More on aldosterone biosynthesis inhibition and resistant hypertension: a Phase-2 study with lorundrostat

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Comment on ‘Aldosterone Synthase Inhibition with Lorundrostat for Uncontrolled Hypertension: The Target-HTN Randomized Clinical Trial’ which was published in the JAMA, https://doi.org/10.1001/jama.2023.16029.

Key points

• The Target-hypertension (HTN)1 is an industry-funded, multicentre, randomized, placebo-controlled, Phase-2 dose-ranging trial, which tested the dose-dependent efficacy and safety of lorundrostat, an aldosterone-synthase inhibitor, in patients with treatment-resistant hypertension [systolic automated office blood pressure (AOBP) > 130 mmHg] while taking two or more antihypertensive medications.

• The primary efficacy endpoint was the change in systolic AOBP from baseline to 8 weeks. Adverse events of special interest consisted of hyperkalaemia with a need of dosage changes, symptomatic hypotension, and adrenal insufficiency.

• The study enrolled an initial cohort of 163 participants with suppressed plasma renin activity (PRA) ≤ 1.0 ng/mL/h and elevated plasma aldosterone >1.0 ng/dL and a second cohort of 37 participants with PRA >1.0 ng/mL/h. Key exclusion criteria included orthostatic hypotension, type 1 diabetes, concomitant use of epithelial sodium channel inhibitors, or mineralocorticoid receptor antagonists (MRA), estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m². A systolic AOBP ≥175 mmHg, diastolic AOBP ≥100 mmHg, or serum potassium level >5.2 mmol/L were exclusion criteria in Cohort 1, whereas exclusion criteria in Cohort 2 were a systolic AOBP ≥160 mmHg, diastolic BP ≥100 mmHg, or serum potassium level >4.8 mmol/L. The mean age was 65.7 years, 60% of patients were women, 48% had a body mass index >30 kg/m², and 40% had type 2 diabetes. Patients in Cohort 1 had mean baseline systolic and diastolic AOBP of 142 and 81 mmHg, respectively. Systolic and diastolic AOBP were 139 and 79 mmHg in Cohort 2.

• Participants underwent 2–4 weeks of pre-screening, a 2-week placebo run-in period to ensure eligibility, and then were randomly assigned in a 1:1:1:1:1:1 ratio to placebo or one of five lorundrostat doses (12.5 mg, 50 mg, or 100 mg once daily or 12.5 mg or 25 mg twice daily).

• Following 8 weeks of treatment in participants with suppressed PRA, systolic AOBP reductions were 14.1, 13.2, 6.9, and 4.1 mmHg with 100, 50, and 12.5 mg once daily of lorundrostat and placebo, respectively. Lorundrostat 25 and 12.5 mg twice daily reduced systolic AOBP by 10.1 and 13.8 mmHg, respectively. Among participants without suppressed PRA, a systolic AOBP reduction of 11.4 mmHg was achieved with 100 mg of lorundrostat once daily. All doses of lorundrostat reduced serum aldosterone, whereas serum aldosterone level was increased in the placebo group.

• Six participants had increases in serum potassium >6.0 mmol/L that required dose reduction or drug discontinuation, whereas cortisol insufficiency was not recorded.

Comment

Insufficient control of blood pressure (BP) accounts for up to 60% of hypertensive patients who receive BP-lowering medications.2 Of these, a proportion ranging between 5% and 10% has treatment-resistant hypertension.3 Therefore, new pharmacological and non-pharmacological strategies targeting different pathophysiological pathways have been developed in recent years aimed at achieving BP control in the more difficult-to-treat patients.4–6 Elevated aldosterone production has been long viewed as a key player in causing and maintaining sustained high BP levels and, in fact, MRAs are recommended by international guidelines as an add-on strategy in those patients who do not achieve BP levels <140/90 mmHg despite treatment with three different antihypertensive drugs including a diuretic, according to the European Guidelines for defining resistant hypertension.7,8 Due to the frequent adverse effects reported with this pharmacological class, mostly related to hyperkalaemia, worsening renal function, and gynecomastia, the inhibition of aldosterone...
biosynthesis has gained growing attention as a potential innovative therapeutic strategy, in view of a more selective effect on the adrenal steroid pathway based on upstream blockade of aldosterone production.

The recent Phase-2 Brighhten (HTN) study has shown a dose-dependent BP-lowering effect of baxdrostat, a selective aldosterone-synthase inhibitor, in patients with treatment-resistant hypertension. Systolic blood pressure was significantly reduced at 12 weeks compared to placebo in patients treated with the 2 and 1 mg doses (−11 mmHg and −8 mmHg, respectively). Moreover, the use of baxdrostat led to sustained, dose-dependent decreases in serum aldosterone levels without causing major adverse effects and a reduction in cortisol levels.

The Target-HTN study confirmed these results by demonstrating the efficacy of lorundrostat in reducing both BP levels and serum aldosterone independently of baseline PRA. Although the relatively short half-life of lorundrostat limited the efficacy of the 12.5 μg once daily dose, the higher doses tested were effective in reducing BP, with a remarkable interindividual variability in the in the BP-lowering effect. Similar to baxdrostat, aldosterone-synthase inhibition with lorundrostat did not modify cortisol levels.

Some limitations of the study should be emphasized. First, unattended measurements using an automated oscillometric sphygmomanometer were used to determine BP. Although AOBP has been proposed as a better approach to reduce the white-coat effect and shown to have a better correlation with organ damage and ambulatory BP compared to standard office BP measurement, the latter approach remains the standard recommended by international guidelines. Moreover, the use of attended office BP is associated with a definition of treatment-resistant hypertension which is different from that adopted in the present study. In addition, only a small percentage of enrolled patients (55%) was treated with diuretics and 24-h ambulatory BP monitoring was not used to confirm the diagnosis of resistant hypertension before randomization. Secondly, a relevant proportion of subjects were obese, and this may have influenced the results since obesity is associated with a dysregulation of aldosterone production, and treatment with lorundrostat appeared to be particularly effective in subjects with a body mass index >30 kg/m². Third, an eGFR < 60 mL/min/1.73 m² was considered an exclusion criterion thus preventing an extension of the current observations to patients with hypertension and moderate chronic kidney disease. Fourth, beside diabetes and heart failure, no information is available about relevant comorbidities associated with an increased occurrence of resistant hypertension such as obstructive sleep apnoea and thyroid disorders. Fifth, the authors did not report data about the adherence to prescribed medications before enrolment into the trial; thus one cannot exclude the confounding impact of pseudo-resistant hypertension. Finally, the follow-up period was limited to 8 weeks and the potential occurrence of adverse effects with a longer exposure to the drug cannot be ruled out.

The relatively short half-life of lorundrostat could translate into safety benefits compared to aldosterone-synthase inhibitors or receptor blockers with longer half-life, although this may require higher doses and a twice daily regimen to maintain a 24-h BP control. In addition to the lack of influence on cortisol levels, it should be mentioned that lorundrostat is highly selective for CYP11B2 vs. CYP11B1, and does not increase the production of 11-deoxycorticosterone, a mineralocorticoid receptor agonist.

The Target-HTN study confirms the short-term efficacy and tolerability of the new aldosterone-synthase inhibitor lorundrostat in patients with treatment-resistant hypertension, by tackling key molecular pathways involved in the development and persistence of this threatening clinical manifestation of hypertension. Further clinical development of this compound will need to address the long-term safety and the selectivity of the pharmacological inhibition of aldosterone synthase as well as its impact on the pituitary–adrenal axis by measuring cortisol and the adrenocorticotropic hormone. Besides, it would be of great interest to test in appropriately designed and sized studies the potential benefits of aldosterone-synthase inhibitors, such as lorundrostat and baxdrostat, also in a broader range of hypertensive patients, beyond the boundaries of treatment-resistant hypertension.

Declarations

Disclosure of Interest

M.V. reports personal fees for speaker bureau and/or consulting in Advisory Boards from, Astra Zeneca, Menarini Int, Novartis Pharma, Novo Nordisk, and Sanofi Pasteur, outside the submitted work. L.G. reports no conflict of interest.

References