NEW PAPERS

Baxdrostat, an aldosterone synthase inhibitor, a novel mechanism for uncontrolled hypertension

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Primary aldosteronism has been recognised as a cause of hypertension since 1955, when Conn's syndrome was first described. However, it is now recognised that adenomas are not the only presentation for aldosterone dysregulation which is a spectrum of disease due to somatic mutations, that lead to inappropriately elevated aldosterone levels, relative to the sodium status of the patient – effectively generating a salt sensitive state which is the hallmark of most hypertension. In many cases, there is no visible adenoma, just microadenomas, or even aldosterone producing cell clusters, all of which are undetectable by conventional imaging. It is likely that aldosterone dysregulation is a major cause of difficult to control hypertension.

Aldosterone acts in the principal cell of the cortical collecting duct of the kidney to increase sodium reabsorption, thereby increasing blood pressure. Hypertension due to inappropriate aldosterone is associated with excessive cardiovascular and kidney disease due to increased oxidative stress, inflammation and fibrosis. There is also an increased risk for insulin resistance, further driving fibrosis and inflammation.[1]

The mainstay of treatment for aldosterone-driven hypertension has been to block the mineralocorticoid receptor (MR). MR antagonists have been around for the treatment of hypertension since 1957, when spironolactone was found to improve blood pressures. However, MR antagonists can have intolerable side effects that hinder their use. The three final steps in aldosterone synthesis are catalysed by aldosterone synthase (CYPIIB2), an enzyme in the adrenal gland. Thus, blocking this enzyme has become an attractive target to decrease circulating aldosterone and control blood pressure.

Aldosterone synthase inhibitors (ASI's) represent a novel class of antihypertensives. In a phase two trial in patients with resistsnt hypertension, the ASI baxdrostat reduced blood pressure over a three month period[2]: the placebo adjusted blood pressure changes for baxdrostat 1mg and 2mg were 8.1/2.6 mmHg and 10.9/5.1 mmHg, respectively. Another ASI, lorundrostat, has also demonstrated effective blood pressure lowering with 41% achieving a target systolic blood pressure of <125 mmHg compared to 18% of those on placebo.[3]

The phase three trial results for baxdrostat were released at the European Society of Cardiology meeting with simultaneous publication in the New England Journal of Medicine.[4] This global trial enrolled people over 18 years with uncontrolled (systolic blood pressure between 140-170 mmHg on two agents) or resistant (uncontrolled on 3 or more agents) hypertension, including a diuretic. After a two week run-in period on placebo added to their background antihypertensives, adherent participants were randomised to placebo, 1mg baxdrostat or 2mg baxdrostat for 12 weeks.

The primary efficacy endpoint was the placebo controlled change in seated systolic blood pressure

from baseline to 12 weeks. Of the 2591 patients that were screened, 796 were randomised and 794 received at least 1 dose of treatment. Participants were similar across the three arms of the first part of the trial and representative of typical patient populations with uncontrolled or rersistant hypertension. The mean seated baseline blood pressure was 149/87 mmHg.

The placebo adjusted improvement in systolic blood pressure was -8.7 mmHg and -9.8 mmHg for 1mg and 2mg baxdrostat, respectively at 12 weeks. Respective placebo adjusted improvement in diastolic blood pressure was -3.3 mmHg and -3.9 mmHg. Consistent with the hypothesis that aldosterone dysregulation is playing a key role in patients with difficult to control hypertension, the effect of baxdrostat on blood pressure was remarkably consistent across all patient subgroups.

There was a strong focus on safety in this trial, as this is a new therapy, and the trial is designed to go beyond the primary outcome period of 12 weeks with 3 additional sequential parts, for a total of 52 weeks follow up, to provide longer term safety and efficacy data with baxdrostat. During the initial 12 week study period, baxdrostat was well tolerated with no unanticipated adverse events. A key focus was on potassium and reassuringly, confirmed elevations of potassium > 6mmol/l were detected in around 1% of patients on baxdrostat 1 or 2mg daily. The study also showed that potassium changes usually occurred within the first two weeks of initiating baxdrostat, remaining stable thereafter. Another safety focus was eGFR and this was reduced by about 7 ml/min/1.73m2, and just like potassium, this mainly occurred within the first 2 weeks. Of course, these early studies recruit patients with normal renal function and as with all inhibitors of the renin angiotensin aldosterone system, the risk of hyperkalemia increases in those with more substantially impaired kidney funcrion, i.e. eHGR <45 ml/min/1.73m2. Importantly the BaxHTN trial also included an 8 week placebo controlled randomized withdrawal of treatment between weeks 24 and 32. This showed that the changes in eGFR reversed following treatment withdrawal, suggesting it was functional related to changes in blood pressure.

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The BaxHTN study focussed on seated office BP as its primary end-point but also included a small exploratory ambulatory blood pressure sub study in 56 patients which revealed remarkable reductions in placebo-adjusted 24hr systolic BP of almost 17mmHg and nocturnal BP reductions of almost 12mmHg. It will be fascinating to see if this remarkable effect on 24hr BP is confirmed in the much larger, parallel, global phase III study (Bax24) which is specifically studying the effect of baxdrostat 2mg versus placebo on 24hr ambulatory BP as the primary outcome. This study will present its topline results at the American Heart Association late breaking science sessions in November.

In conclusion, it feels like we are on the cusp of a therapeutic breakthrough for the treatment of difficult to control hypertension with new treatments targeting aldosterone synthase and many new studies are ongoing, either with ASI alone, or in combination with SGLT2-inhibitors. The ASI/SGLT2i combinations are specifically being studied in patients with CKD and at risk of heart failure, or with established heart failure. It is good to see a renewed focus on aldosterone, more than 70 years on from the description of that adrenal nodule by Conn.[5]

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