Editors' Note: The correspondence this week highlights controversial points in 2 recently published articles. Dr. Rammohan and colleagues disagree with the findings of Dr. O'Connor et al. that, after discontinuation of natalizumab therapy, multiple sclerosis (MS) disease activity returns to baseline levels without rebound, based partly on methodologic concerns. In his response, Dr. O'Connor clarifies the study's methodology and justifies the conclusions. In reference to another study, Drs. Mascitelli and Goldstein question the conclusion that statins are beneficial in young patients with strokes of unknown etiology based on other literature showing that higher cholesterol is associated with decreased stroke severity and poststroke mortality. Putaala et al. contend that their study focused on reducing future vascular events rather than stroke outcomes and that their data show a likely benefit to statin use in this population.

Megan Alcauskas, MD, and Robert C. Griggs, MD

DISEASE ACTIVITY RETURN DURING NATALIZUMAB TREATMENT INTERRUPTION IN PATIENTS WITH MULTIPLE SCLEROSIS

Kottil W. Rammohan, Milissa R. Ortega, Silvia R. Delgado, Leticia Tornes, Miami: We disagree with the conclusions of O'Connor et al.¹ that there is return of disease activity to baseline levels, but not rebound, after discontinuation of natalizumab therapy. Their findings conflict with other studies that have suggested otherwise.^{2,3} Every placebo-controlled clinical trial in MS has shown that both quantitative gadolinium enhancement and relapse rates decrease over time in both treatment and placebo groups.^{4,5} Accordingly, a comparison of postcessation disease activity to baseline disease activity from 24 months earlier is not an acceptable metric concerning rebound recurrence. A more appropriate metric is the comparison of the relapse rate and gadolinium enhancement postcessation of natalizumab to similar metrics at the end of the study in the placebo arm. In the absence of such a comparison, the observation of a return of disease activity to baseline levels following cessation of natalizumab treatment can only be construed as evidence for rebound.

Author Response: Paul W. O'Connor, Toronto:

Rammohan et al. state that "a comparison of post-cessation disease activity to baseline disease activity from 24 months earlier is not an acceptable metric concerning rebound recurrence." However, "baseline disease activity from 24 months earlier" was not the metric we chose for relapse comparisons, as can be seen in figures 2 (relapse rates in all patients and in AFFIRM patients) and 3 (relapse rates in those on alternative treatments and highly active cases).¹ In the relapse data, "baseline" is the on-study placebo rate, not the prestudy placebo rate as Rammohan et al. contend.

Regarding gadolinium-enhancing lesions, figure 4¹ shows both the prestudy as well as the last on study data for the natalizumab-treated patients together with data points to greater than 6 months after treatment cessation. At greater than 6 months postcessation, it is clear that for natalizumab-treated patients the number of enhancing lesions (1.2) is higher than at the end of the study (0.3) but not as high as the prestudy number (1.6).

We defined "rebound" as "worsening of disease activity beyond pretreatment levels." By this definition, rebound was not seen in this assessment of by far the largest group of natalizumab-treated patients in the literature. We used this definition because it seemed reasonable but other definitions could be considered.

These data came from a large group of patients and the data are depicted in terms of means and standard deviations. As in any group, some patients will be outliers and have a higher or lower than average level of disease activity, which may account for some of the smaller case series in the literature.

It is clear that relapse and MRI activity does return when natalizumab is stopped, which makes decisions about when and why to stop this medication and what, if anything, to replace it with even more complex. There is a risk in staying on the drug but also a risk in stopping it.

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STATINS AFTER ISCHEMIC STROKE OF UNDETERMINED ETIOLOGY IN YOUNG ADULTS

Luca Mascitelli, Udine, Italy; Mark R. Goldstein, Naples, FL: Putaala et al.¹ studied a group of young patients with a first stroke of undetermined etiology and found that individuals who used statin poststroke had lower rates of vascular events in long-term follow-up. However, when the whole young population was studied after first-ever ischemic stroke, it was found that dyslipidemia did not predict the occurrence of future arterial thrombotic events.² The present study¹ suggests that higher cholesterol levels actually are protective after ischemic stroke of undetermined etiology.

It is well known that baseline total cholesterol levels of statin-treated populations are higher than those of the general population. Cholesterol levels of the statin-treated patients in this study¹ were significantly higher than those of the non-statin-treated patients. Higher serum cholesterol concentrations have been shown to be associated with better outcome after stroke.³ Furthermore, an inverse relation between cholesterol and stroke severity and poststroke mortality has recently been reported, suggesting that higher cholesterol favors the development of small-vessel disease and therefore less severe strokes are associated with lower mortality.⁴ Therefore, we question the usefulness and safety of long-term treatment with statins on all young patients with stroke of unknown etiology. Regarding cholesterol and outcomes after stroke, perhaps more is better.

Author Response: Jukka Putaala, Elena Haapaniemi, Markku Kaste, Turgut Tatlisumak, Helsinki: We thank Drs. Mascitelli and Goldstein for their comments on our article. We showed that young patients with ischemic stroke of undetermined etiology are likely to benefit from statin treatment in prevention of new strokes, myocardial infarctions, or other vascular events.¹

Several issues mentioned by Mascitelli and Goldstein need clarification. First, the group treated with statins not only had a poorer lipid profile, but were also older and had overall greater burden of vascular risk factors. Despite these features, they had fewer vascular events compared with those never on statins. This strongly supports the beneficial pleiotropic effects of statins on secondary prevention in this patient group. Furthermore, it has been shown that statins initiated before or immediately after ischemic stroke improved early and long-term survival and functional outcomes.⁵ Second, higher serum total cholesterol and triglycerides are shown to be associated with better functional outcome and reduced long-term mortality after ischemic stroke,^{3,4} but not with decreased risk for recurrent vascular events in the long term, which was the scope in our study. Third, our study included only patients with undetermined stroke etiology with no signs of small-vessel disease or any other probable or possible cause. Moreover, the comparison groups had similar symptom severity and anatomic lesion distribution. The beneficial effects of statins cannot then be due to underlying factors that might have favored development of smaller lesions.

Randomized data show that the risk of future vascular events can be safely and effectively reduced in patients with a recent TIA or stroke.⁶ Our observational study adds to that evidence and supports the view that statins should be considered in every young patient with stroke of unknown cause.

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Neurology 2011;77;1930-1931

DOI 10.1212/WNL.0b013e31823c1200

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