Pimavanserin and dementia related psychosis: Can HARMONY prevail?

Delusions and hallucinations are common in people with dementia[1], and although risperidone and olanzapine show efficacy for the treatment of psychosis in Alzheimer's disease, their use has been linked to cardiovascular adverse events including increased risk of death [2]. Safe and effective treatments are needed when non-pharmacological interventions have been unsuccessful and symptoms continue to distress or place the patient and others at risk.

Pimavanserin, a selective 5-HT_{2A} inverse agonist and antagonist, which differs from other drugs of this class in having low affinity for dopamine or histamine receptors, was approved by the US Food and Drug Administration (FDA) in 2016 for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. In July, 2020, the manufacturer of pimavanserin sought a wider licensing indication for the treatment of dementia-related psychosis.[3] This approach is based on the assumption that the symptoms of psychosis seen in patients with any dementia diagnosis, regardless of the underlying neuropathology, will respond to the same pharmacological treatment. Such license would open up a large potential market for pimavanserin.

HARMONY was a phase 3, randomised, double-blind discontinuation trial[4] done at 101 clinical sites in Europe and America. The trial randomly assigned 217 individuals with dementia-related psychosis, whose symptoms of psychosis had been judged by the treating clinicians to have responded to 12 weeks of open-label treatment with 20–34 mg per day pimavanserin. Among the study participants, 137 (63%) had Alzheimer's disease, 42 (19%) had Parkinson's

disease dementia, 25 (12%) had vascular dementia, ten (5%) had dementia with Lewy bodies, and three (1%) had frontotemporal dementia. 105 partici pants were randomly assigned to continue receiving pimavanserin and 112 received placebo for up to 26 weeks in a double-blind phase.

The HARMONY trial was stopped early, when interim analyses indicated that the drug had met prespecified endpoints for efficacy. Although 217 participants had been randomly assigned when the trial was discontinued, only 194 (89%) participants had been assigned (95 [49%] to pimavanserin and 99 [51%] to placebo) at the time of the interim analysis that led to discontinuation. 12 (13%) of the 95 participants who received pimavanserin and 28 (28%) of the 99 participants who received placebo were reported to have a relapse of psychosis (the primary outcome; hazard ratio 0·35; 95% CI 0·17 to 0·73; p=0·005). Almost all this difference was driven by patients with Parkinson's disease dementia. Adverse events were similar in both treatment groups, although headache, constipation, urinary tract infections, and asymptomatic QT prolongation were more frequent in participants who received pimavanserin.

What can potential prescribers draw from these study findings? The trialists acknowledge that their inclusion requirement of a sustained response during the open-label phase reduced the ability of the study to assess efficacy in other patients. Although randomised-withdrawal trial designs are encouraged by the FDA to enrich the ability to detect drug versus placebo differences,[5] their validity for assessing relapsing-remitting psychiatric illnesses has been questioned.[6] The HARMONY study[4] does not answer an important question that clinicians

may have: will this treatment be effective in the untreated symptomatic patients who I see? The effect of withdrawing a treatment cannot be assumed to simply negatively mirror the effect of commencing it because both non-specific withdrawal effects—such as reduction of sedation—and specific effects on the expression of symptoms of psychosis might contribute to an impression that the patient's psychosis has relapsed.

The FDA are not convinced by the results of HARMONY, or those of an earlier phase 2 trial of pimavanserin (NCT02035553), and rejected the request from the manufacturer for its approval as a treatment for hallucinations and delusions associated with dementia-related psychosis. The decision of the FDA was based on concerns about data from HARMONY,[4] including a lack of statistically significant benefits and small numbers of participants within the dementia diagnostic groups.[8] Furthermore, the FDA did not consider that the earlier phase 2 trial, in which nursing home residents were recruited who had Alzheimer's disease and vascular dementia, had been adequately done or well controlled.[8] The concerns of the FDA echoed those of some who believe that the significant differences between pimavanserin and placebo detected in the phase 2 study had been seen only at a single timepoint, and appeared to be driven by symptom worsening in the placebo group.[9]

Expression of symptoms of psychosis in patients with different types of dementia has generally been considered distinctive, reflecting the differential anatomical distribution of neuropathology, and different neurotransmitter and cognitive deficits.[10] Viewing dementia-related psychosis as one condition with a corresponding single treatment would potentially provide a shortcut, and remove the traditional licensing requirement to establish efficacy

within each dementia diagnosis. The FDA's rebuff of the approval request for pimavanserin, and their criticisms of the data from HARMONY,[4] suggest that the regulators are not yet ready to accept dementia-related psychosis as a license indication for pimavanserin without confirmation of its safety and efficacy in larger numbers of patients in diagnosis subtypes.

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