Editorial

Arteriovenous malformations

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Years ago, my late colleague Ladislau Steiner expressed disappointment to me about the lack of substantial improvement in radiosurgical obliteration of arteriovenous malformations (AVMs) during the more than 4 decades after his seminal work.2,5,7 Obliteration, after all, is the ultimate goal for AVM radiosurgery. Although radiosurgery for AVMs seems to have become safer, we have largely failed to improve the obliteration rate or shorten the latency period after radiosurgery.

In the current study by Reddy et al., the authors use a preclinical AVM model to study a novel vascular-targeting strategy for AVM thrombosis.4 Using a lipopolysaccharide (LPS) and soluble tissue factor (sTF) conjugate, they compellingly demonstrate augmentation of stereotactic radiosurgery–induced vessel thrombosis. Thrombosis induced by LPS/sTF and radiosurgery proved durable and fairly specific to vessels within the targeted volume. Moreover, the phenomenon of thrombosis increased for up to 3 months after treatment. Reddy et al. temper their enthusiasm by noting potential safety concerns for nonligand-targeted approaches such as LPS in humans. Ligand-based techniques may obviate some of these risks. We have been exploring the use of MR-guided focused ultrasonography and microbubbles to effectuate favorable changes on microvasculature; others have explored the direct occlusive properties of MR-guided focused ultrasonography.1,3,4 Although much more study of MR-guided focused ultrasonography for AVMs is needed, this technique could have the target specificity of radiosurgery without the latency period.

Ever since the Data Safety and Monitoring Board closed the ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations) trial early, there has been a keen awareness of the need to improve the safety and efficacy of AVM treatment options. Proponents of ARUBA may contend that treatment of a patient with an unruptured AVM is not warranted. A broader discussion about ARUBA and the optimal management of patients with AVM seems best left for another day. Nevertheless, although it remains clear that stereotactic radiosurgery will continue to play an important role in AVM treatment, improvements in the benefit-to-risk profile for stereotactic radiosurgery can and should be made. The current study provides one avenue for augmenting the extent of stereotactic radiosurgery–induced AVM obliteration. I look forward to future research in this field by Reddy and colleagues.

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Disclosure

The author reports no conflict of interest.

References

Response

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The comments by Dr. Sheehan are acknowledged and appreciated. He notes the findings of the ARUBA study, and although we agree that an in-depth analysis is beyond the scope of this discussion, our view is that comparing the results of intervention to the short-term natural history of AVMs is not a valid comparison. Regardless, our work is aimed at developing a new treatment for AVMs that are currently untreatable without unacceptable risks.

The LPS/sTF approach is intended to be a proof-of-concept study. The goal, rather than to enhance the normal biological response to radiosurgery, is to use radiosurgery to alter the AVM endothelium so that it can be targeted with biological therapies delivered into the systemic vasculature. We are currently working on ligand-based treatments, which we expect will be more specific and more effective than the non-ligand LPS/sTF approach.

Dr. Sheehan suggests that MR-guided focused ultrasonography might have a role in AVM treatment. We also have been exploring this technique as an alternative to radiosurgery for altering AVM endothelial characteristics. In this context, focused ultrasonography would work by heating the vessel wall and inducing molecular expression changes that could be targeted in the same way that we proposed with the radiosurgery and vascular-targeting approach. Some concerns with this technique are the ability of the focused ultrasonography to heat the endothelium while there is high blood flow adjacent to the endothelial surface and the possibility that heating thin vessel walls could lead to rupture. However, we agree that the technique has much promise and is worthy of further exploration.

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