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NEUROLOGY

COMMENTARY

Natalizumab is an adhesion-molecule inhibitor. The study by Polman and colleagues is a randomized, placebo-controlled trial to test the efficacy of this agent in relapsing multiple sclerosis. Decreased long term disability is reported in the drug-treated group. These findings are promising and further studies are needed to extend their influence into clinical practice.

After many disappointing trials related to neuroprotective agents in ischemic stroke, an encouraging result has been reported by the SAINT-I investigators. NXY-059 is a free-radical scavenger that showed marginal benefit in the treated group. The findings are unlikely to impact clinical practice, although they are promising for ongoing research in this field and are likely to trigger new studies.

The study by Bhatt et al looks at a burning question in secondary stroke prevention, namely, whether addition of clopidogrel to aspirin offers added benefit in reducing recurrent events. It is a large, well-conducted study looking at standard vascular outcomes and end-points. As with the MATCH trial, the authors conclude that the combination offers no advantage over aspirin alone.

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Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, Phillips JT, Lublin FD, Giovannoni G, Wajgt A, Toal M, Lynn F, Panzara MA, Sandrock AW; AFFIRM Investigators.

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A RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF NATALIZUMAB FOR RELAPSING MULTIPLE SCLEROSIS

BACKGROUND: Natalizumab is the first alpha4 integrin antagonist in a new class of selective adhesion-molecule inhibitors. We report the results of a two-year phase 3 trial of natalizumab in patients with relapsing multiple sclerosis. **METHODS:** Of a total of 942 patients, 627 were randomly assigned to receive natalizumab (at a dose of 300 mg) and 315 to receive placebo by intravenous infusion every four weeks for more than two years. The primary end points were the rate of clinical relapse at one year and the rate of sustained progression of disability, as measured by the Expanded Disability Status Scale, at two years. **RESULTS:** Natalizumab reduced the risk of sustained progression of disability by 42 percent over two years (hazard ratio, 0.58; 95 percent confidence interval, 0.43 to 0.77; $P < 0.001$). The cumulative probability of progression (on the basis of Kaplan-Meier analysis) was 17 percent in the natalizumab group and 29 percent in the placebo group. Natalizumab reduced the rate of clinical relapse at one year by 68 percent ($P < 0.001$) and led to an 83 percent reduction in the accumulation of new or enlarging hyperintense lesions, as

detected by T2-weighted magnetic resonance imaging (MRI), over two years (mean numbers of lesions, 1.9 with natalizumab and 11.0 with placebo; $P < 0.001$). There were 92 percent fewer lesions (as detected by gadolinium-enhanced MRI) in the natalizumab group than in the placebo group at both one and two years ($P < 0.001$). The adverse events that were significantly more frequent in the natalizumab group than in the placebo group were fatigue (27 percent vs. 21 percent, $P = 0.048$) and allergic reaction (9 percent vs. 4 percent, $P = 0.012$). Hypersensitivity reactions of any kind occurred in 25 patients receiving natalizumab (4 percent), and serious hypersensitivity reactions occurred in 8 patients (1 percent). **CONCLUSIONS:** Natalizumab reduced the risk of the sustained progression of disability and the rate of clinical relapse in patients with relapsing multiple sclerosis. Adhesion-molecule inhibitors hold promise as an effective treatment for relapsing multiple sclerosis. (ClinicalTrials.gov number, NCT00027300.).

N Engl J Med. 2006 Feb 9;354(6):588-600

Lees KR, Zivin JA, Ashwood T, Davalos A, Davis SM, Diener HC, Grotta J, Lyden P, Shuaib A, Hardemark HG, Wasiewski WW; Stroke-Acute Ischemic NXY Treatment (SAINT I) Trial Investigators

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NXY-059 FOR ACUTE ISCHEMIC STROKE

BACKGROUND: NXY-059 is a free-radical-trapping agent that is neuroprotective in animal models of stroke. We tested whether it would reduce disability in humans after acute ischemic stroke. **METHODS:** We conducted a randomized, double-blind, placebo-controlled trial involving 1722 patients with acute ischemic stroke who were randomly assigned to receive a 72-hour infusion of placebo or intravenous NXY-059 within 6 hours after the onset of the stroke. The primary outcome was disability at 90 days, as measured according to scores on the modified Rankin scale for disability (range, 0 to 5, with 0 indicating no residual symptoms and 5 indicating bedbound, requiring constant care). **RESULTS:** Among the 1699 subjects included in the efficacy analysis, NXY-059 significantly improved the overall distribution of scores on the modified Rankin scale, as compared with placebo ($P=0.038$ by the Cochran-Mantel-Haenszel test). The common odds ratio for improvement across all categories of the scale was 1.20 (95 percent confidence interval, 1.01 to 1.42). Mortality and rates of serious and nonserious adverse events

were each similar in the two groups. NXY-059 did not improve neurologic functioning as measured according to the National Institutes of Health Stroke Scale (NIHSS): the difference between the two groups in the change from baseline scores was 0.1 point (95 percent confidence interval, -1.4 to 1.1; $P=0.86$). Likewise, no improvement was observed according to the Barthel index ($P=0.14$). In a post hoc analysis of patients who also received alteplase, NXY-059 was associated with a lower incidence of any hemorrhagic transformation ($P=0.001$) and symptomatic intracranial hemorrhage ($P=0.036$). **CONCLUSIONS:** The administration of NXY-059 within six hours after the onset of acute ischemic stroke significantly improved the primary outcome (reduced disability at 90 days), but it did not significantly improve other outcome measures, including neurologic functioning as measured by the NIHSS score. Additional research is needed to confirm whether NXY-059 is beneficial in ischemic stroke. (ClinicalTrials.gov number, NCT00119626.)

N Engl J Med. 2006 Apr 20;354(16):1706-17. Epub 2006 Mar 12.

Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, Cacoub P, Cohen EA, Creager MA, Easton JD, Flather MD, Haffner SM, Hamm CW, Hankey GJ, Johnston SC, Mak KH, Mas JL, Montalescot G, Pearson TA, Steg PG, Steinhubl SR, Weber MA, Brennan DM, Fabry-Ribaudo L, Booth J, Topol EJ; CHARISMA Investigators

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CLOPIDOGREL AND ASPIRIN VERSUS ASPIRIN ALONE FOR THE PREVENTION OF ATHEROTHROMBOTIC EVENTS

BACKGROUND: Dual antiplatelet therapy with clopidogrel plus low-dose aspirin has not been studied in a broad population of patients at high risk for atherothrombotic events. **METHODS:** We randomly assigned 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg per day) plus low-dose aspirin (75 to 162 mg per day) or placebo plus low-dose aspirin and followed them for a median of 28 months. The primary efficacy end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes. **RESULTS:** The rate of the primary efficacy end point

was 6.8 percent with clopidogrel plus aspirin and 7.3 percent with placebo plus aspirin (relative risk, 0.93; 95 percent confidence interval, 0.83 to 1.05; $P=0.22$). The respective rate of the principal secondary efficacy end point, which included hospitalizations for ischemic events, was 16.7 percent and 17.9 percent (relative risk, 0.92; 95 percent confidence interval, 0.86 to 0.995; $P=0.04$), and the rate of severe bleeding was 1.7 percent and 1.3 percent (relative risk, 1.25; 95 percent confidence interval, 0.97 to 1.61 percent; $P=0.09$). The rate of the primary end point among patients with multiple risk factors was 6.6 percent

with clopidogrel and 5.5 percent with placebo (relative risk, 1.2; 95 percent confidence interval, 0.91 to 1.59; P=0.20) and the rate of death from cardiovascular causes also was higher with clopidogrel (3.9 percent vs. 2.2 percent, P=0.01). In the subgroup with clinically evident atherothrombosis, the rate was 6.9 percent with clopidogrel and 7.9 percent with placebo (relative risk, 0.88; 95 percent confidence interval, 0.77 to 0.998; P=0.046).

CONCLUSIONS: In this trial, there was a suggestion of benefit with clopidogrel treatment in patients with symptomatic atherothrombosis and a suggestion of harm in patients with multiple risk factors. Overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes. (ClinicalTrials.gov number, NCT00050817.).