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Aldosterone Synthase Inhibitors for Treatment of Hypertension and Chronic Kidney Disease

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Abstract

Aldosterone excess is known to worsen hypertension and kidney function. Three selective aldosterone synthase inhibitors (ASIs) were evaluated in 3 phase 2 trials. In the first study, the ASI baxdrostat 2 mg orally once daily decreased systolic blood pressure (SBP) by 11.0 mmHg compared with placebo after 12 weeks in patients with treatment-resistant hypertension. In the second study including patients with uncontrolled hypertension, placebo-corrected reduction in SBP with lorundrostat 50 mg once daily was 9.6 mmHg after 8 weeks. Patients receiving thiazides and those with body mass index (BMI) > 30 kg/m^2 had the optimum blood pressure (BP) response to lorundrostat, whereas plasma renin activity (PRA) did not affect its antihypertensive potency. In the third trial including patients with chronic kidney disease (CKD), the ASI BI 690517 (10 mg once daily) decreased urinary albumin creatinine ratio (UACR) by 39% after 14 weeks compared with 3% reduction with placebo. Reduction in UACR was generally similar in presence or absence of concomitant treatment with empagliflozin. The 3 ASIs mildly decreased (by <15%) estimated glomerular filtration rate (eGFR) compared with placebo. The most common adverse effects of ASIs were hyperkalemia occurring in 2.9% and 7.9% among patients randomized to baxdrostat and lorundrostat, respectively versus none in the placebo groups. In patients with CKD, frequency of hyperkalemia was higher: 14.2% and 6.0% with BI 690517 and placebo, respectively. Adrenal insufficiency was reported in 1.3% of patients randomized to BI 690517 versus 1.0% with placebo. Preliminary data suggest that selective ASIs are effective in lowering BP in patients with resistant and uncontrolled hypertension and decreasing albuminuria in CKD. Phase 3 clinical trials should be conducted to assess long-term efficacy and safety of ASIs in a wide spectrum of patients with uncontrolled BP and CKD.

Keywords: Aldosterone synthase, Hyperkalemia, Hypertension, Chronic kidney disease, Albuminuria

Introduction

Aldosterone excess causes hypertension through its salt-retaining effect [1]. In addition, accumulating evidence suggests that aldosterone has deleterious effects on the cardiorenal system by promoting inflammation, vascular stiffness, and thrombosis resulting in coronary artery disease, heart failure, and progression of kidney disease [1]. Furthermore, aldosterone may compromise renal function by causing tubulointerstitial inflammation and fibrosis and damage of podocytes [1]. Verma et al. [2] have shown that higher circulating aldosterone levels among patients with CKD were independently associated with increased risk for kidney disease progression (defined as the composite of 50% decline in eGFR or end-stage kidney disease). Thus, each doubling of serum aldosterone value was associated with a 11% increase of CKD progression whether diabetes was present or not [2]. In fact, inhibition of aldosterone receptors by the steroidal aldosterone receptor antagonist spironolactone reduced the risk of death by 30% versus placebo in patients with heart failure and reduced ejection fraction [3]. Moreover, the use of the non-steroidal aldosterone-receptor antagonist finerenone was associated with reduction in cardiovascular (CV) events in patients with type 2 diabetes and CKD [4]. Another approach to achieve aldosterone blockade consists in interference with its synthesis by aldosterone synthase. Because the latter enzyme shares 93% homology with 11-β-hydroxylase, the enzyme responsible for cortisol synthesis, designed ASIs should be highly selective to inhibit aldosterone synthase without inhibition of 11-β-hydroxylase and cortisol production [5].

Recently, several highly selective ASIs have been introduced. For instance, the ASI baxdrostat exhibits 100 times more potency with respect to aldosterone synthase inhibition versus 11-β-hydroxylase inhibition [5]. Since aldosterone excess is implicated in uncontrolled and resistant hypertension and CKD, 3 phase 2 clinical trials were recently published aiming at the evaluation of the 2 ASIs, baxdrostat and lorundrostat for BP reduction, and the third ASI, code BI 690517, for lowering albuminuria in patients with CKD [6-8]. Table 1 depicts an overview of these trials. The main purpose of this article is to provide an appraisal of these 3 ASIs as a novel strategy for management of patients with hypertension and CKD.

Baxdrostat for Treatment of Resistant Hypertension

The ASI baxdrostat was evaluated in a phase 2, randomized, placebo-controlled trial called BrigHTN conducted at community-based practices in the USA for management of treatment-resistant hypertension [6]. The latter was defined as mean seated blood pressure of at least 130/80 mmHg in patients receiving stable doses of ≥ 3 antihypertensive drugs including a diuretic [6]. Patients (n=248, 55% men, mean age 62 years, 28% African Americans, 38% with type 2 diabetes) were randomized to 1 of 3 doses of baxdrostat (0.5 mg, 1 mg, 2 mg) taken orally once a day or matched placebo for 12 weeks [6]. Mean baseline blood pressure was 148/88 mmHg [6]. The primary outcome was the change in SBP from baseline to week 12. There was dose-dependent decrease in SBP of -20.3 mmHg, -17.5 mmHg, -12.1 mmHg, and -9.4 mmHg with baxdrostat 2 mg, 1 mg, 0.5 mg, and placebo respectively [6]. The placebo-corrected decrease in SBP was -11.0 mmHg (95% CI, -16.4 to -5.5; P< 0.01) with the 2 mg dose, and -8.1 mmHg (95% CI, -13.5 to -2.8; P=0.003) with the 1 mg dose, but the difference in SBP was not significant between the 0.5 mg dose and placebo [6]. Baxdrostat significantly decreased diastolic blood pressure (DBP) compared to placebo with the 2 mg-dose only; difference being -5.2 mmHg (95% CI, -8.7 to -1.6; P value not calculated) [6]. No effect on body weight was demonstrated with baxdrostat [6].

Lorundrostat for Treatment of Uncontrolled Hypertension

In a randomized, dose-ranging, multicenter trial conducted in the USA, (called Target-HTN), Laffin et al. [7] evaluated the effects of the ASI, lorundrostat, on BP in patients with uncontrolled hypertension. The latter was defined as a systolic automated office BP (AOBP) of ≥ 130 mmHg on ≥ 2 antihypertensive agents [7]. The study included 2 cohorts. Cohort 1 participants (n=163) had suppressed PRA ≤ 1.0 ng/ml/h and serum aldosterone of ≥1 ng/dl and were randomly assigned to placebo or one of the following lorundrostat doses: 12.5 mg, 50 mg, or 100 mg once daily, or 12.5 mg or 25 mg twice daily. Cohort 2 participants (n= 37) had PRA >1.0 ng/ml/h and were randomized to placebo or lorundrostat 100 mg once daily in a 1:6 ratio [7]. Patients' mean age was 65.7 years, 40% men, 36% African Americans, 48% had BMI >30 kg/m^2, and 40% had type 2 diabetes [7]. The primary outcome was the change in systolic AOBP from baseline to the trial end at week 8 after intervention [7]. At week 8, placebo-subtracted change in systolic AOBP was -9.6 mmHg (90% CI, -15.8 to -3.4; P=0.01) in the 50 mg group and -7.8 mmHg (90% CI, -14.1 to -1.5; P=0.04) in the 100 mg group. Only the 50 mg-dose had significant reduction in DBP compared with placebo, -5.5 mmHg (90% CI, -9.4 to -1.5; P=0.02) [7]. No significant changes in BP were recorded with other doses of lorundrostat [7]. In cohort 2, lorundrostat 100 mg decreased systolic AOBP similar to patients randomized to 100 mg in cohort 1 (-11.4 mmHg compared to baseline), i.e. lorundostat effect on systolic AOBP was independent of PRA [7]. Mean 24-hour ambulatory BP decreased by -7.5 mmHg, -9.9 mmHg, and -2.1 mmHg with 50 mg, 100 mg lorundrostat and placebo respectively (statistical significance was not calculated) [7]. Interestingly, prespecified exploratory endpoints showed that patients taking thiazide diuretics exhibited greater response to lorundrostat than those not taking thiazide-type diuretics [7]. Moreover, obese patients with BMI >30 kg/m^2 had greater systolic AOBP reduction with lorundrostat compared with those with BMI between 25-30 kg/m^2, placebo-subtracted with the 50 mg-dose, -16.7 mmHg [7]. Unfortunately, lorundrostat effects on body weight were not reported. This parameter should be measured in future trials to see whether the BP lowering action of lorundrostat may be mediated in part by weight loss. Another subgroup analysis of interest was the finding that African American patients exhibited less systolic AOBP response to lorundrostat compared with other races, -7.1 mmHg versus -9.4 mmHg with the 50 mg-dose. Yet, the number of subjects in these subgroups were too small (15 in each subgroup) to draw a definitive conclusion [7].

BI 690517 for Treatment of Chronic Kidney Disease

In a phase 2 trial, Tuttle et al. [8] evaluated efficacy and safety of an ASI called BI 690517 in patients with CKD on top of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin-receptor blocker (ARB) and with or without the sodium-glucose co-transporter 2 (SGLT2) inhibitor empagliflozin. Patients were randomized in an initial run-in phase to empagliflozin 10 mg/d or placebo for 8 weeks followed by a second randomization to BI 690517 in doses of 3, 10, or 20 mg orally once daily or placebo for 14 weeks [8]. The primary outcome was the change in UACR from the end of run-in period (week 8) to 14 weeks after starting BI 690517 [8]. At study entry, median UACR was 426 mg/g (IQR 205 to 889), and mean eGFR was 51.9 ml/min/1.73 m^2 [8]. Prevalence of type 2 diabetes ranged from 62 to 88% across different patient groups, with an average of 71% [8]. In subjects receiving BI 690517 without empagliflozin, the percentage change in UACR from baseline to end of treatment at week 14 was -3% (95% CI, -19 to +17), -22% (95% CI, -36 to -7), -39% (95% CI, -50 to -26) and -37% (95% CI, -49 to -22) with placebo, BI 690517 3 mg, 10 mg, and 20 mg, respectively [8]. Interestingly, these reductions

in UACR were similar in patients receiving background empagliflozin suggesting an additive effect between BI 690517 and empagliflozin due to different mechanisms of actions [8]. Regarding the effects on BP, placebo-corrected decrease in SBP was approximately 4-6 mmHg with different doses of BI 690517, and there was a tendency towards greater decrease in SBP, 7-8 mmHg reduction versus placebo, when BI 690517 was added to empagliflozin [8].

Hormonal Effects of Aldosterone Synthase Inhibitors

As expected, the 3 ASIs resulted in decrease of serum aldosterone levels by approximately 42-66% versus placebo when administered at their maximum effective doses [6-8]. The maximum reduction in circulating aldosterone levels was reached after 15 days in case of baxdrostat and was generally sustained to the end of the trial [6]. In the case of BI 690517, the reduction in aldosterone levels was obvious after day 1 and continued to progress up to the end of follow-up at week 14 [8]. PRA increased with the 3 ASIs as a compensatory response [6-8]. Importantly, the 3 ASIs did not exert any significant effects on serum cortisol concentrations whether measured without or after cosyntropin stimulation [6-8]. This finding supports the selectivity of the ASIs for aldosterone synthase with no evidence of inhibition of cortisol synthesis through inhibition of the closely related enzyme 11-β-hydroxylase. Levels of aldosterone precursors, 11-deoxycorticosterone and 11-deoxycortisol, may increase due to their back-up accumulation as a result of aldosterone blockade and exert a hypertensive effect. The latter may virtually counteract the ani-hypertensive effects of ASIs action [5]. Unfortunately, these precursors were not measured in the 3 trials.

Effects on Aldosterone Synthase Inhibitors on Glomerular Filtration Rate

The use of the 3 ASIs was associated with mild decline in eGFR by approximately 15% or less compared with placebo [6-8]. The authors attributed this decline to diuretic effect or decrease in intraglomerular pressure [6]. This reduction in eGFR was also observed with the aldosterone receptor agonist finerenone during the first 4 months of use, then eGFR decline was slower than placebo thereafter [4].

Safety of Aldosterone Synthase Inhibitors

Hyperkalemia

Moderate hyperkalemia (K 5.6-5.9 mmol/L) occurred more frequently with the 3 ASIs, particularly with BI 690517 and lorundrostat (**Table 1**) [6-8]. Frequency of severe hyperkalemia (serum K ≥ 6 mmol/L) requiring treatment interruption or dose reduction was uncommon occurring in 1.3%, 2.4%, 3.6% with BI 690517, baxdrostat, and lorundrostat, respectively versus none with placebo (**Table 1**) [6-8]. As expected, incidence of severe hyperkalemia was higher with BI 690517, despite the fact that serum K >4.8 mmol/L was an exclusion criterion, because patients had concomitant CKD (**Table 1**) [8]. Interestingly, the

Table 1. Overview of trials of aldosterone synthase inhibitors.

	Baxdrostat [6]	**Lorundrostat [7]**	**BI 690517 [8]**
Design	Randomized, double-blind, placebo-controlled, multicenter, phase 2 trial	Randomized, placebo-controlled, dose-ranging, multicenter in the USA, phase 2 trial	Randomized, placebo-controlled, multinational, phase 2 trial
Disease	Treatment-resistant hypertension defined as seated BP ≥130/80 mmHg on ≥3 medications including a diuretic	Uncontrolled hypertension defined as automated office SBP ≥130 mmHg	CKD with eGFR 30 to <90 ml/min/1.73 m^2, UACR of 200 to <5000 mg/g on ACEI or ARB.
Patients' characteristics	N=275, mean age 62 years, 55% men, 70% Whites, 28% Blacks, 38% with type 2 diabetes	Cohort 1 with PRA ≤ 1.0 ng/ml/h (n= 163), cohort 2 PRA >1.0 ng/ml/h (n=37). Mean age 65.7 years, 40% men, 36% Blacks, 48% Hispanics, 40% with type 2 diabetes	n=586, mean age 63.8 years, 67% men, 58% Whites, mean eGFR 51.9 ml/min/1.73 m^2, median UACR 426 mg/g, 71% with type 2 diabetes
Mean SBP at baseline	148 mmHg	142 mmHg (cohort 1), 139.1 mmHg (cohort 2)	134 mmHg
Intervention	Baxdrostat 0.5 mg (n=69), 1 mg (n=70), 2 mg (n=67) and placebo (n=69)	Lorundrostat 12.5 mg, 50 mg, or 100 mg once daily, 12.5 mg or 25 mg bid	Empagliflozin vs placebo in the run-in phase followed by another randomization to BI 690517 at doses of 3, 10, 20 mg vs placebo

Primary outcome	Change in SBP from baseline to week 12	Change in office SBP from baseline to week 8	Change in UACR from second randomization (start of BI 690517) to week 14
Follow-up	12 weeks	8 weeks	Run-in phase: randomization to empagliflozin for 8 weeks, phase 2: randomization to BI 690517 in doses 3,10,20 mg/d or placebo for 14 weeks, then 4 weeks wash-out
Effect of ASI on primary outcome	Difference between baxdrostat 2 mg and placebo -11.0 mmHg (95% CI, -16.4 to -5.5; P <0.001). Difference between baxdrostat 1mg and placebo -8.1 mmHg (95% CI, -13.5 to -2.8; P=0.003)	Difference from placebo in SBP with 100 mg: -7.8 mmHg (90% CI, -14.1 to -1.5; P=0.04), with 50 mg: -9.6 mmHg (90% CI, -15.8 to -3.4; P=0.01). Reductions in SBP with other doses vs placebo were not significant.	Placebo-corrected reductions in UACR were -20% (95% CI, -39 to 3), -37% (95% CI, -52 to -18), and -35% (95% CI, -51 to -14) with BI 690517 3mg, 10 mg., and 20 mg, respectively.
Proportions of subjects with any adverse effects	48-52% versus 41% with placebo	43-57% versus 40% with placebo	61-62% versus 54% with placebo
Frequency of hyperkalemia (K 5.6-5.9 mmol/L)	6/205 (2.9%) with baxdrostat vs none with placebo	13/164 (7.9%) vs none with placebo	62/436 (14.2%) vs 9/147 (6%) with placebo
Frequency of serum K ≥ 6.0 mmol/L	5/205 (2.4%) with baxdrostat vs none with placebo	6/164 (3.6%) vs none with placebo	6/436 (1.3%) vs 1/147 (0.6%) with placebo
Incidence of adrenal insufficiency	None	None	7/436 (1.3%) vs 1/147 (0.6%) with placebo
Hypotension	1 severe case at day 64 who discontinued baxdrostat	2/110 (1.8%) vs none with placebo	7/436 (1.6%) vs 1/147 (0.6%) with placebo
Comments	Baxdrostat 2 mg decreased DBP by -5.2 mmHg versus placebo	Better SBP response in patients taking thiazides and with BMI >30 kg/m^2, and less SBP response in African Americans	Placebo-corrected decrease in SBP was -7 to -8 mmHg with BI 690517 + empagliflozin vs -4 to -6 mmHg with BI 690517 without empagliflozin

addition of empagliflozin to BI 690517 attenuated the severity of hyperkalemia [8]. However, it should be emphasized that in real practice, incidence of hyperkalemia with these 3 ASIs will likely to be much higher due to 2 main reasons. First, patients with high-normal baseline serum K (4.8-5.0 mmol/L) were excluded from the 3 studies [6-8]. Second, kidney function was almost normal in the baxdrostat and lorundrostat trials, and relatively preserved in the BI 690517 trial [6-8].

Hyponatremia

Hyponatremia occurred in 1.5-4.3% with baxdrostat versus none with placebo and led to drug discontinuation in one patient [6]. Likewise, 1 patient discontinued lorundrostat due to worsening hyponatremia [7].

Adrenal insufficiency

Ruling out adrenal insufficiency was crucial to prove that ASIs do not block cortisol formation through non-specific inhibition of 11-β-hydroxylase. Adrenal insufficiency occurred in 7 of 436 (1.6%) patients receiving BI 690517 versus 1 of 147 (0.6%) with placebo (**Table 1**) [8]. No cases of adrenal insufficiency were reported with baxdrostat and lorundrostat (**Table 1**) [6,7].

Other adverse effects

Urinary tract infections occurred in 10.4% with baxdrostat versus 4.3% with placebo [6]. In the trial of baxdrostat, 3 patients withdrew from the study due to the following serious adverse effects: the first due to severe hypotension (day 64 of use), the second due to hyponatremia as mentioned above, and the third patient due to urosepsis [6].

Advantages of Aldosterone Synthase Inhibitors

The ASIs proved effective in decreasing BP significantly in patients with resistant and uncontrolled hypertension versus placebo [6-8]. Moreover, BI 690517 reduced UACR in subjects with CKD [8]. Available results showed that the 3 agents were selective in inhibition of aldosterone and not cortisol formation [6-8]. In terms of safety, ASIs were fairly tolerated in

most patients. Their easy once-daily administration is another advantage. Therefore, ASIs may represent a potential useful addition to current anti-hypertensive agents.

Limitations of Aldosterone Synthase Inhibitors

Trials of the 3 ASIs had multiple exclusion criteria that limit generalsability of the results to patients with hypertension and CKD. Thus, in order to decrease likelihood of hyperkalemia, subjects with serum K at high normal range and those with significant CKD were excluded. Even in the kidney trial of BI 690517, mean eGFR was not profoundly affected with a mean eGFR of 51.9 ml/min/1.73 m^2 [8]. Other exclusion criteria were severe hypertension, SBP ≥ 180 mmHg or DBP ≥ 110 mmHg in the baxdrostat trial [6]. Although the 3 trials included 38-71% of patients with type 2 diabetes, results by diabetes status were not reported likely due to small numbers of subjects in various subgroups. In addition, the short-term duration of the trials did not allow to see if their effects were sustained over time. Finally, methodology for BP measurement was not identical across the 3 trials of ASIs [6-8].

Conclusions and Future Directions

Preliminary results suggest that the 3 ASIs baxdrostat, lorundrostat, and BI 690517 are effective in lowering BP. Furthermore, BI 690517 decreases albuminuria in patients with CKD. Hyperkalemia represents their major limitation. Well-designed long-term trials should examine the effects of ASIs for treatment of hypertension and CKD in patients with different races and with a broad spectrum of BP, kidney function, and BMI. These trials should have CV events and mortality as primary outcome. In addition, head-to-head trials comparing safety and efficacy of ASIs with the non-steroidal aldosterone receptor blocker finerenone should be performed. This comparison will clarify whether inhibition of aldosterone synthesis or blocking its receptors is the ideal approach to target aldosterone. Trials designed to evaluate baxdrostat as treatment for patients with primary hyperaldosteronism and those with uncontrolled hypertension and CKD are underway [9]. Standardization of the proper methodology of BP measurement is crucial in future trials to validate comparison between different ASIs [10].

Abbreviations

SBP: Systolic Blood Pressure; CKD: Chronic Kidney Disease; eGFR: Estimated Glomerular Filtration Rate; UACR: Urine Albumin to Creatinine Ratio; ACEI: Angiotensin-Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; PRA: Plasma Renin Activity; DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure; BMI: Body Mass Index

Conflict of Interest

The author does not have any conflict of interest to declare.

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