aiming to test a new therapy to prevent progression of CKD has to use the conventional clinical trial end points of death, such as dialysis and doubling of the serum creatinine level (more recently, a 30%–40% reduction in glomerular filtration rate is beginning to be used). This requirement means that a clinical trial could take 5+ years and hundreds of millions of dollars to conduct. In marked contrast, a new therapy for rheumatoid arthritis could use a primary end point of a change in the 12-week American College of Rheumatology-20 score.2 Thus, the lack of validated kidney-specific surrogate end points leads to longer clinical trials and discourages the pharmaceutical industry from developing products for the diagnosis and treatment of kidney disease.

Two important papers by Perrone et al.3,4 published in the current issue of Kidney International Reports, describe for the first time a body of data that takes important steps toward the development of total kidney volume as (i) a potential future surrogate end point for the prevention of progression of autosomal dominant polycystic kidney disease and (ii) an enrichment tool for novel therapies for autosomal dominant polycystic kidney disease.

In brief, the authors describe the development of a uniform set of data standards that allows them to combine 5 existing databases into a single data set. The single data set is then analyzed to demonstrate that increased total kidney volume does, in fact, identify a group of subjects who have a greater risk of disease progression. More important, perhaps, is the second paper,4 which describes joint modeling data that have resulted in both the US Food and Drug Administration (FDA) and the European Medicines Agency agreeing to the use of total kidney volume as an enrichment tool for identifying subjects whose autosomal dominant polycystic kidney disease is more likely to progress. The inclusion of such high-risk patients in clinical trials for autosomal dominant polycystic kidney disease could demonstrate the benefits of a treatment effect with a smaller number of patients (faster product development).

The above discussion brings up numerous issues that need to be considered with regard to product
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PROS AND CONS OF SURROGATE END POINTS

It is important to emphasize that the process for identification of a biomarker as a surrogate end point is well described and requires biological plausibility, epidemiologic data, and clinical trial outcomes. Of note, the FDA has described an accelerated pathway whereby a biomarker that is “reasonably likely” to predict clinical benefit in a serious or life-threatening condition could be used as a surrogate, with the expectation that post-marketing studies will be performed. With regard to the use of surrogate markers for enrichment, while clearly an important step forward, it should be noted that enrichment could result in a population of subjects who are different from the general population. In addition, although enrichment procedures could identify those subjects at high risk of progression, it could also make it more difficult to recruit patients into clinical trials, the latter balancing out a potential higher event rate.

A WAKE-UP CALL FOR THE KIDNEY COMMUNITY

It is a matter of some concern that the described papers are among the first (with the exception of the National Kidney Foundation Workshop on the use of a 30–40% estimated glomerular filtration rate reduction as a potential end point for CKD progression studies) that address the importance of future surrogate end points and enrichment strategies in the context of developing new therapies for kidney disease. The papers by Perrone et al. need to function as a wake-up call to the kidney community to develop projects and consortia to encourage drug development tools that will accelerate the pace of innovation in this field. Of note, one cannot underestimate the importance of patient advocacy in the push to develop such drug development tools. The Polycystic Kidney Disease Foundation has been at the forefront of this initiative, and one hopes that other kidney groups will participate in future similar initiatives. Finally, creating platforms that involve all the stakeholder groups in this area (health professional organizations, patient groups, industry partners, and federal agencies) could also contribute to the creation of such drug development tools. One example of such a platform is the Kidney Health Initiative, which is a public-private partnership between the FDA and the American Society of Nephrology. The Kidney Health Initiative has identified clinical trial design as a priority area and has initiated numerous projects on clinical trial end points, which could facilitate product development.

THE FDA AS A CATALYST

Finally, recognition needs to be given to the important role that the FDA has played as a catalyst for regulatory science innovation, particularly with regard to developing partnerships with organizations such as the Critical Path Institute and the Kidney Health Initiative that promote both innovation and patient safety.

In summary, the 2 papers by Perrone et al. describe the important first steps in creating a pathway to the treatment of kidney disease that uses surrogate markers as a validated tool to accelerate the pace of drug development. This approach is of critical importance to the field of nephrology, which currently suffers from a paucity of new therapies.

The widespread availability and use of such tools could generate (i) hope for our patients, (ii) excitement for our profession, and (iii) confidence and enthusiasm of our industry partners. As quoted in a recent publication that addresses the challenges and opportunities in this field:

If we fail then we fail our patients who will continue to suffer unnecessarily while observing the cascade of cures for other diseases and wonder why not them and why not now!

DISCLOSURE

PR-C is a consultant or advisory board member of WL Gore, Bard Peripheral Vascular, Medtronic, TVA, Akebia, and Humacyte; a founder and chief scientific officer of Inovasc; and the ASN Co-Chair of the Kidney Health Initiative.

REFERENCES

1. Strippoli GF, Craig JC, Schena FP. The number, quality, and coverage of randomized controlled trials in nephrology. J Am Soc Nephrol. 2004;15:411–419.
2. Taylor PC, Keystone EC, van der Heijde D, et al. Baricitinib versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med. 2017;376:652–662.
3. Perrone RD, Mouksassi M-S, Romero K, et al. Total kidney volume is a prognostic biomarker of renal function decline and progression to end-stage renal disease in patients with autosomal dominant polycystic kidney disease. Kidney Int Rep. 2017;2:442–450.
4. Perrone RD, Mouksassi M-S, Romero K, et al. A drug development tool for trial enrichment in patients with autosomal dominant polycystic kidney disease. Kidney Int Rep. 2017;2:451–460.
5. Levey AS, Inker LA, Matsushita K, et al. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. Am J Kidney Dis. 2014;64:821–835.
6. Linde PG, Archeacon P, Breyer MD, et al. Overcoming barriers in kidney health-forging a platform for innovation. J Am Soc Nephrol. 2016;27:1902–1910.