NEW PLAYERS IN NEURODEGENERATIVE DISEASES: SAFINAMIDE AND PARKINSON'S DISEASE

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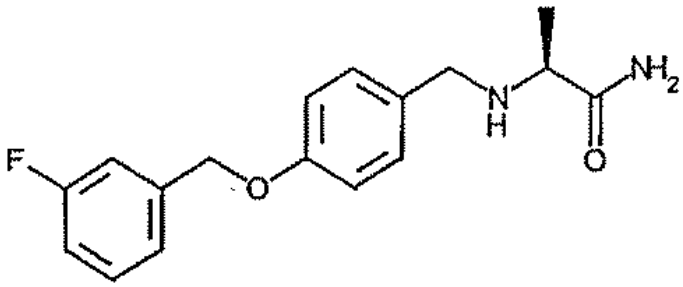
Introduction

Parkinson's disease (PD) is a complex brain disorder, involving dopaminergic and non-dopaminergic pathways. Dysfunction in these pathways is an important contributor to motor symptoms, non-motor symptoms and motor complications such as dyskinesia. The aim of treatment is, therefore, to normalise dopaminergic and non-dopaminergic activity, thus improving the broad spectrum of symptoms.

Pharmacology of safinamide

Safinamide is an α-aminoamide in Phase III clinical development as add-on therapy to dopamine agonists (DAs) or L-dopa in PD. Safinamide has both dopaminergic and non-dopaminergic mechanisms of action, including monoamine oxidase-B (MAO-B) and dopamine reuptake inhibition, activity-dependent sodium channel antagonism and inhibition of glutamate release *in vitro*.

Safinamide is rapidly absorbed after oral administration, reaching peak plasma levels in 1.8–2.0 hours, and has an elimination half-life in humans of 21–24 hours. In non-human primates, safinamide produces a brain-to-plasma concentration ratio of 9, probably reaching high micromolar levels in the central nervous system (CNS). Thus, a dose of 100 mg in clinical trials might be anticipated to produce a brain concentration in the order of 30 μM, although the concentration of unbound, active compound available for pharmacological action at specific sites is not known. The drug is 92% bound in plasma and only a small proportion is excreted unchanged. There is no significant accumulation at steady state.



Structure of safinamide

Laboratory studies

Using *in vivo* models, safinamide was shown to increase dopamine levels when co-administered with L-dopa and to reverse the 'wearing-off' response to L-dopa. Its effect on wearing off was greater than that seen with the glutamate inhibitor, MK801. *In vitro*, safinamide was shown to protect against kainic acid- and veratridine-induced cell loss. The latter effect was mediated by blockade of voltage-dependent sodium and calcium channels.

After long-term administration to monkeys, safinamide significantly increased dopamine levels in the putamen and prefrontal cortex, without affecting regions that are devoted to rewarding/reinforcing circuitry, e.g. mesolimbic structures. More recently, it has been shown that acute administration of safinamide to monkeys pretreated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) significantly reduced L-dopa-induced dyskinesia whilst simultaneously prolonging its antiparkinsonian effects. The antidyskinetic effect of safinamide was dose-related and both the intensity and duration of dyskinesia were reduced. While the prolongation of L-dopa's antiparkinsonian effect most probably reflects the dopaminergic effects of safinamide, its antidyskinetic effect is likely due to its non-dopaminergic properties.

Clinical studies in early PD

In a three-month, placebo-controlled study, 172 patients with early PD received placebo or safinamide (0.5 or 1.0 mg/kg). At three months, the response rate (≥30% improvement in Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor) scores) was 37.5% in the 1 mg/kg group (mean 70 mg/day), 30.9% in the 0.5 mg/kg group and 21.4% in the placebo group ($p<0.02$ for 1 mg/kg versus placebo). In patients on a DA at baseline, response rates

were 47.1%, 36.4% and 20.6%, respectively ($p<0.03$ for 1 mg/kg versus placebo). The mean improvement in motor scores from baseline was 4.7 units for the 1 mg/kg dose ($p<0.05$), 4.0 for the 0.5 mg/kg dose (not significant) and 1.4 for placebo. The statistical benefit of the lower dose may have been undermined by the high placebo response. Nevertheless, the significant response in motor performance with safinamide added to a DA (either ergot or non-ergot) is of great interest, particularly given the current use of agonists as an alternative to L-dopa in early disease. Safinamide thus has the potential to extend the duration of effective PD treatment prior to L-dopa introduction. It is of note that the higher dose was anticipated to produce pharmacological effects of safinamide beyond MAO-B inhibition, i.e. ion channel blockade and inhibition of glutamate release.

The benefit of safinamide added to DA monotherapy was reproduced in a small, six-week, open-label study. There was a rapid (by two weeks) and significant improvement in UPDRS Part III scores, which reached 4.2 ($p<0.001$) by the end of the study.

In the placebo-controlled study, the overall incidence of adverse events (AEs) in the safinamide plus DA groups was 32–38% compared with 50% in the placebo group. Rates of CNS, cardiovascular and psychiatric AEs were similar between treatment groups, as was AE severity.

Clinical studies in advanced PD

In a large, double-blind, placebo-controlled study, 669 patients with PD (mean Hoehn and Yahr Stage, 2.8; mean daily OFF time, 5.2 hours) on stable L-dopa doses were randomised to safinamide 50 or 100 mg/day or placebo for 24 weeks. Completion rate was 89%. For the primary endpoint, ON time without troublesome dyskinesia, there was a significant increase for safinamide 50 mg/day (1.28 h) and safinamide 100 mg/day (1.32 h) versus placebo (0.69 h; $p=0.008$ and $p=0.005$, respectively). Mean UPDRS Part III scores were also significantly improved for both doses compared with placebo. Treatment-emergent side effects included mild to moderate dyskinesia. The proportion of patients who discontinued the study due to an AE was similar in the safinamide 50, 100 mg and placebo groups (4.9%, 6.3% and 5.4%, respectively).

Safinamide 100 mg/day was also associated with significant improvements in rating scale scores for depressive symptoms, activities of daily living and quality of life versus placebo. In a post-hoc analysis of patients with more troublesome dyskinesia at baseline (>30 min), safinamide 100 mg/day significantly improved UPDRS Part IV (complications of therapy) scores for dyskinesia compared with baseline.

Overall, these data suggest that safinamide improves both motor and non-motor symptoms and may have a beneficial effect in patients with troublesome L-dopa-induced dyskinesia.

Ongoing clinical trials

Further Phase III studies are ongoing to confirm the efficacy and tolerability of six months' treatment with safinamide as add-on to DAs in early PD (MOTION) and as add-on to L-dopa in mid to late PD (SETTLE). An 18-month, double-blind, placebo-controlled extension study for MOTION will also be conducted.

Conclusions

Safinamide has a combined dopaminergic and non-dopaminergic mechanism of action. It has been shown to improve motor function in PD when used as add-on therapy to DAs and L-dopa. In patients with mid to late PD, it also improved non-motor symptoms and may have a beneficial effect in patients with troublesome L-dopa-induced dyskinesia.

Further reading

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Conflicts of interest

Professor Stocchi has served as an advisor to Boehringer Ingelheim, GlaxoSmithKline, Lundbeck, Merck Serono, Newron, Novartis, Pfizer and Teva.