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New considerations in the medical management of early Parkinson's disease: Impact of recent clinical trials on treatment strategy

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SUMMARY

The best approach to medical management of early Parkinson's disease remains controversial. Recent studies suggest that early use of MAO-B inhibitors may improve long-term outcome. Long-term follow-up to a delayed-start rasagiline study indicated that patients who were treated with rasagiline from the start did better through 5.5–6 years of treatment (with all PD medications) than patients who began rasagiline after a delay of 6 months. In a long-term selegiline study, patients randomized to treatment with selegiline did better over 7 years than patients randomized to treatment with placebo. Dopamine agonists provide moderate symptomatic benefit, delay the need for levodopa, and delay the emergence of motor complications, especially dyskinesia. Long-term studies have not demonstrated a clear overall benefit to introducing a dopamine agonist prior to levodopa in general PD populations, but treatment regimens tend to become increasingly similar over time, most studies have had high drop-out rates, and there may be subsets of patients who experience greater benefit with this strategy. Levodopa remains the most efficacious oral medication for the treatment of motor signs of PD but is associated with the development of motor complications. Long-acting levodopa formulations are now under development and it will be important to determine whether they cause fewer motor complications than standard levodopa. The current approach to treatment of early PD depends in part on individual patient factors including age, severity of motor signs, presence of cognitive dysfunction, and other co-morbidities.

1. Introduction

Major categories of medications commonly used in the treatment of early Parkinson's disease (PD) include MAO-B inhibitors, dopamine agonists, and levodopa. Although clinical trials have provided a relatively clear picture of the short-term efficacy and side effects of these medications, less is known about their long-term efficacy and side effects, and only a few studies have addressed the relative pros and cons of various possible treatment strategies using these medications. This review will focus on recent trials that impact physician thinking about treatment strategy in the management of motor symptoms in early PD.

1.1. MAO-B inhibitors

MAO-B inhibitors provide mild symptomatic benefit in early PD and are usually very well tolerated [1,2]. They can initially improve parkinsonian signs and symptoms, but the disease continues to progress and after a few months to a few years, more efficacious dopamine replacement therapy must be added. Nonetheless, recent studies suggest that selegiline and rasagiline improve long-term outcomes even after dopamine agonist and levodopa therapy are initiated.

1.2. Selegiline

Palhagen et al. [3] conducted a 7 year, randomized, double-blind study in which 157 subjects with early PD were randomized to treatment with selegiline or placebo. Once the subject had reached a level of disability requiring initiation of levodopa, study medication (selegiline or placebo) was withdrawn for 8 weeks, and then re-instituted along with levodopa. The levodopa dose was adjusted over time as appropriate to manage symptoms. Subjects were followed until they required other PD medications (slow release levodopa or dopamine agonist) or until 7 years after randomization. In the initial (monotherapy) phase of the study [4], progression of symptoms was significantly slower in the selegiline group, and the time to need for levodopa was significantly delayed. In addition, the selegiline group remained significantly better after 8 weeks of study medication wash-out. When levodopa was added, both groups experienced substantial benefit. Through 78 months, subsequent deterioration was more pronounced in the placebo than the selegiline group for UPDRS

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ON scores ($p = 0.003$), motor scores ($p = 0.002$), and ADL scores ($p = 0.0002$). Even though investigators could increase the levodopa dose as needed, differences in UPDRS scores between the two groups increased over time. Tremor, bradykinesia, and rigidity were more improved in the selegiline group, and there was a trend for less wearing-off ($p = 0.053$). In addition, the selegiline group consistently required lower levodopa dosages ($p = 0.0002$). Overall, after 5 years of combination therapy, UPDRS total scores were nearly 10 points higher, or 35% worse, in the placebo group while the mean levodopa daily dose was 19% higher ($p = 0.0002$). This seems quite remarkable for a medication that only provides modest symptomatic improvement as monotherapy in early disease. A major limitation of the study is that only 39% of subjects completed the 7 years of follow-up as 15% reached the termination point (needing other medications) while 46% discontinued prematurely. Several other long-term selegiline studies have found similar results [5,6].

1.3. Rasagiline

Rasagiline was evaluated in a delayed-start study (TEMPO) by the Parkinson Study Group [7]. Four hundred and four subjects with early PD were randomized to rasagiline 1 mg/day for 12 months, rasagiline 2 mg/day for 12 months, or placebo for 6 months followed by rasagiline 2 mg/day for 6 months (delayed-start group). Both early-start rasagiline groups experienced less progression of clinical symptoms over 12 months than the delayed-start group. Subjects treated with rasagiline 2 mg/day for 12 months experienced a 2.29 unit smaller increase in mean adjusted total UPDRS scores compared to subjects treated with placebo for 6 months followed by rasagiline 2 mg/day for 6 months ($p = 0.01$). Subjects treated with rasagiline 1 mg/day for 12 months experienced a 1.82 unit smaller increase in total UPDRS scores compared to subjects treated with placebo for 6 months followed by rasagiline 2 mg/day for 6 months ($p = 0.05$). The observed differences in outcome at 1 year cannot be explained by a simple symptomatic effect of rasagiline and suggest that earlier initiation (and longer duration of exposure) is associated with a better outcome. Nonetheless, the differences at 1 year are small and it was thought important to follow these patients over time to determine whether there are any enduring benefits to early initiation of rasagiline.

The TEMPO study was followed by an open-label extension in which subjects continued on rasagiline, and other PD medications were added as appropriate [8]. Investigators and subjects remained blinded to the subjects' original assignment. Three-hundred and six subjects chose to participate in this open-label extension and were followed for up to 6.5 years from original randomization. Average duration in the study was 3.6 ± 2.1 years and 177 subjects received rasagiline for 5 years. Over the entire 6.5 years of observation, the adjusted mean difference in change from baseline in total UPDRS scores was 2.5 units ($p = 0.021$) or 16% ($p = 0.006$) in favor of the early-start rasagiline group compared to the delayed-start group. The early-start group had numerically better UPDRS scores at all timepoints, and the interaction between treatment and time was significant, with a greater difference observed with longer duration of follow-up. Changes in UPDRS subscale scores also favored the early-start group with mean differences from baseline between groups of 11.9% ($p = 0.046$) for UPDRS motor scores and 39.1% ($p = 0.028$) for UPDRS ADL scores. Daily levodopa equivalent doses were not statistically different between groups. Thus, this extension study suggests that early initiation of rasagiline, compared to a delay of 6 months, offers long-term benefits that are enduring and apparent even as other PD medications are added and adjusted over time. A limitation of the trial is that only 44% of subjects originally enrolled in TEMPO and 58% of subjects entering the extension study completed it. In addition, it is not possible to exclude the possibility that non-significant difference in levodopa equivalent doses could have produced a significant clinical difference.

More recently, rasagiline was evaluated in a very large and rigorous delayed-start study (ADAGIO) [9]. A total of 1176 subjects with very early PD were randomly assigned to rasagiline 1 mg/day or 2 mg/day for 72 weeks (early-start groups) or placebo for 36 weeks followed by rasagiline 1 mg/day or 2 mg/day for 36 weeks (delayed-start groups). To achieve a positive result for either dose comparison, the early start group had to meet three hierarchical endpoints based on UPDRS scores: (1) superiority to placebo in rate of change (i.e., less progression) between weeks 12 and 36, (2) superiority to delayed-start treatment in change from baseline to week 72 (i.e., better outcome), and (3) non-inferiority to delayed-start in rate of change from week 48 to 72 (groups not converging). The 1 mg/day early-start group met all three hierarchical endpoints and the difference in change from baseline to endpoint (week 72) was −1.68 units ($p = 0.02$). This result is consistent with a disease modifying effect. The 2 mg/day early-start group did not exhibit significantly less worsening from baseline to endpoint (week 72). The reason this dose failed to show an enduring difference between early- and delayed-start groups is not clear. One possibility is that the 2 mg dose provided greater symptomatic benefit, and in the context of floor effects, masked the study's ability to detect a disease modifying effect for this dose. When a post-hoc analysis was performed in the quartile of subjects with the worst baseline UPDRS scores (to get away from a potential floor effect), all three hierarchical endpoints were met comparing 2 mg/day early and delayed-start groups. An extension to the ADAGIO study is planned.

On balance, these studies suggest that earlier initiation and longer duration of exposure to MAO-B inhibitors improves long-term outcome. The mechanism remains unclear and it will be important to determine if other types of medications yield similar results in delayed-start studies. In addition, it will be important to evaluate outcomes beyond UPDRS scores including cognition, mobility, balance, and quality of life. Nonetheless, these selegiline and rasagiline studies suggest that physicians should consider initiating an MAO-B inhibitor at or near the time of diagnosis.

1.4. Dopamine agonists

Dopamine agonists provide moderate symptomatic efficacy and commonly control parkinsonian motor signs and symptoms as monotherapy for a few years before levodopa is required. Compared with levodopa, dopamine agonists are associated with a higher rate of certain dopaminergic adverse events including hallucinations, peripheral edema, somnolence, sudden onset sleep, and impulse control disorders (ICDs) [10]. Ropinirole [11], pramipexole [12,13], pergolide [14], and cabergoline [15] have been compared to levodopa for the treatment of early PD in large, randomized, double-blind trials of up to 5 years duration. In these studies, initial treatment with a dopamine agonist was associated with fewer motor complications, especially dyskinesia, but levodopa provided greater symptomatic benefit as assessed by UPDRS scores. More recently, long-term follow-up studies have provided evaluations over 6–14 years of observation.

The Parkinson Study Group recently reported long-term results of the Comparison of the Agonist Pramipexole with Levodopa on Motor Complications of PD (CALM-PD) trial [16]. The CALM-PD trial was a 4-year study that enrolled 301 early PD patients who were in need of dopaminergic therapy, with 151 randomized to initial (double-blind) treatment with pramipexole and 150 randomized to levodopa. Additional open-label levodopa could be added when necessary. Two-hundred twenty two of these subjects enrolled in the CALM Cohort study and were followed for up to an additional 2 years; all PD medications could be used as appropriate.