IS THE EFFECT OF MAO-B INHIBITORS CLINICALLY RELEVANT: NO

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Dopamine (DA) is a catecholamine synthesized in the brain from the amino acid tyrosine. Tyrosine is metabolized to dihydroxyphenylalanine (DOPA) by the enzyme tyrosine hydroxylase. DOPA is then metabolized to DA via aromatic amino acid decarboxylase. DA is mainly metabolized by monoamine oxidase type B (MAO-B) and catechol-O-metyl transferase (COMT). Therefore, inhibition of one and/or both of these enzymes would decrease DA metabolism and result in increased concentration of DA in the brain. The use of MAO-B inhibitor to potentiate the action of DA formed from l-dopa had always been considered logical. Moreover, the recognition of multiple forms of MAO and the discovery of l-deprenyl, a selective MAO-B type-devoid of the 'cheese effect' –have led to the application of these drug in combination with l-dopa for the treatment of PD. L-deprenyl (also known as selegiline) was the first MAO-B inhibitor approved for the use in PD patients since 1974. Rasagiline is also a selective, irreversible but more potent MAO-B inhibitor, without the amphetamine metabolites. Contrary to selegiline, rasagiline is approved as monotherapy and as an adjunt to levodopa.

In the largest clinical study, known as DATATOP, in early PD not on dopaminergic therapy, patients were randomized on selegiline, tocopferol, a combination of both drugs, or placebo. Patients randomized to selegiline had a mild symptomatic benefit. On clinical diagnosis of PD there is approximately 70% loss of DA, while many studies have reported the loss of striatal DA with ageing. Thus, MAO-B inhibition seems as promising therapy if 'disease-modification' effect could be confirmed. But contrary to substantial amount of evidence from experimental PD models that showed the neuroprotective effects of MAO-B inhibitors, controlled clinical studies did not confirm disease-modification and/or neuroprotective effects of MAO-B inhibitors. Increased life expectancy resulting from addition of selegiline to l-dopa treatment in PD patients was indicated only in an open, uncontrolled study. On the contrary, rasagiline was tested for its neuroprotective effects in two prospective, double-blind, placebo-controlled, parallel-group, randomized clinical studies in early PD patients (TEMPO, ADAGIO). Both studies used a delayed-start design in an attempt to separate confounding symptomatic from disease-modifying effects. But the ADAGIO study results raised some debate and concerns, in particular, the divergent and paradoxical outcome between different daily doses. Thus, using delayed-start design still did not provide insights in disease-modification effects of MAO-B inhibitors in PD.