Effectiveness and safety of safinamide in the Toledo Movement Disorders Unit

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Introduction. The management of motor fluctuations in Parkinson's disease (PD) can be challenging, and current therapeutic options include the use of monoamine oxidase B inhibitors (MAO-B inhibitors), among others. The aim of this study was to evaluate the effectiveness and safety of safinamide in the clinical practice carried out in the Toledo Movement Disorders Unit.

Patients and methods. This is a retrospective study in which data were collected at baseline and at six months from PD patients who were started on safinamide as an add-on therapy with a stable dose of levodopa in line with standard clinical practice. An analysis was performed by subgroups: patients who were given low-dose safinamide and patients who previously received rasagiline.

Results. Ninety patients (47 previously received rasagiline) completed the six-month follow-up. A statistically significant decrease in morning akinesia, nocturnal akinesia, wearing off, unpredictable off phenomenon and Unified Parkinson's Disease Rating Scale-III was observed both in those who previously received rasagiline and in those treated with low doses of safinamide. No variation was found in the dyskinesias. The adverse events described were mild, with generalised weakness, dizziness, nausea, headache and alopecia.

Conclusions. Safinamide has been shown to be effective and safe in improving motor fluctuations, motor symptoms and the subjective perception of disease severity in PD patients previously receiving rasagiline and in those receiving low-dose safinamide, all of which is accompanied by a good safety profile.

Key words. Dyskinesia. Fluctuations. Motor symptoms. Parkinson disease. Rasagiline. Safinamide.

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease. It currently affects approximately 2-3% of people over the age of 65. Bearing in mind that age is the main risk factor for developing PD, its incidence and prevalence are expected to increase in the coming years [1,2].

PD is characterised by progressive degeneration of nigrostriatal dopaminergic neurons, leading to a progressive deficit of dopamine, followed by impairment of other neurotransmitters, such as glutamate, gamma-aminobutyric acid or serotonin [2-5]. The resulting dopamine depletion in the dorsal striatum gives rise to the hallmark motor symptoms of PD, i.e. bradykinesia, rigidity, resting tremor, postural instability and gait abnormalities. Although it is the motor manifestations that lead to the diagnosis, PD is not only a movement disorder, but is often associated with a variety of debilitating nonmotor symptoms, such as cognitive impairment, psychiatric symptoms, sleep disorders, autonomic disorders, pain and fatigue, which increase the clinical and economic burden of the disease. Furthermore, in the mid-advanced stages of PD, the combination of motor and nonmotor symptoms often results in marked functional disability in patients, and hence there is an urgent need to find an individualised treatment strategy [6,7].

Among the drugs approved for the symptomatic treatment of PD, levodopa remains the standard-of-care therapy. Yet, disease progression, long-term high-dose levodopa administration and pulsatile stimulation of the drug are considered important risk factors for the development of motor and nonmotor complications. Although several strategies have been used to treat or even delay the onset of these motor complications, long-term control of these side effects has not yet been achieved. Moreover, as the disease progresses, they become in-

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creasingly more difficult to control [8-13]. Fluctuations can appear soon after starting levodopa treatment (50% of patients have motor fluctuations within two years of starting treatment) [14]. Furthermore, fluctuations are underdiagnosed in routine neurological assessment [15]. Therefore, it is recommended to initiate levodopa treatment when symptoms are disruptive, using the lowest dose that provides satisfactory clinical control, especially in younger patients and women, who are more likely to develop dyskinesia. Thereafter, the dose should be increased gradually. A suggested threshold of 400 mg/day is recommended, provided that the clinical requirements for dopaminergic therapy are met [2,14,16].

A common strategy to manage adverse events and decreased levodopa efficacy is to combine it with other drugs that increase dopaminergic transmission in the dorsal striatum, thus reducing the need for high doses of levodopa to control motor symptoms. Complementary treatments include monoamine oxidase B inhibitors (MAO-B inhibitors) (selegiline or rasagiline), catechol-O-methyl transferase inhibitors (COMTI) (entacapone or opicapone), dopamine agonists (ropinirole, pramipexole or rotigotine transdermal patch) or combined-action drugs such as safinamide (MAO-B inhibitor + glutamatergic modulator) [16-18]. Comprehensive treatment of PD should also minimise the negative impact of non-motor symptoms on patients' functioning and quality of life [19].

Safinamide is a multimodal drug with a dual mechanism of action, namely dopaminergic (selective and reversible MAO-B inhibition) and non-dopaminergic (modulation of abnormal glutamate release by blocking presynaptic voltage-dependent Na^+ and Ca^{2+} channels), that offers an innovative approach to the management of motor and non-motor symptoms and motor complications [20-24]. None of the drugs for PD already marketed in Spain have this unique dual mechanism of action, so the Movement Disorders Society has included safinamide in a class of drugs distinct from selegiline and rasagiline (MAO-B inhibitors + channel blockers) [25,26].

In order to gain further insight into the effectiveness and safety profile of safinamide, a retrospective study on the use of safinamide in PD patients in real clinical practice was conducted. In addition, the effectiveness of switching from rasagiline to safinamide (to corroborate its clinical benefit and the impact of the dual mechanism of action in the treatment of the disease) and the use of low doses of safinamide were evaluated.

Patients and methods

Study design

This is a retrospective study carried out in the Movement Disorders Unit of the Neurology Service of the Complejo Hospitalario de Toledo (Toledo, Spain), in which the effectiveness, safety and tolerability of safinamide in patients with PD were evaluated over a six-month follow-up period. Data were obtained from a review of anonymised medical records.

The study received approval from the research committee of the Toledo University Hospital Complex, under the project 'Study of the efficacy and safety of safinamide in routine clinical practice. Appraisal of the switch from rasagiline and low-dose treatment'.

Patients

Data were collected from non-age-restricted patients from the outpatient clinics of the Movement Disorders Unit who met the diagnostic criteria of the UK PD Society Brain Bank [27] and in whom treatment with safinamide had been initiated in accordance with standard clinical practice. The recruitment period was between January 2018 and December 2021 (both inclusive). Patients with insufficient medical data in the clinical follow-up reports were excluded.

Procedure

All patients had received safinamide as add-on therapy to a stable dose of levodopa. They were assessed at least twice: in an initial visit and in a first follow-up visit at six months. Demographic and clinical data were collected at both baseline and in the follow-up visits, including the presence of dyskinesia and motor fluctuations, modified Hoehn and Yahr scale, mean daily dose of levodopa, treatment with dopamine agonists, COMTI, MAO-B inhibitors, amantadine and its levodopa equivalent dose. The main assessment criteria used were a change in part III (motor examination) of the Unified Parkinson's Disease Rating Scale (UPDRS-III), presence and/or severity of motor fluctuations, and a variation in the Clinical Global Impression (CGI) scale.

Data from patients who had previously received rasagiline (1 mg/day) and those who maintained a low dose of safinamide (50 mg/mL) at six months were evaluated independently.

Statistical analysis

The primary objective was to assess the clinical motor effect of safinamide using the UPDRS-III and CGI scales, and the presence/severity of motor fluctuations and dyskinesias, both in the total population treated with safinamide and in the subgroup of patients who had previously received rasagiline. As a secondary objective, these effects were assessed with the lowest dose of safinamide.

Statistical analyses were performed with SPSS software v. 21.0 (Wilcoxon rank sum test).

Results

Of the 93 PD patients who initially received safinamide, 90 completed the six-month follow-up and three had to discontinue treatment in the first month due to adverse events (headache and general malaise). Regarding the dose of safinamide administered, of the 93 patients who started treatment, 45 were treated with a dose of 50 mg/day, 26 received 50 mg/day initially, which was increased to 100 mg/day at one month and 22 received directly a dose of 100 mg/day. Of the 90 patients who completed the six-month follow-up, 47 had previously been treated with rasagiline (1 mg/day).

Just over half the patients were female (52.7%), mean age at baseline was 67.8 years (minimum 34 and maximum 85; standard deviation: 10.9). At the start of treatment with safinamide, the mean duration of PD was 8.3 years (minimum 0 and maximum 24; standard deviation: 5.3).

As concomitant treatments, 64 patients (68.8%) were being given dopamine agonists (18 with rotigotine, 16 with ropinirole and 30 with pramipexole). All patients were receiving levodopa (11 with levodopa/benserazide, 53 with levodopa/carbidopa, 27 with levodopa/carbidopa/entacapone and 2 with levodopa/carbidopa intestinal gel). As regards COMTI, 27 received entacapone and 15 were given opicapone.

After six months of follow-up, there was a statistically significant decrease in morning akinesia compared to baseline (66.7 vs. 33.4%; $p = 0.001$), nocturnal akinesia (19.4 vs. 8.1%; $p = 0.003$), wearing off (65.6 vs. 31.2%; $p < 0.001$), unpredictable off phenomenon (8.7 vs. 6.5%; $p = 0.03$) and UPDRS-III (24.72 vs. 20.28; $p < 0.001$). No variation was observed in the dyskinesias. According to the CGI severity perception scale, after six months of treatment, 67.8% of patients reported feeling better, 28.9%, reported feeling the same and 3.3%, reported feeling worse with the addition of safinamide (Table I).

Table I. Clinical parameters and progress of all patients who completed the six-month follow-up ($n = 90$).

	Start	Six months	*p*
Morning akinesia, %	66.7	33.4	0.001
Nocturnal akinesia, %	19.4	8.1	0.003
Wearing off, %	65.6	31.2	<0.001
Unpredictable off, %	8.7	6,5	0.03
UPDRS-III	24.72 (SD: 11.28)	20.28 (SD: 10.45)	<0.001
Hoehn and Yahr, %			
I	13.3	12.1	
II	68.8	70	
III	13.3	12.2	
IV	4.4	5.5	
CGI, %			
Better		67.8	
Equal		28.9	
Worse		3.3	

CGI: Clinical Global Impression; SD: standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale.

In the subgroup analysis, patients who were switched from rasagiline also experienced significant improvement in all the variables studied compared to the baseline visit: morning akinesia (59.2 vs. 29.8%; $p = 0.003$), nocturnal akinesia (18.4 vs. 6.5%; $p = 0.006$), wearing off (69.4 vs. 40.4%; $p = 0.001$), unpredictable off phenomenon (8.2 vs. 4.3%; $p = 0.006$) (Fig. 1) and UPDRS-III (20.53 vs. 18.42; $p = 0.014$) (Fig. 2). Furthermore, according to the CGI severity perception scale, after switching from rasagiline to safinamide, 61.7% of patients reported feeling better, 36.2%, the same and 2.1%, worse after six months of treatment (Fig. 2). A significant decrease was also observed in all the variables in the subgroup of patients who maintained the lowest dose of safinamide (50 mg/day) (Table II).

Ten patients reported adverse events and treatment had to be discontinued in seven of them (three in the first month and four at six months). Adverse events reported were generalised weakness ($n = 3$), dizziness ($n = 3$), nausea ($n = 2$), headache ($n = 1$) and alopecia ($n = 1$).

Figure 1. Clinical parameters and progress of patients who previously received rasagiline (1 mg/day) and switched to safinamide (*n* = 47).

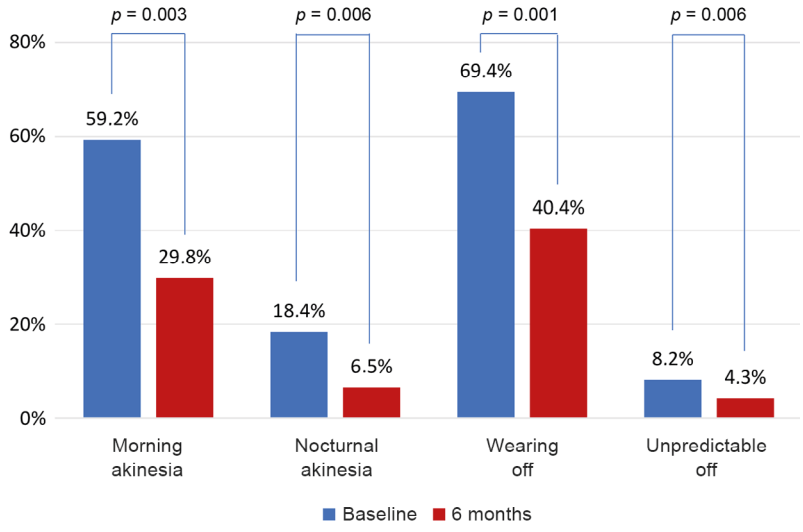
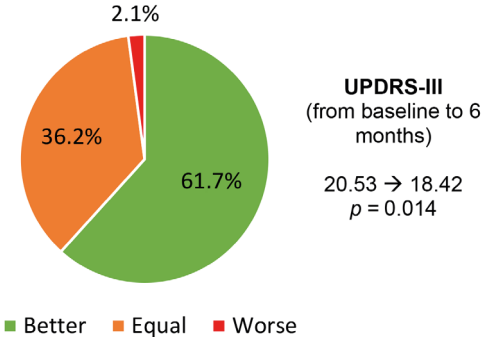


Figure 2. Results according to the severity perception scale (CGI) and Unified Parkinson's Disease Rating Scale-III in patients who previously received rasagiline (1 mg/day) and switched to safinamide (*n* = 47).



CGI: Clinical Global Impression; UPDRS: Unified Parkinson's Disease Rating Scale.

Discussion

The results regarding effectiveness and safety obtained in the present study confirm those previously obtained both in randomised studies, in which safinamide was shown to provide a significant improvement in on-time, off-time and UPDRS-III in patients with PD [20-22], and in studies conducted in clinical practice, the most relevant of which is the phase IV SYNAPSES study, which enrolled 1,500 patients and lasted for one year [26]. This study confirmed the safety and tolerability of safinamide as an add-on therapy in patients with fluctuating PD and in specific subgroups of subjects. Neither advanced age nor comorbidities nor psychiatric disorders appeared to influence its safety profile. Motor complications and motor scores improved in a clinically significant way and UPDRS results were maintained in the long term [26]. In other studies conducted in clinical practice, safinamide offered significant improvements in UPDRS-III [26,28-37], UPDRS-IV [26,28,29,33,35,36], CGI [33, 36,38,39], off time [30,37,38,40] and the 19-item wearing-off scale (WOQ-19) [18].

Moreover, as in our study, the motor improvement experienced by these patients after switching from rasagiline to safinamide has also been documented. In an expert consensus, all respondents agreed on the benefits of this change [41]. In a study conducted in clinical practice, it was reported that the group previously treated with a MAO-B inhibitor significantly reduced off time, as well as the levodopa dose and levodopa equivalent dose [30]. Another study showed an improvement of 80.4% in motor symptoms and of 32.5% in non-motor symptoms in patients who were switched from rasagiline to safinamide [39]. Following the switch, a significant reduction in WOQ-19 score was also observed (52.9% of patients had a score ≤ 2 on the WOQ-19) [18], as well as significant changes in motor assessments such as the UPDRS-III and UPDRS total score [34]. As already noted in the aforementioned papers, this remarkable motor improvement could be attributed to safinamide's non-dopaminergic mechanism of action. A recent review reported that switching from rasagiline to safinamide improved the wearing off phenomenon that occurs as the effect of the levodopa dose comes to an end until the clinical effect of the next one takes place, which could be useful to reduce the total daily dosage of levodopa, while improving the off and on times without troublesome dyskinesias and being more effective than other MAO-B inhibitors [42].

In addition, it is also important to highlight the safety of this shift, as no drug-related adverse events were reported in the study. In addition, no patients reported hypertension, as previously demonstrated by Stocchi et al. [34]. Switching from other MAO-B inhibitors to safinamide is a safe and tolerable therapeutic opportunity to optimise antiparkinsonian therapy. In this way, the therapeutic treatment of

PD would be approached by restoring the dopaminergic deficit and modulating the existing glutamatergic hyperstimulation, thereby offering a more holistic approach [16]. Moreover, as recently indicated by Sánchez-Alonso et al, switching from a MAO-B inhibitor to safinamide allows for optimisation of the antiparkinsonian treatment, especially before considering possible advanced or second-line therapies [42].

In order to assess the efficacy of the 50 mg/day dose of safinamide, a subgroup analysis was performed in patients receiving that dose. As in previous analyses, an improvement in motor complications and motor scores was observed. This analysis is useful in actual clinical practice, as it demonstrates motor effectiveness at the lowest drug dose and allows a higher drug dose (100 mg/day) to be used in order to maximise the inhibitory effect of MAO-B together with the modulatory effect of excessive glutamate release, which may translate into greater motor and non-motor benefit, and thus an improvement in the patient's quality of life [20-22,35].

The main limitation of the study lies in its design. It is a retrospective study in which comparisons were made with respect to the baseline situation, so it lacks a control group without safinamide treatment. Also, as some of the scales used assessed patients' opinions, there could be a possible placebo effect. The main strength of the study is that it reinforces previous evidence of the benefit of switching from rasagiline to safinamide [18,39,42]. One recently published study was conducted with the aim of determining the levodopa equivalent dose. A 100 mg dose of safinamide was equivalent to a 125 mg levodopa equivalent dose, while 1 mg rasagiline and 50 mg safinamide were equally equivalent to a 100 mg levodopa equivalent dose. Patients who received safinamide at doses of 50 and 100 mg, but not those with 1 mg rasagiline, had lower UPDRS-III scores than controls ($p < 0.001$) [43].

The SUCCESS study is currently under way with the aim of evaluating the effectiveness of safinamide, rasagiline and other treatment standards prescribed as add on treatments to levodopa [44].

Table II. Clinical parameters and progress of patients who maintained low-dose safinamide (50 mg/day) ($n = 45$).

	Start	Six months	*p*
Morning akinesia, %	75.6	44.2	0.026
Nocturnal akinesia, %	20	12.5	0.046
Wearing off, %	57.8	25.6	0.001
Unpredictable off, %	6.8	4.4	<0.001
UPDRS-III	25.59 (SD: 11.69)	20.89 (SD: 11.52)	<0.001
CGI, %			
Better		65.1	
Equal		30.2	
Worse		4.7	

CGI: Clinical Global Impression; SD: standard deviation; UPDRS: Unified Parkinson's Disease Rating Scale.

Conclusions

Administration of safinamide has been shown to improve motor fluctuations, motor symptoms and subjective perception of disease severity in PD patients, even in patients receiving low-dose safinamide (50 mg/day). Worthy of note is the improvement in symptomatology and motor complications in PD patients who had previously taken rasagiline, probably as a consequence of safinamide's anti-glutamatergic mechanism of action, suggesting a clinical benefit and thus an improvement in patients' quality of life after switching from MAO-B inhibitors to safinamide. In addition, safinamide has been shown to have a good safety profile, with the main adverse events being headache, dizziness, alopecia and general malaise.

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Efectividad y seguridad de la safinamida en la Unidad de Trastornos de Movimiento de Toledo

Introducción. El manejo de las fluctuaciones motoras en la enfermedad de Parkinson (EP) puede suponer un reto, que cuenta entre las diversas opciones terapéuticas actuales con el uso de inhibidores de la monoaminooxidasa B (IMAO-B), entre otros. El objetivo de este estudio fue evaluar la efectividad y seguridad de la safinamida en la práctica clínica de la Unidad de Trastornos de Movimiento de Toledo.

Pacientes y métodos. Es un estudio retrospectivo en el que se registraron datos en una visita inicial y a los seis meses de pacientes con EP en los que se inició tratamiento con safinamida como terapia adicional con una dosis estable de levodopa según la práctica clínica habitual. Se realizó un análisis por subgrupos: pacientes que recibieron safinamida en dosis bajas y pacientes que recibieron previamente rasagilina.

Resultados. Completaron los seis meses de seguimiento 90 pacientes (47 recibieron previamente rasagilina). Tanto en los pacientes que recibieron rasagilina previa como en los tratados con dosis bajas de safinamida se observó una disminución estadísticamente significativa de la acinesia matutina, la acinesia nocturna, el *wearing off,* el fenómeno *off* impredecible y la *Unified Parkinson's Disease Rating Scale-III.* No hubo variación en las discinesias. Los acontecimientos adversos descritos fueron leves, y se describieron sensación de debilidad generalizada, mareo, náuseas, cefalea y alopecia.

Conclusiones. La safinamida ha demostrado ser eficaz y segura en la mejoría de fluctuaciones motoras, los síntomas motores y la percepción subjetiva de la gravedad de la enfermedad tanto en pacientes con EP que recibieron previamente rasagilina como en los que recibieron safinamida en dosis bajas, todo ello acompañado de un buen perfil de seguridad.

Palabras clave. Discinesia. Enfermedad de Parkinson. Fluctuaciones. Rasagilina. Safinamida. Síntomas motores.