Opportunity

Abstract

Parkinson’s disease psychosis (PDP) is a complication that affects 40-60% of patients with Parkinson’s disease (PD). The visual hallucinations and sensory disturbances experienced by patients contribute to the overall burden of disease. PDP is due to death of substantia nigra dopaminergic neurons in the brain while psychosis is associated with excessive dopamine transmission, presenting a predicament for the treatment of PDP. Treatment options have been limited to off-label use of the atypical antipsychotics clozapine and quetiapine, until the FDA approved pimavanserin (Nuplazid), the first drug indicated for treatment of PDP. ACADIA Pharmaceuticals set out to create a pure S-HT2A inverse agonist based on evidence of increased S-HT2A neurotransmission in patients with PDP.

This review assesses the evidence for pimavanserin for treatment of PDP by analyzing the pharmacology, preclinical studies and clinical trial data for its use in PDP. ACADIA developed a high-throughput receptor assay which identified ACP-103 (pimavanserin) as a highly selective, orally bioavailable S-HT2A inverse agonist. Later, animal models predictive of antipsychotic activity, ACP-103 decreased head twitch, prepulse inhibition, and amphetamine-induced locomotor hyperactivity without causing motor impairment. In two clinical trials, significant placebo effects caused discontinuation but in a third trial, pimavanserin demonstrated statistically significant reductions in hallucinations (p=0.017) without worsening PD motor symptoms. Given the available evidence, pimavanserin presents as a logical treatment for PDP. Further studies with greater statistical power are needed to confirm the efficacy of reducing S-HT2A neurotransmission in PDP. Post-marketing studies on the long-term effectiveness of pimavanserin will ultimately establish its place in therapy.

Background

1. What is Parkinson’s Disease (PD)?
   - A chronic and progressive movement disorder caused by the death of dopamine neurons in an area of the brain called the substantia nigra.
   - Hallmark symptoms include tremor, rigidity, slowness of movement, and postural instability.
   - Dopamine receptor agonists, L-DOPA, and MAO inhibitors are commonly used to treat the motor symptoms of PD.

2. What is Parkinson’s Disease Psychosis (PDP)?
   - A psychiatric complication seen in 40-60% of PD patients.
   - Common symptoms include visual hallucinations, delusions, and sensory disturbances.

3. What causes PD?
   - The mechanism is unknown but may be multifactorial.
   - Use of dopaminergic medications for PD may cause over-stimulation of dopamine receptors in unintended brain areas, resulting in psychiatric symptoms.
   - Serotonin 5-HT2A receptor activity is elevated in visual brain areas in PD patients with visual hallucinations, suggesting a causal role for excessive S-HT2A receptors.

4. What are the current therapies available for PD?
   - Prior to pimavanserin, there were no FDA-approved medications for PD.
   - The atypical antipsychotics clozapine and quetiapine have been used off-label in clinical practice. They are dopamine receptor antagonists as well as S-HT2A inverse agonists.

5. What is pimavanserin’s role in therapy for PDP?
   - Pimavanserin is the first FDA-approved drug for treatment of PDP (approved in 2016).
   - It has a unique mechanism of action as an inverse agonist at S-HT2A receptors and no activity at dopamine receptors.

Approach

Review of published articles evaluating pimavanserin’s pharmacology, preclinical studies, and clinical trials

Results

Pimavanserin is a highly selective S-HT2A inverse agonist.

- Inverse agonists bind to receptors and produce effects opposite to that of an agonist.
- In an experimental assay, pimavanserin was shown to decrease basal activity of S-HT2A receptors with greater selectivity than S-HT2C receptors (graph at left).
- ACADIA’s Receptor Selection and Amplification TechnologyTM demonstrated pimavanserin’s higher affinity and selectivity for S-HT2A receptors than other antipsychotic drugs (shown in table).

Pimavanserin decreased psychotic symptoms in animal models of PDP.

- PD symptoms were induced in rats by bilateral lesions of the substantia nigra dopamine neurons.
- Several weeks later, motor impairments and psychosis-like behaviors spontaneously developed in lesioned rats.
- Three behaviors used to assess antipsychotic efficacy were head twitch, prepulse inhibition, and amphetamine-induced hyperactivity.
- In each of these models, pimavanserin significantly reduced psychosis-like behaviors compared to vehicle-treated controls, but it did NOT impair L-DOPA’s reversal of motor symptoms.

In Phase 2b/3 clinical trials, pimavanserin did not worsen PD motor symptoms but placebo effects led to early discontinuation.

- Study 021:
  - Randomized, double-blind, placebo controlled
  - Pimavanserin 10 mg vs. pimavanserin 20 mg vs. placebo
  - Primary outcome: reduction of psychosis using the SAPS-H+D scale
  - A 42% placebo effect precluded statistically significant separation of pimavanserin treatment arm from placebo
  - Confirmed motor safety in humans

- Study 024:
  - Pimavanserin 10 mg vs. pimavanserin 20 mg vs. placebo
  - Primary outcome: reduction of psychosis using the SAPS-H+D scale
  - Initiated before outcome of Study 012 was known
  - Discontinued based on similarity in design and subsequent results of Study 012
  - Limited data prior to study discontinuation showed no statically significant separation of pimavanserin from placebo

Impact

The unique feature about my innovation/research is its review of pimavanserin’s novel pharmacology and breakthrough clinical indication.

This addresses the problem of treating Parkinson’s disease psychosis without worsening motor function.

References

1. References to journal articles and case studies to support the evidence for the use of pimavanserin in PDP.
5. ACADIA’s Receptor Selection and Amplification TechnologyTM demonstrated pimavanserin’s higher affinity and selectivity for S-HT2A receptors than other antipsychotic drugs (shown in table).