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See related article, "ACE Inhibition Is Renoprotective among Obese Patients With Proteinuria," on pages 1122–1128.

# Trials and Tribulations of New Agents, Novel Biomarkers, and Retarding Renal Progression

Adeera Levin and Monica C. Beaulieu
Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada

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Inflammation and fibrosis are important processes that mediate progression of kidney disease. Agents that interfere with these processes need to be studied in sufficient detail in humans so we may begin to offer some hope to patients and populations with kidney disease. Diabetic nephropathy remains the most common cause of end-stage renal disease (ESRD) worldwide, and as there are an increasing number of people developing diabetes, in both developed and developing countries, the need for treatments that delay progression or attenuate the course of the disease is ever pressing.

Sharma *et al.*, in the current issues of *JASN*, describe the results of a small, randomized control trial with an oral antifibrotic, anti-inflammatory agent, pirfenidone.[1] This agent has shown promise in animal studies of diabetes or lung fibrosis and small human open-label studies in patients with FSGS and with pulmonary fibrosis.[2–5] This study enrolled 77 patients who were randomly assigned to placebo or two different doses of the pirfenidone. All patients received baseline medication for renin-angiotensin system blockade and the majority were type 2 diabetics. Overall, the study reports only the results of those who actually completed the study ($n = 52$) over a period of one year and notes the relatively high number of dropouts, particularly in the high-dose pirfenidone group. The authors describe statistically different changes in eGFR between low-dose pirfenidone and placebo, and a nonsignificant result when the placebo group was compared with those who received pirfenidone at any dose. The authors acknowledge the shortcomings of the trial but are encouraged by the results and then call for larger studies.

Close review of this paper and accompanying literature, however, reveals that there are a number of unanswered questions that need to be carefully considered before embarking on these larger trials. First, those on the higher dose of pirfenidone had a greater drop in their eGFR in the first 3 mo of the study than either placebo or low dose groups. This is not explained and is counterintuitive. The higher-dose group had substantial side effects, mostly gastrointestinal, so that tolerability of the drug is an important issue for future consideration. There are no changes in the inflammatory or pro-fibrotic serum biomarkers over time, despite their correlation with eGFR at baseline, nor are there any changes in these serum biomarkers as a function of treatment, despite the purported mechanism of action of the agent being the inhibition of TGF$\beta$ production and subsequent matrix accumulation. Furthermore, even in patients with response to the drug, there are no changes in urine levels of the albumin-creatine ratio or TGF$\beta$ over the study duration. The end point in this study is a surrogate: eGFR using standardized creatinine measurements and the four variable MDRD equation

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**Correspondence:** Dr. Adeera Levin, Department of Nephrology, Street Paul Hospital, 1081 Burrard Street Room 6010A Providence Wing, Vancouver, British Columbia V62 1W8 Canada. Phone: 604-682-2344, x62510; Fax: 604-806-8120; Email: alevin@providencehealth.bc.ca

but no direct measurements of GFR. Interestingly, previous studies using this agent that have been conducted over the last decade have not yet led to any larger scale studies.

These specific issues and inconsistencies serve to caution enthusiasm and give reason to ponder the best study design and framework in which to study such agents. Given the increasing interest in biologic pathways and agents that interfere with them, it is important to set up a framework in which new agents that modulate biologic pathways should be evaluated.

In particular, given the heterogeneity of the human disease conditions, it would be prudent to phenotype individuals and randomize them according to more precise descriptors rather than presence or absence of diabetes. Many have acknowledged the biologic variability of kidney disease itself,[6] so that it behoves us to take that into account in the design of clinical studies. More precise biomarker profiles could have been determined at baseline,[7] and stratification by level of pro-fibrotic or pro-inflammatory markers could have been conducted. Second, in studies of renal progression, there is a need to correlate biomarkers with tissue damage, and the use of kidney biopsies should be encouraged,[8] both at baseline and serially if possible. Third, given the importance of the question regarding progression, estimates of kidney function are not acceptable in small trials. Simple, but robust, direct measurements such as iohexal or radionucleotide measurements should be undertaken. And last, evaluation of these new therapies should be undertaken over a minimum duration of 18 to 24 mo.

Imagine that the current study had serial biopsies, direct measurements of GFR instead of estimates, and that patients were all either type 1 or type 2 diabetics, with no differential in baseline kidney function or albumin excretion. If the same results were described, but with biopsy confirmed evidence of regression or lack of progression with respect to tissue fibrosis, staining for TGF$\beta$ or other biomarkers, we may be less concerned about some of the inconsistencies noted in the presented results. Similarly, if the biopsy results were not supportive of any real change in fibrosis or matrix expansion, then the encouraging results of eGFR changes would have been tempered, especially since no changes in any of the inflammatory biomarkers studied were noted.

Clinical studies of human kidney disease with biologic agents that address key pathologic processes are needed. The excitement of preliminary studies with specific agents needs to be tempered with caution, given the absence of consistent and robust data. Furthermore, the probability of any single agent being effective in the context of the complexity of fibrosis[9] and inflammatory pathways[10] is suspect, and needs to be considered in the design of the studies. The addition of new agents to current standard of care, as was done in this study, is important. The conduct of clinical trials is difficult, fraught with numerous regulatory and ethical hurdles. The study by Sharma *et al.* is a reasonable start,[1] but carefully performed physiologic studies are required before embarking on larger-scale clinical trials.

We would propose a consistent framework of study for these new agents that includes harder end points (as in measured GFR and biopsies where feasible), better phenotyping of individuals enrolled in studies, and longer duration of follow-up. The systematic evaluation of a series of different agents could then be conducted using this framework, which would help with comparisons between different molecules and extend our knowledge of pathobiology of disease. In so doing, we would establish a standard that would move the scientific community forward at a significant pace. Until that time, the results of this and other similar trials must be looked upon with cautious optimism but tempered enthusiasm.

## DISCLOSURES

None.

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See related article, "Pirfenidone for Diabetic Nephropathy," on pages 1144–1151.