Rasagiline, Parkinson neuroprotection, and delayed-start trials

Still no satisfaction?

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ABSTRACT

Rasagiline has been studied as a Parkinson disease (PD) neuroprotective agent in 2 major clinical trials, utilizing the delayed-start design in an attempt to separate symptomatic drug benefits from a disease-modifying effect. The ostensibly positive outcomes of these studies, however, are obscured by potential confounding factors that seem intrinsic to this trial design, including 1) very small changes in clinical outcome measures that could easily be overshadowed by other influences; 2) probable incomplete blinding to study end; 3) subjective components of the Unified Parkinson's Disease Rating Scale (UPDRS) scoring system; and 4) practice influences from repeated scoring. Interpretation of the recent Attenuation of Disease Progression with Azilect Given Once-daily (ADAGIO) trials is especially problematic given 1) divergent results with the 2 symptomatically beneficial doses and 2) variability in UPDRS scores with active rasagiline, which was twice the magnitude of the major finding of the study. These studies further illustrate the difficulty in documenting a disease-modifying effect when considering a PD drug with symptomatic benefit. ***Neurology*® 2010;74:1143–1148**

GLOSSARY

ADAGIO = Attenuation of Disease Progression with Azilect Given Once-daily trial; **PD** = Parkinson disease; **TEMPO** = TVP-1012 in Early Monotherapy for PD Outpatients study; **UPDRS** = Unified Parkinson's Disease Rating Scale.

A fundamental goal of Parkinson disease (PD) research is development of drugs to halt or at least slow disease progression.[1] We have efficacious drugs for treating dopamine-deficiency PD symptoms, but no drug is proven to attenuate PD causative/pathogenic factors.[2] This primarily relates to the fact that we do not know what causes most cases of PD.

PD PROGRESSION IS DIFFICULT TO MEASURE Compounding this problem has been the difficulty simply measuring PD progression. PD is a complex disorder affecting not only motor, but cognitive, behavioral, and autonomic systems. Measurement of progression in any of these domains might be meaningful. Because PD is primarily clinically defined as an extrapyramidal motor disorder with a dopaminergic substrate, this has been the measurement focus in neuroprotective trials.

Many of the drugs proposed to slow progression improve dopaminergic neurotransmission and treat PD symptoms. This has confounded clinical assessments, where it has proven very difficult to separate symptomatic effects from a true effect on disease progression. This is exemplified by the prior experience with the MAO-B inhibitor, selegiline, in the DATATOP trial, the largest and most expensive NIH-sponsored drug trial of its time.[3,4] The DATATOP results were initially interpreted as demonstrating neuroprotection; only later was the confounding symptomatic benefit recognized, associated with a pharmacologic effect exceeding the duration of study-drug washout (40-day half-life of brain MAO-B inhibition).[5] Subsequent follow-up studies in this cohort cast doubt on a true disease-modifying effect from selegiline,[6,7] although this topic remains controversial.

Most drugs being contemplated as PD-slowing agents have potential symptomatic properties, including nondopaminergic drugs such as creatine, which may have some nonspecific effects improving energy or sense of well-being. A valid, measurable biomarker of the biologic process causing PD would be the ideal outcome measure, but since we understand little about the pathogenic substrates for PD, this is not currently possible.

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Dopaminergic brain imaging as a biomarker of PD progression. Theoretically, brain imaging of nigrostriatal dopaminergic integrity should be an ideal strategy for documenting PD progression in clinical studies. This outcome measure was employed in 2 large clinical trials assessing whether the dopamine agonists, pramipexole[8] or ropinirole,[9] had a favorable effect on PD progression compared to levodopa therapy. Striatal dopaminergic imaging changes in these 2 studies suggested disease-modifying effects, although clinical outcomes were opposite to the imaging. The confounding influences of the study drugs on the radioligand binding or metabolism were subsequently recognized.[10,11] Consensus opinion therefore concluded that dopaminergic brain imaging is unproven as a strategy for measuring PD progression in clinical trials using agents interacting with dopaminergic neurotransmission.[12]

Inhibitors of apoptosis: No symptomatic effect, but not neuroprotective in PD clinical trials. Apoptosis has been proposed as fundamental to the PD neurodegenerative process. This has led to clinical trials of apoptosis inhibitors, which have been devoid of PD symptomatic effects. Absence of symptomatic benefit allowed clinical batteries to be used for outcome measurements (Unified Parkinson's Disease Rating Scale [UPDRS]), a more straightforward assessment strategy. Unfortunately, independent clinical trials of 2 different antiapoptosis drugs revealed no evidence of any disease-modifying effects in PD.[13,14]

Delayed-start trial design to assess PD progression. The delayed-start clinical trial design has been proposed to overcome confounding by drug symptomatic effects in PD progression trials.[15-17] With this scheme, untreated patients with PD are randomized to receive the study drug for (a) the full study duration, or (b) only the last half of the trial. With trials spanning a year or more, the presumption is that drug symptomatic effects will stabilize and be equivalent in both groups by study end. A clinical rating scale, the UPDRS, is utilized to document changes over time. If there is a disease-slowing effect, the group administered placebo for the first half of the study should never catch up to the other group.

Obviously, a sufficiently long trial is necessary to allow measurable clinical decline to accrue in this slowly progressive disorder. This requires selection of patients who have a high likelihood of remaining in the investigation despite being untreated during the first half of the study (placebo phase). Moreover, if the study drug, itself, provides only limited symptomatic benefit, patient selection is additionally crucial, so that patients with PD in the active arm of the study will not drop out in order to start levodopa or dopamine agonist therapy. Thus, patients in such a study may be restricted to those with mild and early PD. However, with mild PD, and only very slow progression, the modest changes in measurable parameters challenge this study design, even with long study durations.

RASAGILINE Reminiscent of the early selegiline experience, the newer PD drug, rasagiline, is proposed to have a neuroprotective effect.[16] Rasagiline and selegiline are, in fact, structurally and pharmacologically very similar, including selectively blocking brain MAO-B. Both drugs inhibit apoptosis in vitro, which appears independent of MAO inhibition.[16] Unlike selegiline, however, rasagiline does not generate l-amphetamine metabolites; apoptosis blockade by these drugs tends to be reversed by such l-amphetamines.[18] Like selegiline, rasagiline mildly improves PD symptoms.[19-21]

Rasagiline and delayed-start clinical trial outcomes. The delayed-start design has been utilized in 2 major clinical trials to assess whether rasagiline has disease-modifying effects. The initial trial compared 1 year to 6 months of rasagiline in the TVP-1012 in Early Monotherapy for PD Outpatients (TEMPO) study.[15] Data analysis revealed that patients with PD receiving rasagiline for 1 year were statistically superior at study end to those administered rasagiline for only the last 6 months of that trial. Thus, one interpretation was that the findings ". . . may be due to a disease-modifying activity of the drug."

The second rasagiline trial, designated ADAGIO (Attenuation of Disease Progression with Azilect Given Once-daily),[16,22] has been the stimulus for recent publicity. It employed the same design as the TEMPO study but a larger N (total of 1,176, vs 404 initial subjects in the TEMPO trial); it was also longer, with 9 months in each of the 2 phases, vs 6 months in each of the 2 phases of the TEMPO trial. In this 72-week ADAGIO trial, there were 4 study arms: 1) rasagiline, 1 mg daily during the entire study; 2) placebo during the first phase (36 weeks), then 1 mg rasagiline daily in the second phase (weeks 36–72); 3) rasagiline, 2 mg daily during the entire study; 4) placebo during the first phase, then 2 mg rasagiline daily in the second phase.

The outcome of the ADAGIO study, however, differed from TEMPO: only the group administered 1 mg daily for the full study had significantly better UPDRS scores at study end than the delayed-start group. Unlike the TEMPO study, the group receiving 2 mg daily for the entire ADAGIO trial was no different at study end than the group starting this dose 9 months into the study. The authors concluded that a disease-modifying effect is "possible," at least in the 1 mg group.

The ADAGIO study specified 2 additional primary endpoints that were not utilized in the TEMPO study: the graphed slopes of UPDRS changes were compared between groups during the first, and also the second half of the study. However, the fundamental, intuitive rationale for using the delayed-start design relates to comparison of scores over the entire trial, study end vs baseline; this was the sole outcome measure in the TEMPO trial. Hence, we primarily focus our discussion on this, but later address the slope comparisons.

IS THE DELAYED-START TRIAL METHODOLOGY ROCK-SOLID? The primary outcome measure of these delayed-start PD trials is the standard UPDRS total score, parts I through III (31 multiple-choice questions). This includes 2 patient-scored batteries (Mentation and Activities of Daily Living subscales; maximum score for both = 68 units) and the investigator-rated motor evaluation (maximum, 108 units). UPDRS outcomes measured in these delayed-start PD trials are subject to confounding influences for 4 reasons. First, the measured changes over the course of the trials are very small and easily overshadowed by other factors; second, blinding may be partially transparent; third, UPDRS scoring is not entirely objective; fourth, UPDRS repetitions may translate into biased influences from practice effects. Each of these concerns deserves discussion.

Slow progression and small changes. A confounding effect would not need to be substantial to explain the outcomes in either the TEMPO or ADAGIO trials. In each study, the UPDRS difference between the delayed-start and early-start groups was on the order of 2 points. Placed in context, the UPDRS maximum score is 176 points and "2" represents approximately 1% of the maximum. This small change in UPDRS scores reflects that very slow progression of PD, plus selection of less aggressive PD that would allow patients to initially remain untreated if randomized to the delayed-start arm.

Blinding may be broken before the final scoring. Although delayed-start trials are labeled as double-blind, this is true for only the first half of the study, with the last half, open-label. With transition to known symptomatic drug therapy, clinical responses to the open-label active drug may also disclose the randomization status of the initial double-blind phase; e.g., initial placebo treatment, then a clinical response to the active drug in phase 2 may retrospectively unblind these subjects. Since clinical scoring at study end is crucial, unblinding in phase 2 could compromise the findings.

UPDRS is not completely objective. UPDRS scoring has a substantial subjective element, and for some entries, the distinctions are subtle. Thus, consider item 14 of the patient-scored ADL scale, where 1 = "rare freezing when walking; may have start hesitation"; 2 = "occasional freezing when walking." Or consider the clinician scored item 19 (motor scale), facial expression: 1 = "minimal hypomimia; could be normal 'poker face'"; 2 = "slight but definitely abnormal diminution of facial expression."

Note that the UPDRS is subject to substantial placebo effects, including among investigator-raters, which has been well-documented.[23] Thus, patients with biologically stable PD potentially have a range of UPDRS scores that could be recorded, depending on subjective factors.

UPDRS response imprinting. In delayed-start PD trials, subjects are repeatedly scored during the first phase, when one group receives symptomatic benefit from the active drug (rasagiline) while the other group receives placebo. In the TEMPO and ADAGIO trials, a clear symptomatic effect was borne out by the UPDRS scores that diverged right after the drugs were started; the rasagiline groups improved and the placebo groups did not (figure 3 in both the TEMPO[15] and ADAGIO studies[22]).

There is substantial potential for UPDRS choices to become somewhat automatic with repeat testing; the more often a task is repeated, the more likely for responses to become imprinted in memory and habit. In other words, there is potential for scores during the placebo-controlled phase to become locked-in; less thought is given as the UPDRS battery continues to be readministered. Thus, UPDRS scoring in the placebo-controlled phase may well influence UPDRS scores in the last half of the study when all subjects receive the study drug; each group may be more likely to retain some of the entries from the first phase when there was differential treatment (rasagiline or placebo).

ADAGIO: DIVERGENT OUTCOMES FROM DIFFERENT RASAGILINE DOSES The ADAGIO trial generated counterintuitive findings based on dose. For the 1 mg rasagiline dose, the difference between the baseline and end-of-study UPDRS scores declined significantly less in the ADAGIO early-start group compared to the delayed-start group. Surprisingly, this was not the case for the 2 mg arm, where the baseline to end-of-study UPDRS changes were nearly identical in the 2 groups.[22] Moreover, note the simple rankings of best to worst total UPDRS score changes in the 4 groups over the

18 months of the trial: 1) early 1 mg (18 months rasagiline), declined by 2.82 points; 2) delayed 2 mg (9 months rasagiline), declined by 3.11 points; 3) early 2 mg (18 months rasagiline), declined by 3.47 points; 4) delayed 1 mg (9 months rasagiline), declined by 4.5 points.

The difference between the early- vs delayed-start 2 mg group favored the delayed-start group by 0.36 points; this actually was slightly more than the 0.29-point difference between the top 2 groups above (early-start 1 mg vs delayed-start 2 mg).

There is no intuitive reason that 1 mg and 2 mg should have generated different outcomes. The study authors proposed that the symptomatic effect may have been greater with the 2 mg dose and this might have overshadowed a disease-modifying effect. However, the measured symptomatic effect was nearly identical between the 1 mg and 2 mg doses in the initial placebo-controlled phase of this study (as assessed by the secondary endpoint). Moreover, the symptomatic effect from rasagiline is thought to occur via MAO-B inhibition; rasagiline is an irreversible inhibitor of MAO-B (like selegiline) and both doses should have completely inhibited this brain enzyme, with a half-life of 40 days.[5] Thus, why one dose should have induced a disease-modifying effect but not the other is not obvious.

Analysis of the individual 9-month outcomes suggests potential for confounding influences. The delayed-start design assumed that the symptomatic benefit would have plateaued early in each of the 2 9-month study phases, presumably by 12 weeks.[22] Thus, the primary influence on scores should then be due to the neuroprotective effect, slowing the progressive decline in UPDRS scores. Note, however, the best-to-worst ranking of total UPDRS score changes during the 9-month study phases where active rasagiline was administered: 1) delayed-group, active-phase 2 mg rasagiline: improved by 1.16 points; 2) delayed-group, active-phase 1 mg rasagiline: declined by 0.23 points; 3) early-start group, first active-phase 2 mg rasagiline: declined by 1.11 points; 4) early-start group, first active-phase 1 mg rasagiline: declined by 1.26 points; 5) early-start group, second active-phase 1 mg rasagiline: declined by 1.56 points; 6) early-start group, second active-phase 2 mg rasagiline: declined by 2.36 points.

Consider these UPDRS score changes in the context of the major positive finding of this ADAGIO study where the early-start 1 mg rasagiline group differed from the delayed-start 1 mg group by 1.68 points at study end; this is less than half of the range of 9-month scores listed above (3.52 points). Restated, variability in rasagiline scores in these 9-month epochs was twice the magnitude of the major positive finding of this study. Thus, small influences could easily bias study outcomes not only in this trial, but in delayed-start PD trials in general.

Other ADAGIO primary outcome measures: Slope comparisons. ***ADAGIO phase 1 primary endpoint: Initial slopes.*** If rasagiline has a neuroprotective effect beyond symptomatic benefit, the ADAGIO authors proposed that this should already be apparent in the initial phase, when 2 of the 4 groups were administered placebo.[22] Assuming that the symptomatic effect would be fully developed by 12 weeks, they compared the UPDRS rate-of-change slopes for the last 24 weeks of the 36-week placebo-controlled phase. Indeed, the rate of change during this 24-week phase was significantly better with rasagiline.

Visual inspection of the actual curves for this 24-week phase, however, gives a different impression (figure 3 in the ADAGIO article[22]). Whereas the slopes do diverge during the first 12 weeks of this 24-week placebo-controlled phase, the opposite is apparent during the second half of this phase. During the last 12 weeks of this phase, the 1 mg and placebo slopes start to converge, not diverge. Correspondingly, the 2 mg arm and placebo slopes no longer diverge, but run parallel during the second half of this 24-week phase. Thus, whereas the authors assumed that any symptomatic effect should have fully plateaued by 12 weeks, this graphic appearance suggests otherwise.

ADAGIO phase 2 primary endpoint: Terminal slopes. The TEMPO trial results indicated that even if rasagiline is neuroprotective, it does not halt progression; UPDRS scores continue to deteriorate and the progression slopes never plateau despite rasagiline. However, a partial neuroprotective effect from early-start rasagiline should translate into UPDRS rate-of-change slopes that do not converge with the early-placebo curves at the end of the study. In other words, the slope analysis should confirm that the early-placebo group never "caught up" with the early rasagiline group. In fact, this was not the outcome in the early-start 2 mg rasagiline analysis; the early- and delayed-start curves converged to exactly the same data point at study end (figure 3B in the ADAGIO article[22]). The 1 mg analysis did demonstrate persistent separation of the early- and late-start curves at study end (figure 3A in the ADAGIO article[22]); whether this reflects the potential confounding influences discussed above is open to speculation.

Long-term follow-up of the TEMPO trial. Additionally arguing for a rasagiline neuroprotective effect was the outcome of the TEMPO open-label extension study, which also generated recent publicity.[24] Thus, subjects in the original TEMPO trial were

subsequently monitored for up to 6.5 years while continuing rasagiline treatment (but allowed to add other PD drugs). Interestingly, the group whose rasagiline was delayed 6 months had significantly poorer PD scores at every point in time thereafter. This was a striking finding indeed, given that only a 6-month delay of rasagiline still had an impact more than 5 years later.

Confounding interpretation of this follow-up study is the number of patients dropping out. By 1.5 years, approximately 20% of the original 404 subjects were lost and by 3 years, this jumped to 37%, with 59% lost by 5.5 years. Clinical trial analyses are notoriously sabotaged by high dropout rates, opening the potential for biased outcomes. Perhaps this explains the marked and otherwise inexplicable graphic divergence of the 2 groups beginning after the fourth year of the study (shown in figure 2 from that study[24]). Early-start patients completing the extension study were also more likely to have been treated with levodopa (69%) than the delayed-start group (56%), which obviously could account for the later-developing UPDRS differences. Finally, in an open-label study with the blind broken, rating bias is possible; investigators knew the study hypothesis and might have been consistently more sympathetic to the early-start group. In summary, so many potential sources of confounding were present in this long-term follow-up study that interpretation is impossible.

But rasagiline is neuroprotective in the laboratory . . . Numerous in vitro and in vivo studies have documented evidence of neuroprotective effects with rasagiline,[16] although one might question whether these models truly replicate the disease process. Arguably, they support the initial interpretation of these clinical trials as demonstrating a disease-modifying effect. However, nearly all the dopamine-active drugs used to treat PD have similarly been reported to demonstrate in vivo and in vitro evidence of neuroprotective influences, including all the dopamine agonists[25] and even levodopa.[26,27] In fact, it has been proposed that early treatment with any dopaminergic drug may have a long-term favorable effect in PD.[25]

Practical problems with prescribing rasagiline in clinical practice. One might argue that rasagiline should be prescribed to all patients with PD on the chance that it might be neuroprotective (hedging one's bets, so to speak). However, balanced against this are considerations of potential drug interactions and expense.

The package insert lists numerous drugs that are contraindicated with rasagiline, including most antidepressants. Many of the listed drugs are likely to be considered in patients with PD. At the very least, this has medical–legal implications, whereby the drug combination might well be blamed for a variety of coincidental problems. A second issue is the considerable expense of rasagiline. Retail price is approximately $10 per tablet, not inconsequential even with pharmaceutical plans requiring copayments.

DISCUSSION Twenty years ago, selegiline was prescribed to nearly all patients with PD because of faith in or hope for a possible neuroprotective effect. Now, the very similar drug, rasagiline, is being touted for the same purpose. However, like the earlier DATATOP trial assessing a possible selegiline neuroprotective effect, the current TEMPO and ADAGIO investigations raise more questions than provide definitive answers. This delayed-start study design came under the scrutiny of the American Academy of Neurology Quality Standard Subcommittee after the TEMPO trial and they concluded then that "no treatment has been shown to be neuroprotective."[2] This still appears to be an appropriate conclusion.

These studies have implications beyond rasagiline. Unfortunately, they illustrate the collective frustrations with measures to assess PD progression in clinical drug trials. "Unmet needs" has become a buzzword for pharmaceutical companies touting PD drugs in the last few years. Clearly, an unmet need for the PD community is a valid and reliable means of simply assessing PD progression.

DISCLOSURE

Dr. Ahlskog received the Fred Springer Award from the American Parkinson's Disease Association; receives royalties from publishing *The Parkinson's Disease Treatment Book* (Oxford University Press, 2005) and *Parkinson's Disease Treatment Guide for Physicians* (Oxford University Press, 2009), *Parkinson's Disease and Movement Disorders* (Humana Press, 2000), and *Surgical Treatment of Parkinson's Disease and other Movement Disorders* (Humana Press, 2003); has received honoraria for lectures or educational activities not funded by industry; and receives research support from NIH/NINDS [P50 NS 40256-R (Co-I)]. Dr. Uitti serves as an Associate Editor of *Neurology*®; has received research support from Advanced Neuromodulations Systems and from the NIH/NINDS (P50NS 40256 [Co-I]); and his institution receives annual royalties from the licensing of the technology related to PARK8/LRRK2.

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The delayed-start study in Parkinson disease

Can't satisfy everyone

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Drs. Ahlskog and Uitti correctly point out the difficulty in identifying a disease-modifying therapy for Parkinson disease (PD).[1] While there are many promising candidate drugs, endpoints employed in the past did not permit detection of a disease-modifying effect because of potential symptomatic or pharmacologic confounds.[2] A validated biomarker would obviously be helpful, but one does not currently exist.

The delayed-start design was proposed to address these problems.[3] In this 2-period design, patients are randomized to receive placebo or active drug in the first period, while patients in both groups receive the active drug in the second period. Keys to defining a positive outcome are evidence that early treatment provides benefits at study end that cannot be achieved with delayed-treatment despite both groups receiving the same treatment, and evidence that the slopes of deterioration in the Unified Parkinson's Disease Rating Scale (UPDRS) in the 2 groups are not converging, indicating that the benefit is not readily explained by a symptomatic effect.

There are many issues that must be addressed in designing a delayed-start study. The periods must be sufficiently long to permit disease modification to occur in period 1, and for the drug to reach its full symptomatic effect in period 2. Dropouts (especially differential dropouts between the groups) must be minimized as the primary analysis requires data from each of the 2 periods. Analytic methods must be used to account for missing data. Finally, there should be sufficient numbers of visits to permit meaningful slope analyses.[4]

In the ADAGIO study, rasagiline 1 mg dose met all endpoints of the primary analysis, consistent with the possibility that the drug has a disease-modifying effect.[5] This was supported by multiple sensitivity and imputation analyses, reinforcing the robustness of this result. Rasagiline 2 mg failed. While the reason for this is unknown, we hypothesize that it could be due to a greater or more prolonged symptomatic effect of this dose, masking disease modification in this very mildly affected population. Indeed, the subset of patients treated with 2 mg in the highest quartile of baseline UPDRS scores met criteria for performing a subgroup analysis,[6] and met all primary endpoints.[5] The 2 mg dose was also positive in another delayed-start study where patients had higher UPDRS scores at baseline.[7]

Drs. Ahlskog and Uitti raise their own set of concerns. They argue the UPDRS is an insensitive scale and that there may have been disproportionate learning from repeated evaluations. But this is no different than other placebo-controlled trials in PD where multiple UPDRS evaluations are routinely employed. They point out that the UPDRS is somewhat subjective, but the same scale was used for patients in both groups, the study was blinded, and this scale is used in virtually every trial in PD. They argue that because the study enrolled patients with early and mild PD "modest changes in measurable parameters challenge the study design." We agree that slow progression makes it more difficult to detect disease modification, but the study was still positive for the 1 mg dose. They conclude that variability in UPDRS scores was

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greater than the effect size based on an inappropriate comparison of data from different cohorts, different placebo groups, and different phases of the study. Still, this does not negate statistical significance, which takes variability into consideration. They criticize the separation of slopes in the first period, saying that "visual inspection of the curves gives a different impression." But it is an error to eyeball slopes from a graph of raw means derived from the endpoint II/III cohort and compare this to slope estimates derived from a model which includes covariate effects and uses data from the endpoint I cohort. They question the integrity of the double-blind because patients in both groups were on active treatment in the second period, but physicians and subjects remained blind as to treatment in period 1, which is the critical component of the study. Indeed, a placebo benefit was observed in the early-start group at onset of period 2, supporting preservation of the blind.

None of the issues raised by Drs. Ahlskog and Uitti invalidate the fact that early treatment with rasagiline 1 mg provided benefits that could not be achieved with delayed treatment with the same drug. The arguments they pose are primarily based on flawed comparisons and generalized speculations, while ignoring the rigorous statistical analyses that were performed in the ADAGIO study based on consultation with the Food and Drug Administration, experts in PD and statistics, and an open public forum.[8] The delayed start is the best design currently available for ensuring that benefits seen at the end of a study are not due to a short-term symptomatic effect. These benefits could be due to preservation of a compensatory mechanism rather than a true neuroprotective effect, and early treatment with any dopaminergic agent might have a comparable effect. However, this is still disease modification, and the recently reported PROUD study testing pramipexole in a delayed-start study was negative.[9]

The difference between the early and delayed-start groups was only 1.7 UPDRS points. But this represents a 38% reduction in the rate of decline, and reflects the impact of only 9 months of treatment. Further, a delayed-start study is not conducted to determine the clinical significance of a disease-modifying effect, but to determine if there are benefits that cannot be accounted for by an effect on symptoms alone. Long-term studies measuring the effect of the rasagiline on cumulative disability will be required to address clinical significance. As always, physicians will have to use their judgment in determining whether to use this drug based on its potential benefits and adverse event profile.

DISCLOSURE

Dr. Olanow has served on scientific advisory boards for and/or received funding for travel from Teva Pharmaceutical Industries Ltd., Lundbeck Inc., Novartis, Orion Pharma, Merck Serono, Boehringer Ingelheim, Ceregene, Solvay, and Schering Plough; serves as Chief Editor of *Movement Disorders*; has received speaker honoraria from Teva Pharmaceutical Industries Ltd. and Lundbeck Inc.; has received research support from the Lowenstein Foundation; and has served as a medico-legal consultant to the welding industry. Prof. Rascol has served on scientific advisory boards for Bial, Boehringer Ingelheim, Eisai Inc., GlaxoSmithKline, IMPAX Laboratories, Inc., Lundbeck Inc., Merck Serono, Merz Pharmaceuticals, LLC, Oxford BioMedica, Schering Plough, Servier, Solvay Pharmaceuticals, Inc., Teva Pharmaceutical Industries Ltd., UCB, and Xenoport, Inc.; serves on the editorial boards of the *European Journal of Neurology*, the *Journal of Neural Transmission*, *Lancet Neurology*, *European Neurology*, and *Core Evidence*; receives royalties from the publication of the *European Handbook of Neurological Management (First Edition)* (Blackwell Publishing Ltd., 2006); received a speaker honorarium from the Movement Disorders Society; and has received research support from Boehringer Ingelheim, GlaxoSmithKline, Orion Pharma, Teva Pharmaceutical Industries Ltd., Lundbeck Inc., Servier, PHRC National (n°06 008 01 and n°07 201 01), France Parkinson, and the Michael J Fox Foundation.

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REPLY TO DRS. OLANOW AND RASCOL

As clinicians with active Parkinson disease (PD) practices, we took publication of the Attenuation of Disease Progression with Azilect Given Once-daily (ADAGIO) study results very seriously. Should rasagiline be prescribed to all patients with PD? After carefully considering this and other relevant trials, we concluded that there are insufficient data to support this practice. This parallels the scenario that played out 2 decades ago relating to investigation of another MAO-B inhibitor, selegiline.[1,2]

Our interpretation differs substantially from that of our colleagues, Drs. Olanow and Rascol. They argue that the ADAGIO statistical comparisons seemingly make other analyses "inappropriate" and "an error"; apparently this includes visual inspection of graphs and perusal of raw data. However, statistical analyses are only valid if the study design is sound and without potential confounding influences. With this drug (rasagiline), and with the delayed-start study design, the potential for confounding is substantial, as we outlined in our article. Statistics, no matter how "rigorous," will not salvage a flawed study with faulty premises. Thus, incomplete blinding (open-label conditions in the last half of the study), sequential and perhaps unbalanced placebo effects, a partially subjective scale (Unified Parkinson's Disease Rating Scale [UPDRS]), and the potential for asymmetric practice effects could easily have influenced outcomes, especially when the measured differences were so small (1.7 UPDRS points).

Defending use of the UPDRS, Drs. Olanow and Rascol comment that ". . . this scale is used in virtually every trial in PD." In fact, the UPDRS evolved from earlier rating scales that were developed primarily to assess the symptomatic effects of PD drugs. In that setting, where robust symptomatic responses translate into marked differences in UPDRS scores, the utility of this measure is obvious. However, adapting the UPDRS to analyze parkinsonism progression, where very small differences accrue over long periods of time, seriously challenges this scale.

The statement that "the delayed start is the best design currently available" bears on a larger issue: Are our current approaches for assessment of PD progression truly "futility trials"[3]? When drugs with symptomatic effects are studied for neuroprotection, current study designs seemingly are inadequate, and generate far more questions than answers. Thus, we agree with Drs. Olanow and Rascol that "a validated biomarker would obviously be helpful."

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