Natalizumab in acute ischemic stroke (ACTION II)
A randomized, placebo-controlled trial

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Study objective
This study tested the hypothesis that natalizumab improves functional outcomes in patients with acute ischemic stroke (AIS).

Classification of evidence
Class I.

What is known and what this paper adds
Natalizumab is a humanized monoclonal antibody targeting alpha-4 integrin within VLA-4. Preclinical research has supported blocking VLA-4 as a strategy to reduce infarct size and improve functional outcomes after stroke, and a small trial suggested improvement on some clinical outcomes. This larger study did not find evidence that natalizumab improved functional outcomes.

Participants and setting
This international, multicenter, double-blinded, phase 2b trial enrolled 277 adults with supratentorial AIS (64% male; mean (SD) age 66 (10) years, median NIHSS score 9 (IQR 6–14), 63% treated with tPA) with NIHSS scores 5–23 or 5–15 if treatment was initiated ≤9 hours or 9 and 24 hours from onset, respectively.

Design, size, and duration
Patients were randomized 1:1:1 to one intravenous infusion of placebo (n = 94) or natalizumab at 300-mg (n = 91) or 600-mg (n = 92) doses. Randomization was stratified for clinical and demographic variables. All efficacy analyses were performed for the modified intent-to-treat (MITT) population (i.e., all patients who were randomized and received the entire infusion of study treatment; n = 267) and safety outcomes for all patients. Generalized estimating equation (GEE) models with the logit link function were used to estimate the odds ratio (OR) and 95% confidence interval (CI) for overall improvement across the modified Rankin Scale (mRS) and Barthel Index (BI).

Primary outcome measures
The primary outcome was a composite measure of excellent outcome (defined as mRS score ≤1 and BI score ≥95) at day 90 assessed in all patients receiving a full dose.

Main results and the role of chance
Natalizumab-treated patients were less likely than placebo-treated patients to achieve excellent outcomes (OR = 0.60; 95% CI, 0.39–0.93). There was no effect modification by time to treatment or use of thrombolysis/thrombectomy.

Harms
For natalizumab 300 mg, 600 mg, or placebo, there were no differences in incidence of adverse events (90.0%, 92.1%, and 92.3%, respectively), serious adverse events (25.6%, 32.6%, and 20.9%, respectively), or deaths (6.7%, 4.5%, and 5.5%, respectively). Adverse events in this study were consistent the natalizumab’s established safety profile.

Bias, confounding, and other reasons for caution
This Phase 2b trial had a relatively small sample size.

Study funding/potential competing interests
This study was funded by Biogen. Some authors report additional competing interests. Go to Neurology.org/N for full disclosures.

Table
Associations between natalizumab treatment and the primary composite endpoint and its individual components at 90 days

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Odds ratio (95% confidence interval) in natalizumab groups vs placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global composite excellent outcome (primary outcome)</td>
<td>0.60 (0.39–0.93)</td>
</tr>
<tr>
<td>Modified Rankin Scale score ≤1</td>
<td>0.60 (0.34–1.06)</td>
</tr>
<tr>
<td>Barthel Index score ≥95</td>
<td>0.55 (0.31–0.98)</td>
</tr>
</tbody>
</table>

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The corresponding author(s) of the full-length article and the journal editors edited and approved the final version.

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