In Reply We thank Merschhemke et al and Andrade for their interest in our article.1 We appreciate Merschhemke et al highlighting that data have been collected on patients participating in fingolimod trials for up to 3 months after drug cessation. However, these data have not, to our knowledge, been subjecting infingolimod trials for up to 3 months after drug cessation.

In the 2013 abstract cited,2 while 1033 and 1153 participants completed the FREEDOMS and TRANSFORM trials, respectively, only 164 participants in the fingolimod group and 110 in the placebo group fulfilled the named criteria to be included in the rebound analysis (ie, at least 3 months taking the drug and 14 days of data after discontinuation). With only about 10% of patients evaluated, significant bias may be present. Fewer patients had magnetic resonance imaging scans after study drug discontinuation. We cannot determine from the abstract how patients were treated after cessation and if/when new medications were started. To be included in the analysis, only 14 days of data after discontinuation were required; thus, many cases may have had follow-up of less than 3 months. Later rebound events may have been missed (we observed rebound phenomenon occurring between 4 to 16 weeks after discontinuation). Furthermore, only months of fingolimod exposure was required to be included in this trial analysis, significantly less time exposed than for the cases in our series. Short exposures may be less likely to result in rebound on discontinuation. Last, there are multiple examples in the literature of differences between clinical trial and postmarketing experience of medications, often attributed to differences in the patients exposed, therapy duration, or other real-world factors.3

With respect to our cases merely being examples of resumed disease activity or expressions of disease heterogeneity, 4 of the 5 cases from our center had imaging prior to fingolimod administration and, although some had a long course and worsening progression over the years, none had development of increase in gadolinium-enhancing lesions and new T2 lesion development comparable with post-fingolimod magnetic resonance imaging activity at any single point. As such, the dramatic increase in magnetic resonance imaging activity (>30 gadolinium-enhancing lesions in our most severe case) seen shortly after fingolimod cessation, we believe distinguishes these cases from a typical relapse and can be considered a rebound.

Regarding Andrade’s concerns for medication transitions for the cases from our center, these details are provided in the article; 2 patients stopped disease-modifying therapy for pregnancy, 2 started new therapies (dimethyl fumarate within 12 days and rituximab within 6 weeks of fingolimod cessation), and the last case self-discontinued medication. We agree that larger, prospective studies of this phenomenon will more precisely estimate its frequency.

More in-depth analysis and publication on the trial patients have the potential to contribute significantly to this topic. If available, immunological data from this safety period may help identify markers of those who may be at risk for a post-cessation severe episode. Sequencing of medications will remain an increasing concern in the field of multiple sclerosis. These issues are critical for all multiple sclerosis therapies with significant immune effects.

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CORRECTION

Error in Figure: In the Review Article titled “A Clinical Approach to the Diagnosis of Traumatic Encephalopathy Syndrome: A Review,” published in the June issue of JAMA Neurology, an error occurred in the Figure. The answer above the arrow connecting the box for “Suspected TES” and the diamond for “Delayed onset?” should have been yes instead of no. This article was corrected online.