
Response:
The hypothesis that sulfonylurea agents may limit neurological injury through blockade of the SUR1 receptor, expressed under ischemic conditions, is both novel and promising. It is clearly disappointing that the largest clinical study to date to examine this hypothesis, in the robustly validated Virtual International Stroke Trial Archive (VISTA) registry of patients with acute stroke, identified no association between clinical outcome and sulfonylurea treatment.1

Foremost among the concerns raised by Simard and colleagues is the potential for misclassification regarding treatment. We analyzed a subset of VISTA in which complete information existed on concomitant medications, including start and end dates of administration, derived from trials with comprehensive data including annotated case report forms available for confirmation. These trials were subjected to rigorous monitoring and source data verification to meet worldwide regulatory standards. These trials were subjected to rigorous monitoring and source data verification to meet worldwide regulatory standards.

We identified patients on sulfonylureas at the time of acute stroke. Given the long half-life of most sulfonylureas, the treated patients likely had therapeutic levels at stroke onset and during the relevant time period described in preclinical work.2,3 Pre-stroke use thus offers the possibility of prophylactic neuroprotection, avoiding the paradox of delivering drug to an area with impaired blood supply. Unfortunately, no signal of clinical benefit was observed with prior use. However, SUR1 is upregulated after ischemia and may require prolonged exposure. Subjects who continued sulfonylureas were quite similar to those who discontinued them with respect to major stroke prognostic indicators (ie, in each group, median baseline National Institutes of Health Stroke Scale score was 11 and mean age was 70 years). The point estimates favored continued sulfonylurea use, but the result did not achieve significance.

The issue of possible effect modification by stroke subtype is intriguing, because preclinical studies suggest that gray matter is more amenable to neuroprotection than white matter. Unfortunately, assessment of subtype in the hyperacute setting is notoriously unreliable as is such assessment retrospectively. Nevertheless, data were not available on subtypes in our data set and we cannot exclude a subtype-specific effect.

The issue of safety remains unresolved. Although treatment was not associated with worse outcomes in our study, the risk of hypoglycemia was not examined. Clearly sulfonylureas may predispose to potentially harmful hypoglycemia in diabetic and nondiabetic patients alike.

Potential confounding is of course a limitation inherent to all nonrandomized analyses. However, unlike the prior small retrospective studies that reported beneficial outcomes with sulfonylureas,4 the risks of error due to chance or bias are substantially less in VISTA because it provided a meticulously characterized prospective cohort and a much more powerful analysis. Consequently, the lack of an association in our study represents an ominous signal.

Certainly only a randomized clinical trial can provide a definitive answer as to whether sulfonylureas are beneficial. The more pertinent question is whether the sulfonylurea hypothesis has yet been sufficiently evaluated to justify progression to a clinical trial. It is essential that before investing valuable resources and asking our patients to participate that the available data fully optimize the chances of success. Issues of dose (in relation to hypoglycemia), timing and duration of therapy, and potentially [un]suitable stroke subgroups remain to be defined in human subjects.

Our findings from VISTA do not preclude a clinical trial in the future. However, they should be considered alongside existing clinical and preclinical data, particularly in guiding further investigation before launching such a trial. Furthermore, because patients without diabetes are not treated with sulfonylureas in practice, we cannot make presumptions about their safety or efficacy in that population.

Disclosures

None.

Peter Higgins, MD
University of Glasgow
Glasgow, Scotland

Christopher G. Favilla, BA
Michael T. Mullen, MD
University of Pennsylvania
Philadelphia, PA

Myzoon Ali, PhD
University of Glasgow
Glasgow, Scotland; and
NMAHP Research Unit
Glasgow Caledonian University
Glasgow, Scotland

Scott E. Kasner, MD
University of Pennsylvania
Philadelphia, PA

On behalf of the VISTA Collaboration

Response to Letter by Simard et al Regarding Article, "Sulfonylurea Use Before Stroke Does Not Influence Outcome"

Peter Higgins, Christopher G. Favilla, Michael T. Mullen, Myzoon Ali and Scott E. Kasner

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