Long-term outcomes with pimavanserin for psychosis in clinical practice

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ABSTRACT

Introduction: Pimavanserin is the only medication FDA-approved for the treatment of Parkinson disease (PD) psychosis (PDP), but reports of long-term, real-world clinical experience are lacking.

Methods: A retrospective chart review of all patients treated with pimavanserin was conducted at our large Movement Disorders practice in Providence, Rhode Island, USA. Demographic and clinical data for each patient were collected and descriptive analyses were performed.

Results: We identified 54 patients (23 female) who initiated pimavanserin, whose median age was 70 years (range 44–87 years) and the median duration of pimavanserin therapy was 26 weeks. Initial improvement was seen in 47% of the entire group, and 50% of the DLB patients. Additional antipsychotic medication was needed concomitantly with pimavanserin to maintain a positive response for 40% of patients. Only 15% of the entire group had effective treatment of their condition with pimavanserin monotherapy over a median of 52 weeks. Among the initial responders, 32% continued on pimavanserin monotherapy. Among the non-responders, the mean trial period for patients who did not improve was 27 weeks, for patients who worsened was 16 weeks, and for those who experienced adverse effects was 1–2 weeks. Reported sex was similar across responders (60%), non-responders (56%), and the overall cohort (57%).

Conclusion: Our real-world experience shows that pimavanserin is safe and tolerable, with a lower response rate than reported in other publications. While it has been proven to be effective in short-duration clinical trials, our clinical experiences, however, demonstrate less promising results in the long term.

1. Introduction

Psychosis in Parkinson's disease (PDP) is common and burdensome on patients, their caregivers, and the healthcare system. The management of people with PDP is complicated by the fact that conventional anti-psychotic medications block dopamine which worsens the motor symptoms of PD. Prior to FDA-approval of pimavanserin for PDP in 2016, two atypical dopamine-receptor blocking drugs (DRBDs) – quetiapine and clozapine – had been used to treat PDP [1]. Clozapine has been shown to be effective for treating PDP, but because of the risk of agranulocytosis, requires frequent blood testing. While quetiapine does not worsen motor problems in PD, and does not require frequent blood monitoring, it has been shown not to be more effective than placebo at treating PDP in double blind placebo controlled trials [2]. Because open label studies have reported efficacy and tolerance, quetiapine is still used for PDP treatment [1].

Pimavanserin is a novel 5-HT2a antagonist/inverse agonist without adrenergic, histaminergic, muscarinic or dopaminergic activity, and thus is not expected to worsen PD symptoms. Pimavanserin was FDA approved for PDP over 5 years ago, and long-term data – especially of real-world experience – are sparse. To gain insights from real-world experience, we sought to examine outcomes in the patients treated with pimavanserin at our large Movement Disorders practice.

2. Methods

After approval of the institutional review board, we conducted a retrospective chart review of patients treated with pimavanserin by the co-author (JHF) at our large Movement Disorders practice in Providence, Rhode Island, USA. Since pimavanserin was FDA-approved in 2016, our review included charts from 2016 until July 2021. We identified 54 patients who initiated treatment with pimavanserin. Data collected for each patient included diagnosis, sex, age at disease onset, disease duration, the initial response to pimavanserin after 4 weeks of

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treatment, duration of pimavanserin therapy, if pimavanserin was discontinued and why, which antipsychotic replaced pimavanserin or was added to it, and the long-term response to treatment. Patients were categorized into responders (versus non-responders) based on clinician's global impression of the patient's condition based on his discussion with the patient and the caregiver. Patients who did not improve or could not tolerate pimavanserin were labeled non-responders. Descriptive analyses were performed.

3. Results

Of the 54 patients (31 male, 23 female) who initiated pimavanserin, 45 had PD, 8 had Dementia with Lewy Bodies (DLB), 1 had atypical parkinsonism (not further specified), and 1 was lost to follow-up, and thus removed from the analysis.

The median age at disease onset was 70 years (range 44–87 years) and the median duration of pimavanserin therapy was 26 weeks (range 1–260 weeks).

All patients but one had hallucinations, and 24 had delusions. Of the patients with PD, 27 were demented (60%) and 18 were not. Anti-dementia medications (cholinesterase inhibitors and/or memanine) had been tried by 9 patients (33%) without benefit; 12 patients (44%) had never been treated with any; and 6 patients (22%) were still on treatment when started on pimavanserin.

Initial improvement (determined by the clinician after at least 4 weeks of therapy) was seen in 47% of the entire group (n = 25 of 53), and 50% of the DLB patients (n = 4 of 8). Excluding patients with < 4 weeks of therapy, 56% of the entire group (n = 25 of 45), and 67% of the DLB patients (n = 4 of 6) experienced improvement. Due to inadequate control of symptoms with pimavanserin, addition of another antipsychotic medication was needed to maintain a positive response for 40% (n = 10 of 25) of patients. Out of the patients who had an initial positive response, 32% (8 of 25) continued on pimavanserin monotherapy with a positive response. Thus, only 15% of the entire group (n = 8 of 53) had effective treatment of their condition with pimavanserin monotherapy over a median 52 weeks (range 28–208 weeks).

Pimavanserin was the initial treatment in all but 3 cases; it was added to quetiapine in 2 cases and it replaced clozapine in 1 case due to neutropenia, but clozapine resumed when neutrophils recovered, as symptoms were not as well controlled. The clozapine re-challenge was well-tolerated and both medications were continued.

Among the non-responders, the median trial period was 6 weeks (range 1–208 weeks), and excluding patients with therapy < 4 weeks was 6 weeks (range 4–208 weeks); and 1–2 weeks for those who experienced adverse effects.

Quetiapine was added to pimavanserin in 3 cases; clozapine in 4; lurasidone (by a psychiatrist) in 1 case.

Age at onset and sex did not seem to affect response to pimavanserin treatment. Reported sex was similar across responders (60%), non-responders (56%), and the overall cohort (57%).

Of the 7 patients who developed worsening psychosis on pimavanserin, 3 were within the first 4 weeks, and the duration for the remaining ranged from 4 to 84 weeks, median 10 weeks. No patient was withdrawn from an alternative antipsychotic so there was no withdrawal effect. An additional 5 patients discontinued pimavanserin due to other side effects, including sedation (1), bad dreams (1), confusion (1), worsening gait (1), and gastrointestinal symptoms (2).

There were 14 deaths during the study period; 8 patients died while taking pimavanserin with median duration of treatment 32 weeks (range 1–88 weeks); 6 patients died after being on pimavanserin for median of 4 weeks (range 2 days to 84 weeks) and after discontinuing it for a median of 10 weeks (range 3–24 weeks).

4. Discussion

PDP is an often disabling problem which pimavanserin treat without

worsening motor symptoms through its novel mechanism of action.

A phase 3 randomized-controlled trial showed that pimavanserin-treated patients improved 37% on the scale for assessment of positive symptoms (SAPS-PD) versus placebo (14% improvement), with a statistically significant difference of 23% [3]. The clinical global impression improvement was seen in 49% of the pimavanserin treated cohort, which is similar to the rate in our group. AEs were reported by 11% of pimavanserin-treated patients vs 4% in the placebo group. Notably, 6 of the 10 discontinuations in the pimavanserin-treated group were for psychosis.

An open-label study (spanning 11 years) of 459 patients treated for a median 454 days showed long-term safety of pimavanserin for PDP. At least 1 AE was reported by 85% of patients, serious AEs occurred in 41%, and AEs that resulted in study termination or dose discontinuation occurred in 29% [4].

Wei et al (2021) published their single-center experience with 45 pimavanserin-treated patients and reported improvement in 71% of patients and AE rate of 30% [5].

Sellers et al conducted a retrospective chart review of 91 patients on pimavanserin and showed that 76% of patients improved initially, 22% experienced side effects, and after a mean duration of 56 weeks, 18% of the initial cohort were on dual antipsychotic therapy and 36% remained on pimavanserin monotherapy [6]. These findings differ from our group's but given the lack of clinical measures and rating scales, comparing the two groups is difficult.

In a review of the literature summarizing the findings of various pimavanserin studies, the authors concluded that the variability of efficacy in clinical trials may be due to the varying study designs, and when trial design was adjusted to blunt the placebo effect, pimavanserin was found to be safe, tolerable and effective [7].

In our real-world experience, approximately half of the patients treated with pimavanserin had an initial positive response, and one-third of them were maintained on pimavanserin monotherapy with good response. Of the overall cohort, pimavanserin monotherapy adequately controlled symptoms in only 15% of patients, long term, over a median duration of 52 weeks and had an AE rate of 9%.

A high discontinuation rate is not specific to pimavanserin. A retrospective cohort study of commercially-insured PD patients treated with antipsychotic medications found that the discontinuation rate after the first prescription was 39%, and after 6 months, the rate was highest for DRBDs and lowest for pimavanserin (23%) [8]. A retrospective chart review study reported a similar discontinuation rate of 36% for pimavanserin and 21% for quetiapine [9].

The difference in response rate and AE rate in our cohort compared to others' reports is likely explained by the differences in practice patterns and healthcare systems. In our practice, quetiapine is used first when a rapid response, within a week is required, and clozapine is used first for emergencies when hospitalization is refused by the family. We use pimavanserin for patients whose symptoms are not so severe that a response lag time of 4–6 weeks would be intolerable, as the response to clozapine is much faster [10]. We use donepezil only infrequently to treat PDP in demented patients.

The 10 patients in our cohort who used pimavanserin concomitantly with another antipsychotic tolerated the dual therapy well without report of adverse effects to raise concern regarding safety.

While there were 14 deaths during the study period (8 patients died while taking pimavanserin and 6 patients died after stopping pimavanserin), it is important to note that PD patients in routine clinical care are often "lost to follow-up" at advanced stages of disease because of death or because the patient/caregiver do not find routine neurology care beneficial, or the nursing home might be providing on-site neurology care. Since our data were not collected as part of a prospective clinical trial, data regarding mortality should be interpreted cautiously.

While we did not assess other comorbid problems (e.g. sleep disorders, dementia) which could have affected the severity of PDP and

response to treatment, we provide a large real-world experience with pimavanserin for PDP, including patients who were previously reported [11,12].

5. Conclusion

Pimavanserin has a novel mechanism of action to treat PDP without causing motoric worsening. A review of our real-world experience shows that pimavanserin is safe and tolerable, with a lower long-term response rate than reported in other publications. While it has been proven to be effective in clinical trials lasting 6 weeks, and, when effective, lasting up to 26 weeks [13] in people with dementia, in general, our clinical experiences, however, demonstrate less promising results. More research is needed to understand the ideal candidate for pimavanserin treatment and to develop more effective treatments for PDP [14].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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