Schizophrenia Research 208 (2019) 217–220

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Successful treatment of clozapine-nonresponsive refractory hallucinations and delusions with pimavanserin, a serotonin 5HT-2A receptor inverse agonist

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ARTICLE INFO

Article history:
Received 7 January 2019
Received in revised form 20 February 2019
Accepted 25 February 2019
Available online 2 March 2019

Keywords:
Schizophrenia
Refractory hallucinations and delusions
Clozapine
Pimavanserin
Serotonin 5HT-2A inverse agonist

ABSTRACT

Background: Clozapine was the widely accepted gold standard treatment for treatment resistant psychotic symptoms. Clozapine has efficacy of about 50% and some responding patients have to discontinue it due to serious adverse effects. The search for novel agents to use for clozapine-non-responders continues. One such possible agent is the non-dopaminergic antipsychotic pimavanserin, an inverse agonist of serotonin 5-HT2A receptors which was recently approved for the hallucinations and delusions of Parkinson's Disease Psychosis. We report here the successful results of using pimavanserin in patients with refractory hallucinations and delusions who failed to respond to clozapine. We also report similar results in refractory psychosis patients who did not receive clozapine.

Methods: We present ten cases of patients with schizophrenia and schizoaffective disorder with refractory hallucinations and delusions who received a trial of pimavanserin when clozapine or multiple antipsychotics failed. Six of ten patients had not responded to a clozapine trial. The subjects' ages ranged between 21 and 77 years and were followed up for several months.

Results: All 10 patients with refractory hallucinations and delusions showed marked response to pimavanserin 34 mg/day within 4–8 weeks, with continuation of the response for several months of follow-up. Improvements in negative symptoms and social functioning were also observed in several patients.

Discussion: This series of 10 cases of patients with refractory psychosis who responded to pimavanserin is an important new finding that has never been reported before. Controlled studies comparing clozapine and pimavanserin in refractory schizophrenia are warranted to confirm these clinical observations.

1. Introduction

Clozapine is widely recognized as the last resort agent for persistent hallucinations and delusions that are refractory to first or second generation antipsychotic drugs (Meltzer, 1997; McEvoy et al., 2006). A significant proportion of patients with schizophrenia are estimated to be treatment-resistant or refractory to multiple antipsychotics (Siskind et al., 2017), which makes clozapine a vital part of the psychopharmacological toolbox for the management of chronic schizophrenia.

However, response to clozapine in treatment-resistant/refractor psychosis is limited and estimated to be about 40% of cases (Siskind et al., 2017), leaving a large segment of refractory psychosis cases with no viable alternative. Researchers have reported several adjunctive agents that may improve clozapine-resistant refractory hallucinations and delusions including Lamotrigine (Tiihonen et al., 2009) and Sodium Benzoate (Lin et al., 2017). However, there are still no widely accepted adjunctive pharmacotherapies for clozapine non-responders, and certainly no alternatives to clozapine itself in refractory psychosis.

Pimavanserin, an inverse agonist of the serotonin 5HT-2A receptor and to a lower extent 5HT-2C receptor (Meltzer et al., 2010), was recently approved for the treatment of the hallucinations and delusions that occur in up to 50% of patients with Parkinson's Disease (Hacksell et al., 2014). Since pimavanserin does not bind at all to dopamine D2 receptors, it is the first non-dopaminergic antipsychotic since the discovery of the first dopamine antagonist, chlorpromazine, in the early 1950s. It is an ideal pharmacotherapy for Parkinson' Disease psychosis because it can treat the psychotic symptoms without exacerbating the motor symptoms of Parkinson's disease, which can be exacerbated with all current antipsychotic drugs because they all reduce dopamine neurotransmission.

Because pimavanserin has been demonstrated to exert efficacy on hallucinations and delusions in a major psychotic disorder like Parkinson's Disease Psychosis, it seems reasonable that it be used as we an adjunctive therapy to clozapine in desperately sick patients with refractory hallucinations and delusions who failed to respond to

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https://doi.org/10.1016/j.schres.2019.02.018
0920-9964/

a trial of clozapine. We report here how that clinical strategy in a clinical setting of a residential treatment facility for patients with chronic psychotic disorders serendipitously revealed that the addition of pimavanserin to clozapine in patients with refractory hallucinations and delusions led to remission of the refractory psychotic symptoms which had failed to respond to several months of clozapine treatment. Following that important clinical observation in several patients pimavanserin was administered in monotherapy to patients with refractory hallucinations and delusions prior to using clozapine with the intention to resort to clozapine only if pimavanserin does not exert clinical efficacy on refractory psychosis.

2. Methods

This is a retrospective report of patients with refractory psychosis who responded to pimavanserin. Our clinical use of pimavanserin initially as adjunctive therapy and as subsequently as monotherapy for treatment-refractory psychosis was done as clinical management for desperately sick refractory patients, not as a research study. No rating scales are used in the residential treatment facility and improvement is determined clinically by the treating psychiatrist [RM] and documented as usual in the medical record. It was over a year later, after success was noted in several patients, that we felt it was important to report those encouraging findings in a peer reviewed journal so that other clinicians, and researchers, recognize the potential for pimavanserin to be a useful agent in refractory psychosis, even when clozapine, the only approved drug for this condition, fails to suppress refractory hallucinations and delusions.

Thus, those clinical findings ended up serving as a hypothesis-generating observations which may very well set the stage for a controlled trial, now that pimavanserin's efficacy was clinically achieved in refractory patients with or without clozapine. Treatment resistant and refractory schizophrenia is a significant unmet need in psychiatry, and serendipitous findings like this one may lead to a new avenue for treating what is regarded as the most severe forms of psychosis.

3. Results

Pimavanserin did demonstrate efficacy as adjunctive therapy to clozapine-non-responding psychotic symptoms in 6 patients. Pimavanserin was also administered as monotherapy to 4 patients with refractory hallucinations and delusions who had not received clozapine, and observed strong efficacy there as well with very good tolerability and safety after several months of treatment, unlike the serious adverse effects often encountered with clozapine.

The following are brief vignettes of all 10 cases. Detailed clinical data are available on all patients but were not included here due to space considerations. No serum clozapine levels were obtained at the residential treatment facility. In addition, none of the patients is a smoker, so there was no potential reduction of clozapine serum concentrations due to the induction of Cytochrome 1A2 by nicotine.

3.1. Efficacy of pimavanserin as adjunctive therapy with clozapine

The following are 6 brief vignettes of clinical remission of refractory hallucinations and delusions when pimavanserin was added as adjunctive therapy to patients with poor or partial response to clozapine in adequate doses after several months. Interestingly, it was noted that some of the negative symptoms of the patients also improved concurrently with the elimination of the refractory positive symptoms:

3.1.1. Case 1

44-year-old female with auditory and visual hallucinations since age 18, along with severe paranoid delusions. She was started on clozapine 400 mg/day for several months after failing to respond to various antipsychotics, but responded only partially and her hallucinations persisted. Pimavanserin 34 mg/day was then added. Her visual hallucinations disappeared in 1 month, and her auditory hallucinations responded completely after 2 months. In addition, she was also noted to become more friendly, pleasant and less isolative.

3.1.2. Case 2

21-year old male with intense auditory and visual hallucinations, and severe delusions that led him to “argue with inanimate objects”. Clozapine 500 mg/day was started but failed to control his hallucinations or delusions after several weeks. Pimavanserin 34 mg/day was added. His hallucinations remitted fully after 1 month. He also became more sociable and his affect became much less blunted.

3.1.3. Case 3

40-year old male with refractory auditory hallucinations but no visual hallucinations. His command auditory hallucinations prompted him to kill himself. He received multiple antipsychotics and experienced severe EPS. So, he was switched to clozapine 200 mg/day, but continued to receive olanzapine, risperidone, ziprasidone and loxapine, but with no response. Pimavanserin 34 mg/day was then started, and his auditory hallucinations noticeably improved within 1 months, and were completely gone after 2 months. His affect became brighter and he became more friendly and “much happier”.

3.1.4. Case 4

54-year old male with both auditory and visual hallucinations. He did not respond to several antipsychotics. A trial of clozapine 500 mg/day failed to help him and his hallucinations actually worsened after a few months. Addition of olanzapine 30 mg/day did not help either. Pimavanserin 34 mg/day was then added. His auditory hallucinations decreased within 1 month, and both auditory and visual hallucinations completely disappeared at the end of 2 months. He also became more sociable, with improved cognitive ability, and even started working part-time.

3.1.5. Case 5

68-year old male with visual hallucinations and comorbid auditory hallucinations telling him to commit suicide. He sustained several injuries by repeatedly hitting his ears and head. After failing to respond to various antipsychotics for many years, he was started on clozapine 350 mg/day, but with minimal response after several months. Pimavanserin 34 mg/day was then added. His auditory hallucinations decreased after 1 month, and by 3 months he was hitting his head much less frequently (1/week instead of 9 times/week). His hallucinations and head hitting completely disappeared after 5 months. He was also noted to become more social and engaged with much less flat affect and he felt “happier”.

3.1.6. Case 6

61-year old female, with command (suicidal) auditory hallucinations. After failing to respond to many antipsychotics and suffering from EPS, she was given Clozapine that was titrated up to 800 mg/day with no remission of her auditory hallucinations after several months. Pimavanserin 34 mg/day was added. Her auditory hallucinations gradually faded and stopped completely after 2 months. She became more verbal and less aggressive, with a brighter affect.

3.2. Pimavanserin monotherapy in refractory psychosis

The following are 4 brief vignettes of remission of refractory hallucinations and delusions with Pimavanserin when used in patients who had never received Clozapine:

3.2.1. Case 1

44-year-old female with schizoaffective disorder and tardive dyskinesia, who suffered from refractory auditory hallucinations. She also