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Letter by Gauberti and Vivien Regarding Article, “Amplification of Regulatory T Cells Using a CD28 Superagonist Reduces Brain Damage After Ischemic Stroke in Mice”

To the Editor:

The recent article by Na et al1 shows that amplification of regulatory T-cell (Treg) improves stroke outcome in both permanent and transient mechanical vascular occlusion (TMVO) models in mice. Surprisingly, Schuhmann et al2 published the exact opposite finding 1 month before, ie, amplification of Treg worsens stroke outcome by increasing thromboinflammation. One year after publication of a controversy in Stroke on the role of Treg in acute ischemic stroke, we thought how to explain this persisting discrepancy in preclinical research results? We thought that the basis for all the paradoxical results on Treg has not been correctly identified and can be resumed as follows: thromboinflammation is not a universal response to cerebral ischemia-reperfusion, but, rather, a specific feature of TMVO models.

Treg are double-edged sword in acute ischemic stroke. On the one hand, they protect neurons from inflammation-related death and, on the other, they promote secondary microthrombosis (the final step of the thromboinflammatory reaction). Therefore, in permanent models (eg, without secondary microthrombosis), Treg are protective, as consistently shown by several studies. In transient models, the beneficial or deleterious role of Treg depends on the occurrence of thromboinflammation. Whether the thromboinflammation occurs or not in a TMVO model depends most probably on laboratory-specific methods influencing the severity of the ischemia after filament insertion, such as size of the embolus, occlusion time (30 versus 60 minutes), speed of filament retrieval, persistence of common carotid artery occlusion after filament removal (such as in the study of Schuhmann et al2 but not in the study of Na et al), etc. These apparently small but, however, important differences most likely led to the occurrence of thromboinflammation in the study of Schuhmann et al2 but not in the study of Na et al1. Then, who is right? More precisely, who is clinically relevant? Is there thromboinflammation and secondary microthrombosis after stroke in humans? Both are probably right.

The thromboinflammation concept suggests that after arterial recanalization, an inflammatory reaction takes place in the reperfused brain, ultimately leading to the reocclusion of distal vessels (secondary microthrombosis). Hence, despite recanalization and early cerebral blood flow improvement in TMVO models, the cerebral blood flow worsens in a delayed manner in the affected arterial territory. In fact, in TMVO models with thromboinflammation, 80% of the ischemic lesion growth occurs after recanalization because of secondary microthrombosis. Thus, blockade of this phenomenon ≤3 hours after ischemic onset using different strategies in TMVO models allows to reduce ischemic lesion size by ≈80%. Of note, the same neuroprotective strategies are not efficient in non-TMVO models, such as permanent middle cerebral artery occlusion or in situ thrombin-induced ischemia-reperfusion because there is no secondary microthrombosis.3 In fact, there are many putative neuroprotective drugs that are efficient in TMVO but not in other models, probably because they target the thromboinflammation pathway. Notably, secondary microthrombosis does not occur either after ischemia reperfusion in nonhuman primates.3

In humans, the presence of secondary microthrombosis is not observed in all patients. For instance, when recanalization is complete after fibrinolysis, there is almost no further lesion growth as assessed by longitudinal MRI.4 Moreover, whereas argatroban (a direct thrombin inhibitor blocking secondary microthrombosis) reduces ischemic lesion size by ≈70% in rodent TMVO models, no evidence for efficacy has come from the randomized trial of argatroban ARGIS (Argatroban Anticoagulation in Patients With Acute Ischemic Stroke)-1 and anticoagulation therapies have consistently been found to be ineffective in multiple clinical trials. In fact, unlike what was found in TMVO models, once reperfusion is achieved either spontaneously or pharmacologically, the cerebral blood flow does not secondary worsen in the vast majority of patients with stroke. However, intriguing data are available from patients with stroke who benefit from endovascular reperfusion. Indeed, longitudinal MRI data showed that, in 18% of them, there is a delayed infarction,5 which may correspond to thromboinflammation. Moreover, these patients present transient reversal of the cytotoxic edema after reperfusion, another specific and probably thromboinflammation-related feature of TMVO models.

To conclude, the absence of thromboinflammation in non-TMVO stroke models and, probably, in many patients with stroke should be reassuring for further preclinical development of Treg amplification as a potential therapeutic strategy. Nevertheless, we should be particularly cautious about treatments interfering with the thromboinflammatory reaction in patients benefiting from endovascular reperfusion procedures, especially because their number will probably grow in the next future. Moreover, to our opinion, TMVO models should be used with caution as generic ischemic stroke models. Several alternative models are now available (permanent ischemia, thrombin-induced thromboembolic stroke, autologous clot, ferric-chloride–induced thrombosis, etc) and should be considered. The underlying risk is to develop general therapeutics that target pathophysiological mechanisms that exist in only a subgroup of human strokes.

Disclosures

None.

Maxime Gauberti, PhD
Denis Vivien, PhD
INSERM, INSERM UMR-S U919
Serine Proteases and Pathophysiology of the Neurovascular Unit, GIP Cytceron
University Caen Lower-Normandy
Bd Henri Becquerel, Caen, France


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