Use of Surrogate Outcomes in Nephrology Research

Joshua Samuels

Clinical trials are large and expensive and could require exceedingly long-term follow-up for subjects to reach clinically meaningful end points. To combat these methodologic issues, researchers sometimes use biomarkers as surrogate end points. A biomarker is an objectively measured characteristic that is indicative of some underlying phenomenon or process, while a surrogate is a biomarker that "takes the place" of a clinically meaningful outcome, usually earlier in the disease process. This paper reviews the history, strengths, and weaknesses of surrogate outcome use in clinical research and then discusses potential surrogate outcomes in nephrology research.

Key Words: Surrogate, Research, Outcomes, Nephrology, Research methods

One of the greatest advances in modern society is increased longevity. People live longer than ever before in history. Much of this increase is attributable to improved living conditions, diet, and medications to treat illnesses. The advances all came on the heels of clinical research. With few exceptions, however, there is no more expensive or time-consuming form of clinical research than prospective human clinical research. Whether conducted as an observational cohort or an interventional clinical trial, prospective clinical research involves not only enrolling patients and measuring exposures but also careful follow-up and assessment for end point outcomes. The length of follow-up and the ability to find differences between exposure groups depends on multiple outcomes occurring. Even with tens of thousands in each exposure arm of a study, one can make no claims about the association between exposure and outcome unless at least one of the groups has subjects reaching clinical outcomes. This need for outcomes to occur in clinical trials tempts researchers to study common outcomes or to use intermediary biomarkers as surrogates.

Investigators would ideally like trial outcomes that are clinically meaningful to patients and the health care system. In nephrology, these important clinical outcomes might include need to initiate dialysis, death from kidney disease, loss of a kidney transplant, or MI or CVA from hypertension. While clinically important, these outcomes usually require large studies with potentially very long-term follow-up. Instead, in order to have groups reach a trial outcome, investigators often use outcomes that are presumed intermediary to the clinically important outcome. These intermediaries are referred to as surrogate outcomes. While often easier to measure or quicker to occur, these outcomes often have no clinical meaning to patients or providers. Doubling of the estimated glomerular filtration rate (GFR) or decrease in proteinuria might be a surrogate outcome, but no patient really cares what their creatinine value is: only whether their kidneys function enough to keep them feeling well, out of the hospital, and off dialysis or transplantation. These surrogates are only effective, therefore, when their presence truly does predict the clinically meaningful outcome is imminent. A surrogate is a biomarker that "takes the place" of a clinically meaningful outcome, usually earlier in the disease process. A biomarker has been defined as "a characteristic that is objectively measured and evaluated as an indication of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[1] Where did the idea for surrogate outcomes even begin?

The concept of a surrogate outcome in research began back in the 1980s. The earliest biomedical use seems to be a 1985 clinical trial text which used changing tumor size as a "surrogate response variable" for cancer mortality.[2] The use was codified into trial design by the FDAMA legislation of 1996 which gave Food and Drug Administration (FDA) authority to approve new therapeutics for serious diseases using trial end points that are "reasonably likely" to predict clinical benefit. This approval, however, requires drug makers to conduct phase 4 studies postmarketing to prove that the treatment also shows benefit in clinically meaningful ways. Because of this "Subpart H" requirement, few therapies have utilized the streamlined process of approval.

The use of surrogate outcomes in clinical research has many potential advantages.[3] The primary advantage is that a smaller sample size can be followed for a much shorter period of time. With shorter follow-up required, studies become cheaper and often feasible to conduct. Surrogate markers are often cheaper to measure than gold-standard clinical outcomes, and these surrogate markers may be less likely to fluctuate due to other competing treatments. They may allow greater measurement precision. That said, care must be taken not to over read meaningful clinical differences based on surrogate findings: even large findings in surrogate makers might only be associated with small findings in clinically meaningful outcomes.[4]

There are several challenges to the use of surrogate outcomes.[5,6] A major pitfall in the use of surrogate biomarkers is a misunderstanding of the pathophysiology

From the Pediatric Nephrology and Hypertension, University of Texas McGovern Medical School at Houston, Houston, TX.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Address correspondence to Joshua Samuels, MD, MPH, Pediatric Nephrology and Hypertension, 6431 Fannin St, MSB 3-121, Houston, TX 77030. E-mail: Joshua.A.Samuels@uth.tmc.edu

1548-5595/$36.00

http://dx.doi.org/10.1053/j.ackd.2016.11.008

of disease progression as it relates to the surrogate and the mechanism of action of the proposed treatment being investigated. Statisticians continually warn that merely finding a correlation between a surrogate marker and a clinically meaningful outcome is not enough to conclude that the surrogate is a valid substitution for the clinical outcome.

While often proposed with the best intentions, biomarkers and surrogate outcomes do not always convey the intended association.[7] One of the best examples of surrogate outcomes misleading researchers (and the public) is that of the cardiac arrhythmia suppression trial.[8] It was known that persons with frequent premature ventricular contractions (PVCs) are at increased risk of sudden death from fatal arrhythmias. Antiarrhythmic medications such as flecainide and procainamide were proven to decrease the rate of PVCs. The use of "decreased PVCs" seemed a perfectly logical surrogate end point for fatal arrhythmias or cardiac death: it was quick and easy to prove and made perfect biologic sense. These drugs were widely prescribed and touted based on the findings from the surrogate outcome. To prove the clinical utility of the treatment, the cardiac arrhythmia suppression trial study randomized patients who had frequent PVCs that were demonstrated to be suppressed by antiarrhythmic medicine to receive either those medicines or a placebo. This time the study used sudden cardiac death at the true clinical outcome. Not surprising, there was a significant difference in the rate of sudden death between the two treatment groups in the study. Surprising to all, it was the treated patients who had the increased mortality. Placebo patients fared much better. While able to successfully suppress PVCs, this surrogate outcome did not predict the actual clinically important outcome of sudden death.

CLINICAL SUMMARY

- Biomarkers are objectively measured characteristics that indicate some underlying phenomenon or process.
- Surrogate endpoints are biomarkers that replace clinically meaningful outcomes in research, usually because they are easier, cheaper, or faster to measure.
- Surrogates must be interpreted with caution, since they are not universally intermediary and inevitable to their clinical outcome.
- Surrogate outcomes can greatly increase the efficiency of clinical trials, but their use must be tempered by their potential to mislead.

Elevated blood pressure (BP) is often used as a surrogate marker for future cardiovascular risk. While patients with hypertension indeed fare worse than those with controlled BP, studies that use target BP, change in BP, or some other measure of BP response as a surrogate outcome for clinically meaningful survival should be viewed with caution. It is true that observational data suggest that even small differences in systolic or diastolic BP might have large effects on overt cardiovascular outcomes such as stroke, MI, or heart failure. Clinical trials such as SHEP suggested that a 12 mm Hg lowering of systolic BP might reduce heart failure by as much as 50%.[9] On the flip side, ALLHAT found a doubling of clinical heart failure in patients treated with doxazosin compared to chlorthalidone despite only a 2–3 mm Hg difference in BP between those groups.[10] Clearly, only using BP response alone as a surrogate might not provide the entire story to predict future cardiac risk.

Lack of clinical trial data to support therapies is a serious problem in nephrology, and we lag behind many of the other medical specialties such as cardiology in altering disease progression. Progression of kidney disease is often slow and is usually asymptomatic. Because of this, clinically meaningful outcomes require overly long trials with exceedingly long follow-up. There are many possible surrogate outcomes of possible use in nephrology.[11,12] Common surrogate outcomes in the medical literature include changes in serum creatinine or changes in proteinuria (as opposed to clinically diagnosed kidney failure manifested by transplantation or need for dialysis). In hypertension research, changes in BP are often used as a surrogate for cardiovascular risk, including risk of myocardial infarction, heart failure, and cerbrovascular accident. In transplantation, the use of changes in donor-specific antibodies, antibody levels, or even findings on kidney biopsy is often substituted for more patient-centered outcomes such as graft survival or loss.

Declining GFR is a major surrogate biomarker used in nephrology trials. It is indisputably in the pathway toward ESRD, though how well early changes in GFR predict later, clinically meaningful outcomes is unclear. The FDA accepts a doubling of creatinine, assumed to represent a halving of GFR, as an acceptable surrogate for the development of kidney failure in CKD trials of disease progression. However, rising creatinine is often a late finding in CKD, and a 2012 workshop of the National Kidney Foundation and FDA discussed whether it might be appropriate to use smaller rises as an alternative to the standard surrogate. Committee analysis of both observational and trial data indicates that even smaller decreases in GFR might be reasonable surrogates.[13] They suggest that a 40% fall in GFR (1.5× rise in creatinine) is as acceptable as a doubling of creatinine as long as follow-up is at least 2-years duration. In some instances, it may even be reasonable to use only a 30% drop in GFR (1.3× rise in creatinine), though one must be careful to ensure that the therapy in question has no short-term effects on filtration which might disrupt the longer term assumptions in using this early surrogate.

Another main surrogate often proposed in nephrology is the measurement of proteinuria. Many kidney diseases present with proteinuria, and the finding is not only a marker of disease severity but is thought to also predict (and even hasten) poor clinical outcomes. While no study has used targeted changes in proteinuria as an intervention, many trials have evaluated changes in proteinuria