HHS Public Access

Author manuscript

Stroke. Author manuscript; available in PMC 2018 September 01.

Published in final edited form as:

Stroke. 2017 September ; 48(9): e259. doi:10.1161/STROKEAHA.117.018294.

Response by Barreto and Grotta to Letter Regarding Article, "Randomized, multicenter trial of ARTSS-2 (argatroban with recombinant tissue plasminogen activator for acute stroke)"

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In Response

We thank Dr. Shah for his interest and insightful comments on our randomized trial of adjunctive argatroban administered to r-tPA treated stroke patients (ARTSS-2).[1] Compared to r-tPA alone, ARTSS-2 demonstrated safety and improved clinical outcomes in patients that received combination r-tPA and argatroban. In general, we are in complete agreement with Dr. Shah's comments and would like to make the following points.

Dr. Shah correctly points out our hypothesis that adjunctive argatroban enhances recanalization of proximal, large vessel occlusions [LVO]. Although our current study did not show increased recanalization of LVOs, it was underpowered to do so. Previous data suggested an effect of argatroban on increasing recanalization. For example, animal models of embolic stroke found enhanced lysis with r-tPA + argatroban and acute myocardial infarction patients had substantially higher rates of complete reperfusion in argatroban + r-tPA compared to IV-heparin + r-tPA (57% versus 20% p=0.03) with lower rates of major hemorrhage.[2,3] Our pilot study suggested greater 2-hour recanalization rates in argatroban +r-tPA compared to historical r-tPA-alone controls.[4] Lastly, other explanations remain plausible such as clot burden and location as well as the early timing of follow-up imaging.

We agree with Dr. Shah's comment regarding distal vascular patency via thrombin-inhibition. We did not study reperfusion in the microcirculation, which also may be the location of some of argatroban's benefit. Even in light of these considerations and the possibility of argatroban's benefit on reperfusion, we agree with Dr. Shah that the drug may also have a neuroprotective effect as referenced in his letter. Therefore, argatroban's inhibition of thrombin's neurotoxic effects definitely warrants further study.

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To that end, we have proposed a large randomized trial of argatroban + r-tPA embedded in the MOST trial (Multi-arm Optimization of Stroke Thrombolysis). If funded, this study, which will have a wider scope by not being limited only to patients with LVO, will not address mechanism, but should detect a beneficial clinical effect from whatever method argatroban adds to r-tPA.

Acknowledgments

Disclosures

Dr. Barreto reports grants from NINDS and other from DHFSR to UTHSC, during the conduct of the study. Dr. Grotta reports grants from NINDS, other from DHFSRF, during the conduct of the study.

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