DIABETES

Bardoxolone improves kidney function in type 2 diabetes

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Recent clinical studies with bardoxolone methyl have demonstrated improvements in the glomerular filtration rate of diabetic patients with chronic kidney disease (CKD). Although its mechanism of action is uncertain, the persisting effects of bardoxolone methyl in this challenging group of patients are a source of optimism for the management of CKD.

The management of advanced chronic kidney disease (CKD) in patients with type 2 diabetes mellitus is not easy, and currently has few rewards. Although substantial progress has been made towards understanding the pathogenesis of diabetic kidney disease, conventional therapy achieves, at best, only modest slowing in the relentless decline in kidney function. Despite treatment, many of these patients still progress to end-stage kidney disease, making type 2 diabetes mellitus the leading cause of end-stage kidney disease in the Western world.[1] The need for new approaches to manage the exponentially increasing number of patients with type 2 diabetes mellitus and CKD is urgent. One such approach might be to augment the natural cytoprotective responses of the body using small molecule activators such as bardoxolone methyl. In a phase II, double-blind, randomized, placebo-controlled trial recently published in the *New England Journal of Medicine*, bardoxolone methyl increased the estimated glomerular filtration rate (eGFR) by 5–10 ml/min/1.73 m² in patients with type 2 diabetes mellitus and impaired renal function.[2]

Bardoxolone methyl is an oral modulator of Nrf2 (nuclear factor erythroid 2-related factor 2) that, with its negative regulator KEAP1 (Kelch-like ECH-associated protein 1), triggers cytoprotective responses that affect over 300 genes coding for detoxification, antioxidant and anti-inflammatory molecules. Nrf2/KEAP1 is considered one of the central players in cellular defense and a modifier of chronic disease in which its expression and activity are often increased in response to oxidative stress and oxidant-induced injury. For example, the expression of Nrf2 is increased in the diabetic kidney in parallel with raised levels of reactive oxygen species and activation of nuclear factor κB.[3]

Mice that are deficient in Nrf2 have increased sensitivity to a variety of stressors, including hyperglycemia and dyslipidemia. Nrf2-knockout mice develop accelerated renal damage following the induction of diabetes mellitus, which is associated with increased oxidative and nitrosative stress.[3,4] These mice also have higher levels of vascular reactive oxygen species and more endothelial dysfunction when fed a high-fat diet than do wild-type mice.[5] A range of putative Nrf2 activators have been shown to have renoprotective effects in experimental diabetes mellitus (Box 1). For example, sulforaphane, an Nrf2 activator found in *Brassica* species such as broccoli, is able to attenuate vascular damage associated with hyperglycemia.[6] Diallyl sulfides (from garlic, onion and chives), curcumin (from turmeric) and caffeic acid phenethyl ester (found in many plants and bee hives) are also weak activators of Nrf2.

Interest in this pathway has led to the development of a range of selective activators of Nrf2. The first of these agents to undergo formal clinical investigation is bardoxolone methyl, which was originally explored because of its potential anticancer properties. However, improvements in kidney function were also noted in phase I studies,[7] prompting a range of further trials. The largest of these trials with the longest duration has just been published. In this phase II study, Pergola and colleagues randomly assigned 227 adults with CKD to receive placebo or bardoxolone methyl at a dose of 25 mg, 75 mg or 150 mg once daily, in addition to standard therapy that included blockade of the renin–angiotensin system.[2] Within 4 weeks of patients receiving bardoxolone methyl, mean eGFR had increased significantly from baseline in all groups, with the greatest increases of 6–8 ml/min/1.73 m² observed in those taking the 75 mg and 150 mg doses. Importantly, improvements at each dose were sustained during 1 year of active treatment, suggesting that increasing renal function has no adverse effects on failing kidneys. After bardoxolone methyl was withdrawn, renal function returned towards baseline levels. Although the eGFR was still significantly higher than baseline levels 4 weeks after stopping the drug, this increase (0.7–2.5 ml/min/1.73 m²) was only approximately one-quarter of what was observed while patients were receiving bardoxolone methyl. These data indicate that the actions of bardoxolone methyl on eGFR are most likely a reversible modulation of impaired glomerular function. Indeed, the reported actions on eGFR in nondiabetic patients with cancer would support this hypothesis.[7]

> **❝ Within 4 weeks of patients receiving bardoxolone methyl, mean eGFR had increased significantly... ❞**

That an Nrf2 activator would increase GFR is entirely consistent with its role in detoxification pathways through its interaction with the antioxidant response element in the regulatory domains of target genes. Advanced CKD includes both functional and structural components that contribute to the impairment of renal function. Structural components include glomerulosclerosis, tubular atrophy and nephron dropout, which are effectively irreversible, especially within a 4-week window. However, renal function can also be

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Box 1 | Putative activators of Nrf2

- Astaxanthin
- Bardoxolone methyl
- Caffeic acid phenethyl ester
- Celastrol
- Curcumin/dimethyl curcumin
- Diallyl sulfides
- Dimethyl fumarate
- Ebselen
- Ferulic acid
- γ-Tocopherol
- Oltipraz
- Resveratrol
- Sulforaphane
- Tertiary butylhydroquinone

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functionally downregulated by oxidative stress and hypoxia, partly via activation of tubuloglomerular feedback. Heme oxygenases inhibit tubuloglomerular feedback, both directly and indirectly by reducing superoxide.[8] Bardoxolone methyl, which acts to increase the expression of heme oxygenase in renal tubules and reduces superoxide, would also be predicted to inhibit tubuloglomerular feedback, leading to a reduced afferent arteriolar vasoconstriction and subsequently an increase in GFR.

Although the eGFR was improved in the patients included in the study by Pergola *et al.*, whether bardoxolone methyl truly improved kidney function remains to be established. The eGFR relies on serum creatinine levels for its calculation. As bardoxolone methyl also affects muscle (and muscle spasms are its major side effect), it is possible that this agent may also affect creatinine metabolism. Against this hypothesis, serum urea levels were also reduced and 24 h urinary creatinine clearance improved in response to bardoxolone methyl in Pergola *et al.*'s study. Nonetheless, it is surprising that studies of noncreatinine-based markers of GFR, such as cystatin C or isotopic GFR testing, have not been published to allay such concerns.

Although the study by Pergola and co-workers focused on the induction of reversible changes in the eGFR by bardoxolone methyl, direct renoprotective actions are also possible. Certainly, the proportion of patients experiencing a decline in eGFR was lower in patients receiving the three different doses of bardoxolone methyl (20%, 21% and 27%, respectively) than in those receiving placebo (54%).[2] Experimental studies have also suggested that activation of Nrf2 is able to inhibit the promoter activity of transforming growth factor β1,[3] a key growth factor implicated in the development and progression of renal fibrosis.

The BEACON trial will test bardoxolone methyl in a much larger cohort of patients with type 2 diabetes mellitus, with results available in 2013.[9] Other Nrf2 activators are also under active investigation. If similar improvements in kidney function can be reproduced it will represent a major advance on conventional therapy. The much-lauded renoprotective effects of losartan in the RENAAL trial slowed the decline in renal function by less than 1 ml/min/1.73 m[2] per year.[10] Angiotensin-converting-enzyme inhibition or other standard therapies do not come close to the improvement in renal function achieved with bardoxolone methyl.

Although much remains to be established, if these effects are reproducible and sustained it could mean a delay of dialysis for these patients by 2–3 years, at the very least.

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Competing interests
M. C. Thomas and M. E. Cooper declare an association with the following company: Abbott. See the article online for full details of the relationship.

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TRANSPLANTATION

mTOR inhibition in kidney transplant recipients

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The ASCERTAIN study has confirmed previous findings that conversion from calcineurin inhibitors to mammalian target of rapamycin (mTOR) inhibitors does not seem to improve glomerular filtration rate in renal transplant recipients, although it does seem beneficial in patients with better renal function at baseline. Questions remain regarding the role of mTOR inhibitors in kidney transplantation.

The standard immunosuppression regimen in renal transplant recipients has evolved to include the combination of a calcineurin inhibitor (CNI) and an antiproliferative agent, with or without steroids. Use of such a regimen has reduced the risk of graft rejection and has improved short-term allograft survival; however, CNIs carry the burden of renal toxic effects. These toxic effects include both a reversible hemodynamic decrease in renal blood flow and glomerular filtration rate (GFR) as well as an association with interstitial fibrosis. Mammalian target of rapamycin (mTOR) inhibitors exhibit no hemodynamic effects on the kidney nor are they associated with interstitial fibrosis. These agents have therefore been pursued as a means of decreasing the potential nephrotoxicity of CNIs. Numerous well-designed studies have investigated the minimization or elimination of CNIs from immunosuppressive regimens, using the mTOR inhibitors sirolimus or everolimus to replace the CNI. For the most part, these studies have shown rather mixed results and no clear answer to the question of where the use of mTOR inhibitors fits into routine clinical practice.

In general, studies of mTOR inhibition can be split into three classes: use of an mTOR inhibitor with a CNI, *de novo* mTOR inhibition without a CNI, and conversion of a CNI to an mTOR inhibitor. Of these study types, those investigating