

Reexamination of the TEMPO Study

Recent claims in the lay press that rasagiline (N-propargyl-1[R]-aminoindan) mesylate (TVP-1012) can reduce the progressive functional decline in patients with Parkinson disease prompted a colleague to ask me to look again at the article reporting the results of the TEMPO study.¹ Examination of the article raised a concern regarding the inclusion of certain subjects in the primary analysis.

The TEMPO study used a variation on a trial design first used in our study "Effects of Coenzyme Q₁₀ in Early Parkinson's Disease," which is commonly referred to by the nickname QE2.² This design uses the change in total Unified Parkinson's Disease Rating Scale (UPDRS) score from the baseline visit to the last visit, which is either the point at which the subject with Parkinson disease has developed disability warranting beginning dopaminergic therapy or, if the subject does not develop this level of disability, the final study visit (16 months in the QE2 study and 12 months in the TEMPO study). If the subject does need dopaminergic therapy prior to the end of the study, then the total UPDRS score at the visit when that judgment is made is carried forward, using the last-observation-carried-forward technique. The TEMPO study also incorporated a randomized start design in which the subjects were randomized to rasagiline, 1 mg/d for 12 months; rasagiline, 2 mg/d for 12 months; or matching placebo for 6 months followed by rasagiline, 2 mg/d, for 6 months. Blinding was maintained in all phases of the TEMPO study. The randomized delayed-start design was intended to separate an immediate symptomatic effect from an effect on disease progression.

Use of this primary response variable (change in the total UPDRS score) was based on analysis of the data from the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism study³ in which treatment with deprenyl postponed the time until the end point of disability requiring treatment with levodopa by approximately 9 months. The response variable (change in the total UPDRS score) captured 3 distinct aspects of the observed effect of deprenyl on symptoms of disease. First, because the number of subjects on deprenyl who reached the end point was lower than the number of subjects on placebo reaching the end point, the average worse score of patients at end point compared with that of patients not reaching end point translated into a better average score among patients assigned to deprenyl than among those assigned to placebo. Second, among patients who did not reach the end point, the mean UPDRS score at the final visit was better among patients assigned to deprenyl than that among patients assigned to placebo. Third, among

patients who did reach the end point, the mean score when the end point was reached was better among patients assigned to deprenyl than among those assigned to placebo. The reason for this third component is not obvious, but it may have to do with the ability of deprenyl, which is an irreversible inhibitor of monoamine oxidase-B, to reduce the metabolism of dopamine. Rasagiline, which like deprenyl is an irreversible inhibitor of monoamine oxidase-B, caused an improvement in the total UPDRS score at the 1-month visit, as deprenyl had done in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism study.

A problem appears to be the inclusion of subjects who developed disability warranting treatment with a dopaminergic agent prior to the 6-month point, when subjects on placebo were switched to rasagiline, 2 mg/d. In this situation, the last-observation-carried-forward technique would carry forward any difference due to the third component discussed here. An analysis of the data without these subjects would be informative.

The most easily interpreted data are clearly those from subjects who completed the 52 weeks without needing dopaminergic therapy. Approximately two thirds of the subjects in each group did this, with more than 80 subjects in each group completing the study without needing dopaminergic therapy. The authors are to be commended for inclusion of these data in Figure 3B. I was surprised that with more than 80 subjects in the groups, the results in this analysis did not achieve statistical significance, but they did not. (*P* value for this secondary analysis was not provided but should be provided.) I thought that this lack of significance was probably due to a lack of power, but then I looked at Figure 3B. The figure suggests that the 3 groups were coming together, particularly at week 42.

Can rasagiline slow the functional decline in patients with Parkinson disease? I hope so. Has the data presented to date convincingly shown that it does such? Not yet, but additional analysis of data from the TEMPO study could clarify the issues raised here.

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2. Shults CW, Oakes D, Kieburtz K, et al; Parkinson Study Group. Effects of coenzyme Q₁₀ in early Parkinson disease: evidence of slowing of the functional decline. *Arch Neurol.* 2002;59:1541-1550.
3. Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med.* 1993;328:176-183.