Tolerability and efficacy of switching from swallowed selegiline to Zydis selegiline (Zelapar®) in patients with Parkinson's disease

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ABSTRACT

Background: Zydis selegiline is a novel preparation that results in higher and more consistent serum selegiline levels, and lower levels of amphetamine metabolites. The drug increases "on" time in fluctuating PD subjects compared to placebo but there is little efficacy data comparing oral vs. Zydis selegiline preparations.

Methods: We conducted a multi-center, open label switch trial of PD patients taking stable doses of oral selegiline. Patients were assessed with a series of motor (UPDRS) and non-motor scales, including PDQ-8, Epworth sleepiness scale, PD fatigue severity scale, and Beck depression scale at entry (oral selegiline) and six weeks after switching to Zydis selegiline, 2.5 mg/day. We also assessed global impressions, visual analogue scales of change, drug preferences, and adverse events.

Results: Five sites enrolled 48 subjects (11 female, age 71.1 (8.8) years). Follow-up data was available on 46. Of these, 25 preferred Zydis selegiline, 13 preferred oral selegiline, and 8 had no preference. UPDRS part II "on" scores significantly improved with Zydis selegiline, whereas part II "off" scores and part III scores showed trends toward improvement. A battery of non-motor assessments did not change. Adverse events were minimal and expected.

Discussion: An acute switch from oral selegiline to Zydis selegiline was well tolerated and patients tended to prefer the Zydis preparation.

INTRODUCTION

Selegiline is a monoamine B specific inhibitor used to treat Parkinson's disease (PD) for more than 20 years. It has also been used for depression and attention deficit disorder, among other things. 1, 2 In PD, selegiline produces a modest symptomatic effect, which has obfuscated the clinical determination of whether it possesses long term disease modifying properties. Conflicting long term clinical data further complicate assessments of oral selegiline. 3-8

Although multiple potential mechanisms of neuroprotection exist, the original hypothesis suggested that MAO-B inhibition would reduce dopamine turnover, thus reduce non-enzymatic metabolism of dopamine, which produces toxic oxidative stress inducing compounds. One possible explanation for the lack of overt neuroprotection is that metabolites of selegiline (i.e. methamphetamine) potentially increase endogenous dopamine release and thus negate the dopamine sparing properties of the parent compound.

Recently, a sublingually absorbed Zydis preparation of selegiline (Zelapar®, Valeant) has been approved as adjunct therapy to levodopa. This novel preparation results in higher and more consistent serum selegiline levels, and importantly, lower levels of amphetamine metabolites. 9 The drug increases "on" time in fluctuating PD subjects compared to placebo 10, 11 but there is little efficacy data comparing oral vs. Zydis preparations.12 Therefore we conducted a multi-center open label switch study from oral selegiline to Zydis selegiline.

METHODS

This was a multicenter, 6 week, open label study evaluating the conversion from oral selegiline to orally disintegrating (Zydis) selegiline in PD patients. Inclusion criteria were a clinical diagnosis of PD using standard criteria, age 30-90, Hoehn and Yahr stage 1-4, who were taking a stable dose of oral selegiline for greater than one month. Exclusions criteria included dementia, the use of rasagiline, and other medications contra-indicated with selegiline in the package insert. Patients maintained their other PD medications throughout the study.

All subjects signed appropriate informed consent from their institutions. The study was registered on ClinicalTrials.gov NCT00640159. It was funded by Valeant Pharmaceuticals, who had no role in data acquisition (individual sites), data management (AD), statistical analysis (AD and WO), or manuscript preparation (WO).

At visit 1, patients underwent a baseline "on" UPDRS (parts I, II, III, IV), PD Quality of Life-8 (PDQ-8), Beck Depression Inventory (BDI), Epworth sleepiness scale (ESS), PD Fatigue Severity Scale (PDFSS), orthostatic blood pressure and pulse. Demographics, medical histories, concurrent medications, and physical examinations were also assessed. Patients then discontinued oral selegiline and the next day started 1.25 mg Zydis selegiline for 10 days, followed by 2.5 mg Zydis selegiline for 30 days. On day 10, a telephone call reminded subjects to increase the dose to 2.5 mg daily, and assessed any adverse effects and gross efficacy. The final assessment occurred at week 6 (day 40). The entire test battery from Visit 1 was repeated. Patients and physicians provided global evaluation of improvement (100 mm V.A.S. scales and on 7 point Clinical Global Impression-Improvement scales), and patients recorded how much their dyskinesia changed (V.A.S. scale). Patient drug preference and reason for preferences were queried. Adverse events were also assessed. If patients desired to discontinue we attempted an early termination visit while on Zydis selegiline.

The primary efficacy point was drug preferences. All other assessments were secondary. Statistical analysis was performed using Stata version 8.0 (Stata Corporation, 4905 Lakeway Drive, College Station, TX, 77845, USA) Tabulations were performed on nominal variables, and means and standard deviations calculated for continuous variables. Comparisons of nominal variables used Pearson's Chi-Square test, and for continuous variables Student's t-test was used.

RESULTS

Forty-eight subjects (11 female) were recruited over 12 months from 5 sites. The mean age was 71.1 (8.8) and the duration of PD was 9.4 (4.7) years. H & Y staging at entry was 1 (4), 1.5 (1), 2 (28), 2.5 (4), 3 (7), and 3.5 (1). The daily dose of oral selegiline was 7.5 (3.5) mg equally distributed between 5 mg/day and 10 mg/day.

Five subjects stopped the Zydis selegiline prior to their scheduled follow-up visit. Three underwent a termination visit and are included in the analysis whereas two were lost to follow-up and not included in the comparative analysis. At the final analysis 25 patients preferred Zydis selegiline, 13 preferred oral selegiline, and 8 felt they were similar. Reasons for preferring Zydis selegiline (N=25) included placement on the tongue (20), convenience (9), better PD control (9), better mood (7), and fewer adverse events (3). Clinical global impressions showed that about half of all subjects felt at least mildly better on Zydis selegiline. [Table 1] Per clinician impressions, patients who were "fluctuating" decreased from 28 to 19 ($\chi 2$, $p<0.01$), patient "wearing off" decreased from 32 to 22 ($\chi 2$, $p<0.001$) and patients with "dyskinesia" decreased from 15 to 11, (NS) On Zydis selegiline, UPDRS part II "on" scores improved and part II "off" and part III "on" scores showed a trend toward improvement. [Table 1] Other non-motor assessments did not change. Vital signs did not change.

Any adverse event was reported by 10/48 subjects. These included: increased dyskinesia (2), orthostatic hypotension (2), bad taste (1), fatigue (1), freezing (1) fall (1), freezing (1), dry mouth (1), anxiety (1), confusion (1), insomnia (1), blurred vision (1), and weakness (1).

	Oral Selegiline N=46	Zydis Selegiline N=46	P value
UPDRS part II "on"	10.7 (5.6)	9.4 (4.6)	0.006
UPDRS part II "off"#	13.5 (6.3)	12.8 (6.7)	0.18
UPDRS part III "on"	23.8 (11.7)	21.6 (11.6)	0.10
PD Qol -8	8.4 (5.7)	8.6 (5.5)	NS
Epworth sleepiness scale	8.9 (4.8)	9.5 (5.1)	NS
PD Fatigue Rating Scale	41.7 (16.5)	41.3 (16.2)	NS
Beck Depression Scale	6.8 (5.2)	7.3 (6.6)	NS
V.A.S. Overall PD*		53.8 (18.5)	
V.A.S. Dyskinesia*		48.7 (14.5)	
Global assessments Patient *		Very Much Worse 1 Much Worse 3 Mildly Worse 3 No Change 18 Mildly Improved 16 Much Improved 2 Very Much Improved 3	
Global assessments Clinician *		Very Much Worse 0 Much Worse 2 Mildly Worse 3 No Change 17 Mildly Improved 18 Much Improved 7 Very Much Improved 0	

* V.A.S. 1-100 where 1 is much worse and 100 is much better and 50 is no change
# If patients were not fluctuating, part II "on" and "off" were identical

DISCUSSION

Conversion from oral to Zydis selegiline was well tolerated. Patients tended to prefer the Zydis preparation for a variety of reasons. PD scale sub-sets showed some improvement while a series on non-motor assessments did not change. These results suggest that it may be reasonable try Zydis selegiline in subjects currently stable on oral selegiline.

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