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BRIEF REPORT

Aldosterone synthase inhibitor "Baxdrostat" for resistant hypertension: A clinical approach or futuristic idea?

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The American College of Cardiology/American Heart Association defines resistant hypertension (RH) as a clinical blood pressure (BP) reading of >130/80 mmHg in patients taking three antihypertensive drugs, including a renin–angiotensin system inhibitor, a calcium channel blocker (CCB), and a diuretic at well-tolerated doses.[1,2] It is reported from multiple population-based surveys that in the United States, there is an approximately 12%–15% prevalence of RH among adults diagnosed with hypertension.[2] A prospective study demonstrates that 20% of people diagnosed with RH had primary hyperaldosteronism.[3,4] In addition to the classic three antihypertensive drugs, spironolactone and mineralocorticoid are also administered for RH. However, with respect to the safety profile of spironolactone, it has been reported to have several side effects such as low testosterone production, menstrual irregularities, and excessively raised serum potassium levels, leaving the drug unfit for the longitudinal therapeutic purpose of treating RH.[5]

Clinical research has demonstrated that aldosterone synthesis inhibitors lower circulating aldosterone levels by directly blocking the synthesis of aldosterone rather than blocking its receptor activity, subsequently lowering BP.[6] The first aldosterone synthase inhibitor to be developed was Osilodrostat (LCI699), which was intended to reduce serum aldosterone levels and manage hypertension. It was soon discovered, nevertheless, that Osilodrostat also inhibits 11-beta hydroxylase (CYP11B1), which lowers serum cortisol levels.[7]

Perhaps due to decreased cortisol levels, there were many reasons for the administration of Osilodrostat; thus, what was needed for the resistance was a selective aldosterone inhibitor, which was conceived and licensed by CinCor Pharma Inc. Baxdrostat, a drug in phase 2 clinical trials, exemplifies exceptional selective suppression of aldosterone synthase without blocking 11-beta hydroxylase.[8]

Animal model studies conducted on cynomolgus monkeys suggested that this drug inhibits the production of aldosterone without influencing the increase in cortisol caused by adrenocorticotropic hormone.[9] Furthermore, research involving healthy volunteers validated these findings (ClinicalTrials.gov Identifier: NCT01995383).[8] Multiple ascending doses of Baxdrostat were later investigated for safety, pharmacokinetics, and pharmacodynamics in a Phase I trial, which found that Baxdrostat was well tolerated, safe, and caused a dose-dependent decrease in plasma aldosterone but not cortisol.

Baxdrostat was tested in a Phase II trial[8,10] that was randomized, double-blind, placebo-controlled, and dose-ranging in adults with treatment-resistant hypertension (BrigHTN, Clinicaltrials.gov Identifier: NCT04519658). Individuals who are eligible must[8,10] (1) Be 18 years old and taking three stable antihypertensives, along with a diuretic, at the highest dosage tolerable. (2) If necessary, stop using potassium-saving diuretics and switch to nonpotassium-saving ones. (3) Have a mean seated BP of 130/80 mmHg (130/80 at the third visit if stopping a mineralocorticoid receptor antagonist). (4) Adhere to the recommended contraception practices: women should use contraception, and men should refrain from sperm donation. (5) Grant

participation in the study with informed consent. Supplemental material is available for more information (Table 1).

From July 30, 2020 to June 14, 2022, the BrigHTN trial took place.[8,10] A total of 779 people were screened, and 274 were chosen at random. Sixty-nine participants received placebo, 69 recipients of 0.5 mg Baxdrostat, 69 recipients of 1 mg Baxdrostat, and 67 recipients of 2 mg Baxdrostat.[8,10] A screening period of up to 8 weeks was included in the trial design before randomization. To evaluate drug compliance, a 2-week run-in period was used.[8,10] Out of the 29%–46% diabetic participants, black individuals made up 28% of the total group.[8,10] Twelve weeks after randomization, Baxdrostat at 1 and 2 mg dramatically decreased systolic blood pressure compared to placebo, leading to the early termination of the trial.[8,10] Differences in diastolic blood pressure, the secondary objective, were achieved at the 2 mg dose.[6] Baxdrostat was shown to reach its maximal plasma level in 4 h, causing a dose-dependent drop in serum aldosterone without changing cortisol levels as one of the exploratory endpoints.[8,10] The background medication utilized in the experiment was the same for all groups. All of the patients received a diuretic, and 64%–70% of them received a CCB, while 91%–96% of the patients received an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.[8,10]

TABLE 1 Inclusion and exculsion criteria for clinical trial (NCT04519658).

Inclusion criteria	Exclusion criteria
1. Is on a stable regimen of ≥3 antihypertensive agents (one of which is a diuretic) for at least 4 weeks before randomization.	1. Has a seated SBP ≥ 180 mmHg or DBP ≥ 110 mmHg.
2. Be at least 70% compliant to their antihypertensive medication regimen.	2. Has a BMI > 40 kg/m^2.
3. Has a seated BP ≥ 130/80 mmHg.	3. Has an upper arm circumference <7 or >17 inches.
4. Agrees to comply with the contraception and reproduction restrictions of the study.	4. Has been on night shifts at any time during the 4 weeks before Screening.
5. Able to understand and willing to comply with all study visits, procedures, restrictions, and provide written informed consent according to institutional and regulatory guidelines.	5. Is using a beta blocker for any primary indication other than systemic hypertension (e.g., migraine headache).
	6. Is not willing or not able to discontinue an MRA or a potassium-sparing diuretic as part of an existing antihypertensive regimen.
	7. Is not willing or not able to discontinue taking a potassium supplement.
	8. Has documented eGFR < 45 mL/min/1.73 m^2.
	9. Has known and documented New York Heart Association stage III or IV chronic heart failure.
	10. Has had a stroke, transient ischemic attack, hypertensive encephalopathy, acute coronary syndrome, or hospitalization for heart failure within 6 months before Screening.
	11. Has known current severe left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy and/or severe aortic valvular disease diagnosed from a prior echocardiogram.
	12. Major cardiac surgery (e.g., CABG, valve replacement), peripheral arterial bypass surgery, or PCI within 6 months before Screening.
	13. Has chronic permanent atrial fibrillation.
	14. Has uncontrolled diabetes with glycosylated hemoglobin >9.5% at Screening.
	15. Has planned dialysis or kidney transplant during the course of this study.
	16. Potassium <3.5 mEq/L.
	17. Potassium >5.0 mEq/L.
	18. Is positive for HIV antibody, hepatitis C virus RNA, or hepatitis B surface antigen.
	19. Has typical consumption of ≥14 alcoholic drinks weekly.

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; SBP, systolic blood pressure.

The researchers concluded that none of the side effects were significant or specifically linked to Baxdrostat.[8,10] The fact that none of the patients had to stop the experiment because of hyperkalemia is also remarkable.[8,10] When patients taking Baxdrostat did experience hyperkalemia, it usually went away quickly with standard dietary recommendations. The experiment did not include patients whose estimated glomerular filtration rate was higher than 45 mL/min/1.73 m^2; however, since this is crucial to mention.[8,10] A major exclusion criterion that restricted the generalizability of the findings was having a mean seated systolic blood pressure of 180 mmHg or a diastolic blood pressure of 110 mmHg.[8,10] It is crucial to note that Baxdrostat's effectiveness was only evaluated in comparison to a placebo and that additional studies, such as phase III trials, are required to evaluate Baxdrostat's performance against other antihypertensive medications.[8]

In conclusion, Baxdrostat emerges as a highly potent aldosterone synthesis inhibitor, distinguishing itself from previous drugs by not impacting cortisol levels. Remarkably, it demonstrated a favorable safety profile without reported side effects in clinical trials. These findings position Baxdrostat as a promising candidate for reducing aldosterone levels and effectively treating RH. While further trials are required to establish this as the standard of care, current research highlights its potential as a groundbreaking solution in the management of RH, providing a ray of hope in an otherwise challenging landscape.

AUTHOR CONTRIBUTIONS

Muhammad Osama Siddiqui: Conceptualization; writing and reviewing. **Ayaan Ahmed Qureshi**: Writing; reviewing. **Arooba Siddiqui**: Writing; reviewing. **Noor ul ain**: Reviewing.

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The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing statement is not applicable as this is a brief report.

ETHICS STATEMENT

Ethical statement is not applicable as this is a brief report and does not involve active patient participation.

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