Bardoxolone—the Phoenix?

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There is a desperate need to identify treatments for CKD. Drug development for CKD is stifled. With few exceptions, there have been no new treatments for common or rare causes of CKD since irbesartan and losartan were Food and Drug Administration (FDA) approved for treatment of nephropathy in type 2 diabetes 14 years ago. This is not for lack of trying: several large-scale trials in people with diabetic CKD have been conducted over the past 15 years.1–4 However, they failed.

Bardoxolone is anti-inflammatory and tissue protective. Inflammation and fibrosis of all compartments of the kidney are common histopathologic features of many diseases causing CKD, regardless of the primary underlying mechanism. Bardoxolone acts by releasing Nrf2 from KEAP1, allowing it to suppress NF-κB and activate transcription of many anti-inflammatory and antioxidant genes. In recent years, many laboratories have investigated its kidney and metabolic effects. In preclinical models, increases in GFR have been attributed to increases in glomerular surface area by suppression of glomerular inflammation.5 In many, but not all, rodent models of CKD, including diabetes, hypertension, and hyperfiltration, bardoxolone administration mitigates renal injury and inflammation.6–8

There have been clinical trials of bardoxolone in CKD. In 2011, bardoxolone was shown to increase eGFR in patients with type 2 diabetes and stage 3 CKD over a 52-week period.9 At the time, this finding energized the nephrology community and the sponsor, Reata Pharmaceuticals, to design and conduct the Bardoxolone Methyl Evaluation in Patients with CKD and Type 2 Diabetes Mellitus: The Occurrence of Renal Events (BEACON) Trial. The BEACON Trial was a phase 3, randomized, double-blind, placebo-controlled trial designed to determine whether bardoxolone would reduce ESRD and cardiovascular events.2 The BEACON Trial included patients with more advanced CKD, but the excitement among nephrologists was such that trial recruitment rate exceeded projections. Unfortunately, there was an excess of heart failure hospitalizations among those assigned to bardoxolone, and the trial was discontinued. These disappointing results led to a plunge in enthusiasm for this agent, and drug development for CKD waned.

In an attempt to understand the unexpected safety finding, post hoc analysis indicated that heart failure hospitalization occurred within the first month of the trial and suggested that sodium and fluid retention related to bardoxolone suppression of endothelin signaling may have been responsible.10 Risk factors were identified, allowing at-risk patients to be excluded from future trials.11 Given more than a decade of failed clinical trials for preventing progression of CKD, perseverance led to a community of scientists, including nephrologists, pharmaceutical scientists, and the FDA, to reconsider bardoxolone for rare causes of CKD.

Bardoxolone’s resurrection was with the CARDINAL Program. Lessons learned from the BEACON Trial have proven useful for rekindling efforts to pursue bardoxolone as a potential beneficial agent for patients with CKD. The rationale is strong: chronic inflammation is a constant histologic feature of common and rare causes of CKD. The CARDINAL Program is an international, multicenter, phase 2/3 trial to assess the safety, tolerability, and efficacy of bardoxolone methyl in patients with Alport syndrome (AS). AS is progressive with no known treatment, which uniformly leads to ESRD. The CARDINAL Program is designed to determine if bardoxolone will slow progression of kidney disease as assessed by eGFR decline. The rationale for the CARDINAL Program is on the basis of the fact that progression of kidney disease in AS is accompanied by inflammatory changes in the glomeruli, tubules, and interstitium. The hypothesis is that bardoxolone will slow progression of kidney disease by inhibiting inflammation that undoubtedly contributes to progression of AS. The phase 3 portion is randomized, double blind, placebo controlled, and 2 years in duration, and it will enroll up to 180 participants. The primary end point is the change in eGFR at week 48, and the key secondary end point is the change at week 52 after a 4-week withdrawal. Importantly, patients will then restart treatment and be followed for an additional year. Therefore, the study is designed to ensure the acquisition and subsequent promulgation of critical information on both efficacy and safety of bardoxolone in this population.

Why would increasing GFR be associated with slowing progression to ESRD? Progression of kidney disease to end stage in AS is inevitable with current treatment. Theoretically, by increasing GFR and preventing its decline, it is possible to prolong the time to ESRD. Preliminary data presented at the American Society of Nephrology Annual Meeting in 2017 show that administration of bardoxolone to patients with type 2 diabetes and stage 3 and 4 CKD increased measured GFR determined by renal clearance of inulin. Furthermore, increases in inulin clearance were observed both with and without corrections for body weight.

This finding puts to rest the longstanding concern that bardoxolone increases in eGFR owing to alterations in creatinine metabolism.
Two questions arise concerning the potential benefit of an increase in GFR. First, will an increase in GFR result in hyperfiltration, glomerular hypertension, and an acceleration in decline in GFR in the long run? Second, will an increase in urine albumin excretion result in an acceleration in the rate of decline in GFR owing to tubular and interstitial damage from excessive albumin filtration? Regarding hyperfiltration, it is not known whether the increase in GFR is accompanied by glomerular hypertension, because there are no studies of glomerular capillary pressure in animals with CKD administered bardoxolone. Although it is not proven, one possible mechanism by which bardoxolone increases GFR is favorably affecting glomerular surface area.3 Consistent with the mechanism of GFR increase being distinct from increases in glomerular pressure, the drug preserves kidney function and reduces fibrosis in the 5/6 nephrectomy model of hyperfiltration.7 Regarding urine albumin excretion, it has not been proven that increased albumin excretion rate is the cause of tubular injury in humans. Clinical studies with bardoxolone indicate that albumin excretion is correlated with increase in GFR in diabetic CKD, suggesting that this is not a toxic effect of bardoxolone on glomerular structure and function.9

Will an increase in GFR slow progression of CKD? We do not yet have the answer to this question. However, recent post hoc analyses of the BEACON Trial showed that increases in eGFR in patients randomized to bardoxolone were durable for a year and that bardoxolone significantly reduced the risk of reaching a composite renal endpoint.12 Furthermore, patients who were treated for at least 1 year in the BEAM and the BEACON Trial and then withdrawn for 4 weeks showed a significant placebo-corrected increase in eGFR, suggesting that some of the effect persists and that the mechanism and clinical profile of bardoxolone are not likely to be deleterious. The CARDINAL Program, although smaller and involving a rare disease, will help us answer this important question. In addition, this program will provide new longer-term data on the trajectory of eGFR during treatment with bardoxolone. If successful and safe, longer-term use of bardoxolone with careful clinical monitoring will provide the evidence needed to determine its risks and benefits.

Will bardoxolone be proven safe in treatment of rare diseases? Bardoxolone is undergoing testing in nonrenal diseases, including pulmonary hypertension and interstitial lung disease, on the basis of its anti-inflammatory and antifibrotic properties. Although the Orphan Drug Act for regulatory approval is an important tool for encouraging research on rare diseases, there is the potential for both approval of drugs used for a broader range of indications than anticipated in the original approval process and long delays in the recognition of unanticipated harm. These are valid concerns. It is precisely because of these concerns that the CARDINAL Program Data Monitoring Committee meets regularly to carefully monitor all unblinded data for the entire 2-year period of the trial. The Data Monitoring Committee reviews all SAEs in real time, including those reported from nonrenal trials of bardoxolone (e.g., pulmonary hypertension), and it is empowered to recommend termination of the trial for safety or efficacy reasons at any time. The CARDINAL Program is exemplary of the Orphan Drug Act’s intent to allow the pursuit of promising compounds that have the potential to improve human health, pioneering clinical trials for evaluating such compounds that would not exist in the United States. We need new effective and safe drugs to stop the progression of CKD and relieve the suffering of our patients.

DISCLOSURES
R.D.T. is a member of the Data Monitoring Committee for the CARDINAL Study and a paid consultant to Reata Pharmaceuticals.

REFERENCES


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