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Editorial

Sulodexide for Diabetic Nephropathy: Another One Bites the Dust

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In this issue of the *American Journal of Kidney Diseases*, Lewis et al,[1] on behalf of the highly accomplished Collaborative Study Group, report the findings of an industry-funded randomized controlled trial investigating the use of sulodexide for kidney protection in patients with type 2 diabetes and microalbuminuria. In brief, this multicentered trial recruited patients with type 2 diabetes and urine albumin-creatinine ratios (ACRs) of 35-200 mg/g in males and 45-200 mg/g in females along with a serum creatinine level <1.5 mg/dL. They randomly assigned 1,056 eligible patients to sulodexide therapy or matching placebo and studied the effect on ACR during 26 weeks of therapy and 8 weeks after cessation of the treatment. Regardless of how the investigators looked for differing effects on ACR, the study intervention had no discernible impact on it, with similar proportions of patients in the active-treatment and placebo-control groups achieving a >50% decrease in ACR from baseline, similar numbers achieving normalization of ACR, and distributions of changes in ACR during the study period that were virtually identical between groups.

The investigators' rationale for conducting this study was that sulodexide potentially could interfere with the abnormal biochemistry of the glomerular capillary wall in patients with diabetic nephropathy, particularly with respect to heparan sulfate content. Despite encouraging results from small pilot studies cited by the investigators, they conclude from this larger study that sulodexide does not decrease urine albumin excretion in patients with type 2 diabetic nephropathy and microalbuminuria. The implication is that sulodexide does not have a role in the management of diabetic nephropathy and is not likely to slow the progression of this dreadful complication of diabetes.

This study raises a number of interesting issues that make it an important publication above and beyond the points raised in the investigators' conclusions. First and foremost, this is a negative (or neutral) study that refutes earlier suggestions from smaller less rigorous studies that sulodexide may be efficacious in diabetic nephropathy. Randomized controlled trials, when carried out with methodologic rigor and adequate statistical power, support or refute positive findings of less rigorous trials or those with quasi-experimental design. One need only recall the lessons learned from studies of erythropoiesis-stimulating agents in the chronic kidney disease population to see the importance of and desperate need for appropriately designed and controlled studies.[2] A well-conducted positive trial can provide irrefutable evidence for the benefit of an intervention, serving to change medical practice and improve public health. A well-conducted negative trial can serve to prevent investigators and patients from wasting time and money on ineffective therapies and possibly provide additional insights into the biology of disease, steering future endeavors in more fruitful directions. At the extreme, such trials may uncover previously unrecognized harms of therapies for which the benefits are uncertain. Sadly, enlightened as we are about the need for excellent quality studies, be they positive or negative, evidence still exists for publication bias that favors the dissemination of positive results and tends to suppress that of negative results.[3]

What are some of the features of this negative trial that merit its publication? The investigators went to great lengths to pick an appropriate sample size that would allow them an adequate chance to discern a statistically and clinically important difference in albuminuria while recognizing the significant intrasubject variability in this measurement and avoiding type II error (incorrectly accepting the null hypothesis of no treatment effect). Furthermore, sample size calculation was based on a power of 90%, meaning the chance of committing a type II error would be <10%. A remarkable 93.4% of participants completed this large placebo-controlled study with valid baseline and 26-week follow-up results and an exceptional rate of adherence. Important cointerventions that could influence the outcome were rigorously controlled, such as the use of maximal doses of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for at least 120 days, and equivalent control of blood pressure. All other important covariates and interventions were well balanced by virtue of randomization, sample size, and blinding. Many of the threats to a clinical trial that tend to bias toward the null hypothesis, such as high numbers of dropouts or crossovers, were avoided, with early termination limited to ~5% in both the treatment and placebo groups.

Another factor to consider in a negative trial is whether the study population has a reasonable chance to benefit from a truly effective intervention due to

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dose chosen, duration of therapy, or severity of disease. In the Lewis et al[1] study, dose selection was based on the best available evidence from earlier trials. Participants were eligible based on the presence of microalbuminuria, rather than overt or macroalbuminuria. In an earlier study of patients with type 2 diabetes with microalbuminuria, blockade of the renin-angiotensin system with the angiotensin receptor blocker irbesartan led to significant differences in albumin excretion that were apparent at the first 3-month follow-up visit, in a much smaller study than the present trial.[4] Thus, it would seem that the population studied in the present trial should have had ample opportunity to respond to the intervention if it was truly effective. Furthermore, when the investigators limited the analysis to the subgroup of 330 patients with a greater degree of albuminuria (ACR >125 mg/g), 20.3% assigned to sulodexide versus 25.8% assigned to placebo achieved a successful decrease in albumin excretion ($P = 0.3$). In the end, presentation of the study results using multiple analytical approaches leaves little doubt that sulodexide at 200 mg daily has no clinically discernable or meaningful effect on albuminuria in this population.

An additional important issue relevant to this trial is the utility of surrogate outcomes. For many years, a change in albuminuria generally has been believed to be a suitable surrogate for important kidney disease progression and an independent predictor of adverse cardiovascular events. Previous work from the Collaborative Study Group in type 1 and type 2 diabetic nephropathy convincingly showed that improvement in urinary protein excretion was associated with slowing of kidney disease progression in patients treated with blockade of the renin-angiotensin system with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, respectively.[5,6] In the latter study, the Irbesartan Diabetic Nephropathy Trial, the investigators showed that patients in the irbesartan group had an unadjusted relative risk of reaching the primary composite end point of doubling of baseline serum creatinine level, end-stage renal disease, and all-cause mortality that was 20% lower ($P = 0.02$) than those receiving placebo and a similar 23% lower risk than in the amlodipine group ($P = 0.006$).[6] The unadjusted relative risk of end-stage renal disease was 23% lower in the irbesartan group than the amlodipine or placebo group ($P = 0.07$). The irbesartan group had a 33% decrease in daily protein excretion compared with 6% in the amlodipine group and 10% in the placebo group. However, several recent studies, including ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) and the ROADMAP (Randomized Olmesartan and Diabetes MicroAlbuminuria Prevention) study, have shown favorable effects on albuminuria, but detrimental effects on kidney failure and cardiovascular outcomes, respectively,[7,8] and the recently published BEAM (Bardoxolone in Chronic Kidney Disease) study showed favorable effects on kidney function while albuminuria actually increased.[9]

What does this mean for sulodexide? We are all familiar with the folly of relying heavily on positive changes in surrogate outcomes when the real outcomes of interest turn out to be unaffected or, worse yet, affected detrimentally. However, less attention has been placed on the converse situation in which surrogate outcomes are unaffected or "worsened" by an intervention, but the same intervention turns out to have important benefits on the clinical outcome. Studies of clinically beneficial treatments that have a negative impact on surrogate outcomes may fail for a number of reasons. For example, the intervention may affect the true clinical outcome through pathways different from that of the surrogate end point, or the intervention may have direct positive effects on the true clinical outcome that counter the negative effects on the surrogate. If the hypothesis is that sulodexide should interrupt the pathophysiologic process leading to worsening diabetic nephropathy through its influence on albuminuria, this trial does not provide us with even a shred of optimism. However, if sulodexide has any positive role in the progression of diabetic nephropathy beyond the simple surrogate of albuminuria, we must rely on other surrogates, such as changes in serum creatinine, cystatin C, or estimated (or measured) glomerular filtration rate (GFR) values, all of which have their own limitations. Even the "hard outcome" of end-stage renal disease can be problematic because initiation of dialysis therapy is highly dependent on subjective signs and symptoms of uremia, volume overload, and clinical judgment. Until the nephrology community finds a reproducible, minimally invasive, and reliable biomarker that can predict with a high degree of accuracy the outcomes we deem to be clinically important, we must continue to rely on albuminuria and changes in GFR as our signposts, imperfect and at times contradictory as they may be. Without the slightest indication of a favorable change in either albuminuria or serum creatinine level in the present trial, it seems likely that sulodexide as a treatment strategy for diabetic kidney disease will be relegated to the ash heap of history. What a shame it will be if our signposts are ultimately proved to have pointed us in the wrong direction.

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REFERENCES

1. Lewis EJ, Lewis JB, Greene T, et al. Sulodexide for kidney protection in type 2 diabetes patients with microalbuminuria: a randomized controlled trial. *Am J Kidney Dis*. 2011;58(5):729-736.

2. Singh AK. The controversy surrounding hemoglobin and erythropoiesis-stimulating agents: what should we do now? *Am J Kidney Dis*. 2008;52(6)(suppl):S5-S13.

3. Song F, Parekh S, Hooper L, et al. Dissemination and publication of research findings: an updated review of related biases. *Health Technol Assess*. 2010;14(8):iii, ix-xi, 1-193.

4. Parving HH, Lehnert H, Brochner-Mortensen J, et al. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*. 2001;345(12):870-878.

5. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. the Collaborative Study Group. *N Engl J Med*. 1993;329(20):1456-1462.

6. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345(12):851-860.

7. Mann JF, Schmieder RE, McQueen M, et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET Study): A multicentre, randomised, double-blind, controlled trial. *Lancet*. 2008;372(9638):547-553.

8. Haller H, Ito S, Izzo JL Jr, et al. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. *N Engl J Med*. 2011;364(10):907-917.

9. Pergola PE, Raskin P, Toto RD, et al. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. *N Engl J Med*. 2011;365(4):327-336.