New hope for Parkinson's disease progression delay

A recent trial indicates that rasagiline might slow down Parkinson's disease progression, and also highlights challenges for the development of disease-modifying drugs.

Bethan Hughes

A pioneering Phase III trial designed to assess whether rasagiline (Azilect/Agilect; Teva/Lundbeck) can slow down the progression of Parkinson's disease (PD) has shown success. The top-line results of the ADAGIO delayed-start study, which were presented at the 12th Congress of the European Federation of Neurological Societies, Madrid, Spain, 23–26 August 2008, indicated that early treatment with rasagiline provided benefits that were not obtained with later initiation of the drug. This is the first time that a prospective large-scale, randomized, double-blind trial has provided evidence that a drug might slow down PD progression.

Increasing preclinical and clinical evidence has suggested that rasagiline — a selective, irreversible monoamine oxidase B (MAO-B) inhibitor — could delay the progression of PD. However, as rasagiline also alleviates the symptoms of PD to some extent, it has been difficult for trial investigators to rule out confounding factors when analysing clinical results.

"The problem we have faced is that we really didn't have a study design that told us if positive results in a clinical trial occurred because the study intervention actually slowed the disease process or simply provided symptomatic or pharmacological effects that masked ongoing neurodegeneration," explains Warren Olanow, Professor and Chairman of the Department of Neurology, Mount Sinai School of Medicine, New York, USA, and ADAGIO co-principal investigator. To try and overcome this, a new treatment design called the delayed-start study was introduced.

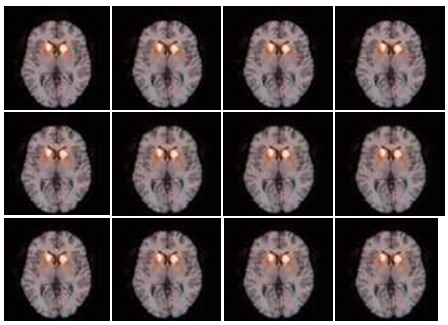

Image kindly provided by Ken Marek, President, Institute for Neurodegenerative Disorders, New Haven, Connecticut, USA.

This study design randomizes patients into two groups: one group that starts drug treatment early and a delayed-start group that receives placebo. After an initial treatment phase, all patients are put on the same treatment in the second phase of the study. The key aspect then is whether a difference in measures of disease between the early group and the delayed-start group seen after the initial treatment phase is still present at the end of the second phase.

In the ADAGIO study, all the primary end points chosen to demonstrate an effect of the drug on disease progression using this design were met for patients receiving the 1 mg per day dose of rasagiline. "This means that early treatment provided a benefit that could not be achieved with later introduction of the same drug. This finding cannot be readily explained by a symptomatic effect, as both groups were on the same treatment, and is consistent with the possibility that the drug has a neuroprotective effect," says Olanow.

According to Moussa Youdim, Professor of Pharmacology, Technion-Rappaport Family Faculty of Medicine and Institute, Haifa, Israel — whose lab discovered rasagiline and co-developed it with Teva — there is significant *in vitro* and *in vivo* preclinical evidence that rasagiline is neuroprotective, and increasing evidence that it might also be neurorestorative.

He explains: "Rasagiline upregulates the anti-apoptotic BCL2 family of proteins and downregulates the pro-apoptotic members BAX, BAD and BIM. It also prevents the opening of mitochondrial permeability transition pores, a sign of traumatic brain injury [*Drugs Today* 41, 369–391; 2005]." In addition, preliminary studies suggest that rasagiline increases levels of the brain- and glial-derived neurotrophic factors (BDNF and GDNF), which might promote neurorestoration.

Importantly, says Youdim, the *S*-isomer of rasagiline, TVP1022, has similar neuroprotective activity and is not an MAO-B inhibitor, which suggests that the neuroprotective activity of rasagiline is not related to its MAO-B inhibitory action. In addition, his group has reported evidence that rasagiline's metabolite aminoindan also contributes to the neuroprotective activity.

Nevertheless, achieving an FDA-approved label stating that a drug is disease-modifying based on clinical data such as those obtained during the ADAGIO study seems very challenging. "Proving that you are modifying the disease in a neuropathological, anatomical, electrophysiological or neurochemical sense is currently almost impossible to do. So, to try to infer that only from clinical data is a monumental leap, and I don't think that the regulatory agencies are likely to let you say are modifying the course of the disease," says Gene Johnson, Professor of Molecular Biology and Pharmacology, Washington University School of Medicine in St Louis, Missouri and Chief Scientific Advisor at The Michael J. Fox Foundation for Parkinson's Research (MJFF), USA.

To achieve this, continues Johnson, will require a biomarker that is "wedded to the disease", perhaps even linked both genetically and neuropathologically. Unfortunately, there are currently no validated biomarkers for PD progression, but the MJFF is extensively funding research in this field. "Several rounds of big funding have been going to a range of projects from imaging to blood-based markers," says Jonathan Brotchie, Director of Atuka Ltd, a clinical research organization specializing in the development of novel therapeutics and diagnostics for PD.

Another major hurdle for development of disease-modifying therapies is the lack of reliable animal models, says Brotchie. "In the absence of any proven disease-modifying agent, we just don't know the validity of any of the models. So you have a significant hurdle relatively early on in the development process." In turn this affects investment, says Johnson. "Without a very good predictive animal model, it's difficult to generate sufficient confidence in a particular approach. People don't want to invest 10s or 100s of millions of dollars just to find out that it doesn't work."

Until these problems are addressed, it will remain challenging to translate laboratory findings for PD into the clinic. Olanow concludes: "The hope is that with advances in science we will be able to more accurately determine the precise cause of cell death in PD in order to develop neuroprotective drugs, that we will have better models that more accurately reflect the aetiology and pathogenesis of PD in which to test them, and study designs that provide an accurate measure of the effect of the intervention on disease progression."