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Short Communication

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Novel Therapies for Hypertension Treatment

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Abstract

Control rates for hypertension continue to decline due to poor medication adherence by patients despite over 120 different antihypertensive medications. Hence, cardiovascular outcomes have been worsening in the United States. Despite the plethora of antihypertensive medications available, the prevalence of resistant hypertension is estimated to be 13.7%. Single-pill combinations are highly effective in improving medication adherence rates as seen in various studies.

Four relatively novel classes of promising medications and two procedural interventions are being developed to expand our treatment arsenal for patients with resistant hypertension. This article presents a short overview of these medications and procedures most in the early stages of development. These new pharmacological agents are also from novel classes of medications including non-steroidal mineralocorticoid receptor antagonists, dual endothelin receptor antagonists, aldosterone synthetase inhibitors, a mutant atrial natriuretic peptide, and an RNA interference as well as a knockout molecule of hepatic angiotensinogen. Additionally, an update on renal denervation is presented. Based on the available data and assuming no new issues with safety develop, it will be at least 12-18 months for any of these new pharmacological agents to get approved.

Keywords: *Hypertension; Novel therapy; Aldosterone, Endothelin; Denervation*

Introduction

Resistant hypertension (RH) is defined as office systolic blood pressure (SBP) ≥130mmHg or diastolic blood pressure (DBP) ≥80mmHg while receiving at least three antihypertensive medications at maximally tolerated doses, one of which is a thiazide-type diuretic [1,2]. Despite the more than 100 medications approved to treat hypertension, the prevalence of RH is estimated to be 13.7% (95% CI, 11.2-16.2%) based on a meta-analysis of 20 observational studies [3]. However, it is imperative to exclude "apparent from true resistant hypertension" by evaluating medication adherence, accurate office blood pressures, and ambulatory blood pressures [1]. Patients with true RH are at a significantly increased risk for cardiovascular mortality and worsening of kidney function compared to hypertensive patients without RH [4].

There are five different classes of antihypertensive medications being developed for resistant or difficult-to-treat hypertension as well as renal denervation by two different methods. These are briefly discussed.

Therapeutic Classes Under Development

Non-steroidal mineralocorticoid receptor blockers (ns-MRA)

NS-MRAs are a new class of agents distinct in many ways from their steroidal cousins and were developed, in part, to have less hyperkalemia. Unlike spironolactone and eplerenone, nsMRAs are bulky, have a higher selectivity for the MR, and stimulate various genomic reactions, thus contributing to a better overall efficacy and safety profile [5].

While there are five different nsMRA only one, finerenone has outcome data indicated to slow the decline of kidney function and reduce cardiovascular outcomes in patients with diabetic nephropathy when added to traditional therapies across a wide range of eGFRs [6]. Compared with spironolactone and eplerenone, which primarily accumulate in the kidneys, finerenone is distributed evenly between the heart and the kidneys [7]. This may explain why finerenone reduces cardiovascular events in patients with diabetic nephropathy with less hyperkalemia [6,8]. There are data with finerenone demonstrating significant blood pressure lowering ability at systolic pressures above 140 mmHg [9],

however, it is not being developed as an antihypertensive agent.

Of the other four nsMRAs esaxerenone [10,11] and Ocedurenone [12] have been developed as antihypertensive agents, Esaxerenone is available only in Japan, and Ocedurenone focused exclusively on advanced kidney disease and difficult to treat hypertension [12,13].

Ocedurenone has higher selectivity for the mineralocorticoid receptor when compared to steroidal MRAs, spironolactone, and eplerenone [12]. BLOCK-CKD was a phase 2b, international, multicenter, randomized, double-blind, placebo-controlled, parallel-group study that evaluated the effect of Ocedurenone on 162 patients with uncontrolled hypertension and CKD stage 3b-4. There was a significant reduction in placebo-subtracted systolic blood pressure of 7mmHg (p = 0.0399) in the group that received 0.25mg daily and a drop of 10.2 mmHg (p=0.0026) in the group that received 0.5mg daily. The incidence of mild hyperkalemia (K 5.6-5.9 mmol/L) was similar among the groups: 8.8% in the placebo group, 11.8% in the 0.25mg treatment group, and 16.7% in the 0.5mg treatment group.

The soon to be completed CLARION trial is a Phase 3, randomized, double-blind, placebo-controlled, 2-arm, parallel-group, multicenter study with randomized withdrawal to evaluate the efficacy, safety, and durability of Ocedurenone in 600 adult participants who have stage 3b/4 chronic kidney disease (CKD) (estimated glomerular filtration rate [eGFR) ≥15 to ≤44 mL/min/1.73 m^2) and uncontrolled hypertension (systolic blood pressure (SBP) ≥140 and <180 mm Hg and taking two or more antihypertensive medications [14].

Dual endothelin antagonists

There are two types of endothelin (ET) receptors: ETA and ETB [15]. Both are found on vascular smooth muscle cells where they mediate vasoconstriction, but only ETB receptors are present on endothelial cells and can mediate vasodilation [15]. Both selective and non-selective endothelin receptor antagonists (ERAs) have been studied to treat resistant hypertension. The failure of previously studied ERA's was due to edema development and prompted research into drugs that more selectively target the ETB receptor rather than the ETA receptor.

Aprocitentan is a non-selective ERA but has a 16-fold higher affinity for the ETB receptor [16]. It has a longer half-life of 44 hours which facilitates once-daily dosing. A randomized, double-blind, dose-response study was conducted on 409 patients comparing placebo, lisinopril 20mg, and ascending doses of aprocitentan (5, 10, 25, 50mg) [16].

The primary endpoint was the mean trough in sitting AOBP from baseline to week 8. Compared to placebo, significant reductions were seen for the three higher doses of aprocitentan. The placebo-subtracted reduction in SBP/DBP was -7.05/4.93mmHg for aprocitentan 10mg, -9.90/6.99mmHg for aprocitentan 25mg, and -7.58/4.95mmHg for aprocitentan 50mg. The lisinopril 20mg group had a placebo-subtracted reduction of -4.84/3.81mmHg. These reductions occurred at week two and persisted until week eight. No serious adverse events were caused by aprocitentan. However, there was a dose-dependent decrease in hemoglobin and a dose-dependent decrease in uric acid.

Aldosterone synthetase inhibitors

Aldosterone synthase inhibitors (ASIs) are an emerging class of medications used in patients with hyperaldosteronism [17]. The first ASI studied in humans was baxdrostat, an imidazole derivative, which showed a dose-dependent decrease in plasma and urine aldosterone levels with no change in plasma cortisol [18]. A total of 248 patients completed the Phase 2 trial [19]. Dose-dependent changes in systolic blood pressure of -20.3 mm Hg, -17.5 mm Hg, -12.1 mm Hg, and -9.4 mm Hg were observed in the 2-mg, 1-mg, 0.5-mg, and placebo groups, respectively. No deaths occurred during the trial, no serious adverse events were attributed by the investigators to baxdrostat, and there were no instances of adrenocortical insufficiency. Baxdrostat-related increases in the potassium level to 6.0 mmol per liter or greater occurred in 2 patients, but these increases did not recur after withdrawal and reinitiation of the drug.

A Mutant Atrial Natriuretic Peptide Analog

Atrial natriuretic peptide (ANP) activates natriuretic peptide receptor type A, which is coupled to the guanylyl cyclase A (GC-A) receptor, thereby increasing cyclic GMP (cGMP) levels [20].

M-atrial natriuretic peptide (MANP) is a MANP, 40 amino acid designer natriuretic peptide, that activates the GC-A receptor stimulating the generation of its second messenger, cGMP. After binding to GC-A in the kidney, the vasculature, and the adrenal gland, MANP mediates natriuresis, vasodilatation, and aldosterone inhibition [21]. This is due to MANP's resistance to enzymatic degradation. In a study of normotensive canines, MANP was superior to native ANP in cGMP increase, blood pressure reduction, natriuresis, GFR increase, and aldosterone suppression [22].

The first human study of MANP was published in 2021 [23]. It was an open-label, sequential, single-dose ascending design that involved three cohorts with four subjects, each receiving different amounts of MANP subcutaneously at 1μg/kg, 2.5μg/kg, and 5μg/kg. All antihypertensives were stopped 14 days before MANP administration. Blood pressure, reductions in both SBP and DBP were observed in each cohort between 2-12 hours post-administration. However, at 24 hours, both SBP and DBP remained reduced in the 5μg/kg group, while only SBP remained reduced in the 2.5μg/kg group. No serious adverse

events occurred in this study, with minor side effects being mild headache, light headedness, and orthostatic vasovagal syncope. Future studies with subcutaneous injection are being developed and these studies are just starting.

Attenuators of hepatic angiotensinogen

Targeting the upstream enzyme, angiotensinogen (AGT), blocks RAAS and confers additional advantages [24,25]. By silencing AGT in the liver as opposed to the kidneys, there may be a lower incidence of hyperkalemia and renal dysfunction.

IONIS-AGT-LRx is an antisense oligonucleotide (ASO) that reduces plasma AGT levels by AGT mRNA knockdown in the hepatocytes [25].

Two phase 2 studies were conducted – one monotherapy and the other as add-on therapy. The first was a randomized, double-blind, placebo-controlled trial in patients with well-controlled hypertension on two antihypertensive medications (one of which is an ACEi/ARB and the other is BB, CCB, or diuretic) [25]. The subjects were randomized 2:1 to receive 80mg of the study drug (17 patients) or placebo (8 patients). They received a subcutaneous injection with the loading dose followed by once weekly injections for six weeks. The subjects were then followed for 12 additional weeks. The two groups had similar baseline AGT levels. AGT levels declined slightly during the washout period, and blood pressures rose somewhat compared to on-treatment measurements.

Post-treatment, the IONIS group had significantly lower absolute AGT levels (-11.2 ± 6.0 μ g/ml vs 2.0 m ± 4.6 μg/ml, p<0.001) and a significantly higher percentage reduction in AGT (-54 ± 24.8% vs. 12.6 ± 23.3%, p<0.001) when compared to the placebo group [25]. These differences were noted on day eight and lasted until day 78. There was a trend towards more significant SBP reduction (-8 mmHg, 95% CI -17 to +2) and DBP reduction (-1 mmHg, 95% CI -8 to +5) in the treatment group. There were no serious adverse events, hypotension, hyperkalemia, or GFR decreases.

The second phase 2 study had a very similar design to the first, except it included patients with uncontrolled hypertension on a stable dose of 2-3 antihypertensive medications (one of which is an ACEi/ARB and the other is BB, CCB, or diuretic) [25]. The subjects were randomized 2:1 to receive 80mg of the study drug (18 patients) or placebo (9 patients). They received a subcutaneous injection with the loading dose followed by once weekly injections for eight weeks. The IONIS group had significantly lower absolute AGT levels (-17.0 ± 4.1 μg/ml vs. -1.1 ± 4.5 μg/ml, p<0.001) and significantly higher percent reduction in AGT (-67 ± 14.1% vs. 3.4 ± 17.8%, p<0.001) when compared to the placebo [25]. These differences were noted on day eight and lasted until day 92. There was no significant difference in the effect between patients on 2 or 3 antihypertensives at baseline.

In addition to antisense technology, there is another approach: interference with angiotensinogen mRNA. Zilebesiran is an investigational subcutaneous RNA interference (RNAi) therapeutic targeting liver-expressed angiotensinogen (AGT) in development for the treatment of hypertension. In a phase 1 study, patients with hypertension were randomly assigned in a 2:1 ratio to receive either a single ascending subcutaneous dose of zilebesiran (10, 25, 50, 100, 200, 400, or 800 mg) or placebo and followed for 24 weeks (Part A). Part B assessed the effect of the 800-mg dose of zilebesiran on blood pressure under low- or high-salt diet conditions, and Part E the effect of that dose when co-administered with irbesartan. The authors found that of 107 patients enrolled, 5 had mild, transient injection-site reactions. There were no reports of hypotension, hyperkalemia, or worsening of renal function resulting in medical intervention. In Part A, patients receiving zilebesiran had decreases in serum angiotensinogen levels that were correlated with the administered dose. Single doses of zilebesiran (≥200 mg) were associated with decreases in systolic blood pressure (>10 mm Hg) and diastolic blood pressure (>5 mm Hg) by week 8; these changes were consistent throughout the diurnal cycle and were sustained at 24 weeks. Results from Parts B and E were consistent with attenuation of the effect on blood pressure by a high-salt diet and with an augmented effect through coadministration with irbesartan, respectively [26].

A just completed Phase 2 trial, KARDIA 1, was a randomized, double-blind (DB), placebo-controlled, dose-ranging study to evaluate the efficacy and safety of zilebesiran as monotherapy in adults with mild-to-moderate hypertension. This global, multicenter trial enrolled about 375 adults with untreated hypertension or stable on therapy with one or more anti-hypertensive medications. Those receiving prior anti-hypertensive medications had a four-week wash-out before randomization. Randomization to one of five treatment arms during a 12-month double-blind period and double-blind extension period occurred to the following dose schedule: 150 mg zilebesiran subcutaneously every six months; 300 mg zilebesiran subcutaneously every six months; 300 mg zilebesiran subcutaneously every three months; 600 mg zilebesiran subcutaneously every six months; or placebo. Those receiving a placebo were randomized to one of the four initial zilebesiran dose regimens at six months. The study's primary efficacy endpoint is the change from baseline in 24 hr. ambulatory systolic blood pressure at month three [27].

Procedural Interventions

Renal denervation

Renal denervation has emerged as a possible treatment for resistant hypertension and was just reviewed by the FDA with a decision pending by this fall. There are two different types of denervation methods, one involves catheter-based radiofrequency ablation of

the renal nerve and the other high-frequency ultrasound, thereby reducing sympathetic activity, and is associated with a 4-8 mmHg placebo-subtracted blood pressure fall.

The radiofrequency ablation procedure uses the Spyral catheter to deliver energy at the hilum of the kidney's renal artery and its branches. Multicenter, international, single-blind, randomized, sham-controlled trials were conducted in hypertensive patients off medication and on medication [28,29].

A meta-analysis of seven randomized, blinded, sham-controlled renal denervation trials, which included 1,368 patients, found significant reductions in ambulatory and office blood pressures after denervation compared to the sham procedure [30]. This procedure is up for approval by the Food and Drug Administration.

A second approach to denervation is the use of radiofrequency ultrasound. This procedure had two different positive outcome trials for BP reduction [31,32] and the RADIANCE-HTN TRIO trial was very instructive [31]. TRIO was a randomized, international, multicentre, single-blind, sham-controlled trial done at 28 tertiary centers in the USA and 25 in Europe. Eligible patients were switched to a once-daily, fixed-dose, single-pill combination of a calcium channel blocker, an angiotensin receptor blocker, and a thiazide diuretic. After 4 weeks of standardized therapy, patients with a daytime ambulatory blood pressure of at least 135/85 mm Hg were randomly assigned (1:1) by computer (stratified by centers) to ultrasound renal denervation or a sham procedure. Participants were enrolled and 136 were randomly assigned to renal denervation (n=69) or a sham procedure (n=67). Full adherence to the combination medications at 2 months among patients with urine samples was similar in both groups (42 [82%] of 51 in the renal denervation group vs. 47 [82%] of 57 in the sham procedure group; p=0.99). Renal denervation reduced daytime ambulatory systolic blood pressure more than the sham procedure (-8.0 mm Hg [IQR -16.4 to 0.0] vs -3.0 mm Hg [-10.3 to 1.8]; median between-group difference -4.5 mm Hg [95% CI -8.5 to -0.3]; adjusted p=0.022); the median between-group difference was -5.8 mm Hg (95% CI -9.7 to -1.6; adjusted p=0.0051) among patients with complete ambulatory blood pressure data. There were no differences in safety outcomes between the two groups.

Conclusion

Starting in 2024 and by 2028 some or possibly all of these therapies will be available. However, keep in mind the lessons learned from the TRIO study using high-frequency ultrasound where a single pill containing 3 complementary medications led to 90% control rates of hypertension [31,33], yet insurance companies will not pay for these agents. Even these need agents except the Angiotensinogen injections will be add-on or substitution therapy to our current hypertension mainstays. What is needed is a change by the medical system to spend more time with patients explaining the importance and implementation of lifestyle changes and their significance to lowering BP to improve medication adherence as noted in all guidelines and generally ignored because physicians and the healthcare system are not given the time to implement.

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