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The Use of Safinamide for Patients with Parkinson's Disease

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ABSTRACT

Safinamide is a selective, reversible, monoamine oxidase B inhibitor for the treatment of patients with Parkinson's disease (PD) and motor fluctuations. This was a post hoc analysis of the SETTLE study, in which patients with PD and motor fluctuations were randomly assigned to 24-week treatment with safinamide (50 mg/day for 2 weeks, increased to 100 mg/day if tolerated) or placebo. In the present analysis, responders were defined according to their treatment responses at Week 2 and Week 24 based on changes in ON-time without troublesome dyskinesia from baseline with cutoffs of 1 hour. It was found that 81% (103/127) of the responders at Week 2 maintained the response through Week 24 in the safinamide group. Other outcomes did not necessarily coincide with the ON-time response; however, "Early" responders who showed a treatment response at both Week 2 and Week 24 had substantial improvements from baseline in OFF-time, UPDRS Part II and III scores, and PDQ-39 summary index scores through Week 24. The safinamide group had a higher proportion of early responders than the placebo group (39% vs 20%, $p < 0.0001$). At baseline, early responders in the safinamide group had significantly higher UPDRS Part II and III scores, shorter ON-time, and longer OFF-time than the other responder populations. In conclusion, the results of the present post hoc analysis suggest that patients with a short ON-time, severe motor symptoms, and highly compromised activities of daily living can benefit from safinamide early in treatment and over the long term.

KEYWORDS: *safinamide, Parkinson, patients, populations, responders, compromised*

INTRODUCTION

Safinamide is a highly selective, reversible MAO B-inhibitor recently marketed in European and North American countries. To better define clinical indications regarding motor and non-motor symptoms, targeted population and safety of this compound, ten movement disorders specialists, experts in their field, convened and developed a panel of statements on: the role of glutamate in Parkinson's disease, introduction to fluctuations, efficacy of safinamide on motor symptoms, motor complications and non-motor symptoms, quality of life, safety of safinamide and target population for use. Strong consensus was reached for all the statements on the efficacy of safinamide on motor symptoms, motor fluctuations, quality of life and safety. Among non-motor symptoms, a positive consensus was reached for the symptoms sleep/fatigue, mood, and pain while there was a lack of consensus for the statements regarding the efficacy of safinamide in improving cognition, urinary and sexual functions.[1,2] The statement on orthostatic hypotension obtained a negative consensus. The consistent and large agreement reached in this Delphi panel perfectly reflects the perception of efficacy, safety and tolerability of safinamide as evident from pivotal trials and clinical practice and shows how these findings may guide movement disorders specialists in their clinical therapeutic approach. The impact of non-motor symptoms in PD is considerable, and management remains an unmet need. In this context, the ability of safinamide to impact some non-motor symptoms may represent the most promising and distinctive feature of this compound and deserves further investigations.

Monoamine oxidase B inhibitors represent an important treatment option in the management of Parkinson's disease (PD), both in the early and in the advanced stages of motor complications1·2. The clinical benefit of MAO-B inhibitors arises from the ability of these medications to enhance the level of dopamine by decreasing its catabolism in the brain.3. Among MAO-B inhibitors, safinamide has a dual-mechanism of action since it is able to inhibit (a) MAO-B, potentiating dopaminergic transmission and (b) glutamate release by blocking voltage-dependent sodium channels and modulating calcium channels4·5. Safinamide is a benzylamine derivative which acts as potent, highly selective, and reversible MAO-B inhibitor. Due to its reversibility4·6, treatment with safinamide is associated with reduced risk of hypertensive crises or serotonergic syndrome7·8 as well as drug interaction4·6.

Safinamide is marketed in Europe and in North America under the brand name of Xadago® (Zambon Pharma) and Onstryv® (Valeo Pharma); it was approved in 2015 as adjunctive therapy to levodopa in mid- to late-stage fluctuating patients and became commercially available in the spring of 2016. While its efficacy in controlling motor symptoms and improving motor fluctuations is well established9·10·11, uncertainty remains on its potential ability to control dyskinesias in the long term or to address the many non-motor symptoms that are typical of the advanced stages of the disease. The aim of this study was to obtain a European Consensus on the use of safinamide, considering the efficacy of this compound on motor symptoms and motor complications, its effect on non-motor symptoms (NMS), quality of life in patient with PD and how its clinical effect is perceived by clinicians. Moreover, we wished to identify an ideal target population and delineate the safety in different PD patient sub-populations.

Hundred and nineteen panelists among movement disorders specialists were identified in the following countries: Italy, UK, Belgium, Spain, Germany, Sweden, Austria, Netherlands. The response rate was 76% (n = 90)[3,4] which was considered high, taking into account that the study was performed during the COVID 19 pandemic and related lockdown in most countries.

Strong consensus was reached for all the statements regarding the efficacy of safinamide on motor symptoms, motor fluctuations, quality of life and safety (29/34 statements, 85,2 % of agreement, mean score 91.5),

suggesting a shared view of European movement disorders specialists on these topics. Among NMS, a common, positive consensus was achieved for the symptoms sleep/fatigue, mood, and pain while there was a lack of consensus for the statements regarding the efficacy of safinamide in improving cognition, urinary and sexual functions. No agreement was reached either on the tolerability of safinamide in patients with hallucinations. The statement on orthostatic hypotension obtained a negative consensus.

A second round of questionnaire was deemed unnecessary by the Board, since all the statements with no or negative agreement were considered clearly stated and results obtained reflected trends in clinical practice.

DISCUSSION

Safinamide is a novel anti-parkinsonian drug with possible anti-dyskinetic properties. Parkinson's disease (PD) is a complex disease. The objective of this systematic review and meta-analysis is to evaluate the efficacy and safety of safinamide administration compared to placebo in PD patients on multiple outcomes.

PubMed, EMBASE, Cochrane CENTRAL, LILACS, and trial databases were searched up to 23 December 2020 for randomized controlled studies (RCTs) comparing safinamide to placebo, alone or as add-on therapy in PD. Data were extracted from literature and regulatory agencies. Primary outcomes were ON-time without troublesome dyskinesia, OFF-time, and Unified Parkinson's Disease Rating Scale (UPDRS) section III (UPDRS-III). Secondary outcomes included any dyskinesia rating scale (DRS), ON-time with troublesome dyskinesia, UPDRS-II, and Parkinson's Disease Questionnaire 39 (PDQ-39). In order to estimate mean difference (MD) and odds ratios with 95% confidence intervals (CI), generic inverse variance and Mantel–Haenszel methods were used for continuous and dichotomous variables, respectively. Analyses were performed grouping by PD with (PDwMF) or without (PDwoMF) motor fluctuations, safinamide dose, and concomitant dopaminergic treatment. Summary of findings with GRADE were performed.

Six studies with a total of 2792 participants were identified. In PDwMF patients, safinamide 100 mg as add-on to levodopa (L-dopa) significantly increased ON-time without troublesome dyskinesia (MD = 0.95 h; 95% CI from 0.41 to 1.49), reduced OFF-time (MD = − 1.06 h; 95% CI from − 1.60 to − 0.51), [5,6]and improved UPDRS-III (MD = − 2.77; 95% CI from − 4.27 to − 1.28) with moderate quality of evidence. Similar results were observed for the 50 mg dose. However, the quality of evidence was moderate only for ON-time without troublesome dyskinesia, whereas for OFF-time and UPDRS-III was low. In PDwoMF patients taking a single dopamine agonist, safinamide 100 mg resulted in little to no clinically significant improvement in UPDRS-III (MD = − 1.84; 95% CI from − 3.19 to − 0.49), with moderate quality of evidence. Conversely, in PDwoMF patients, the 200 mg and 50 mg doses showed nonsignificant improvement in UPDRS-III, with very low and moderate quality of evidence, respectively. In PDwMF patients taking safinamide 100 mg or 50 mg, nonsignificant differences were observed for ON-time with troublesome dyskinesia and DRS, with high and low quality of evidence, respectively. In the same patients, UPDRS-II was significantly improved at the 100 mg and 50 mg dose, with high and moderate quality of evidence. In PDwoMF, UPDRS-II showed a little yet significant difference only at 100 mg, with low quality of evidence. PDQ-39 resulted significantly improved only with the 100 mg dose in PDwMF, with low quality of evidence.

Overall, safinamide is effective in PDwMF patients taking L-dopa both at 100 and 50 mg daily. Evidence for efficacy in early PD is limited. Further trials are needed to better evaluate the anti-dyskinetic properties of safinamide.[7,8]

RESULTS

In March 2017, the FDA approved safinamide (Xadago) for clinical use in the United States. Safinamide is the first new drug approved by the FDA to treat Parkinson's disease in more than 10 years. It is a form of adjunctive, or add-on treatment, used in combination with levodopa.

Parkinson's disease is a movement disorder which gradually progresses and typically begins at around age 60. Symptoms include trembling, stiffness, slowed movement, and poor balance. This disease eventually results in difficulties with walking, talking, and other routine activities of daily living. In the United States, about 50,000 people are diagnosed with Parkinson's disease each year.[1]

Although there is no cure for Parkinson's disease, there are treatments that help with symptom management, including the following:

- levodopa
- dopamine agonists (e.g., apomorphine, bromocriptine, ropinirole, and pramipexole)
- monoamine oxidase inhibitors or MAO-B inhibitors (e.g., selegeline and rasagaline)
- catechol-O-methyl-transferase (COMT) inhibitors (e.g., entacapone and tolcapone)
- amantadine
- anticholinergic drugs, such as Artane and Cogentin (usually given to younger people in whom tremor is the main symptom)

0 seconds of 1 minute, 44 seconds Volume 90%

Unfortunately, there are no treatments that slow or stop the progression of Parkinson's disease.

Levodopa is the most potent and prominent drug used to treat Parkinson's disease; however, its effect tends to wear off over time and can lead to negative side effects including dyskinesia.[2]

Drugs including COMT inhibitors, dopamine agonists, and non-dopaminergic treatments—such as anticholinergic treatments and amantadine—can be used as alternatives to levodopa, in addition to levodopa, or in combination with one another.

In people with advanced Parkinson's disease, when medications fail, deep brain stimulation (brain surgery) can be considered to help alleviate symptoms.[11,12]

Typically, medications are reserved for people whose symptoms have become severe enough to interfere with activities of daily living. Levodopa is usually the drug of choice in people aged 65 and older whose lifestyles are seriously compromised. People younger than 65 can be treated with a dopamine agonist.

Drugs are started at the lowest effective dose and treatment is typically delayed as long as possible. However, the

research supporting the guiding tenet of "start low and go slow" with dosages of levodopa is mixed. According to author Peter Jenner:[3]

"The introduction of L-Dopa [levodopa] in those with longer disease duration or in high doses may result in a shortened period of good effect before motor complications appear. Very recently, keeping the dose of L-dopa below 400 mg per day in early PD was shown to reduce the risk of dyskinesia induction."

However, Jenner goes on to note the following:
"The early use of L-dopa was also shown to be the most effective treatment for motor symptoms and not to affect the long-term risk of dyskinesia."

Verily, such conflicting evidence underscores how little we know about the pathology and treatment of Parkinson's disease.

In people with Parkinson's disease, the brain doesn't produce enough of a neurotransmitter called dopamine. The cells that produce dopamine either die or become impaired. Dopamine is necessary for proper motor control and movement.

Specifically, dopamine transmits signals in the brain that are involved in smooth, purposeful movements like eating, writing, and typing. Like selegeline and rasagaline, safinamide is a type of MAO-B inhibitor, which prevents the breakdown of dopamine and thus increases its levels in the brain.

Of note, safinamide also modulates glutamate release; however, the specific effect of this action on the drug's therapeutic actions is unknown.

Unlike other MAO-B inhibitors, which can be prescribed alone for those with early-stage Parkinson's disease, safinamide is intended to be used in conjunction with other types of antiparkinson drugs for the later-stage disease, most notably levodopa as well as dopamine agonists.

When people first start treatment for Parkinson's symptoms, drugs tend to work pretty well and symptoms are controlled throughout the day. Between five and 10 years, however, the efficacy of conventional Parkinson's drugs wanes in many people, and symptom control becomes more difficult to alleviate.

Specifically, in people with mid- to late-stage Parkinson's disease, motor fluctuations or involuntary muscle movements (dyskinesia and freezing) begin to crop up.

Dyskinesia is most pronounced in people taking levodopa and is an adverse effect of drug treatment. The manifestation of dyskinesia bodes poorly with respect to prognosis and should preferably be delayed as long as possible. Furthermore, non-motor symptoms, such as dementia, depression, and hallucinations, which are affected little if at all by dopaminergic drugs, also become a problem.

Those patients who decompensate after adequate treatment that has lasted some time are difficult to treat in a fashion that maintains mobility and quality of life.

In other words, once levodopa stops working as well, in part because we don't understand the pathology of this decompensation, it's hard to get people back to a stable baseline and a quality of life experienced earlier during disease when levodopa and other dopaminergic agents were working.

Moreover, even if motor difficulties are reined in, non-motor issues like mood disorders, sleep disorders, and dementia become troublesome to those with late-stage Parkinson's disease.[13,14]

Unfortunately, we can't predict which people with late-stage Parkinson's disease will develop fluctuations and motor complications. Overall, disease duration, disease stage, length of treatment with levodopa, levodopa dosages, gender, and body weight are all believed to play a role in eventual decompensation.

"ON time" refers to periods when medications are adequately working and the symptoms of Parkinson's disease are controlled.

"OFF time" refers to periods when the medications wear off and Parkinson's symptoms, such as tremor, rigidity, and difficulty walking reappear.

The addition of safinamide to drug regimens of people with advanced Parkinson's disease taking levodopa increases the amount of ON time and decreases OFF time.

Results from two randomized clinical trials have shed light on the potential benefits of safinamide use among people with more advanced Parkinson's disease. These participants had been diagnosed with Parkinson's disease at either three or five years' duration.

The first clinical trial assessed 669 participants with motor fluctuations.[4] These participants either received safinamide in addition to their other antiparkinson medications or placebo (no safinamide) and their other antiparkinson drugs.

Average ON time for the participants was between 9.3 and 9.5 hours. After six months of testing, ON times increased in both sets of patients; however, ON times were about 30 minutes longer in those taking safinamide.

After two years of treatment, the average ON time stayed about the same in those taking safinamide but decreased in those taking a placebo. Thus after two years on average, participants taking safinamide along with levodopa as well as other antiparkinson medications experienced about one more hour of effective treatment for Parkinson's disease symptoms.

Of note, safinamide reduced OFF time by about 35 minutes. Remember that OFF times refer to periods when antiparkinson drugs wear off, and symptoms like tremor are once again exacerbated.[15,16]

In addition to lengthening ON times and shortening OFF times, safinamide also improved movement (motor scores) in those taking it. Furthermore, at a higher dosage, safinamide also helped with activities of daily living and quality of life.

Similarly results from the second trial, which involved 549 participants, suggest an increase in ON time by about one hour in those taking safinamide as compared with those taking placebo as well as reductions in OFF time. Additionally, improvements in functioning and quality of life scores were also observed.[5]

Because of negative side effects, 3.7 percent of participants taking safinamide dropped out of clinical trials as compared with 2.4 percent of those taking a placebo.[5]

Common adverse effects observed during these clinical trials included the following:

- jerky or fragmented motions (i.e., dyskinesia)
- falls
- nausea
- insomnia

Of these symptoms, dyskinesia was about twice as common in people taking safinamide as compared with those not taking it (i.e., those taking placebo).

Less common but more serious adverse effects include the following:

- worsening high blood pressure
- visual hallucinations and psychotic behavior
- falling asleep during the day
- serotonin syndrome (when used with MAO inhibitors, antidepressants, and opioids)
- problems with impulse control or compulsive behavior (think OCD)
- fever and confusion
- retinal problems

Here are some drugs that you shouldn't take if you're also taking safinamide:

- certain antidepressants (serotonin-norepinephrine reuptake inhibitors, tricyclics, and tetracyclics)
- cyclobenzaprine
- dextromorphan (found in certain cough medications)
- opioids
- St. John's Wort

Although people with kidney impairment can take safinamide, those with severe liver problems should not take the drug.

Safinamide is most useful in those with mid- to late-stage Parkinson's disease who experience motor fluctuations (i.e., dyskinesia) and a decrease in the effectiveness of their medications (i.e., OFF times). Safinamide could be a better add-on therapy to primary treatment with levodopa than other add-on treatments, including other MAO-B inhibitors as well as COMT inhibitors. Safinamide is not used alone.

The most common negative side effect of safinamide is dyskenesia or an increase in involuntary movements. People with severe liver problems or those taking certain antidepressants or other medications should not take safinamide. [17,18]

CONCLUSIONS

The FDA has approved safinamide (marketed as Xadago) for treating increased symptoms of Parkinson disease. The drug is indicated as add-on therapy for patients in whom levodopa/carbidopa is not working well (i.e., they are experiencing "off" episodes).

Safinamide increases dopamine availability by blocking the enzyme monoamine oxidase B, blocking sodium and potassium channels, and reducing glutamate release. In two randomized studies comprising some 1200 patients, safinamide improved "on" time, that is, reduced Parkinson symptoms without exacerbating dyskinesia. Safinamide patients also had better motor function scores than patients given placebo.

Patients using the following medications or supplements should avoid using safinamide: certain antidepressants, cyclobenzaprine, dextromethorphan, monoamine oxidase inhibitors, opioids, and St. John's wort. Additionally, it should not be given to patients with severe liver problems.

Falls, insomnia, nausea, and uncontrolled involuntary movement are among the most common side effects associated with safinamide.[19,20]

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