Letter to the Editor

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Letter by Elkins et al Regarding Article, “Blocking of α4 Integrin Does Not Protect From Acute Ischemic Stroke in Mice”

To the Editor:

We read with interest the article by Langhauser et al1 that reported no benefit of blocking α4 integrin in a mouse model of acute ischemic stroke. The authors identified several reasons that might account for the discrepancies between their results and those of 3 prior studies2–4 that did observe a benefit of blocking α4 integrin in stroke models. The authors and accompanying editorialists then went on to suggest that more animal studies should be performed before human trials of blocking α4 integrin are undertaken. Although we agree with the need to bring greater standardization to preclinical stroke studies, we do not agree that the ongoing phase II biomarker-driven clinical trial to assess the effect of natalizumab on infarct volume in acute ischemic stroke (NCT019555707) should be halted or delayed pending further studies in stroke models.

There are multiple lines of experimental evidence that point to a role for lymphocytes in promoting secondary injury after acute stroke, as Langhauser et al1 acknowledge: “…there is little doubt that certain immune cell subsets are critically involved in secondary infarct expansion.” In fact, the study of Langhauser et al1 did show that blocking α4 integrin significantly reduced infiltration of lymphocytes and reduced upregulation of adhesion molecules in the mouse stroke model. Although there is clearly much to learn about this process and its potential impact on stroke outcome in humans, it is unlikely that preclinical stroke models will be able to provide all the answers. Natalizumab cannot be used in rodent models, and furthermore, there are key differences in α4 integrin expression between rodents and humans1 that cast substantial doubt on the ability of such models to accurately recapitulate the immunologic effects that natalizumab will have in human stroke. Natalizumab has a well-established clinical and pharmacological profile and has demonstrated potent and rapid efficacy in reducing central nervous system inflammation in its approved indication for multiple sclerosis. Its most significant risk, progressive multifocal leukoencephalopathy, has been well studied and is limited to long-term use of natalizumab. The ongoing clinical trial of natalizumab in acute ischemic stroke is a small, single-dose, proof-of-concept trial using MRI measures as a marker of efficacy that is the first stroke trial to test an approved medication with demonstrated ability to block lymphocyte transmigration into the brain in the setting of neurological disease. Ultimately, whether natalizumab can improve outcomes in patients with stroke is a question that will require a clinical trial to resolve. The stroke community will most likely need a combination of preclinical and clinical studies to understand the relevance of posts ischemic inflammation to stroke outcomes as well as the therapeutic potential of immune-targeted therapies. Although animal models have taught us key lessons about mechanisms of injury in stroke, their track record for predicting therapeutic success in clinical trials is far from perfect. In this instance, rather than delay a clinical trial of a therapy with established efficacy in other neurological diseases so that related compounds can be reevaluated in animal models, both clinical and preclinical studies should be used in concert to advance stroke therapy.

Disclosures

Dr Elkins is a full-time employee of Biogen Idec, which is the sponsor of the ACTION trial (Effect of Natalizumab on Infarct Volume in Acute Ischemic Stroke). Dr Elkind has received consulting fees from Biogen Idec related to the design of clinical trials involving natalizumab and stroke. Drs Elkind and Johnston are members of the advisory committee for the ACTION trial.

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