UPDATES IN DRUG THERAPY

mhc MENTAL HEALTH CLINICIAN

LITERATURE REVIEW Open Access

Pimavanserin (Nuplazid™) for the treatment of Parkinson disease psychosis: A review of the literature

Katie T. B. Touma, PharmD, BCPP, BCPS[1]
Daniel C. Touma, MD[2]

How to cite: Touma KTB, Touma DC. Pimavanserin (Nuplazid™) for the treatment of Parkinson disease psychosis: a review of the literature. Ment Health Clin [Internet]. 2017;7(5):230-4. DOI: 10.9740/mhc.2017.09.230.

Abstract

Introduction: Pimavanserin (Nuplazid™) is an atypical antipsychotic currently indicated for the treatment of hallucinations and delusions associated with Parkinson disease psychosis. The antipsychotic effects of this new agent are believed to occur via selective inverse agonist activity at serotonin 5-HT_{2a} receptors.

Methods: Study authors completed a literature review of 2 published randomized controlled trials of pimavanserin for the treatment of Parkinson disease psychosis. The Food and Drug Administration Briefing Document by the Psychopharmacologic Drugs Advisory Committee for the review of pimavanserin dated March 29, 2016, was reviewed for additional information on 2 unpublished trials.

Results: Pimavanserin has demonstrated no worsening of motor symptoms of Parkinson disease, but only 1 of 4 trials has shown consistent statistically significant improvements in psychotic symptoms compared with placebo.

Discussion: Options for the treatment of Parkinson disease psychosis are limited. The selective receptor profile of pimavanserin offers advantages for tolerability. Further studies are warranted to better provide clinicians and patients with information regarding the clinical utility of this agent.

Keywords: Pimavanserin, Parkinson disease, psychosis

[1] (Corresponding author) Clinical Pharmacy Specialist, Mental Health, WJB Dorn VA Medical Center – Anderson Community Based Outpatient Clinic, Anderson, South Carolina, Katherine.Blissit@va.gov, ORCID: http://orcid.org/0000-0002-1792-5929; [2] Postgraduate Year Three Family Medicine Resident, Spartanburg Regional Healthcare System, Spartanburg, South Carolina, ORCID: http://orcid.org/0000-0001-8791-1058

Disclosures: The authors have nothing to disclose in terms of financial conflict of interest.

Introduction

Pimavanserin (Nuplazid™) is an atypical antipsychotic currently indicated for the treatment of hallucinations and delusions associated with Parkinson disease psychosis (PDP).[1] Pimavanserin is reported to be a selective inverse agonist at serotonin 5-HT_{2a} receptors and an antagonist at 5-HT_{2c} receptors, with a 40-fold higher affinity for 5-HT_{2a} receptors. It has no affinity for dopaminergic, histaminergic, adrenergic, or muscarinic receptors.[2] It is the first medication approved for treating psychotic symptoms in any of the movement disorders. The recommended starting dose of pimavanserin is 34 mg once daily, and there is no dose titration. It is currently only commercially available as a 17-mg tablet. Each tablet contains 20 mg of pimavanserin tartrate, which is equivalent to 17 mg of pimavanserin free base. This new medication is a major substrate of CYP3A4 and therefore is subject to clinically significant interactions. The maximum recommended daily dose is 17 mg when it is administered concomitantly with a strong CYP3A4 inhibitor. Steady-state blood concentrations are reached in 10 to 12 days. Pimavanserin is not recommended in patients with an estimated creatinine clearance $<$30 mL/min or patients with hepatic impairment because it has not been studied in subjects with these characteristics.[1]

Psychotic symptoms occur in 20% to 40% of patients with Parkinson disease.[3] Characteristics of PDP predominantly include visual hallucinations, paranoid delusions, and other sensory disturbances. The exact cause of PDP is unknown; it may be multifactorial as research suggests intrinsic factors of visual processing abnormalities, sleep dysfunctions, and structural and neurochemical changes as contributors.[3] Blockade of acetylcholine is thought to induce psychosis in Parkinson disease. Excess dopaminergic activity in the limbic system and cerebral cortex is thought to be involved in the development of psychosis, which can be caused by the dopaminergic agents used to treat the motor symptoms of Parkinson disease. Dose reduction in dopaminergic agents is part of the treatment of PDP.[4]

More traditional antipsychotics have also been evaluated based on this pathophysiology; however, the doses of most antipsychotics needed to block D_2 receptors in the limbic system also block dopamine in the nigrostriatal pathway, which can worsen motor symptoms of Parkinson disease. Clozapine, when used at significantly lower doses than in schizophrenia, has been shown to be efficacious for PDP. These low doses are thought to selectively block 5-HT_{2a} and H_1 receptors and not block D_2 receptors.[2] Other antipsychotics that were available for use before pimavanserin have been evaluated as well. Quetiapine also possesses 5-HT_{2a} and H_1 antagonism in combination with moderate D_2 blockade and has mixed evidence in PDP. It is thought to be less effective than clozapine in the treatment of PDP.[3] D_2 blockade has been associated with a worsening of motor symptoms and competes with dopaminergic agents that are mainstay treatments in Parkinson disease; therefore, this mechanism is a significant disadvantage of the use of more traditional antipsychotics. H_1 blockade is associated with sedation and is unlikely to contribute to an antipsychotic effect; hence, the blockade of 5-HT_{2a} may be a viable mechanism for treating PDP.[2,5]

The progression of Parkinson disease has been associated with an upregulation of 5-HT_{2a} receptors in the cerebral cortex, and upregulation of 5-HT_{2a} receptors in the prefrontal cortex and visual/temporal cortex may only occur in patients with PDP.[5,6] This change theoretically causes visual hallucinations. Inverse agonism of this receptor, the mechanism of action of pimavanserin, may provide relief of these symptoms. An inverse agonist produces a conformational change in a receptor that yields a functional reduction in signal transduction. In contrast to an antagonist that blocks signal transduction, an inverse agonist decreases transduction below baseline levels.[7] It is unclear whether this differentiation is of clinical significance as second-generation antipsychotics that are known to be antagonists at 5-HT_{2a} receptors are also considered to be inverse agonists.[8,9] The purpose of this review is to discuss the clinical data that lead to the Food and Drug Administration (FDA) approval of pimavanserin for the treatment of hallucinations and delusions associated with PDP.

Methods

Study authors searched the MEDLINE database through December 2016 using search terms "pimavanserin," "Parkinson's disease," and "psychosis." Studies were included if they were randomized controlled trials of pimavanserin published in English in a peer-reviewed journal and evaluated the use of this new medication in human subjects for the treatment of psychosis in Parkinson disease. The FDA Briefing Document by the Psychopharmacologic Drugs Advisory Committee (PDAC)[10] for the review of pimavanserin dated March 29, 2016, was reviewed for additional information on unpublished studies. One phase II trial has been completed and published.[11] Three phase III trials have been conducted, 1 of which has been published and will be reviewed here.[12] Relevant information from unpublished trials found in the FDA Briefing Document will be discussed briefly.

Literature Review

Data from 2 randomized, placebo-controlled, double-blind trials evaluating pimavanserin tartrate in PDP are available. As noted in the previous section, the results of 2 phase III trials have not been published, but a summary is available in the FDA Briefing Document by the PDAC for the review of pimavanserin dated March 29, 2016. This document notes similar dosing evaluated (ie, 10 to 40 mg) over 6 weeks. One study did not show efficacy with the use of pimavanserin up to 40 mg/day for PDP and showed a large placebo response.[2,10] The other study was similar in design to the phase III trial with negative findings, but it evaluated lower doses and was terminated early based on the prior phase III trial's negative findings.[2,10]

In the phase II trial[11], pimavanserin was compared with placebo and powered to detect a difference of 5 points on the Unified Parkinson's Disease Rating Scales (UPDRS) II and III over 4 weeks. The UPDRS II assesses activities of daily living, and UPDRS III assesses motor function in Parkinson disease. This was a randomized, double-blind, flexible dose (20 mg, 40 mg, and 60 mg), placebo-controlled, multicentered (United States only) study with inclusion criteria of patients with moderate to severe PDP (psychosis severity score $\geq$4 assessed by the hallucinations and delusions sections of the Neuropsychiatric Inventory) for at least 4 weeks. Subjects were required to be on stable antiparkinsonian drugs for at least 1 week before study entry and through the 4-week treatment.

The use of other antipsychotics was not allowed. Presence of any other medical condition contributing to psychosis, dementia, myocardial infarction within prior 3 months, pregnancy and significant premorbid psychiatric disorder other than major depressive disorder were exclusion criteria. Sixty subjects were enrolled, and ultimately 28 subjects in each group completed the 4-week study. The per-protocol population included 52 subjects (24 receiving pimavanserin and 28 patients receiving placebo). The efficacy measures were the Scale for the Assessment of Positive Symptoms (SAPS), the Parkinson's Psychosis Rating Scale, and the Clinical Global Impression-Severity Scale (CGI-S). Analyses of the SAPS global severity ratings, domain scores for hallucinations (SAPS-H) and delusions (SAPS-D), and the combination of the 2 domains (SAPS-H+D) were performed. The 2 groups were well matched with baseline characteristics. Subjects were primarily white men around the age of 70 years; however, the pimavanserin group consisted of approximately 90% male subjects, whereas the placebo group was 64.5% male ($P=.03$). Of the 60 subjects enrolled, 15 subjects in each group received levodopa/carbidopa only for Parkinson disease; however, 11 subjects received levodopa/carbidopa plus a dopamine agonist in the pimavanserin group and 19 subjects received levodopa/carbidopa plus a dopamine agonist in the placebo group. The authors did not note if this difference was statistically significant.

The design of this trial consisted of subjects receiving pimavanserin 20 mg once daily (or placebo) on the first day, and the daily dose could be titrated to 40 mg or 60 mg on the 8th and 15th days, respectively. Dose increases depended on individual responses. Subjects were evaluated at baseline and day 1, 8, 15, and 28. Safety data were observed at day 57 (4-week follow-up period beyond 4 weeks of treatment). The mean dose of pimavanserin at the end of four weeks was 44.8 mg. An analysis of covariance model was used in the analysis of the primary safety outcome using the last observation carried forward. This noninferiority assessment was a per-protocol analysis. There were no statistically significant differences between pimavanserin and placebo for the safety outcomes of UPDRS II, UPDRS III, and combined UPDRS II and III, which suggested no worsening of Parkinson disease symptoms. Statistically significant differences were observed in favor of pimavanserin with the SAPS global severity rating of hallucinations (least squares mean difference of –1; $P=.02$), persecutory delusions (least squares mean difference of –1; $P=.009$), SAPS global severity rating of delusions (least squares mean difference of –1; $P=.03$), and SAPS global severity ratings total (least squares mean difference of –1.89; $P=.02$). Differences in individual and combination domain scores (SAPS-H, SAPS-D, and SAPS-H+D), visual hallucinations, Parkinson's Psychosis Rating Scale, and CGI-S were not statistically significant. The most common adverse effects reported by Meltzer et al[11] (incidence $\geq$5% and greater than rates in placebo group) included peripheral edema, asthenia, increased blood urea nitrogen, balance disorder, somnolence, and freezing phenomenon; however, no significant differences were found between placebo and pimavanserin. There were no clinically meaningful changes in electrocardiogram measurements.

Notable strengths of this phase II trial[11] are the study design, extended 4-week follow-up for safety monitoring, and the use of clinically relevant and appropriate rating scales, including the SAPS, which is a scale the Movement Disorder Society Task Force on Rating Scales for Parkinson's disease recommends to measure PDP.[13] This study was powered to find a difference in the safety outcomes instead of efficacy outcomes in order to highlight changes in motor function, which would set pimavanserin apart from other antipsychotics. The occurrence of freezing, which is a clinical presentation of Parkinson disease, was seen in 2 patients receiving pimavanserin, potentially raising concern as this effect was not seen in the placebo groups. The presence of freezing could indicate worsening of this specific motor symptom. Freezing could also be related to the fact that there were fewer pimavanserin subjects on dopaminergic agents compared with placebo, although a statistically significant difference was not reported. Considering that dose reduction in dopaminergic agents is part of the treatment of PDP, a higher percentage of subjects in the placebo group receiving dopaminergic agents could have contributed to the difference found in the efficacy outcomes. Notable limitations of this trial were its smaller sample size, unclear criteria for dose increase, and dose increases at day 8, prior to pimavanserin reaching steady state.

In a pivotal phase III clinical trial,[12] pimavanserin 40 mg daily was compared with placebo with the primary outcome measured as change in the Scale for Assessment of Positive Symptoms Adapted for Parkinson's Disease (SAPS-PD) from baseline to day 43. This study was powered to detect a 3-point difference in the SAPS-PD between groups. The SAPS-PD is a 9-item scale with a maximum score of 45 that is adapted from the SAPS and focuses more on hallucinations and delusions as these are more prominent symptoms in PDP. The data analysis for the development and validation of this scale was funded by the manufacturer of pimavanserin.[14] Assessments were performed at 2-week intervals. This trial was a randomized, double-blind, parallel-group, placebo-controlled, multicentered (United States and Canada) study with principal participant criteria of age >40, PDP with psychotic symptoms developing after Parkinson disease diagnosis, and Mini-Mental Status Examination score of at least 21 out of 30. The investigators excluded potential participants if their psychosis was believed to be

secondary to toxic or metabolic disorders or to concurrent dementia, or if the onset of psychosis occurred after ablative stereotaxic surgery. An additional exclusion was serious medical illness. After selection, participants were not allowed to receive adjustments to their antiparkinsonian regimens during the trial and for 1 month prior to enrollment; other antipsychotic drugs were prohibited. After screening 314 subjects, 199 were randomly allocated to either the treatment or placebo arm (105 to treatment arm; 94 to placebo arm). One subject in the treatment arm did not receive at least 1 dose of pimavanserin and 13 subjects discontinued treatment prior to post-baseline measurements, which left 95 and 90 subjects, respectively, included in the full analysis. Ultimately, 89 subjects receiving pimavanserin and 87 subjects receiving placebo completed the study treatment. The 2 arms appeared to be well matched in terms of baseline characteristics although *P* values were not reported. Overall, subjects were primarily white men around the age of 72 years, though the treatment group was 67% male, and the placebo group was 58% male. Close to 20% of subjects had received a prior antipsychotic trial, most commonly quetiapine, within 21 days before baseline. A vast majority of subjects were receiving dopaminergic agents during the study. Approximately 1/3 of subjects in each group were receiving acetylcholinesterase inhibitors. There were no differences between groups regarding the use of dopaminergic agents or acetylcholinesterase inhibitors.

The design of this trial included a 2-week lead in phase of psychosocial therapy in efforts to induce a placebo response prior to baseline (follow-up was done after 3 and 7 days). Inclusion was then set with a minimum score of at least 3 on both the SAPS and the SAPS-PD. In addition to the primary outcome assessed as the change in the aforementioned SAPS-PD, key secondary outcomes included a change in the CGI-S and Clinical Global Impression-Improvement Scale (CGI-I), a caregiver burden scale, and assessments related to sleep-wake cycle. A mixed-model repeated measures analysis was performed for numerical outcomes, including the primary outcome. Non-inferiority was assessed between pimavanserin and placebo with analysis of covariance using the change in UPDRS II and III scores. The primary analysis was performed on all subjects who received at least 1 dose of pimavanserin. The change in SAPS-PD least squares means score for pimavanserin vs. placebo was −5.79 versus −2.73, respectively ($P = .0014$). This correlated with a 37% versus 14% change in SAPS-PD scores, respectively ($P = .0006$). The change in domain scores for SAPS-H, SAPS-D, and SAPS-H+D were also in favor of pimavanserin, and these differences were statistically significant. Safety analyses indicated no sign of treatment-related worsening of motor function in either arm; however, 10 patients dropped out of the pimavanserin group because of an adverse event compared with 2 in the placebo group. The most common adverse effects reported by Cummings et al[12] (incidence $\geq$5% and rates more than 2 times the rate in placebo) included peripheral edema and confusional state. Adverse effects that led to discontinuation in this study included hallucinations (some occurred before pimavanserin was at steady state), urinary tract infections, and fatigue. A 7.3 ms increase in QTc interval from baseline was noted in the treatment arm, but this phenomenon was not related to adverse clinical events.

Strengths of this phase III trial[12] include use of centralized raters to reduce differences among raters as this study included 52 centers, use of an independent source for statistical analysis, and a study design that included a 2-week lead-in period of psychosocial therapy that may have reduced risk for placebo response. It is important to note that the objective scale used to measure the primary outcome of this trial was changed from the SAPS to the SAPS-PD approximately 16 months after final data collection.[15] Based on the data prior to this study, this change in primary outcome measurement raises questions with respect to efficacy and clinical meaningfulness. This is the first study to utilize the SAPS-PD; therefore, the findings cannot be compared with those of previously published studies that evaluated the use of other antipsychotics for this indication. Voss et al[14] reported a clinically meaningful change to be a 1-unit change in the CGI-I scale and that this is associated with a 2.33 point change in the SAPS-PD. This unit of change on the 7-point CGI-I scale is considered minimally improved within 1 subject. The FDA Briefing Document reported that large percentages of subjects that were "minimally improved" or "no change" per the CGI-I scale within this study had a $\geq$3-point change in SAPS-PD (44% for minimally improved; 31% for no change).[10] The threshold of a 3-point change on the SAPS-PD, which was used for the power analysis, may not provide enough data on the clinical significance of these results.

Discussion

Pimavanserin is the first antipsychotic without affinity for dopamine receptors. Its selective receptor profile offers advantages for its side-effect profile, especially in regards to the potential worsening of motor symptoms in Parkinson disease with D_2 blockade that other antipsychotics exhibit. An additional advantage in relation to its receptor profile is that there is not an interaction with dopaminergic agents. The reviewed studies provide data regarding the use of the medication primarily in elderly white men, and neither demonstrated worsening of motor symptoms, which is noteworthy. Both the published phase II and phase III trial primarily utilized the UPDRS II and III to assess motor symptoms. The non-inferiority analysis in both studies showed that pimavanserin did not worsen

activities of daily living or motor function more or less than placebo. The primary efficacy measure was different in the trials reviewed. In the phase II trial, the results of the SAPS efficacy measures were mixed. The SAPS-PD was created for the pivotal phase III trial after pimavanserin failed to show statistically significant improvements in psychosis symptoms using the SAPS in the prior trials. The SAPS-PD became the primary outcome measure after final data collection. The efficacy data are not profound in regards to clinical significance because the threshold of a 3-point change set for SAPS-PD in the phase III trial correlates with "minimally improved" on the CGI-I scale.[10] The exact mechanism of PDP is not well understood; therefore, there may be other targets of drug therapy that pimavanserin does not address given the selectivity of its mechanism of action. The statistically significant findings from the pivotal phase III trial that facilitated the FDA approval of pimavanserin may not correlate with a significant clinical utility, and this is a major limitation of pimavanserin. This is the first review article to include information available from the FDA Psychopharmacologic Drugs Advisory Committee meeting prior to this medication's approval, which enables clinicians to have a broader perspective of the data beyond the published studies. Further studies are warranted to provide clinicians and patients with better information regarding the efficacy of this agent.

References

1. Nuplazid (pimavanserin) [prescribing information]. San Diego (CA): Acadia Pharmaceuticals Inc; April 2016.
2. Hacksell U, Burstein ES, McFarland K, Mills RG, Williams H. On the discovery and development of pimavanserin: a novel drug candidate for Parkinson's psychosis. Neurochem Res. 2014; 39(10):2008-17. DOI: 10.1007/s11064-014-1293-3. PubMed PMID: 24682754.
3. Zahodne LB, Fernandez HH. Pathophysiology and treatment of psychosis in Parkinson's disease: a review. Drugs Aging. 2008; 25(8):665-82. PubMed PMID: 18665659.
4. Thanvi BR, Lo TC, Harsh DP. Psychosis in Parkinson's disease. Postgrad Med J. 2005;81(960):644-6. DOI: 10.1136/pgmj.2004.032029. PubMed PMID: 16210460.
5. Weiner DM, Vanover KE, Brann MR, Meltzer HY, Davis RE. Psychosis of Parkinson's disease: serotonin 2A receptor inverse agonists as potential therapeutics. Curr Opin Investig Drugs. 2003;4(7):815-9. PubMed PMID: 14619402.
6. Ballanger B, Strafella AP, van Eimeren T, Zurowski M, Rusjan PM, Houle S, et al. Serotonin 2A receptors and visual hallucinations in Parkinson disease. Arch Neurol. 2010;67(4):416-21. DOI: 10.1001/archneurol.2010.35. PubMed PMID: 20385906.
7. Stahl SM. Stahl's essential psychopharmacology: neuroscientific basis and practical applications. 4th ed. Cambridge (UK): Cambridge University Press; 2013.
8. Stahl SM. Parkinson's disease psychosis as a serotonin-dopamine imbalance syndrome. CNS Spectr. 2016;21(5):355-9. DOI: 10.1017/S1092852916000602. PubMed PMID: 27686027.
9. Stahl SM. Mechanism of action of pimavanserin in Parkinson's disease psychosis: targeting serotonin 5HT2A and 5HT2C receptors. CNS Spectr. 2016;21(4):271-5. DOI: 10.1017/S1092852916000407. PubMed PMID: 27503570.
10. US Food and Drug Administration. Psychopharmacologic Drugs Advisory Committee (PDAC) Meeting: FDA Briefing Document. March 29, 2016. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM492452.pdf
11. Meltzer HY, Mills R, Revell S, Williams H, Johnson A, Bahr D, et al. Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of Parkinson's disease psychosis. Neuropsychopharmacology. 2010;35(4):881-92. DOI: 10.1038/npp.2009.176. PubMed PMID: 19907417; PubMed Central PMCID: PMC3055369.
12. Cummings J, Isaacson S, Mills R, Williams H, Chi-Burris K, Corbett A, et al. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet. 2014;383(9916):533-40. DOI: 10.1016/S0140-6736(13)62106-6. PubMed PMID: 24183563.
13. Fernandez HH, Aarsland D, Fénelon G, Friedman JH, Marsh L, Tröster AI, et al. Scales to assess psychosis in Parkinson's disease: Critique and recommendations. Mov Disord. 2008;23(4): 484-500. DOI: 10.1002/mds.21875. PubMed PMID: 18175343.
14. Voss T, Bahr D, Cummings J, Mills R, Ravina B, Williams H. Performance of a shortened Scale for Assessment of Positive Symptoms for Parkinson's disease psychosis. Parkinsonism Relat Disord. 2013;19(3):295-9. DOI: 10.1016/j.parkreldis.2012.10.022. PubMed PMID: 23211417.
15. ACADIA Pharmaceuticals. A study of the safety and efficacy of pimavanserin in patients with Parkinson's disease psychosis. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 [cited 2017 Jan 7]. Available from: http://clinicaltrials.gov/show/NCT01174004