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Worldwide, diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease (ESKD), and its global incidence and prevalence are both increasing. More than 10 years ago, the Irbesartan Diabetic Nephropathy Trial, the Reduction of Endpoint in NIDDM with the Angiotensin II Antagonist Losartan, and similar trials demonstrated that blockade of the renin-angiotensin-aldosterone system delays DKD progression. Yet patients continue to experience progression to ESKD and to die of it.

The 5-year survival of a dialysis patient with DKD is less than 25 percent—worse than most cancers—yet the number of active clinical trials testing therapeutic agents to slow the progression of DKD to dialysis is less than one-tenth of the number of active trials for breast cancer, prostate cancer, or colon cancer (1). Unfortunately, the results of recent large clinical trials testing novel therapies for DKD have been negative or have been complicated by cardiorenal safety concerns. New treatments are desperately needed to spare this high-risk patient population. In order for DKD trials to enter the mainstream of drug development, key hurdles to facilitating trial feasibility, patient identification, and recruitment must first be overcome.

Endpoints

Historically, global regulatory and payer stakeholders have mandated demonstration of efficacy against “hard” clinical endpoints, such as delaying time to dialysis or death. This approach requires that enrolled study participants be late in the course of disease and have already experienced loss of renal function. Trial sample sizes must also be in the thousands, and have a long follow-up period to account for the fact that such endpoints have event rates that are relatively low.

Highly predictive dynamic biomarkers of efficacy and safety are lacking. With regard to efficacy, proteinuria (specifically albuminuria) is typically used in phase 2 clinical trials as an early marker for hard outcomes such as doubling of serum creatinine, ESKD, or both. Albuminuria does have some prognostic significance in assessing risk (e.g., for ESKD) but has significant liabilities. Key limitations include its substantial intrapatient variability, its nonlinearity in predicting risk, and the fact that substantial cohorts of patients exist who have advanced DKD but are normoalbuminuric. Highly predictive safety biomarkers are also sorely needed to provide early clues to the salutary or harmful effects of novel therapeutic agents. The nephrology community needs to continue developing the evidence to identify precise safety and efficacy biomarkers that are acceptable to the regulatory agency, payers, nephrologists, and ultimately our patients.

Feasibility

Most nephrologists consider patients with DKD to be a “dime a dozen” and are surprised that enrollment in trials is a challenge. But for patients to be suitable for an endpoint trial, a very select subset of patients with DKD with rapid progression must be identified. If a sufficient number of patients do not experience progression over the duration of the trial, the trial will fail. Typically, some loss of renal function reflected by an above-normal serum creatinine level, coupled with proteinuria, is used to select these patients. Identifying an “enriched” patient population at highest risk of progression using a criterion such as urine albumin-to-creatinine ratio (UACR) above 300 significantly narrows the eligible patient pool and thus has an impact on the feasibility of a clinical trial. According to the Kidney Early Evaluation Program (KEEP), fewer than 2 percent of diabetes patients with estimated GFR 60 to 90 mL/min/1.73 m² have macroalbuminuria (UACR >300), and fewer than 10 percent of those with estimated GFR 30 to 60 mL/min/1.73 m² have macroalbuminuria (2). As noted earlier, substantial intrapatient variability is a limiting factor here, too, because study participants on some occasions will qualify by this standard but at other times will not.

Slow patient enrollment makes a trial with a large sample size impractical because of prolonged time and cost. The overall recruitment rates for a DKD trial are approximately 0.25 patients per site per month (p/s/m) which is one-fourth the number of patients enrolled per month for a diabetes trial (at 1 p/s/m) (clinicaltrials.gov). Although the size of clinical trials may be similar for studies of cardiovascular conditions and diabetes, the rate at which patients enroll into DKD trials significantly delays the timelines and increases cost. This reality often stifles drug development in DKD by pharmaceutical companies. In addition, factors such as high screen failure rates (resulting from lack of prescreening or narrow inclusion/exclusion criteria) and high dropout rates have a significant impact on trial feasibility. Aside from the need for pragmatic study designs to avoid patient burden and minimize dropout, investigators need to fully educate patients about trial requirements and study commitments.

The last two issues would be favorably affected by a long-term substantial investment in an international clinical trial “infrastructure,” built initially on a country-by-country basis where significant numbers of clinical trials are and would be performed. In each country this could take many forms, three of which include the following: 1) establishment of a free-standing, independent DKD national clinical trial network (where developers could simply pay fees into the network and benefit from pre-established infrastructure at member “go-to” DKD sites within the network); 2) establishment of a national DKD public database, where clinical outcomes data from all studies could be shared, particularly the standard-of-care comparison arm data; and 3) establishment of a virtual registry of DKD patients. All DKD (not only those seeking research physicians) would be encouraged to go online to register their information, find out about their disease, and obtain information about ongoing trials. This registry could also have an opt in/opt out choice for being contacted about future trials. Although we are aware that some regional centers are creating such infrastructures, a global outreach is needed to facilitate execution of the number of ongoing and upcoming trials in DKD (Figure 1).

Lack of patient awareness

According to 2011 KEEP data, only 23 percent of participants with CKD were aware that they had kidney disease (3). Given the lack of awareness and thus the lack of knowledge about the high morbidity and mortality caused by DKD, motivating patients to participate in trials can be challenging. In other diseases wherein patients’ awareness...
and engagement is high (such as polycystic kidney disease), recruitment into trials can occur quickly. Education needs to come ultimately from nurses, physicians, primary care providers, and nephrologists, but as has been observed in the oncology and cardiology fields, national disease societies, such as the American Heart Association and the American Cancer Society, can play a pivotal role in educating the public about important issues connected with a particular disease. New approaches to engage and educate patients and families affected with DKD, such as trial networks and social media, need to be promoted within the nephrology community in order to enhance enrollment into research trials.

Call to action

Whereas there are many practical aspects and challenges to getting therapies to market for patients with DKD, we believe that there needs to be a call to action within the nephrology community to support the rapid advancement of novel therapies through the approval process and into the hands of doctors who treat patients with DKD. Presently, there is a vicious cycle of slow-performing trials, combined with unengaged or poorly informed patients, combined with the large sample sizes demanded because of a lack of precise endpoints, which negatively feeds back upon itself, which in turn makes DKD trials unattractive, unfeasible, or both for innovative therapeutic developers in the diabetic nephropathy space.

We, the nephrology community, need to break this cycle! Practical aspects with regard to improving clinical trial infrastructure, trial endpoints, patient identification, education of patients, and encouraging patient participation in DKD trials as outlined here are some of the first steps we can take toward answering this call so that new and desperately needed therapies for diabetic nephropathy can be expeditiously delivered to our patients.

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