Response to Letter Regarding Article, “Relevance of Blood–Brain Barrier Disruption After Endovascular Treatment of Ischemic Stroke: Dual-Energy Computed Tomographic Study”

We thank Drs Bosche and Macdonald1 for their thoughtful comments on our article.2

We fully agree that a new therapeutic approach using a combination of rapid reperfusion and neuroprotective/vasculoprotective therapies would be of added value for further improving clinical outcome in comparison with rapid reperfusion alone. Indeed, several clinical trials of patients treated with mechanical thrombectomy have recently shown that this therapy is superior to best medical treatment in selected patients with proximal arterial occlusions but also highlighted that despite a high recanalization rate, less than half of the patients allocated to endovascular therapy showed a good functional outcome at follow-up. Poor outcome despite complete recanalization has been related to first penumbra recruitment before recanalization and to reperfusion injury. Therefore, the potential benefits of this combined approach may be multifaceted, including the possibility of freezing the ischemic penumbra while reperfusion is achieved, or to reduce the harmful consequences of reperfusion injury after recanalization.

The therapeutic paradigm of combining reperfusion therapies and neuroprotection was recently tested with promising results in the Efficacy Study of Combined Treatment With Uric Acid and rtPA in Acute Ischemic Stroke (URICO-ICTUS) trial.3 The URICO-ICTUS was a randomized clinical trial designed to assess the neuroprotective effect of the antioxidant uric acid in combination with intravenous alteplase in patients with acute ischemic stroke receiving systemic thrombolysis within 4.5 hours of stroke onset. In comparison with placebo, the addition of uric acid to thrombolytic treatment resulted in an absolute increase of 6% on the rate of excellent outcome at 90 days in the whole study population. The protective effect of uric acid was significantly enhanced in important clinical subgroups, including patients with pretreatment hyperglycemia (15% absolute effect), and in women (12% absolute effect). The results of both the acute phase 1 double-blind randomised placebo-controlled trial and the double-blind phase 2b/3 trial showed a good functional outcome at follow-up. Poor outcome despite complete recanalization has been related to first penumbra recruitment before recanalization and to reperfusion injury. Therefore, the potential benefits of this combined approach may be multifaceted, including the possibility of freezing the ischemic penumbra while reperfusion is achieved, or to reduce the harmful consequences of reperfusion injury after recanalization.

Collectively, we join to the call made by Bosche and Macdonald to encourage the stroke community, specially the research funding agencies, to pursue a combined therapeutic approach for acute ischemic stroke including rapid and complete reperfusion and neurovascular protective therapies. The recent emergence of highly positive clinical trials on endovascular reperfusion therapy and the promising results shown by the URICO-ICTUS trial could be merged into a new clinical trial where patients receiving endovascular therapy would be allocated to receive uric acid or placebo. To minimize the economical costs of the trial and facilitate the identification of the best treatment responders, the entry criteria of the study could be restricted to those patients with proximal arterial occlusions and elevated serum glucose at stroke onset. A conservative estimation of the absolute treatment effect of uric acid over placebo expected in this population is not inferior to 11%, and to reject this null hypothesis would require a study sample of <490 study participants. Never the Holy Grail of effective neuroprotection was so close at hand.

Sources of Funding

We thank the support of the Spanish Ministry of Economy and Competitiveness for grant to Dr Amaro (PI13/01268, Plan Nacional R+D+I and cofinanced by ISCIII-Subdirección General de Evaluación and by the Fondo Europeo de Desarrollo Regional).

Disclosures

None.

Arturo Renú, MD
Sergio Amaro, MD, PhD
Ángel Chamorro, MD, PhD
Department of Neuroscience, Hospital Clinic, Comprehensive Stroke Center
University of Barcelona, August Pi i Sunyer Biomedical Research Institute (IDIBAPS)
Barcelona, Spain

Response to Letter Regarding Article, "Relevance of Blood–Brain Barrier Disruption After Endovascular Treatment of Ischemic Stroke: Dual-Energy Computed Tomographic Study"

Arturo Renú, Sergio Amaro and Ángel Chamorro

*Stroke.* 2015;46:e200; originally published online June 25, 2015; doi: 10.1161/STROKEAHA.115.009183

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/46/8/e200

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/