the basis of the entire dataset; although this is understandable given the limited number of patients available, it does run the risk of overfitting the scheme to fit this particular dataset.

As shown in Figure 4 of the paper by Nickeleit et al.,3 the PVN score at the time of the biopsy was predictive of change in creatinine at 12 months and again, at 24 months, with class 1 doing better than class 2 and class 2 doing better than class 3. As shown in their Figure 5, the authors propose a monitoring schema for patients with renal transplants3 that begins with urinary screening for polyomavirus that is followed, for some patients, with plasma screening for polyomavirus. The finding of BK viral copy numbers >10,000 copies per milliliter, possibly further supported by a positive Haufen test11 (the finding of viral particle aggregates on electron microscopy; Haufen means heap, cluster, or stack in German), would lead to consideration of a kidney biopsy. The rationale for biopsy would be that the diagnosis of PVN would favor reduction in immunsuppressive therapy.

In conclusion, this new grading scheme for PVN, which incorporates clinical and pathology features, shows significant differences in outcomes among the three tertiles in terms of risk for PVN. Although it will be important to validate this approach with new cohorts, it seems to provide useful prognostic information for clinical care and research applications.

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DISCLOSURES

None.

REFERENCES


Editorial Note: From Both Sides Now

Josephine P. Briggs and Thomas H. Hostetter

In this issue of the Journal of the American Society of Nephrology (JASN), the Perspective section features brief essays arguing opposing sides of a tough issue. Baigent and Lennon1 argue that CARDINAL, the ongoing clinical registration trial of bardoxolone for Alport syndrome (NCT03019185) will not adequately address long-term safety. Toto,2 a member of the Data Safety Monitoring Board for the CARDINAL, argues that the trial is safe and well justified.

The argument is in part a debate about competing surrogate markers. In the two previous trials of bardoxolone, BEAM and BEACON, the two intermediate measures used to assess possible benefit went in opposite directions: eGFR increased but so did the albumin-to-creatinine ratio (ACR).3,4 Nephrologists are generally comfortable with albumin excretion as a marker...
surrogate for the health of the glomerulus. The ACR is a noisy measure; it goes up with fever, with running marathons, and with heart failure. Nevertheless, when trended over time, the ACR provides useful information about the development of kidney disease, particularly in the setting of diabetes.

The complexity of interpreting changes in GFR is also familiar to most nephrologists. To paraphrase Joni Mitchell, we have looked at GFR from both sides now, from up and down.

Most of the interventions that have established benefit for CKDs—it is a short list—initially produce a modest fall in GFR. Reflecting this phenomenon, trials of new agents increasingly depend on GFR slope adjusted for the initial decline. Indeed, the initial fall in GFR seen with these agents may reflect hemodynamic changes or reduced hypertrophic drive that is part of the pathway of benefit.

Nevertheless, slowing the inexorable decline in GFR is one of the main goals of treatment of CKD. While a healthy level of glomerular filtration is widely taken as the essence of renal health, can we rely on an increase in GFR as a surrogate measure of benefit, or does short-term gain hasten longer-term decline? And in particular, if GFR goes up but so does albumin excretion, what are the long-term consequences? Baigent and Lennon argue there are long-term risks. Toto, speaking at least in part for the oversight team for CARDINAL, argues that the need for new therapies justifies moving forward, armed with strategies from BEAM and BEACON to minimize risk to patients.

The importance of the debate lies in part in the enormous challenge of mounting definitive trials of new therapies for CKD. Virtually every issue of JASN includes reports of interventions for CKD that look promising in rodent studies, yet very few of these are moving forward into human studies. Surrogate markers are always hazardous. The ideal trial, of course, would study a new intervention for long enough to establish benefits on “hard outcomes”—incidence of ESRD or mortality. But, CKD is a slow-moving adversary. The duration of trials necessary to show benefit, especially of early interventions, is so daunting that we see very little pharmaceutical investment and plenty of caution from federal funders. We urgently need strategies to solve this dilemma. Moving promising interventions from animal studies into people will require strategies built, in part at least, on our available indirect measures of benefit.

A brief comment about disclosure and conflict of interest. The Perspective essay from Baigent and Lennon was an unsolicited submission to JASN. The Editors found the arguments of substantial interest and sent the manuscript out for outside expert review. Our outside reviewers urged publication. The JASN Editors concluded, however, that it would be of value to the JASN readership to also hear the point of view of investigators associated with the trial. The JASN, therefore, issued an invitation to Toto to provide a Perspective that addressed the concerns, disclosing, of course, his relationship with the trial and potential financial conflict.

There are many controversies in nephrology, and we want JASN to be a forum for discourse. We are beginning a Letters to the Editors section, inviting letters that address questions raised by the work that we publish, including the issues raised by Baigent and Lennon and Toto. We welcome Perspective submissions about other questions that matter in nephrology and renal research—including scientific debates and policy arguments. We are also interested in hearing the patient’s voice and about the experience of our trainees.

Therefore, from both sides now, we hope that this debate and future debates about issues of importance to nephrology will continue.

DISCLOSURES

None.

REFERENCES


See related article, “Should We Increase GFR with Bardoxolone in Alport Syndrome,” and “Bardoxolone—the Phoenix?,” on pages 357–359 and 360–361 respectively.