Response to Letter Regarding Article, “Blocking of α4 Integrin Does Not Protect From Acute Ischemic Stroke in Mice”

We thank Elkins et al1 for their interest in our study2 and their thoughtful comments.

We fully agree that preclinical stroke models can only mimic certain aspects of this heterogeneous disease and the decision to enter into clinical trial programs should not only depend on the results from animal studies albeit the predictive value of experimental stroke studies is probably better than previously perceived.3

In fact, based on our neutral findings regarding the efficacy of blocking very late antigen-4 (VLA-4) in mouse models of brain ischemia,2 we never claimed to halt or delay the ongoing Phase 2 ACTION trial (NCT01955707) testing natalizumab in patients with ischemic stroke. Instead, we think that modulating the immune system could become an attractive strategy to positively influence stroke outcome,4 and we appreciate the commitment of any pharmaceutical company in the stroke field in a time when industry, because of countless disappointments, has almost completely pulled out of stroke research.

However, we still doubt whether in ischemic stroke the role of T lymphocytes, which are the main target of any anti-VLA-4 strategy, is already adequately understood to justify large-scale clinical trials. Fundamental questions remain unresolved. For instance, we currently cannot even be sure about the net biological effect (detrimental versus beneficial) of T cells or certain T-cell subsets in the ischemic brain4 and whether or not these complex and highly diverse immune cells contribute to infarct growth or tissue regeneration probably depends on the stage of infarction, that is, acute versus chronic. Accordingly, studies on other immunomodulators (FTY720, glatiramer acetate) derived from the multiple sclerosis field likewise produced conflicting results in preclinical stroke5 and blocking the transmigration of neutrophils into the ischemic brain has proven unsuccessful under clinical conditions.

Safety is another key point. Although we concede that the safety profile of natalizumab is well established in multiple sclerosis, it remains unclear whether this can be easily transferred to the situation in ischemic stroke, which triggers substantial immunodepression. None of the existing preclinical studies on VLA-4 blockade in rodent stroke specifically addressed safety aspects, and although the probability of developing progressive multifocal leukoencephalopathy after a single infusion of natalizumab during the acute phase of an ischemic insult is indeed very low, the consequences of anti-VLA-4 strategies for JC virus homeostasis are still incompletely understood. Moreover, it is at least conceivable that natalizumab induces serious infections other than progressive multifocal leukoencephalopathy in patients with stroke, for example, pneumonia, which is known to worsen stroke outcome.

Finally, we only partly agree on the statement that “natalizumab has a well-established (…) pharmacological profile.” Even if the relevance of VLA-4 for immune cell trafficking is beyond doubt, we still have to learn much more about its effects on different immune cell populations under different disease states. For example, recent findings suggest that lymphocyte trafficking into the central nervous system of patients with multiple sclerosis receiving natalizumab can occur by using the alternative adhesion molecules, P-selectin glycoprotein ligand-1 (PSGL-1) and melanoma cell adhesion molecule (MCAM), the latter representing an exclusive pathway for T helper 17 (TH17) cells to migrate over the blood–brain barrier.6

Taken together, any effort to substantially improve current stroke treatment is greatly appreciated. Clinician scientist should team up with partners from the industries to identify the most promising drug targets. Clearly, the immune system represents one of these innovative approaches, and the results from the ACTION trial are eagerly awaited.

Disclosures

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