MAO B INHIBITORS ARE NOT NEUROPROTECTIVES FOR PARKINSON`S DISEASE

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Parkinson's disease (PD) is unique among other neurodegenerative disorders because the number and variety of completed clinical trials for PD neuroprotection has exceeded those conducted for all other neurodegenerative disorders.

During the years several plausible mechanisms have been considered as possible target for the application of effective treatments for PD (antioxidants, pro-metabolics, antiapoptotics, antiexcitotoxics, and anti-inflammatories , among others) however till now we still have not yet found a solution .

Neuroprotection in PD implies any intervention that can diminish or stop the progressive loss of neurons in the substantia nigra, pars compacta. The ideal method to demonstrate neuroprotection would be to identify a diminished rate of loss of these neurons. Currently measurements of neurons can only be done postmortem en even then determining rate of decline poses a challenge.

From a clinical point of view neuroprotection can be defined by any intervention which causes halting or slowing the emergence or worsening of disability in everyday activities, diminishing the decline of ratings focused on distinctive parkinsonian features, or avoidance of specific clinical milestones (such as the perceived need for starting dopaminergic therapy). The "need for initiation of dopaminergic therapy" has been applied in several investigations. This endpoint despite its apparent imprecision has proven to correlate well with more objective ratings of parkinsonism and was used as the primary endpoint in the first trial of neuroprotection, in the DATATOP study).

Most of the studies which evaluate benefit of drugs for the symptomatic or neuroprotective benefit in PD have utilized the Unified Parkinsonn's Disease Rating Scale (UPDRS). In particular the motor part of the UPDRS has been utilized as the primary outcome measure. However has not been established yet what **changes in UPDRS scores** represent a **clinically relevant improvement**. In 2006 a group of researchers from Europe examined 603 patients to determine the **minimal clinically important change (MCIC)** referred to the status before treatment, for the motor part of the UPDRS, activities of daily living (ADL) and total scores. An anchor based method (CGIC) of seven points global clinical improvement was used. A change of **5 points on the UPDRS motor part** was found to be the most appropriate cutoff score for all Hoehn and Yahr stages I to III, and a change of **8 points** for the **UPDRS total score**.

For the **UPDRS ADL score**, an MCIC of **2 points** for Hoehn and Yahr stages I/I.5 and II and of **3 points** for H&Y II.5/III was the most appropriate cutoff score.

Moreover a group of neurologists from USA. examined 888 patients with idiopathic PD analyzing UPDRS mentation, ADL and motor subscores of the UPDRS. Independent of medication status and cross-sectional and longitudinal analyses, ADL subscores showed a stronger and more stable association between disease duration than other UPDRS subscores after adjusting for age of disease onset. The authors concluded that **the strong association between ADL subscore and disease duration in PD suggests that this measure may serve as a better marker of disease progression than signs and symptoms assessd in other UPDRS sections.**

Recently (2009) a Cochrane review analyzed 10 studies (2422 Pts.) The mean follow up was for **5.8** years. **The conclusions were MAO B inhibitors do not appear to delay disease progression but may have a beneficial effect on motor fluctuations.**

In 2006 a Quality Standards Subcommittee of the American Academy of Neurology published an article analyzing the information available concerning Neuroprotective strategies and alternative therapies for PD (**an evidence based review**). In their conclusions their wrote

"Early use of rasagiline as compared to placebo is associated with less deterioration in the UPDRS scores in a single Class I study. However the additional symptomatic treatment (dopaminergic therapy) and possible symptomatic effect of rasagiline itself confounds the interpretation of whether this represents a neuroprotective effect. **There is insufficient evidence to support or refute the use of rasagiline** (level U) for neuroprotection".

Very recently (20) it was published a cardinal article (the Tempo study) suggesting some neuroprotective properties using rasagiline in early PD. The drug was admistered in a double blind **delayed start approach to 1176 patients**. Although the pretentious from the article if we measure the difference between the **early versus the late addition of rasagiline to PD the crude numbers are quite disappointing**: 1) in the first period (between week 12 and 36) (rasagiline vs placebo) the increase (worsening) measured by UPDRS was **0.09 + 0.02 vs 0.14 + 0.01.(p=0.01).** In the comparison between baseline and week 72 less worsening was recorded in the rasagiline group (**2.82 + 0.52 vs 4.52**

+0.56 in the delayed start group; p=0.02). That means a net difference of **1.7 in the motor UPDRS.**

Although the numbers were significantly different we need to be very cautious before a conclusion can be driven.Statistically significant results don't mean clinical effective results. Specially considering that rasagiline 2mg did not show any difference (authors conclusions).

Final conclusions: **It would be inappropriate to give an agent a neuroprotection license based on small benefits in total UPDRS score which were below the threshold for clinical significance. Larger and longer parallel design placebo-controlled trials would be required to assess the long-term effects of such a therapy, preferably using patient-rated quality of life scales (PDQ 39).**

Such trials should also examine the effects of the agent on the non motor features of PD such as the onset of dementia and falls.