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 fast 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).3,5 In correspondence with these clinical findings, uric acid therapy was also able to reduce infarct growth more effectively than placebo in patients with early recanalization, in women, and in patients with hyperglycemia.6,7 In patients with early recanalization, we think that the reentry of oxygen to the ischemic penumbra boosted redox mechanisms that were minimized with the antioxidant effects of uric acid. It is also likely that a greater availability of glucose during the reentry of oxygen increased the formation of free radicals in the ischemic penumbra, whereas the administration of uric acid allowed a more efficient clearance of free-radicals that limited glucose toxicity.8 At last, it is also arguable that women obtained greater benefits after uric acid replenishment than men because they were in a greater need of antioxidants as the result of their lower constitutional levels of uric acid.9 Overall, these observations supported the key clinical role of oxidative stress after thrombolytic therapy and opened new alternatives to improve the net clinical benefit of reperfusion therapy.

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.

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Disclosures

None.

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