Early monotherapy with rasagiline was efficacious for symptomatic management of Parkinson’s Disease, but there was insufficient evidence of neuroprotection.

Clinical Problem: A 65-year-old patient, recently diagnosed with mild Parkinson’s disease, on no medications, would like to know if there is any treatment that can slow the progression of his disease.

Clinical Question: In patients with early and mild Parkinson’s disease, does early treatment with rasagiline delay disease progression?

Search Strategy: A Medline search was carried out using the keyword “Parkinson Disease”, and limiting to subtopic “therapy”. This was limited to randomized control trials, and 80 results were obtained. “Parkinson Disease” was also combined with keyword “neuroprotective” and limited to randomized control trials, and this search yielded 24 results. The Cochrane Database was also searched and there was one review looking at monoamine oxidase B inhibitors for early Parkinson’s disease. Expert opinion was obtained, and this randomized controlled trial (included in the 24 articles from the Medline search) was recommended by Dr. M. Jog and Dr. M. Jenkins (Movement Disorders Specialists, Western University, London, ON).

Clinical Bottom Lines:

1. Early initiation of treatment with rasagiline 1mg/day (0-72 weeks) slightly improved UPDRS score (1.68/176 points, p=0.02, CI -5.15 to -0.21) at 72 weeks as compared to a delayed-start of treatment (placebo 0 – 36 weeks, followed by rasagiline for 36-72 weeks).
2. There was no change in the UPDRS scores between the early versus delayed-start of treatment with rasagiline at the 2mg/day dosing.
3. Rasagiline was shown to be effective for symptomatic management of Parkinson’s disease.

The Evidence:
Multicenter randomized double-blind controlled trial of 1176 subjects with untreated Parkinson’s disease. Patients were assigned randomly to an early initiation of rasagiline (dose of either 1mg/day or 2mg/day) for 72 weeks or a delayed-start with placebo for 36 weeks followed by rasagiline (dose of either 1mg/day or 2mg/day) for 36 weeks. There were three primary end-points when comparing early to delayed-start treatment groups: 1) rate of change of UPDRS score between weeks 12-36, 2) UPDRS score at 72 weeks, and 3) rate of change UPDRS score between 48-72 weeks. Secondary end-point was change in UPDRS score from baseline to 36 weeks in patients on placebo, 1mg/day or 2mg/day.

Data: Estimated Change in Total UPDRS score from Baseline to week 72

<table>
<thead>
<tr>
<th>Rasagiline Dose</th>
<th>Change in UPDRS score (±SE)</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg / day, early start vs. delayed start</td>
<td>-1.68 (±0.75)</td>
<td>-3.15 to -0.21</td>
<td>0.02</td>
</tr>
<tr>
<td>2 mg / day, early start vs. delayed start</td>
<td>0.36 (±0.68)</td>
<td>-0.99 to 1.70</td>
<td>0.60 (NS)</td>
</tr>
</tbody>
</table>

Comments:
1. Study funding, data was collected and statistical analysis was carried out by sponsoring
pharmaceutical company.
2. The follow-up period was short (18 months)
3. Study had 22.6% total dropout, with 910/1176 patients completing the study. This was underpowered based on the power calculations taken from the TEMPO study (cited in methods section p1270).
4. Intention to treat analysis was not carried out.
5. One of the primary endpoints of the study is the slope of the UPDRS decline over time, and it is assumed to be linear (which it may not be).
6. The clinical significance of a 1-3 point increase on scale of 176 is unclear.
7. Logically, one would expect a similar response or dose-response when comparing the results from the 1mg and 2mg doses of rasagiline. This was not seen.
8. Post-hoc subgroup analysis was proposed after study completion and thus not statistically as robust.

References:


Appraiser: Courtney Casserly and the UWO Evidence Based Neurology Group

Date Appraised: November 10, 2009