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EDITORIAL

Emergence of aldosterone synthase inhibitors for treatment of difficult to treat hypertension

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For the majority of cases of hypertension, blood pressure(BP) is well controlled with a combination of RAS inhibitors, calcium channel blockers and diuretics [1]. However, 10–15% of cases may be resistant to the above mentioned drug combination and are defined as treatment resistant hypertension [2]. Fluid retention and aldosterone excess is an important mechanism of treatment resistant hypertension and based on the PATHWAY-2 trial, steroidal mineralcorticoid receptor(MR) antagonist such as spironolactone is considered the drug of choice [3–5]. However, the use of spironolactone may be limited due to high incidence of side effects such as hyperkalemia, gynecomastia and menstrual irregularities [6, 7]. For example, in the AMBER trial, the incidence of hyperkalemia when spironolactone was administered without patiromer was 64.2% [6, 8]. Recently, potential alternatives to spironolactone are emerging. In a randomized trial comparing amiloride versus spironolactone in subjects with resistant hypertension, amiloride was shown to be non inferior to spironolactone in reducing home SBP at 12 weeks [9]. However, considering the deleterious effect of aldosterone on the cardiovascular system, it would be ideal to have an alternative drug that inhibits both MR dependent and non independent pathway of aldosterone activation while at the same time have lower incidence of side effects [10]. Aldosterone synthase inhibitors are emerging as such new class of drugs.

Baxdrostat is an aldosterone synthase inhibitor that is >100 fold selective to aldosterone synthase(CYP11B2) than 11β-hydroxylase(CYB11B1) [11]. In the phase 2 BrigHTN trial which randomized patients with treatment resistant hypertension to placebo, baxdrostat 0.5, 1.0 mg and 2.0 mg, baxdrostat was associated with dose dependent decrease in SBP, potent reduction in serum aldosterone with no effect on serum cortisol level [11].

For the next phase comes the Baxdrostat hypertension phase 3 program, which consists of the BaxHTN trial, BaxAsia trial and the Bax24 trial [12]. The significance of Baxdrostat hypertension phase 3 program is that it is a comprehensive phase 3 trial that not only recently demonstrated the efficacy of baxdrostat in patients with uncontrolled hypertension and resistant hypertension, but will conduct a separate trial in Asians [13]. As Asian hypertensive subjects have certain characteristics that differ from other ethnicities, the response to aldosterone synthase inhibitors may differ from other ethnicities [14]. Therefore, we commend the investigators for performing a phase 3 trial solely focused on Asians. One important design of the paper was the addition of an additional randomized withdrawal period which allowed for a longer term assessment of drug efficacy while minimizing the exposure to placebo. Another important part of this phase 3 program was a separate trial of resistant hypertension with 24 h ambulatory blood pressure monitoring as the primary endpoint. It will be important to demonstrate the efficacy of baxdrostat in resistant hypertension as it is a separate disease entity from uncontrolled hypertension with needs for separate evaluation.

Recently, results from the BaxHTN trial was reported [13]. It is a phase 3, double-blind, randomized, placebo-controlled trial which enrolled 796 patients with seated SBP between 140–170 mmHg and either uncontrolled hypertension and resistant hypertension. The study subjects were randomized to receive baxdrostat 1 mg, 2 mg or placebo in a 1:1:1 ratio with the primary endpoint being the change in seated SBP from baseline to 12 weeks [13]. At 12 weeks, the change from baseline in the least square mean seated SBP was −14.5 mmHg and −15.7 mmHg with 1 mg and 2 mg of baxdrostat, respectively with estimated difference from

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placebo of −8.7 mmHg for 1 mg of baxdrostat and −9.8 mmHg for 2 mg of baxdrostat. There were small increases in the incidence of hyperkalemia of more than 6.0 mmol/L with baxdrostat 1 mg (2.3%) and 2 mg (3.0%) compared to placebo (0.4%) [13]. The results confirmed the efficacy of a aldosterone synthase inhibitors for treating uncontrolled/resistant hypertension and may give physicians further options for tackling difficult to treat hypertension in the future. One question that needs to be answered is what would be the treatment indication of aldosterone synthase inhibitors going forward? More specifically, what is the benefit of this class of drugs compared to spironolactone? To answer this question, hopefully a head to head trial comparing the efficacy of aldosterone synthase inbitor with spironolactone will be done to compare both the efficacy and safety. Demonstrating similar efficacy with lower degree of side effects for baxdrostat would be important to establish itself as a first line drug for resistant hypertension. Second, considering the high prevalence of resistant hypertension in chronic kidney disease(CKD) [15] and high incidence of hyperkalemia with the use of spironolactone in patients with CKD [8], the efficacy of aldosterone synthase inhibitors in patients with CKD compared to spironolactone needs further investigation. In a recent phase 2 randomized, double-blind, placebo controlled trial, baxdrostat was associated with placebo controlled reduction in SBP of 8.1 mmHg from baseline to week 26 and a high incidence of 41% for hyperkalemia [16]. Therefore, it is still not clear at this time whether baxdrostat has a lower incidence of hyperkalemia compared to spironolactone. Third, as the BaxHTN trial consisted of subjects with both uncontrolled hypertension and resistant hypertension, the degree of efficacy in resistant hypertension needs further clarification, which should be demonstrated in the Bax24 trial in the near future.

Compliance with ethical standards

Conflict of interest S.P. received honoraria from Viatris, Organon, Boryoung, Hanmi, Daewoong, Donga, Celltrion, Servier, Daiichi Sankyo, Handok and a research grant from Daiichi Sankyo. S.P. has received consultation fee from Skylab. Also, S.P has stocks from Mediwhale.

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