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Efficacy and tolerability of rasagiline in daily clinical use—A post marketing observational study in patients with Parkinson's disease focusing on non-motor symptoms and QoL

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ABSTRACT

Rasagiline (Azilect®) is a highly selective irreversible second generation MAO-B inhibitor indicated for the treatment of idiopathic Parkinson's disease (PD) as monotherapy or as adjunct therapy (with levodopa). The 6-month observational study included 871 patients to investigate the efficacy and tolerability of rasagiline in clinical daily practice focussing on non-motor symptoms and quality of life.

Two thirds of the patients received 1 mg rasagiline daily as add-on to their regular PD-medication, the rest as monotherapy.

Efficacy criteria were: (1) CURS, (2) PS-23 scale on Parkinson non-motor symptom strength, (3) UPDRS, part IV B, (4) duration of OFF-periods, (5) QoL by PDQ-8, (6) WHO-5 Well-being Index and (7) change of global clinical impression (CGI-I).

Significant improvements have been observed in total severity of PD: PS-23 total score declined from 46.4 to 42.2. Health and general well-being measured by PDQ-8 improved significantly from baseline 16.3 to 14.3. Emotional well-being according to WHO-5 improved significantly from 14.4 to 16.4.

Positive effects of rasagiline on motor symptoms have been observed: CURS total score improved significantly from 14.8 to 11.4. The proportion of patients without any OFF period increased from 47.1% to 59.1%. Patients reported that OFF periods decreased significantly, most pronounced the morning OFF. Rasagiline has shown to be effective either in monotherapy or in combination with L-Dopa, dopamine agonists or both.

AEs were reported by 6.5% of the patients. The treatment with rasagiline in patients with PD resulted in improvements of motor and non-motor symptoms and led to an improved quality of life.

1. Introduction

Even in early stages of the disease, the daily living activities of many Parkinson patients are impaired. Motor symptoms are predominant in patients with more advanced disease (especially "on-off" fluctuations after long-term treatment with dopaminergic drugs). These motor symptoms are often preceded by non-motor symptoms such as autonomous dysfunction, pain, depression, sleep disturbances and cognitive impairment [1–3]. There is good evidence that these non-motor symptoms have a strong impact on the perception of the disease and impair quality of life (QoL) of the patient [3–5,13].

Rasagiline is a potent, highly selective, and irreversible inhibitor of monoamine oxidase type B (MAO-B). Rasagiline is indicated for the treatment of idiopathic Parkinson's disease (PD) as monotherapy (without levodopa) or as combination therapy (with levodopa) in patients with end-of-dose fluctuations. The efficacy and tolerability of rasagiline was demonstrated in large scale, controlled clinical studies in monotherapy in patients with early PD (TEMPO study) [6–8] and in combination therapy in patients with more advanced PD and motor fluctuations (PRESTO [9] and LARGO [10] studies) and in a previous non-interventional study [11] in a large patient population in routine medical practice in treatment centers across Germany.

The aim of this non-interventional study (NIS) was to document the tolerability and efficacy of rasagiline along with motor symptoms, with special focus on non-motor symptoms in a large

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patient cohort in daily clinical use. Additional attention was drawn on the effects of rasagiline in monotherapy, in combination with levodopa (L-Dopa), with dompamine agonists (DA) or both.

2. Methods/Patients

2.1. Study design and patients

This post marketing observational study was conducted between December 2009 and December 2011 in Germany with 271, mainly office-based-centers participating. 871 patients included in the study received treatment with rasagiline as monotherapy (32.8%) or combination therapy (67.2%) according to their physicians recommendations. The treatment and observation period was scheduled for 6 months with an interim study visit after 3 months.

The age of the patients ranged from 35 to 95 years (mean age: 68 years (±9.2 years standard deviation)). Most patients were male (63.6%). The median duration of idiopathic PD was 3 years. Severity of the disease according to Hoehn & Yahr was between stage II and III in 58.8% of the patients. Table 1 provides more details about the baseline characteristics of the study patients. Besides longer duration of PD and higher severity of the disease, there were no structural differences between patient subgroups with different medication.

2.2. Treatment with rasagiline

Rasagiline was administered in >95% of all patients with a daily dose of 1 mg (as recommended by SPC). This dosage scheme remained unaltered in most of the patients during the treatment and observation period. The median treatment time was 6 months. The efficacy and tolerability of rasagiline treatment were evaluated by the treating neurologist at the following time points-The beginning of the study, after 3 months and at final visit.

2.3. Outcome measures

At baseline demographic patient data and patient history were recorded, including pre-treatment of iPD and concomitant diseases. Severity of PD was rated according to the Hoehn & Yahr scale.

The efficacy of rasagiline was evaluated on the basis of changes on the following scales (between baseline and final visit):

(1) Columbia University Rating Scale (CURS),
(2) PS-23 scale on Parkinson non-motor symptom strength,
(3) Clinical fluctuations subscale of the Unified Parkinson's Disease Rating Scale (UPDRS, part IV B),
(4) Duration of OFF-periods documented in 24 h home diaries,
(5) QoL by Parkinson's Disease Questionnaire (PDQ-8),
(6) WHO-5 Well-being Index and
(7) Change of global clinical impression (CGI-I) rated by participating neurologists.

CURS rates PD symptom severity via assessment of 13 single items: three classical motor items (tremor, rigidity, bradykinesia) and 10 non-classical motor/non-motor items. Item severity is rated from 0 (normal) to 4 (severe). The novel Parkinson-Syndrome-Score PS-23 comprises 23 single items which can be rated from 1 to 5 with increasing severity. PS-23 scores are mapping non-motor symptoms, vegetative symptoms, pain, emotion and cognition. The UPDRS fluctuation subscale is a four-question-segment of the UPDRS-Complications scale which assesses the predictability, appearance and time spent in OFF periods. Questions require a "yes/no" response, apart from question 4 which assesses the proportion of the waking day spent in OFF time. Daily OFF time was also recorded by patients in home diaries, to be completed on the day before a regular study visit. Patient QoL was examined using the PD Questionnaire PDQ-8, a scale especially designed to measure QoL in PD. Emotional well-being was assessed using the WHO-5 questionnaire.

CGI-I is a subscale of the Clinical Global Impression Scale, measuring "improvement" on a sevenfold scale.

Safety and tolerability of rasagiline were assessed via the incidence of adverse drug reactions and a final global rating of the treating physician.

2.4. Statistical analysis

Outcome measures were analyzed using common descriptive statistical summaries. Pre-post comparisons were made with Student's *t*-test (for dependent samples), Wilcoxon test (for rank scale data), and chi-square test (for nominal scale data). Due to the observational character of this study, no specific hypotheses were tested. Resulting *p*-values of the significance tests should be interpreted in an exploratory way, only.

Table 1
Baseline characteristics of the patients.

	Total	L-Dopa + Rasa	DA + Rasa	Rasa (mono)	L-Dopa + Rasa + DA
No. of patients (6 patients could not be allocated to a subgroup)	871 (100%)	217 (24.9%)	143 (16.4%)	286 (32.8%)	219 (25.1%)
Age (years; M ± SD)	68.0 (±9.2)	71.8 (±8.9)	63.2 (±8.8)	66.8 (±8.9)	68.9 (±8.6)
Gender (rel. frequency)	Male: 63.6%:	Männlich: 59,4%:	Männlich: 60,7%:	Männlich: 66,7%:	Männlich: 65,3%:
Duration of PD (years; median)	3	3	2	1	6
Hoehn & Yahr stage (rel. frequency)					
Stage I	33.50%	22.00%	40.00%	56.80%	10.00%
Stage II	42.60%	48.60%	51.40%	34.30%	41.90%
Stage III	16.00%	20.60%	5.00%	6.60%	30.50%
Stage IV	7.10%	8.40%	3.60%	1.50%	15.70%
Stage V	0.80%	0.50%	0.00%	0.70%	1.90%
CURS (total score; M ± SD)	14.8 (±7.8)	16.6 (±8.0)	12.6 (±6.6)	11.6 (±6.5)	18.7 (±7.9)
PS-23 (total score; M ± SD)	46.4 (±13.4))	49.0 (±12.9))	43.8 (±12.4))	42.5 (±12.0))	50.9 (±14.3))
Patients without OFF periods (rel. frequeny)	47.10%	45.30%	60.80%	k.A.	31.20%
Quality of Life (PDQ-8 total score; M ± SD)	16.3 (±5.9)	17.5 (±6.2)	15.1 (±6.0)	14.6 (±5.1)	17.8 (±6.3)
Emotional well-being (WHO-5 total score; M ± SD)	14.4 (±5.9)	13.2 (±5.9)	15.3 (±5.5)	15.4 (±5.9)	13.9 (±6.0)

M = mean; SD = standard deviation.