

RASAGILINE

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Rasagiline (N-propargyl -1 R-aminoindan) is a relatively selective irreversible MAO-B inhibitor at doses recommended for PD. This selectivity is important in avoiding the 'cheese effect' of MAO-A inhibitors. However, higher doses (> 2mg/day) of rasagiline will begin to inhibit MAO-A and so should be avoided. Rasagiline is a propargylamine and so is structurally related to selegiline, but is approximately 10-15 times more potent. It has good central nervous system penetration and long half-life which allows a once-daily dosage schedule. Rasagiline is metabolised to aminoindan in contrast to selegiline which is metabolised to metamphetamine. This difference may have clinical relevance in terms of side effect profile and the potential for disease modification (see below).

Two studies have been published on the use of rasagiline in patients with early PD.^{1,2} Four hundred and four patients with typical PD and Hoehn and Yahr stage no greater than III and who had not received dopaminergic drug therapy were enrolled and randomised to placebo or rasagiline (1 or 2mg/day). In the placebo and rasagiline 1mg and 2mg groups, 81%, 83% and 80% respectively were still on 'monotherapy', there were no statistical differences in the rates for either levodopa supplementation or patient withdrawal. At the end of the six month period, the 1mg rasagiline group had an improved unified PD rating scale (UPDRS) score compared to placebo of 4.2 units ($p < 0.001$), and this was 3.56 ($p < 0.001$) for the 2mg group. Better quality of life scores in the rasagiline arms also accompanied the improvement in motor features. The degree of motor improvement over the six month period was comparable to that seen for selegiline in the DATATOP study,³ but not as great as that seen for dopamine agonists.^{4,5} There were no significant differences in the adverse event profile between the treatment arms and placebo. At six months, the two treatment arms were almost back to their respective baseline UPDRS scores.

The above six month study was extended by a further six months with 380 of the original 404 patients entering the treatment phase.² Patients were continued on their original dose of rasagiline or if on placebo, were given rasagiline 2mg/day. For the whole 12-month period, deterioration from baseline scores was 3.01, 1.97 and 4.17 UPDRS units for the 1mg, 2mg and delayed 2mg cohorts. Those given rasagiline 1mg/day for 12 months compared to those on the 2mg dose for only the last 6 months maintained a total UPDRS improvement of 1.82 UPDRS units ($p = 0.05$). The 12-month rasagiline 2mg group had a 2.29 unit ($p = 0.01$) improvement over the 2mg 6-month group (see fig).

This long-term study provides several important clinical insights into the potential for rasagiline use in early PD. The symptomatic benefits of rasagiline are maintained over 12 months. In the 1mg and 2mg rasagiline groups, 52.5% and 63.8% of patients were considered responders respectively. There are also some interesting implications for a potential disease modifying effect in PD, which is discussed in more detail below.

Two studies have been published on the efficacy of rasagiline in PD patients already taking levodopa. The PRESTO trial investigated a total of 472 patients, mean age approximately 63 years, on stable levodopa with at least 2.5 hours of 'off' i.e. poor motor state.⁶ Patients could also be taking other drugs for PD including a dopamine agonist. The primary end point was a change in mean total daily 'off' time. Placebo decreased 'off' time by 0.9 hours (15% of 'off' time). Rasagiline 0.5mg/day reduced 'off' time by a mean of 1.4 hours ($p = 0.02$ vs placebo), and 1mg/day by 1.9 hours ($p < 0.001$ vs placebo), equating to 23% and 29% reduction of 'off' time respectively. Benefits were seen within 6 weeks of randomisation and maintained throughout the 26 week study period. The improvement in 'off' time was accompanied by a corresponding increase in 'on' time, which in the 0.5mg group was without troublesome dyskinesias, but 32% of the extra 'on' time in the 1mg group was with troublesome dyskinesia but did not lead to any early terminations. The 1mg rasagiline dose also resulted in significant improvements in the UPDRS score. Balance difficulty, weight loss, anorexia and weight loss occurred more commonly in the rasagiline groups, but there was no significant difference in the discontinuation rate between the treatment and placebo arms. Again, there was no increase in hallucinations, confusion or somnolence. Depression was slightly less common in the 0.5mg rasagiline group.

The LARGO study investigated the effect of 1mg/day rasagiline compared to entacapone or placebo in 687 PD patients on stable levodopa but with at least 1 hour of motor fluctuations per day.⁷ Entacapone is a catechol-O-methyl transferase inhibitor and its administration increases levodopa absorption and prolongs its half-life. Its use with levodopa has been demonstrated to increase 'on' time and reduce 'off' time.⁸ 599 patients completed the study; approximately 60% of patients in each arm were also on dopamine agonists. Placebo reduced 'off' time by 0.4 hours, both rasagiline and entacapone decreased 'off' time by 1.2 hours ($p < 0.0001$ vs placebo). There was a comparable and significant increase in 'on' time without dyskinesias of 0.8 hours with both drugs. Again these improvements were established at 6 weeks and maintained for the 18 weeks of the study. Secondary end points including UPDRS and clinical global impression were significantly improved in the treatment groups. Similar benefits were seen in patients above (approximately 28% of subjects) or below age 70 years of age. There was no significant difference in adverse event rates between the placebo and treatment arms but 2% of patients in the rasagiline and entacapone arms had postural hypotension.

These two studies demonstrate that once a day rasagiline (1mg) significantly improves PD control in patients optimised on levodopa with or without additional therapy e.g. dopamine agonist. It is well tolerated and is effective in younger (<70 years) and older (>70 years) patients. Its efficacy is comparable to entacapone, but probably less than that of dopamine agonists which induce a 1-2 hour improvement in PD control.^{9,10}