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Bardoxolone methyl: an anti-oxidative, anti-inflammatory agent for kidney diseases

Kengo Yamawaki
Kyowa-Hakko Kirin Co.,Ltd., Japan

Kidney diseases are highly prevalent worldwide, and significantly reduce the quality of life of patients, creating an urgent need for effective therapeutic modalities. Despite this significant unmet medical need, none of the drugs launched to date have demonstrated promising potential to cure kidney diseases. Currently, the main therapeutic approach for chronic kidney disease (CKD) is to control the blood pressure using renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers). In addition, the beneficial effect of sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin on renal outcomes has also been shown. Although these drugs could be one of the treatment options for CKD, they are still suboptimal approaches and the need to develop new drugs for kidney diseases remains high.

Though the detailed mechanisms of CKD progression are not fully understood, the transition to kidney failure has been suggested to occur via a final common pathway, and oxidative stress and inflammation are thought to be important factors in this pathway. Several clinical trials have been conducted to explore the effects of antioxidants to treat kidney diseases. Despite the multitude of studies showing an association between antioxidants and CKD progression, clear therapeutic effects of antioxidants on kidney diseases are yet to be demonstrated. The underlying problem might be due to the fact that the effects of antioxidants examined to date are insufficient, perhaps because they provide a limited and finite anti-oxidative potential. It is conceivable that the development of new drugs with more potent anti-oxidative effects can significantly advance the treatment of kidney diseases.

Against this background, the Kelch-like ECH-associated protein 1-nuclear factor erythroid 2-related factor 2 (Keap1-Nrf2) system has drawn much attention in recent years for its anti-oxidative and anti-inflammatory properties. The Keap1-Nrf2 system is activated by stimuli such as electrophilic compounds, reactive oxygen species (ROS), and endoplasmic reticulum stress, and controls cellular defense mechanisms against oxidative stress. A key protein in this system is the transcription factor Nrf2. Nrf2 function is negatively regulated by Keap1, which promotes its degradation via the ubiquitin-proteasome system under normal physiological conditions. When the cell is exposed to stimuli such as those mentioned above, modification of specific Keap1 cysteine residues leads to conformational changes in Keap1, which in turn changes its association with Nrf2. Consequently, Nrf2 is released from the proteasome pathway and translocated to the nucleus. Upon translocation to the nucleus, Nrf2 forms a heterodimer with small musculo aponeurotic fibrosarcoma (sMAF) proteins, and activates the transcription of multiple downstream antioxidant gene clusters by binding the gene regulator antioxidant responsive element. A number of reports have described the association between Nrf2 and kidney diseases using genetically modified animals. For example, the Nrf2-KO mutation results in the worsening of lupus-like nephritis, streptozotocin-induced renal disease (including renal function), ferric nitrilotriacetate-induced nephrotoxicity, and ischemia reperfusion (IRI)-induced kidney injury. In contrast, the Keap1-KD mutation is associated with reduced IRI-induced tubular injury and reduced unilateral ureteral obstruction-induced renal fibrosis.

Bardoxolone methyl, a semi-synthetic triterpenoids, is known to be an Nrf2 activator. Similar to the results in genetically modified animals, bardoxolone methyl also leads to reduced kidney injury in

rodent models, indicating the therapeutic potential for treatment of kidney diseases. In a phase 2 clinical trial (BEAM study), 227 patients with diabetic kidney disease (DKD) were enrolled in a 52-week study and marked increases in eGFR were observed and sustained through 52 weeks of administration (Δ eGFR, mean \pm SD [mL/min/1.73m²] =5.8 \pm 1.8 [25 mg], 10.5 \pm 1.8 [75 mg], and 9.3 \pm 1.9 [150 mg]). Although a subsequent phase 3 trial (BEACON study) was prematurely terminated after enrolling 2185 DKD patients due to early-onset fluid overload, a post-hoc analysis revealed the risk factors (a high basal brain natriuretic peptide (BNP) level (>200 pg/mL) and history of hospitalization for heart failure) for this safety concerns and by excluding the patients with those risk factors, another Japanese phase 2 trial (TSUBAKI study, 120 DKD patients) has been successfully completed without any fluid overload-related adverse events including heart failure. Notably, the efficacy of bardoxolone methyl was evaluated by the inulin clearance method in TSUBAKI study (GFR: -0.69 mL/min/1.73m² in the placebo group and +5.95 mL/min/1.73m² in the bardoxolone methyl group after 16 weeks administration), showing that treatment with bardoxolone methyl leads to an improvement in kidney function, which was not associated with creatinine metabolism. Based on those results, now phase 3 clinical trial in DKD (AYAME study) has been started in Japan. Furthermore, phase 2/3 study for Alport syndrome (CARDINAL study) has been conducting globally and another phase 2 study for rare CKD (PHOENIX study for autosomal dominant polycystic kidney disease and others.) has been completed in the US. This presentation summarizes the current situation of bardoxolone methyl and provides its future prospects for treatment of kidney diseases.