Risk Factors for Heart Failure in Patients With Type 2 Diabetes Mellitus and Stage 4 Chronic Kidney Disease Treated With Bardoxolone Methyl

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ABSTRACT

Background: A phase 3 randomized clinical trial was designed to test whether bardoxolone methyl, a nuclear factor erythroid-2–related factor 2 (Nrf2) activator, slows progression to end-stage renal disease in patients with stage 4 chronic kidney disease and type 2 diabetes mellitus. The trial was terminated because of an increase in heart failure in the bardoxolone methyl group; many of the events were clinically associated with fluid retention.

Methods and Results: We randomized 2,185 patients with type 2 diabetes mellitus (T2DM) and stage 4 chronic kidney disease (CKD) (estimated glomerular filtration rate 15 to <30 mL min^{-1} 1.73 m^{-2}) to once-daily bardoxolone methyl (20 mg) or placebo. We used classification and regression tree analysis to identify baseline factors predictive of heart failure or fluid overload events. Elevated baseline B-type natriuretic peptide and previous hospitalization for heart failure were identified as predictors of heart failure events; bardoxolone methyl increased the risk of heart failure by 60% in patients with these risk factors. For patients without these baseline characteristics, the risk for heart failure events among bardoxolone methyl– and placebo-treated patients was similar (2%). The same risk factors were also identified as predictors of fluid overload and appeared to be related to other serious adverse events.

Conclusions: Bardoxolone methyl contributed to events related to heart failure and/or fluid overload in a subpopulation of susceptible patients with an increased risk for heart failure at baseline. Careful selection of participants and vigilant monitoring of the study drug will be required in any future trials of bardoxolone methyl to mitigate the risk of heart failure and other serious adverse events. (*J Cardiac Fail 2014;20:953–958*)

Key Words: Bardoxolone methyl, B-type natriuretic peptide, chronic kidney disease, randomized controlled trial.

Bardoxolone methyl and its analogues are oleanolic acid–derived synthetic triterpenoid compounds that potently induce the nuclear factor erythroid-2–related factor 2 (Nrf2)–Keap1 pathway.[1,2] Through interaction with the Nrf2 repressor molecule, Keap1, bardoxolone methyl promotes translocation of Nrf2 to the nucleus, where it binds to antioxidant response elements in the promoter region of its target genes, leading to induction of many antioxidant and cytoprotective enzymes and related proteins.[3,4] Bardoxolone methyl is also a potent inhibitor of the nuclear factor κB inflammatory pathway through both direct (ie, inhibition of IKKβ kinase activity) and indirect (ie, detoxification of reactive oxygen species) mechanisms.[5] Because of this dual mechanism of action, bardoxolone methyl is hypothesized to have therapeutic potential in a variety of disease settings involving oxidative stress and inflammation.

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Preclinical studies have shown that bardoxolone methyl and close analogues have activity in animal models of kidney disease, including amelioration of murine ischemic acute kidney injury,[1] attenuation of renal interstitial inflammation and fibrosis in mice with proteinuria induced by protein overload,[6,7] and protection against fibrosis in a 5/6 nephrectomy model of chronic kidney disease (CKD).[8] Several phase 2 clinical trials have demonstrated that bardoxolone methyl lowers serum creatinine concentration, along with other markers of kidney function (eg, urea nitrogen, uric acid). A phase 2, double-blind, randomized, placebo-controlled trial enrolling patients with type 2 diabetes mellitus (T2DM) and mild to moderate CKD showed these effects to be sustained for 52 weeks.[9] On the basis of these data, we initiated a multinational, randomized, double-blind, placebo-controlled phase 3 outcomes trial in patients with T2DM and stage 4 CKD: Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes: The Occurrence of Renal Events (BEACON).

The BEACON trial was terminated for safety concerns; the primary reason for study termination was an excess in heart failure events, many occurring soon after bardoxolone methyl treatment was started. We conducted a series of post hoc analyses attempting to identify risk factors for heart failure and fluid overload in the BEACON population.

Materials and Methods

Previous publications have described the BEACON trial design, patient demographics, and baseline characteristics.[10−12] Briefly, 2,185 patients with T2DM and stage 4 CKD were randomized 1:1 to once-daily administration of bardoxolone methyl (20 mg) or placebo. The primary efficacy outcome was the time to first event in the composite outcome defined as end-stage renal disease (ESRD; need for chronic dialysis, renal transplantation, or renal death) or cardiovascular death. The study had 3 secondary efficacy outcomes: 1) change in estimated glomerular filtration rate; 2) time-to-first hospitalization for heart failure or death due to heart failure; and 3) time to first event in the composite outcome consisting of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or cardiovascular death. An independent Events Adjudication Committee (EAC), blinded to study treatment assignment, evaluated whether ESRD events, cardiovascular events, strokes, and fatalities met prespecified definitions of primary and secondary end points, as described in the EAC charter.[10] The study (ClinicalTrials.gov identifier NCT01351675) was approved by Institutional Review Boards at participating study sites and was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

We used classification and regression tree (CART) analysis to identify baseline factors predictive of adjudicated hospitalization or death due to heart failure.[13] We selected CART as the method of choice because we did not want to limit the form of interaction terms to those easily defined by logistic or similar regression models. We constructed separate classification trees for patients randomized to the placebo and bardoxolone methyl groups. We evaluated the following baseline characteristics as potential risk factors: urine albumin-to-creatinine ratio, serum creatinine, B-type natriuretic peptide (BNP), age, prescription of inhibitors of the renin-angiotensin-aldosterone system, and previous hospitalization for heart failure. We used a 10-fold cross-validation testing method and Gini splitting rule[13] in tree development and selected the best tree on the basis of minimum cost, regardless of tree size and complexity. We handled missing values of BNP by substituting surrogate splitters.[13]

In reviewing heart failure case reports (eg, hospital admission notes) we observed that evidence of fluid overload often preceded heart failure events. Because some fluid overload events might have progressed to heart failure, we viewed fluid overload events as potential predictors of a patient's being hospitalized for heart failure. Therefore, we also performed CART analyses to explore baseline factors predictive of EAC-adjudicated heart failure events or potential fluid overload events. The latter were not EAC confirmed.

Fluid overload events were not collected on specific case report forms; rather, they were collected on the general adverse event forms. We identified preferred terms potentially related to fluid overload with the use of terms in the standardized MedDRA (v15.1) query (SMQ) of "cardiac failure" and several other key words (detailed in the Appendix).[14] From this list of potential fluid overload events, we determined which preferred terms were most likely to lead to an EAC-confirmed heart failure event by calculating the probability that a patient would report an identified preferred term as a serious adverse event that started after the 1st dose of study drug and that preceded or occurred on the same day as an EAC-confirmed heart failure event (Table 2). To assess the sensitivity and specificity of the preferred terms used to define fluid overload, we generated 4 definitions that included preferred terms with probabilities reported of ≥80%, ≥70%, ≥50%, and ≥30% of being followed by an EAC-confirmed heart failure event. We used the 80% cutoff to maximize specificity and therefore considered patients to have had a fluid overload event if they reported a preferred term in the 80% fluid overload definition as a post-treatment adverse event (serious or nonserious). For example, 5 of the 6 patients (83%) who reported a serious adverse event of acute pulmonary edema also reported an EAC-confirmed heart failure event that started on or after this serious adverse event; however, in our analyses we consider all 9 patients who reported acute pulmonary edema (serious or nonserious) to have had a fluid overload event.

We also used logistic regression as another method for identifying risk factors. This approach led to the same risk factors identified by CART; however, diagnostics showed that the models were poor fits to the data, probably because they were unable to capture the nature of the interaction among the risk factors.

We used the software package CART v7 (Salford Systems, San Diego, California) to perform the analyses and SAS v9.2 to perform logistic regression.

Results

Overview of BEACON Results

An increase in heart failure events was the major finding that led to the termination of BEACON: 96/1,088 patients (8.8%) randomized to bardoxolone methyl versus 55/1,097 patients (5.0%) randomized to placebo, corresponding to a hazard ratio (HR) of 1.83 (95% confidence interval