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Role of Pimavanserin in Psychosis Treatment

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Abstract: Pimavanserin, a novel agent approved for the treatment of Parkinson's disease psychosis, has potent actions as an antagonist/inverse agonist at serotonin 5HT2A receptors and less potent antagonist/inverse agonist actions at 5HT2C receptors. The *in vitro* and *in vivo* pharmacology of AC-90179 was attractive and, therefore, a major lead optimization effort was launched to develop an orally bioavailable analogue with similar pharmacology .A comprehensive library of marketed CNS drugs were evaluated for activity on a wide range of G-protein coupled receptors (GPCRs) using the Receptor Selection and Amplification Technology™ (R-SAT™) platform, a high-throughput functional assay technology that is well suited for chemical genomics and high-throughput screening (HTS), and is applicable to a wide array of genetic targets including most GPCRs, receptor tyrosine kinases, cytokine receptors, and nuclear receptors. Pimavanserin is a member of the class of ureas and atypical antipsychotic that is used (in the form of its tartrate salt) for treatment of hallucinations and delusions associated with Parkinson's disease. It has a role as an antipsychotic agent, a 5-hydroxytryptamine 2A receptor inverse agonist and a serotonergic antagonist. The most common side effects comparing patients on pimavanserin relative to placebo groups were peripheral edema and confusion.

In this review will discuss treatment strategies involving pharmacological agents, with major emphasis on Pimavanserin and its chemistry.

Keywords: *CNS drugs , Pimavanserin, Psychosis, parkinsonism*

Introduction: Central nervous system (CNS) disease is a broad category of conditions in which the brain does not function as it should, limiting health and the ability to function. The condition may be an inherited metabolic disorder; the result of damage from an infection, a degenerative condition, stroke, a brain tumor or other problem; or arise from unknown or multiple factors [1]. Movement disorders such as Parkinson’s disease, dystonia, and essential

tremor are central nervous system conditions. Parkinson's disease psychosis is common and causes substantial caregiver burden, resulting in a high rate of visits to emergency rooms and admission to nursing homes. The symptoms typically consist of illusions, hallucinations, and more bothersome and distressing paranoid delusions [2]. The etiology and pathogenesis remain incompletely understood. There are currently no disease-modifying treatments for PD, and medical management is predominantly focused on controlling the motor symptoms using drugs. The long-term duration of disease means that patients may take sophisticated medication regimes aimed at controlling the motor symptoms, with a likelihood of problematic side effects.

Pharmacology: The *in vitro* and *in vivo* pharmacology of AC-90179 was attractive and, therefore, a major lead optimization effort was launched to develop an orally bioavailable analogue with similar pharmacology. This effort led to the discovery of pimavanserin (ACP-103) [11], a molecule with similar structural characteristics as AC-90179 but with much greater oral bioavailability. Pimavanserin is an achiral compound which is easy to synthesize in small or large scale from readily available starting materials . Pimavanserin has no structural resemblance to the APDs. Pimavanserin is a potent, selective 5-HT2A inverse agonist, with selectivity over 5-HT_{2C} receptors in binding and functional assays and little to no activity at other GPCRs in contrast to the available APDs . Thus, the structural characteristics and pharmacological selectivity profile of pimavanserin differentiates it from typical as well as atypical APDs. The movement disorder of PD occurs largely due to the selective loss of neurons in the substantia nigra pars compacta [3], with consequent depletion of dopamine in the striatum [4]. Dopaminergic drugs designed to replace the action of dopamine in the deplete striatum form the mainstay of PD treatment at present[5]. There is no gold standard of treatment strategy, with medication regimes being tailored to the individual patient, based on the severity and temporal nature of their symptoms, as well as the side effects that they experience. These drugs include DA receptor agonists, MAO inhibitors, L-DOPA and amantadine. While motor symptoms of PD used to be the focus of treatment, it has now been realized that non-motor symptoms are equally disturbing to the patient [6]. The most common non-motor symptoms include depression, sleep problems, psychosis and dementia. Parkinson’s disease psychosis (PDP) [7, 8], which is characterized by hallucinations and/or delusions, may develop in up to 60 % of PD patients [9], is persistent and progressive and associated with deterioration in quality of life as well as increased morbidity and mortality. Psychosis has been identified as the leading cause of nursing home

placement among PD patients [10]. Currently, there is no effective, tolerated and safe therapy available for treatment of PDP. While low doses of clozapine are approved as a second line therapy in Europe, no first-line therapy is available and no PDP drug is approved in any other major market In the late 1990s ACADIA scientists started a chemical genomics effort aimed at improving the understanding of the targets for drugs acting on the central nervous system.

A comprehensive library of marketed CNS drugs were evaluated for activity on a wide range of G-protein coupled receptors (GPCRs) using the Receptor Selection and Amplification Technology™ (R-SAT™) platform, a high-throughput functional assay technology that is well suited for chemical genomics and high-throughput screening (HTS), and is applicable to a wide array of genetic targets including most GPCRs, receptor tyrosine kinases, cytokine receptors, and nuclear receptors [12]. R-SAT™ utilizes the principles of genetic selection and is based on the observation that oncogenes and many receptors induce proliferation or transformation responses in NIH-3T3 cells. Agonists preferentially select and amplify cells that express functional receptors. In cases where the genetic target exhibits constitutive activity, cellular proliferation occurs in the absence of added agonists. In such cases, inverse agonists can be readily identified by their ability to suppress proliferative responses [13]. Typically, the optimal signal is observed 5–6 days post-transfection, a period of time during which the reporter is amplified in the proliferating cells and diminished in the quiescent cells [14]. GPCRs frequently possess some degree of ligand independent or constitutive activity [15]. Of the various functional assays used for HTS, RSAT™ may provide the most sensitive means of detecting constitutive activity, possibly due to its assay length of 5–6 days which allows for amplification of constitutive responses to occur. For example, a direct comparison of calcium flux, phosphatidyl inositol hydrolysis (PI) and R-SAT™ assays reveals the constitutive activity of the Ghrelin receptor is most easily detected using R-SAT™ [12]. These findings strongly agree with a previous study in which the constitutive responses of wild-type and mutant forms of the 5-HT_{2A} receptor were much more apparent using R-SAT™ assays compared with PI assays . While screening numerous typical and atypical APDs, we discovered that most of the atypical APDs, including clozapine, had one activity in common which separated them from the typical antipsychotic agents. They were potent and fully efficacious inverse 5-HT_{2A} agonists [16] and they were less or much less potent as DA D_2 receptor antagonists. The efficacy of low-dose clozapine in PDP therapy and the observation that atypical APDs appear to have several advantages over the older typical agents led to the hypothesis that selective 5-HT_{2A} inverse agonist activity might be an

appropriate target mechanism to explore in a drug discovery program ; thus we initiated a program to discover novel 5-HT_{2A} receptor inverse agonists.

A functional HTS R-SAT™ assay for 5-HT_{2A} inverse agonists was configured by expression of the human 5-HT_{2A} human receptor in NIH 3T3 cells together with a marker gene to permit signal detection using a colorimetric method. A proprietary compound library of 130,000 chemically diverse small molecules was screened in the HTS assay at a concentration of 3 μM. Of the initial 500 hits, 100 were characterized as potent 5-HT_{2A} inverse agonists. Following further screening for selectivity and subsequent lead optimization, AC-90179 was identified as a selective 5-HT_{2A} inverse agonist [17]. It had nearly 100 fold selectivity for 5-HT_{2A} receptors compared to 5-HT_{2B}, 5-HT_{2C} and 5-HT_6 receptors as an inverse agonist. At concentrations less than or equal to 1 μM, it did not interact with other monoaminergic receptors. Although the oral bioavailability of AC-90179 was very low, it was useful for initial proof of concept studies in rodents. As expected, AC-90179 dose-dependently eliminated head twitches induced by DOI, a behavior mediated by 5-HT_{2A} receptor stimulation. Also, AC-90179 inhibited MK-801-induced but not amphetamine-induced locomotor activity. At the dose that effectively inhibited MK-801-induced locomotor activity, AC-90179 did not reduce spontaneous locomotor activity. Importantly, AC-90179 was effective in restoring prepulse inhibition (PPI) response disturbed by DOI. All these effects were expected based on previous studies describing the pharmacology of MDL-100,907, a selective 5-HT_{2A} antagonist [18, 19].

Clinical Studies:

Efficacy of pimavanserin

In a six-week, randomized, double-blinded, placebo-controlled (RDBPC) study, adults aged ≥ 40 years with PD psychosis were enrolled [20]. Participants were randomly assigned into groups and received pimavanserin 40 mg daily or placebo. The primary outcome measure in this trial was an antipsychotic effect that was assessed by independent raters using the PD-adapted scale for assessment of positive symptoms (SAPS-PD). Pimavanserin was associated with a 5.79-point decrease in SAPS-PD scale compared to the 2.73-point reduction in participants receiving matched placebo, that is a statistically significant difference of 3.06 ($P < .001$) [20]. In another RDBPC trial conducted over the eight weeks included patients at 1:1 ratio, and they received a placebo or pimavanserin [21]. Pimavanserin was started at 20 mg, and depending on the patient's clinical response, the dose was increased to 40 or 60 mg daily

on day 8 and day 15, respectively. There was a statistically significant improvement in the global rating of hallucinations in the pimavanserin group (P = .02, effect size (ES) = .58). Also, some improvements in pimavanserin group was seen in SAPS delusion domain measures, including persecutory delusions (P = .009, ES = .41), and ideas of reference (P = .05, ES = .36). The participants in pimavanserin group showed improvement in the SAPS total domain score (P = .09, ES = .52), i.e., 40% improvement compared with an 11% improvement seen in the placebo group [21].

Safety of pimavanserin

The most common side effects comparing patients on pimavanserin relative to placebo groups were peripheral edema (7%) and confusion (6%) [22]. Other significant adverse drug events were increased risk of fall, urinary tract infections, and hallucinations (5%) and constipation (4%). It is safe to prescribe pimavanserin in patients on carbidopa/levodopa, as no significant drug interactions were observed [21]. It is recommended to reduce the pimavanserin dose by 50% when given along with cytochrome P450 (CYP450) inhibitor. On the contrary, pimavanserin dose may need to be increased if it is given with a CYP450 inducer. An insignificant QT interval prolongation for 9.6 milliseconds was seen in a RDBPC trial at a dose of 34 mg [21]. Pimavanserin is well-tolerated medication for managing psychosis in patients with PD with no serious adverse events [20].

Chemistry: Pimavanserin is a member of the class of ureas in which three of the four hydrogens are replaced by 4-fluorobenzyl, 1-methylpiperidin-4-yl, and 4-(isopropyloxy)benzyl groups (Figure 1). An atypical antipsychotic that is used (in the form of its tartrate salt) for treatment of hallucinations and delusions associated with Parkinson's disease. It has a role as an antipsychotic agent, a 5-hydroxytryptamine 2A receptor inverse agonist and a serotonergic antagonist. Pimavanserin (ACP-103), marketed under the trade name Nuplazid, is a drug developed by Acadia Pharmaceuticals which acts as an inverse agonist on the serotonin receptor subtype 5-HT2A, with 40x selectivity over 5-HT2C, and no significant affinity or activity at 5-HT2B or dopamine receptors. As of September 3, 2009, pimavanserin has not met expectations for Phase III clinical trials for the treatment of Parkinson's disease psychosis. It is in Phase II trials for adjunctive treatment of schizophrenia alongside an antipsychotic medication and is expected to improve the effectiveness and side effect profile of antipsychotics. It is a member of ureas, a member of piperidines, a member of monofluorobenzenes, an aromatic ether and a tertiary amino compound. It is a conjugate

base of a pimavanserin(1+).Pimavanserin tartrate has been approved by the US FDA on April 29, 2016 and marketed at a prescription status in the USA. Abundant pre-clinical research data attach importance to pharmacological and pharmocodynamic studies on animal models. However, as a new drug, there was limited pharmacokinetic information available. Earlier publication rarely reported systematic and mature methods for determination of pimavanserin in rat plasma. Vanover et al. [23]had investigated an 8 h intravenous and oral administration pharmacokinetics of a hydrochloride salt form of pimavanserin in male rats, which was not completed of the validated content and pharmacokinetic parameters. It is necessary to investigate pharmacokinetic profile in rats for longer time

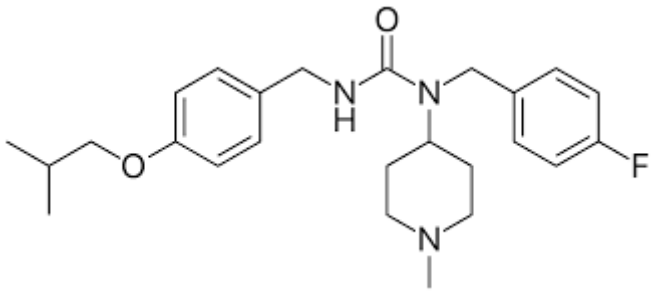

Figure 1: Chemical structure of Pimavanserin

Pharmacokinetics

Pimavanserin demonstrates dose-proportional pharmacokinetics after single oral doses from 17 to 255 mg (0.5-to 7.5-times the recommended dosage). The pharmacokinetics of pimavanserin are similar in both the study population and healthy subjects. The mean plasma half-lives for pimavanserin and the active metabolite (N-desmethylated metabolite) are approximately 57 hours and 200 hours, respectively.

Absorption: The median Tmax of pimavanserin was 6 (range 4-24) hours and was generally unaffected by dose. The bioavailability of pimavanserin oral tablet and pimavanserin solution was essentially identical. The formation of the major circulating N-desmethylated metabolite AC-279 (active) from pimavanserin occurs with a median Tmax of 6 hours. Ingestion of a high-fat meal had no significant effect on rate (Cmax) and extent (AUC) of pimavanserin exposure. Cmax decreased by about 9% while AUC increased by about 8% with a high-fat meal.Administration of one 34 mg capsule once daily results in plasma pimavanserin concentrations that are similar to exposure with two 17 mg tablets once daily.

Distribution

Pimavanserin is highly protein bound (~95%) in human plasma. Protein binding appeared to be dose-independent and did not change significantly over dosing time from Day 1 to Day 14. Following administration of a single dose of NUPLAZID (34 mg), the mean (SD) apparent volume of distribution was 2173 (307) L.

Elimination

Metabolism: Pimavanserin is predominantly metabolized by CYP3A4 and CYP3A5 and to a lesser extent by CYP2J2, CYP2D6, and various other CYP and FMO enzymes. CYP3A4 is the major enzyme responsible for the formation of its major active metabolite (AC-279). Pimavanserin does not cause clinically significant CYP inhibition or induction of CYP3A4. Based on *in vitro* data, pimavanserin is not an irreversible inhibitor of any of the major hepatic and intestinal human CYP enzymes involved in drug metabolism (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4).

Based on *in vitro* studies, transporters play no significant role in the disposition of pimavanserin.AC-279 is neither a reversible or irreversible (metabolism-dependent) inhibitor of any of the major hepatic and intestinal human CYP enzymes involved in drug metabolism (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4). AC-279 does not cause clinically significant CYP3A induction and is not predicted to cause induction of any other CYP enzymes involved in drug metabolism.

Excretion

Approximately 0.55% of the 34 mg oral dose of ^{14}C-pimavanserin was eliminated as unchanged drug in urine and 1.53% was eliminated in feces after 10 days. Less than 1% of the administered dose of pimavanserin and its active metabolite AC-279 were recovered in urine.

Specific Populations

Population PK analysis indicated that age, sex, ethnicity, and weight do not have clinically relevant effect on the pharmacokinetics of pimavanserin. In addition, the analysis indicated that exposure of pimavanserin in patients with mild to moderate renal impairment was similar to exposure in patients with normal renal function.

Drug Interaction Studies

CYP3A4 Inhibitor: Ketoconazole, a strong inhibitor of CYP3A4, increased pimavanserin Cmax by 1.5-fold and AUC by 3-fold. Population PK modeling and simulation show that steady-state exposure (Cmax,ss and AUCtau) for 10 mg pimavanserin with ketoconazole is similar to exposure for 34 mg pimavanserin alone

CYP3A4 Inducer

In a clinical study where single doses of 34 mg pimavanserin were administered on Days 1 and 22, and 600 mg rifampin, a strong inducer of CYP3A4, was given daily on Days 15 through 21, pimavanserin Cmax and AUC decreased by 71% and 91%, respectively, compared to pre-rifampin plasma concentrations. In a simulation with a moderate CYP3A4 inducer (efavirenz), physiologically based pharmacokinetic (PBPK) models predicted pimavanserin Cmax,ss and AUCtau at steady state decreased by approximately 60% and 70%, respectively There is no effect of pimavanserin on the pharmacokinetics of midazolam, a CYP3A4 substrate, or carbidopa/levodopa

Conclusion:

After reviewing existing literature, pimavanserin is useful for treating psychosis (hallucinations and delusions) in PD patients. Dose changes may be required when pimavanserin is used with CYP450 inhibitor or inducer. No dose changes are needed for patients with mild to moderate renal impairment, but pimavanserin is not recommended in PD patients with severe renal or hepatic impairment due to lack of evidence. Pimavanserin has a black box warning on its package labelling, as it increases mortality in older age patients with dementia-related psychosis, and clinicians need to be cautious with the use of pimavanserin with other drugs that prolong QT-interval. As pimavanserin is an effective and safe medication, it may replace current antipsychotic therapy for the treatment of psychosis associated with PD.

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