DISEASE-MODIFYING STRATEGIES

A.H. Schapira
Institute of Neurology, Queen Square, UCL, London UK

Parkinson's disease (PD) usually first manifests clinically through features resulting from the loss of dopaminergic neurons in the substantia nigra pars compacta. These motor symptoms are at first well controlled by dopaminergic therapy. However, as neuronal degeneration continues, not only do the dopaminergic features become more refractory to treatment, but additional non-motor symptoms appear for which no or only limited therapy is available. Thus a major goal of current PD research is to develop strategies to slow or prevent disease progression, which if successful, would be expected to be 'neuroprotective' to dopaminergic and non-dopaminergic systems alike.

The identification of biochemical abnormalities in PD brain has already led to early attempts to modify the course of the disease. Experiments with antioxidants have been disappointing. The potential for the monoamine oxidase B (MAO-B) inhibitor selegiline (deprenyl) to modify the course of PD was examined in the DATATOP study.[1] The results showed that in early PD, selegiline was able to delay the requirement for levodopa by 9–12 months, but this may simply be a modest symptomatic benefit. However, in a long-term follow-up study, patients who had been taking selegiline for seven years had a significantly slower decline, less wearing-off, "on-off" and freezing but more dyskinesias compared to patients who were changed to placebo after five years.[2]

The more potent MAO-B inhibitor rasagiline has demonstrated neuroprotective properties in several laboratory models, independent of its MAO-B inhibition. The 12-month, delayed-start TEMPO study showed that patients with early PD who were randomized to rasagiline at the outset had a better UPDRS score than those who received the drug six months later.[3] The soon-to-be-released results of the large ADAGIO delayed-start study will provide further insight into the potential effect of rasagiline.

Dopamine agonists have also demonstrated neuroprotective properties in *in vitro* and *in vivo* models of PD. Two studies—CALM-PD[4] (pramipexole) and REAL-PET[5] (ropinirole)—have been published, investigating the potential neuroprotective properties of dopamine agonists in early PD patients. Both these studies used imaging of the nigrostriatal system as a surrogate marker of disease progression, and both demonstrated a very similar effect in producing a ~35% decrease in the rate of loss of imaging marker over two years, extending to four years in the case of pramipexole. However, the interpretation of these results remains uncertain.

To test the hypothesis that early administration of pramipexole can modify PD and delay the progression of motor function deterioration in early PD patients, the PROUD study is under way using a delayed-start design combined with SPECT imaging.[6] This is a novel design that combines a primary clinical endpoint with, amongst others, a secondary clinical imaging endpoint. Results, expected in 2009, will provide insight not only into the effect of early pramipexole therapy on motor progression, but also the possible mechanisms that may underlie the effect.

In conclusion, no drug has yet demonstrated unequivocally that it is capable of slowing the progress of PD, although the results of some studies have been promising and warrant further evaluation.

References

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