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LETTER TO THE EDITOR OPEN ACCESS

Inhibiting Serotonin Synthesis for the Treatment of Pulmonary Arterial Hypertension

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Substantial evidence from animal models supports the concept of inhibiting peripheral serotonin synthesis for the treatment of pulmonary arterial hypertension (PAH), as demonstrated by pharmacological blockade or genetic deletion of tryptophan hydroxylase 1 (TPH1) [1–5]. Most recently, we have shown that daily inhalation of TPT-004, a novel class TPH1 inhibitor, can alleviate PAH in the Sugen-hypoxia (SuHx) rat model [1]. However, the clinical phase 2b ELEVATE-2 trial, using the TPH inhibitor rodatristat ethyl (NCT04712669), reported disappointing results, including worsened hemodynamics in PAH patients [6]. Rodatristat ethyl (KAR5585) had previously shown only very mild beneficial effects in the rat monocrotaline model of PAH [2]. However, this model is highly criticized as the histological pulmonary vascular changes are clearly distinct from human PAH, and nearly all published interventions appear to be effective [7]. In the clinically more relevant SuHx rat model, rodatristat ethyl even at a very high dose of 100 mg/kg/d as oral monotherapy, had no significant effect on pulmonary hemodynamics and only marginally reduced the relative pulmonary vessel wall thickness [2]. Rodatristat ethyl was only effective in lowering mean pulmonary arterial pressure (mPAP) when combined with the endothelin antagonist, ambrisentan [2]. In contrast, other published TPH inhibitors with different chemical structure had exerted clear benefits as monotherapy in the SuHx rat model (KAR5416 [2], TPT-001 [3], TPT-004 [1, 4]).

Based on the drug's weak and inconclusive effects on PAH in preclinical rat models, it is not very surprising that rodatristat ethyl did not improve PAH hemodynamics in the ELEVATE-2 trial enrolling PAH patients in WHO functional class 2 and 3 on background PAH-targeted therapy [6]. Indeed, pulmonary vascular resistance (PVR) was significantly increased in both treatment groups (300 and 600 mg twice daily) compared to placebo. Accordingly, the PVR index (PVRi) went up, however, also the systemic vascular resistance index (SVRi) increased markedly (from 36.0 to 390.4 and 329.0 dyn sec cm^{-5} m^2 for 300 and 600 mg, respectively), probably caused by an unwanted systemic effect of the compound. Importantly, a substantial rise in SVRi will increase mean systemic arterial pressure (mSAP), which is not reported in the paper. As a consequence, rodatristat ethyl did not significantly increase the PVRi/SVRi ratio that is the only appropriate hemodynamic indicator of PAH severity in cases when study drug or other medication (such as sedation during catheterization) alter SVRi and mSAP. It is also odd, that only the low (300 mg) but not the high dose (600 mg) of rodatristat ethyl significantly worsened mPAP (+5.1 mmHg vs. baseline) and decreased pulmonary artery compliance (−0.14 mL/mmHg vs. baseline), and that the difference versus placebo is partially driven by an improvement in the placebo group. For TAPSE, an indicator of longitudinal right ventricular systolic function, and other hemodymamic variables, the changes were marginal and without statistical confirmation. Moreover, 50% of the patients in the high-dose group developed

diarrhoea as adverse effect, which may have affected the patients' gastrointestinal uptake of any oral PAH-targeted background medications and thereby impaired their therapeutic efficacy.

Based on these inconclusive results, showing mainly no significant, clinically relevant effects by the rodatristat ethyl treatment on pulmonary and cardiac variables, the conclusion of the authors, that TPH inhibition might not be a suitable option for PAH therapy, is not justified. We posit that adverse systemic effects of rodatristat ethyl, such as diarrhoea and an increase in SVRi and mSAP, have negated the beneficial effects of peripheral serotonin reduction on PAH. Whether these adverse effects are also caused by serotonin reduction or by compound-specific actions independent of serotonin cannot be finally determined, since the off-target profile of rodatristat ethyl has not been reported.

We suggest that other more selective and preclinically more efficient TPH inhibitors than rodatristat ethyl should be tested in future clinical trials before this class of drugs is banned from PAH treatment. To avoid some of the potential adverse effects such as diarrhoea, inhalative application of a TPH inhibitor may be preferred [1], for which rodatristat ethyl, as prodrug [2], would anyhow not be available. Moreover, other therapeutic interventions affecting the serotonin system, such as inhibition of serotonin receptors or transporters, may also be suitable to treat PAH and should be clinically tested.

Author Contributions

Michael Bader and Georg Hansmann have written the manuscript together.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

M.B. is founder and shareholder of Trypto Therapeutics.

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