The Next Treatments of Chronic Kidney Disease: If We Find Them, Can We Test Them?

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Over the last 25 years, the approach to the patient with chronic kidney disease (CKD) has distinctly changed, and that transformation has only accelerated in the recent decade. We have gone from providing only relatively minor adjustments for metabolic derangements and arranging ESRD care to now actively intervening across the whole range of CKD. Many underlying diseases are registered as the causes of ESRD in the annual data report of the United States Renal Data System (1). However, diabetes and hypertension have claimed the increasingly dominant share. Moreover, nephrologists have largely accepted the view that not only these two major categories but also many others, including the varied glomerulonephritides, share common features in their progression to ESRD, features that have yielded to therapeutic intervention. Treatments with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) and to a lesser extent dietary protein restriction have gained acceptance for slowing progression to ESRD in almost all types of CKD. Now physicians can and should do something more than await ESRD. However, these therapies reach too few patients too late, but in most cases they slow without arresting the descent to ESRD. They are an advance but not that of penicillin for pneumococcal disease in 1945.

Two articles in this issue of JASN put forth additional therapies on the basis of studies in two rat models, the remnant kidney and passive Heymann nephritis (2,3). In the former model, pentoxifylline ameliorated injury; in the other, the addition of an ARB to an ACEI lessened damage and the further imposition of a statin provided yet more benefit. These articles identify promising new therapies, but they also provoke important general questions. Which additional new treatments should be chosen for clinical trials? Since any trial will invoke important general questions. Which additional new treatments should be chosen for clinical trials? Since any trial will require that the control group receive ACEI or ARB, how will we test these new ones on that background? Multidrug intervention is the rule in many settings. Some infections such as tuberculosis and HIV require this approach.

Cancer chemotherapy almost always employs several agents sometimes rationally based on documented actions at separate sites in the cell cycle or metabolic pathways of the cancer cell. Similarly, immunosuppression for organ transplantation now routinely entails three drugs. Zoja et al. (3) apply three drugs with escalating success to the model of membranous nephropathy. The first step, a combination of an ACEI and an ARB, has been studied often over the last several years in both animal models and clinical trials with inconsistent results (examples, references 4 and 5). The duration of therapy and, most importantly, the maximization of the baseline ACEI or ARB before addition of the second drug have varied. Too often, those studies have not begun with a maximal dose of the control drug. Thus, the question of whether an ACEI plus an ARB is better than maximal ACEI has not been settled definitively in a long-term trial, and the present study also does not rigorously settle this issue. Recently, further blockade of the aldosterone component of the renin-angiotensin-aldosterone system has received attention, and some clinical reports are promising but preliminary (6–8). Exploration of the nuances of inhibiting this entire system at several sites seems justified if only because of the solid purchase CKD already afforded by ACEI.

Justifications for other potential agents come from many angles. The use of a statin or pentoxifylline with ACEI can be rationalized on their antiinflammatory, antiproliferative, and/or antifibrotic capacities. Even though both drugs began their lives with other more-limited targets, they have gained potential with age, a lesson for us all. However, in the present two reports, the margin gained by these additional treatments was small when compared with ACEI with or without ARB. We may be moving into an era when the gains over ACEI will be modest, at least with the traditional disease models, which are perhaps unrealistically sensitive to ACEI or ARB. Models more faithful to clinical CKD would be welcome.

In answer to the question of which agents should be moved to clinical trials, a logical sequence seems first to test those that show benefits in animals, like the ones in the two articles under discussion (2,3). Then, before large-scale trials, smaller human studies confirming their ability to improve the surrogate marker of proteinuria also appears a reasonable step. Some truly useful combinations might fail this test, but lacking better markers no better approach presents itself. These should be easy steps with established drugs such as a statin or pentoxifylline. Considerably greater barriers would exist for new
compounds. Of course, patent protection will determine the enthusiasm of industry from the outset.

An equally difficult question is how these additional steps, whether new drugs or old, will be proven on the background of ACEI or ARB and on a convincing scale. Ideally they will be so good that an improvement is easy to see. However, the marginal gains may be more difficult to discern in the clinical trial as presently conducted than even in the disease models. The recent trials of ARB in the nephropathy of type 2 diabetes used the now conventional renal progression endpoints: death, ESRD, or halving of GFR (9,10). These trials each required more than 1500 subjects to achieve a result in around three years. Depending on the potency of the additional agent, say a statin, at least twice as many more subjects might be needed for trial over this period with similar subjects and the same outcome events. Even with 1500 participants, these trials are expensive, and ascending costs with yet larger numbers may become prohibitive. Each increment in improvement will become yet more expensive.

One can envision three approaches. First, larger trials of the order of three to five thousand patients could be done to test the next step or two. Recruiting these numbers would be difficult and expensive, but we are experiencing an epidemic of ESRD. Furthermore, current estimates put the number of people with palpable CKD at between 10 and 20 million in the US (11). Thus, nephrologists cannot on the one hand recognize these numbers and on the other claim that there are too few patients for study. To be sure many of these people are not diagnosed, and this deficit represents a barrier to their enrollment in trials to say nothing of depriving them of standard care. Nevertheless, the subjects are there. They represent a large and growing population providing economic incentive for pharmaceutical companies and social and political incentives for the government and nonprofit organizations.

A second approach would be to study only subjects with the higher risks for reaching one of the now-conventional renal endpoints. Growing epidemiologic data make the needed predictions of risk easier (12). With higher event rates, fewer people need be entered into a trial. Of course, the problem with any result would be its validity for the wider population at lower risk. This is not necessarily a fatal criticism. After all, the initial successes ten years ago with ACEI in proteinuric type 1 diabetic nephropathy have spawned a series of studies of ACEI in diseases with lower and lower proteinuria and lower and lower rates of progression (13,14).

Lastly, better markers of progression could supplant the conventional events and enhance trial efficiency. Much enthusiasm exists for proteinuria as such an endpoint or surrogate marker. Indeed, experimental data exist, arguing that proteinuria is directly deleterious on its own and not simply a marker (3). Rightly, the Food and Drug Administration is reluctant to approve drugs on any but the most solid grounds of clinical efficacy. However, further rigorous analyses of available and developing data sets could test the strength of proteinuria abatement as a reliable index of effective therapy. One should note that antihypertensive drugs are approved without the need for demonstrating their efficacy in reducing cardiovascular disease, because the link between high blood pressure and these clinical endpoints is so tight. Perhaps, even more intriguing is the prospect of newer markers. Examples include urinary levels of effector molecules, shed structural components of the nephron, proteomic-derived patterns of urinary composition, or gene expression assayed in urinary components. Such markers should facilitate both large trials and early-phase pilots as well as aiding prognosis and monitoring of therapy in clinical practice.

Pending the next phase in treatment of progressive renal disease, earlier application of current effective, if imperfect, therapy should be pressed. Commenting on the reduction in progression with the an ARB, the authors of one of the recent studies: “Extrapolating from the observed data, we estimate that this reduction corresponds to an average delay of two years in the need for dialysis or transplantation.” (9). Two years is not ideal, but it is still a valuable respite compared with the situation only ten years ago. However, the length of delay to ESRD is dependent on when in the course of CKD the treatment is begun. In that trial, the subjects had an average GFR of about 40 ml/min at the onset. If treatment were begun at a GFR of 70 ml/min, when CKD should be diagnosable in this disease, an average delay of twice as long would result. Thus, the treatment effect would increase substantially just with earlier application. Any new drug will have to be very good to match this. Public and provider awareness may aid in reaching this goal, but here also better markers would promote earlier application of now-standard therapy.

The goal of a monotherapy for CKD as effective as penicillin in 1945 is illusive and perhaps unattainable. Today we can and should do more with what we have, but multidrug approaches will likely be the next improvement. Animal and cellular studies, such as the two reported in this issue, are essential to uncover mechanism, to identify targets, and to test experimental therapies. However, we must devise new approaches for translating their results into established therapy. Otherwise they will remain simply articles in a journal. Better markers of the progression of CKD and its response to therapy will be key tools for that translation.

References
4. Mogensen CE, Neldam S, Tikkanen I, Oren S, Viskoper R, Watts RW, Cooper ME: Randomized controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, mi-

See related articles, “How to fully Protect the Kidney in a Severe Model of Progressive Nephropathy: A Multidrug Approach” (pp. 2898–2908), and “Pentoxifylline Attenuated the Renal Disease Progression in Rats with Remnant Kidney” (pp. 2916–2929).