Protein Kinase C-β Inhibition: A Promise Not Yet Fulfilled

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Kinases transfer the terminal, "high energy" phosphate group of ATP to a site on a target protein, thereby activating the protein, which may be an enzyme, cell membrane receptor, or ion transport channel. The protein kinase C (PKC) family is a group of such enzymes that require specific activator molecules, including diacylglycerol, whose intracellular concentration increases substantially during hyperglycemia. Studies more than a decade ago identified the association between activation of PKC and increased diacylglycerol levels initiated by hyperglycemia with many vascular abnormalities in retinal, renal, and cardiovascular tissues (1,2). Among the various PKC isoforms, the β isoform activates preferentially in the vasculatures of diabetic animals, including those of the renal glomeruli and retina. Glucose-induced activation of PKC increases production of extracellular matrix and cytokines; enhances contractility, permeability, and vascular cell proliferation; induces the activation of cytosolic phospholipase A2; and inhibits Na^+-K^+-ATPase. Activation of the diacylglycerol-PKC pathway (2) may mediate the cellular damage that is induced by the oxidative stress of hyperglycemia.

Since the aforementioned laboratory observations became known, inhibitors of PKC-β isoforms were evaluated to assess their impact on both retinopathy and nephropathy progression. Reviews of clinical outcome trials by various investigators support the notion that systemic inhibitors of the PKC-β isoform were efficacious when used to slow the development of the microangiopathic complications of diabetic retinopathy (3,4).

It is widely known that the presence and the magnitude of diabetic microvascular disease are associated with the presence of diabetic nephropathy in both type 1 and type 2 diabetes (5–8); given this association, it would follow that PKC-β would have a role in mediating concomitant injury in both the retina and the kidney. Note that in most of these studies, renal injury was assessed by magnitude of albuminuria, usually microalbuminuria rather than change in GFR or other renal functional measure. Unfortunately, microalbuminuria is a cardiovascular risk marker and gives information that is more relevant to vascular injury than to kidney disease progression (9–11). If albuminuria rates continue to increase into the macroalbuminuria range (>200 mg/d), however, then nephropathy is present. This limits the strength of the observations regarding worsening of kidney function independent of a functional marker in studies that link retinopathy with early-stage nephropathy.

The article by Tuttle *et al.* (12) in this issue reviews the renal outcomes in three separate diabetic retinopathy trials that primarily assessed the effects of PKC-β inhibition on retinopathy progression. The study participants in these trials had early stage 2 nephropathy (*i.e.*, baseline estimated GFR of 86.8 ± 27.6 ml/min per 1.73 m^2), and the follow-up period was approximately 3 yr. The authors' analysis noted that the frequency of serum creatinine doubling was 6.0%, with progression to higher stages of nephropathy being 3.5%; kidney outcome rates, however, did not differ by treatment assignment. Moreover, the rates of decline in GFR were approximately 3 to 4 ml/min per yr, which is typical for patients who are treated to this level of BP control. From these observations, the authors concluded that long-term kidney outcomes among the patients who were randomly assigned to ruboxistaurin and had diabetic eye disease were similar to the placebo groups.

Although these conclusions are valid, it is difficult to derive any more than a hypothesis from these data for a number of reasons. First, the changes in estimated GFR were not the primary end point. Second, an average of 25% of the patients dropped out of these trials, a very high dropout rate as compared with other kidney outcome trials of similar duration. Last, although the change in albuminuria is in keeping with a prospective study that used this agent in patients with more advanced nephropathy, 33% of albumin:creatinine data were missing (13). Therefore, the authors' observations from these data confirm previous reports that ruboxistaurin is safe (14) and does not worsen kidney function and reduces albuminuria. The reduction in albuminuria may also have major benefits on cardiovascular risk given the mechanism of drug action on the vasculature (9). This also should be the focus of future investigations. In short, use of agents that inhibit PKC-β activity may confer some modest benefits in the vasculature of the eye and the kidney. These benefits have not translated into meaningful outcome differences, but one reason for this may be the intervention at a very early time in progression of nephropathy. Alternatively, this intervention may not offer a significant benefit beyond maximal inhibition of the renin- angiotensin-aldosterone system and BP and glucose control. All of these issues

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should be addressed in a large, meaningfully powered outcome trial.

Disclosures

None.

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See the related article, "Kidney Outcomes in Long-Term Studies of Ruboxistaurin for Diabetic Eye Disease", on pages 631–636.