A Closer Look at Parkinson’s Therapies

AN UPDATE BY PRACTICAL NEUROLOGY STAFF

Current Parkinson’s therapy is largely based on replacing dopamine lost due to deterioration of the substantia nigra, and is most effective in the early stages of the disease. However, the development of motor complications (i.e., motor fluctuations and dyskinesias) inevitably occurs after long-term use of levodopa.

Since the mid-1970s, monoamine-oxidase type B inhibitors (MAO-BIs) have been used to treat the symptoms of PD, by presumably lessening oxidative stress and enhancing the effect of dopamine. Here we take a look at two of these agents, zydis selegiline (Zelapar) and rasagiline (Azilect)—and rotigotine (Neupro).

DRUGS

MAO B inhibitors. These medications include selegiline (Eldepryl, Zelapar) and rasagiline (Azilect). Selegiline, first introduced in 1979 in Austria, has had a checkered history in Parkinson’s disease treatment. Noted to have mild to modest symptomatic benefit, it was also thought to possibly slow the progression of the disease, prompting the performance of the DATATOP trial in the 1980s to evaluate this question. Following the failure to demonstrate a unequivocal evidence of neuroprotective effect, selegiline gradually settled into a background role in Parkinson’s disease treatment, usually being used as an adjunct agent in fluctuators and in the setting of mild, early disease.

Zelapar is a reformulation of selegiline that dissolves quickly in the mouth, leading to absorption through the buccal mucosa rather than the gastrointestinal tract and has been demonstrated to be an adjunct therapy to levodopa. Clinical trials (the Waters et al. 2004 study in Movement Disorders) have demonstrated Zelapar’s effectiveness for reducing off time by up to two hours daily in fluctuating patients.

Published in 2007, Lew et. al’s study found similar results. Long-term selegiline orally disintegrating tablet (ODT) 2.5mg/day was effective, safe, and well tolerated in patients with Parkinson’s disease experiencing off episodes during levodopa therapy. Mean reduction in “off” time from baseline in daily off time was 9.4 percent (1.6 h) for patients previously given selegiline ODT, 6.0 percent (1.2 h) for those switched from placebo, and 8.1 percent (1.4 h) overall. PGI-I and CGI-S ratings indicated little or no change from baseline. Treatment-related adverse events occurred in 132 (52 percent) patients, though this didn’t prompt discontinuation. The open-label extension

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enrolled 254 patients, including 248 from the large phase 3 studies (efficacy analysis) and an additional six from the prior open-label comparison (safety analysis) in order to evaluate a larger population for safety purposes.

One improvement the drug creates is what it does not create: an amphetamine byproduct. The predecessor of zydis selegiline, selegiline, would metabolize into amphetamine compounds that could lead to adverse reactions including central nervous system and cardiovascular effects (sleeplessness, agitation, hallucinations, confusion, elevated blood pressure and rapid heart beat). Fortunately, these side effects are not very common, since the amount of the amphetamine metabolite is quite small, but in sensitive patients, the insomnia can be troublesome.

While in practical experience, the amphetamine byproduct of selegiline metabolism did not have meaningful cardiovascular effects in the clinical setting, the use of Zelapar has negated the issue by eliminating amphetamine metabolite induced by liver metabolism. This is done by bypassing metabolism in the liver, resulting in higher serum levels of selegiline and almost complete elimination of the amphetamine byproduct. This, however, is likely the most distinguishing factor about the formulation. The drug, taken once a day, otherwise does not differ from the orally administered selegiline and there is no evidence that it needs to be taken more frequently to optimize its effect.

As it would be anticipated, the use of zydis selegiline—like the original formulation of selegiline—can increase levodopa’s side effects, including dyskinesias, hallucinations and confusion. Its official status from the FDA is for treatment of motor fluctuations and it is a reasonable option in the treatment of very early PD. Overall, zydis selegiline is minimally to modestly beneficial in a very select group of patients. Zelapar decreases off-time and increases on-time with levodopa in ways comparable to other agents that alter levodopa catabolism.

Selegiline formulations are useful in early PD, when the patient is interested in low-intensity therapy and doesn’t need a DA or levodopa. It has been tried with fluctuators with some success. Dr. Gollomp has a group of patients who want to use it because they subscribe to its potential neuroprotective effect, in spite of the inconclusive findings on DATATOP, partly because of the 2005 Scandinavian study in Annals of Neurology, which suggest a lower incidence of dyskinesias later in the disease if selegiline is used earlier on.

Switching patients doesn’t appear to be a problem. Researchers conducted an open label oral to Zydus switch study to evaluate tolerability of rapid switch, and relative efficacy, in 48 subjects from five sites and found that, overall, patients preferred the Zydis preparation. Per clinician global impressions, fluctuations improved and the “on” UPDRS part II scores improved. Total UPDRS and measures of fatigue and sleep were unchanged and adverse events were concluded as mild. “Patients generally preferred the Zydis selegiline preparation but the modest difference is of unclear clinical significance given the open label nature of the trial,” the authors noted.

AZILECT (RASAGILINE)

As for the second MAO-B inhibitor, rasagiline, experience is similar to that with Zelapar. It’s been met with modest enthusiasm and it resembles selegiline but is more potent and does not have the amphetamine byproducts issue. The well-noted TEMPO, PRESTO and LARGO studies, when taken together, suggest rasagiline may be of benefit in early and late disease, but this is more a function of how these trials were designed and needs elaboration to understand its role in everyday practice.

Efficacy was demonstrated in the PRESTO trial, where rasagiline was used as an adjunct therapy with levodopa. The 26-week placebo-controlled study involved 472 PD patients taking rasagiline 1mg/day or 0.5mg/day given with levodopa. It concluded it drastically decreased off-time in comparison with placebo, and improved motor function.

The 18-week, double-blind, placebo- and active-comparator controlled trial of rasagiline LARGO study sought to assess the efficacy and safety in treating PD patients with motor fluctuations. The 687 patients were randomized to rasagiline 1mg once daily, entacapone 200mg with every levodopa dose, or placebo. As with the PRESTO study, the study showed that when added to levodopa and other PD drugs, once-daily rasagiline provides a reduction in off-time with a corresponding increase in on-time.

The TEMPO study found symptomatic benefits of rasagiline in a series of phase III trials, in which it was administered alone or in combination with standard levodopa therapy. The 26-week TEMPO trial studied rasagiline monotherapy compared with placebo in 404 patients with early PD (not using levodopa), and found treatment with rasagiline was extensively more successful than placebo in regard to change in the Unified Parkinson’s Disease Rating Scale (UPDRS) score from baseline to endpoint. After the treatment was continued for 12 months, patients involved in the two active treatment regimens—1mg and 2mg rasagiline—of the TEMPO trial showed a smaller decline in total UPDRS than those in the placebo group, whose switch to rasagiline was delayed by six months. These studies are certainly of merit; however, rasagiline’s benefit is most effectively had when it is used very early in PD treatment.

In 2013, Elmer published post hoc analyses of the PRESTO and LARGO trials, assessing clinical effects of rasagiline 1mg/day on cardinal PD symptoms and motor

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fluctuations in defined patient subgroups who at baseline were receiving only levodopa, were considered “mild fluctuations” (daily OFF time ≤ 4 h), and who were or were not receiving concomitant DA or COMT-I therapy. When compared with placebo, “rasagiline significantly improved all cardinal PD symptoms and significantly reduced adjusted mean daily OFF time when used as first adjunct therapy in levodopa-treated patients and in patients with mild motor fluctuations,” according to the study. Significant improvement in motor fluctuations was reported with rasagiline regardless of concomitant DA or COMT-I use, and overall incidence of dopaminergic adverse events did not increase with concomitant DA or COMT-I use.

Early speculation led many to believe that rasagiline might generate a neuroprotective effect if given sufficiently early in the course of the disease. The possibility that MAO-Bs could be neuroprotective has raised the hopes and dreams of the entire movement disorder community since the studies by Tetrud and Langston in 1989 and in 1993 by the Parkinson Study Group. Unfortunately, this “holy grail” of therapy is exceedingly difficult to document since the studies by Tetrud and Langston in 1989 and in 1993 by the Parkinson Study Group.

In a 2009 study, Olanow et al. looked at 1176 subjects with untreated Parkinson’s disease who were randomly assigned to receive rasagiline (at a dose of either 1mg or 2mg per day) for 72 weeks (the early-start group) or placebo for 36 weeks followed by rasagiline (at a dose of either 1mg or 2mg per day) for 36 weeks. The found that “early treatment with rasagiline at a dose of 1mg per day provided benefits that were consistent with a possible disease-modifying effect, but early treatment with rasagiline at a dose of 2mg per day did not. Because the two doses were associated with different outcomes, the study results must be interpreted with caution.”

What makes matters difficult with getting neuroprotective language is that the FDA and various other scientific bodies are unable to clearly delineate a precise marker for neuroprotection in any disease, particularly PD. In the Azilect case, the S-enantiomer of rasagiline, which is 1000 times less active on MAO-B, exhibits neuroprotective properties. Furthermore, the neuroprotective activity of rasagiline has been monitored at concentrations below the MAO inhibition threshold as well as in cell systems that do not include MAO-B. Some could contend that rasagiline also possesses neuroprotective activity independent of MAO-B inhibition. The mechanisms where rasagiline has neuroprotective effects are multifactorial and include upregulation of cellular antioxidant activity and antiapoptotic factors. Some studies show rasagiline to suppress oxidant stress in dopaminergic neurons by increasing the expression of antioxidative enzymes superoxide dismutase and catalase.

ROTIGOTINE

After somewhat of a lull in PD drug development, the transdermal patch rotigotine (Neupro, Schwarz Pharma, today a subsidiary of UCB), a non-ergolinic dopamine agonist, shook things up in 2007. It was first approved as a treatment for early stage Parkinson’s, but was then removed from the market in 2008 after a manufacturing issue which caused the medication to crystalize, thereby lowering its effectiveness and making it impossible for the manufacturer to guarantee proper dosing. The problem was caused by distribution and storage, and was re-approved in 2012 for both early and advanced stages, as well as moderate-to-severe restless leg syndrome.

The system delivers rotigotine continuously for the 24 hours that the patch is worn and patches are available in 1, 2, 3, 4, 6 and 8mg/24 hours ranging in size from 5cm² to 40cm². According to UCB Pharma, roughly 45 percent of the drug is released within 24 hours, but an independent study showed that the absolute bioavailability was only 37 percent. Rotigotine is approximately 89.5 percent protein-bound and extensively metabolized in the liver. The manufacturer recommends no dose adjustment for renal or moderate hepatic impairment and no dose adjustment for the elderly between ages 65 and 80, although increased sensitivity may be seen.

A Phase III clinical trial published in Neurology in 2007 found “positive results of its once daily dopamine agonist, rotigotine, for the treatment of early-stage Parkinson’s disease.” According to a January 2007 study published in The Annals of Pharmacotherapy, “In clinical trials of patients with early Parkinson’s disease, rotigotine has decreased combined scores on the motor and activities of daily living sections of the Unified Parkinson’s Disease Rating Scale up to 85 weeks. In patients with advanced Parkinson’s disease, rotigotine reduced mean off-time when used as an adjuvant to levodopa.”
