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New Drugs for Resistant Hypertension: Pending Issue?

İlaç Dirençli Hipertansiyon İçin Yeni İlaçlar: Hâlâ Çözülememiş Bir Sorun mu?

ABSTRACT

Antihypertensive pharmacological treatment, based on currently available drugs, has been shown to reduce the cardiovascular risk profile of treated hypertensive patients by lowering elevated blood pressure. However, the cardiovascular risk in treated hypertensive patients remains elevated. This highlights the need to develop new antihypertensive drugs capable of normalizing the risk associated with high blood pressure. This paper aims to review new antihypertensive drugs for the treatment of drug-resistant hypertension. In particular, it focuses on the results obtained with non-steroidal mineralocorticoid receptor antagonists, aldosterone synthase inhibitors, brain renin-angiotensin blockers, hepatic angiotensinogen inhibitors, atrial natriuretic peptides, and endothelin-1 receptors antagonists.

Keywords: Antihypertensive treatment, new antihypertensive drugs, resistant hypertension

ÖZET

Mevcut ilaçlara dayanan antihipertansif farmakolojik tedavinin, yüksek kan basıncını düşürerek tedavi edilen hipertansif hastaların kardiyovasküler risk profilini azalttığı gösterilmiştir. Ancak, tedavi edilen hipertansif hastalarda risk yüksek kalmaya devam etmektedir. Bu durum, kontrol altına alınamayan yüksek kan basıncına bağlı kardiyovasküler riski normalleştirebilecek yeni antihipertansif ilaçların geliştirilmesi için bir gerekçe oluşturmaktadır. Bu makale, ilaçlara dirençli hipertansiyon tedavisinde kullanılabilecek yeni antihipertansif ilaçların gözden geçirilmesini amaçlamaktadır. İnceleme özellikle steroidal olmayan mineralokortikoid reseptör antagonistleri, aldosteron sentaz inhibitörleri, beyin renin-anjiotensin blokerleri, hepatik anjiyotensinojen inhibitörleri, atriyal natriüretik peptitler ve endotelinin 1 reseptör antagonistleri ile elde edilen sonuçlara odaklanacaktır.

Anahtar Kelimeler: Antihipertansif tedavi, yeni antihipertansif ilaçlar, dirençli hipertansiyon

REVIEW
DERLEME

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Hypertension (HT) is one of the most common risk factors contributing to the high incidence of cardiovascular and renal disease worldwide.[1] A wide range of available antihypertensive drugs, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), thiazide diuretics, beta-blockers, and their combinations, can effectively reduce blood pressure (BP), with a significant associated decrease in the risk of hypertension-mediated organ damage.[2] However, BP control is achieved in only about 40% of patients in Europe1. Several reasons have been proposed to explain this lack of BP control in treated hypertensive patients. These include the routine use of monotherapy, low rates of HT awareness, physician inertia in up-titrating antihypertensive drugs or initiating combination therapy, and, finally, poor patient adherence to prescribed treatment regimens.[3] Additionally, in a variable percentage of patients (12%–18.0%), HT remains difficult to control despite the use of three to four drugs from different classes, administered at recommended daily dosages.[4,5] The prevalence of resistant hypertension (RHT) is particularly high in patients with hyperaldosteronism, advanced chronic kidney disease (CKD), diabetes, the elderly, as well as those with obesity and obstructive sleep apnea.[4] Similar to essential HT, RHT is associated with a high risk of HT-mediated organ damage and cardiovascular events.[5] Hyperaldosteronism, characterized by salt retention and volume expansion, along with sympathetic nervous system hyperactivation, increased secretion of endothelin-1, and altered levels of natriuretic peptides, represents the most common set of pathophysiological mechanisms involved in the development and progression of RHT.[6]

Current Therapeutic Strategy

The aldosterone–mineralocorticoid receptor axis plays an important role in BP regulation. Elevated circulating aldosterone plasma levels, by promoting renal sodium retention and potassium excretion, are involved in the pathophysiology of both HT and RHT.[7] Currently, spironolactone and eplerenone have an established role in the treatment of heart failure and are also used as fourth-line agents for RHT in patients with plasma potassium levels < 4.5 mmol/L and an estimated glomerular filtration rate (eGFR) > 45 mL/min/1.73 m^2. Notably, the PATHWAY-2 trial (Prevention And Treatment of Hypertension With Algorithm-based Therapy-2), a double-blind, randomized, placebo-controlled study, demonstrated that spironolactone (25–50 mg/day), when added to existing antihypertensive therapy, was more effective in reducing BP (Table 1) and achieving BP control in patients with RHT compared with placebo, bisoprolol, and doxazosin.[8] A recent large meta-analysis[9] also confirmed the efficacy of spironolactone in lowering both office and 24-hour ambulatory BP. However, the same analysis reported that, compared with other antihypertensive drugs, spironolactone did not significantly reduce office diastolic BP (Table 1). Despite its effectiveness, the therapeutic use of spironolactone in clinical practice is limited by the risk of hyperkalemia, particularly in patients with advanced CKD or those treated with ACE inhibitors or ARBs, as well as its anti-androgenic and progesterone receptor agonist effects, which can lead to gynecomastia and sexual dysfunction. The combination of spironolactone with potassium binders such as patiromer reduces the risk of hyperkalemia,[10] but does not prevent the hormonal side effects.

Eplerenone is a second-generation mineralocorticoid receptor antagonist, with a lower affinity compared to spironolactone.[11] Several studies, summarized in a meta-analysis,[12] have documented the effectiveness of eplerenone (50–200 mg/day) in the treatment of essential HT. However, strong evidence regarding its efficacy in patients with RHT is lacking. Although few direct comparative studies between eplerenone and spironolactone are available, eplerenone has the notable advantage of causing fewer hormonal side effects than spironolactone. Nonetheless, it also presents some drawbacks, such as higher cost, potential drug-drug interactions due to metabolism via cytochrome P450 pathway, and a shorter half-life, which necessitates twice-daily administration.[11] Like spironolactone, eplerenone is associated with the risk of hyperkalemia, especially in patients with chronic kidney disease or those receiving ACE inhibitors or ARBs.[11] To achieve better BP control in patients with RHT, new pharmacological agents targeting various key pathophysiological pathways have been developed and are currently either in clinical development or have recently been approved.

The aim of this narrative review is to provide an update on emerging drugs for the treatment of RHT. The results obtained with these drugs in patients with essential HT will also be also discussed.

Materials and Methods

We searched PubMed, Google Scholar, and Medline for original randomized clinical trials and open-label studies published between 2019 and 2024, involving new drugs tested in patients with RHT. The following search terms were used: "resistant HT," "treatment of RHT," "drugs for RHT," "new drugs for RHT," and "uncontrolled HT." Studies involving patients with secondary HT, duplicate publications, and expert opinions were excluded. We did not follow a standard protocol for systematic reviews, as this paper is a narrative review aimed at providing an overview of the available evidence. Data on BP reduction are reported as absolute values, while placebo-corrected results are presented in Table 1. Eligible publications were independently selected by two reviewers (FF, RR).

ABBREVIATIONS

ACEi	Angiotensin-converting enzyme inhibitors
ANP	Atrial natriuretic peptides
APA	Aminopeptidase A
ARBs	Angiotensin receptor blockers
AT 1	Angiotensin 1
AT 2	Angiotensin type 2
BLOCK-CKD	Blood pressure lowering with ocedurenone in chronic kidney disease and resistant hypertension
BP	Blood pressure
BrigHTN	Blood pressure reduction in resistant hypertension with baxdrostat
CCBs	Calcium channel blockers
CKD	Chronic kidney disease
DBP	Diastolic blood pressure
EARLY-NH	Efficacy of Esaxerenone in early treatment of nocturnal hypertension
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
ET-1	Endothelin-1
EXCITE-HT	Esaxerenone Comparative evaluation for optimal treatment in uncontrolled hypertension
FDA	Food and Drug Administration
FRESH	Firibastat in Resistant Hypertension
HT	Hypertension
MANP	M-atrial natriuretic peptide
PATHWAY-2 trial	prevention and treatment of hypertension with algorithm-based therapy-2
RECISION	Placebo-Controlled Randomized Study of the Selective Endothelin A Receptor Antagonist Aprocitentan in Resistant Hypertension
RHT	Resistant hypertension
SBP	Systolic blood pressure
Target-HTN	Treatment with lorundrostat in adults with uncontrolled hypertension and elevated aldosterone levels

Emerging Drug Classes for RHT (Figure 1)

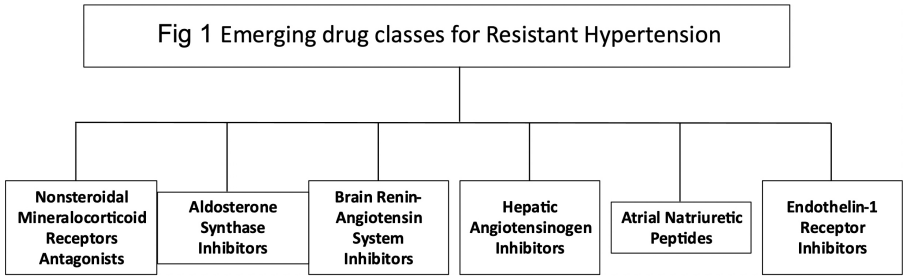
Nonsteroidal Mineralocorticoid Receptor Antagonists

To avoid the hormonal side effects of spironolactone and eplerenone, as well as the risk of hyperkalemia, several nonsteroidal mineralocorticoid receptors antagonists have been approved or are currently under clinical investigation. Esaxerenone, a highly selective nonsteroidal mineral receptor antagonist,[13] has been tested in patients with uncontrolled HT. The multicenter, randomized, open-label, parallel-group, EXCITE-HT (Esaxerenone Comparative Evaluation for Optimal

Table 1. Blood pressure reduction (placebo or active comparator corrected) in patients with resistant or essential hypertension

Drug class	Office SBP/DBP (mmHg)	24-h Ambulatory SBP/DBP (mmHg)
Mineralocorticoid receptor antagonists		
Spironolactone[8]	20.1/-5.7**	-10.3/-3.9**
Office SBP[9]	-6.0**/-0.5	-6.9*/-3.0**
Eplerenone[12,&&]	-9.2/-4.1**	
Nonsteroidal mineralocorticoid receptor antagonists		
Esaxerenone[14]		
Morning home BP	-2.2*/-0.6	
Bedtime home BP	-2.2/-0.9	
Office BP	-3.4/-1.5	
Esaxerenone[17,&&]		
2.5 mg	-0.23/-0.4	
5.0 mg	-4.4/-2.1**	
Ocedurenone[20,21]		
0.25 mg	-7.0*	
0.50 mg	-10.2**	
CKD patients		
0.25 mg	-9.3	
0.50 mg	-10.0	
Diabetes patients		
0.25 mg	-6.9	
0.50 mg	-11.6	
Albuminuria patients		
0.25 mg	-13.1	
0.50 mg	-12.3	
Aldosterone synthase inhibitors		
Baxdrostat[25]		
0.5 mg	-2.7/0.6	
1.0 mg	-8.1**/-2.6	
2.0 mg	-11.0/-5.1**	
Lorundrostat[28]		
12.5 mg	-1.5/-2.1	-5.2
50 mg	-9.6**/-5.5*	-1.8
100 mg	-7.8*/-4.1	-8.9
Brain Renin-angiotensin system inhibitors		
Firibastat[30]	-4.7	-2.7
Hepatic angiotensinogen inhibitors		
IONIS-AGT-LRx[33,&&]	-6.0/-3.0	
Hepatic angiotensinogen inhibitors		
Zilebesiran[35,&&]		
150 mg	-9.6**	-14.1**
300 mg	-12.0**	-16.7**
600 mg	-9.1**	-15.7**
Endothelin-1 receptor inhibitors		
Aprocitentan[44]		
12.5 mg	-3.8/-3.9**	-4.2/-4.3
25 mg	-3.7/-4.5**	
Aprocitentan[45,&&]		
5 mg	-2.4/-1.3	0.9/-0.9
10 mg	-7.0/-4.9**	-4.0/-4.0**
25 mg	-9.9/-7.0**	-4.8/-5.9**
50 mg	-7.6/-4.9**	-3.6/-4.4**

Data are shown as systolic and diastolic blood pressure reductions compared to baseline values. Asterisks (*P < 0.05, **P < 0.01) indicate statistical significance versus control. &&, Essential hypertension; ABPM, Ambulatory blood pressure monitoring; CKD, Chronic kidney disease; DBP, Diastolic Blood pressure; SBP, Systolic blood pressure.



Treatment in Uncontrolled Hypertension) trial[14] compared esaxerenone (2.5–5.0 mg/day) with trichlormethiazide, both administered as add-on therapy to either an ARB or a CCB, in patients with uncontrolled HT. After 12 weeks, BP reductions in home morning, bedtime, and office measurements were not significantly different between the esaxerenone and trichlormethiazide groups. The percentage of subjects achieving morning home BP control (BP < 140/90 mmHg) was nearly identical between the two groups (60.8% vs. 55.8%). Moreover, there was no significant difference between the two drugs in reducing the urinary albumin-to-creatinine ratio (UACR: -38.9% vs. -41.9%) in the subgroup of patients (26%) with diabetes and baseline albuminuria. Overall, the effect of esaxerenone in patients with uncontrolled BP was comparable to that of the diuretic trichlormethiazide (Table 1).

Another open-label study, the EARLY-NH (Efficacy of Esaxerenone in Early Treatment of Nocturnal Hypertension) trial,[15] evaluated the efficacy of esaxerenone in patients with uncontrolled nocturnal HT (systolic BP ≥ 120 mmHg). After 12 weeks of treatment, esaxerenone (2.5–5.0 mg/day), added to either an ARB or a CCB, significantly reduced home nocturnal systolic/diastolic BP, as well as morning and bedtime BP. A post hoc analysis of this study[16] showed that a higher percentage of patients treated with esaxerenone (63.6%) achieved the target nighttime systolic BP of < 120 mmHg. This finding is clinically relevant, as nocturnal HT is associated with an increased risk of cardiovascular events. However, both studies have some limitations: a) the trials were open-label, b) the treatment duration was relatively short, and c) the definition of RHT used in the studies does not align with the current standard definition.

The antihypertensive properties of esaxerenone have also been demonstrated in patients with essential HT, showing a similar BP-lowering effect when used either as monotherapy or in combination with ARBs or CCBs. A recent meta-analysis[17] reported no significant difference between esaxerenone 2.5 mg/day and eplerenone 50 mg/day in reducing systolic BP; however, the highest dose of esaxerenone (5 mg/day) was found to be more effective (Table 1). In patients with type 2 diabetes[18] and proteinuria (urinary albumin-to-creatinine ratio 45 to < 300 mg/g, who were already receiving treatment targeting the renin-angiotensin system, esaxerenone (1.25–2.5 mg/day) was more effective than placebo (44% vs. 11%, respectively) in achieving proteinuria remission (UACR < 30 mg/g creatinine). In these patients, systolic/diastolic BP was significantly reduced from baseline by 10/5 mmHg. Treatment with esaxerenone was associated with elevated renin activity and plasma aldosterone levels, indicating effective mineral receptor inhibition. No hormonal-related adverse effects were reported, and there was no significant difference compared to placebo in terms of drug-related side effects or treatment discontinuation.[17,19] Hyperkalemia (≥ 6.0 or ≥ 5.5 mEq/L) occurred in 9.0% of patients treated with esaxerenone compared to 2.0% in the placebo group. Increases in plasma potassium were particularly evident in individuals with baseline potassium levels ≥ 4.5 mEq/L or with eGFR < 60 mL/min.[18] Therefore, plasma potassium and eGFR should be regularly monitored during esaxerenone treatment. This recommendation is supported by findings from the ESAX-DN (Esaxerenone in Patients With Type 2 Diabetes and Microalbuminuria) trial,[18] conducted in patients with type 2 diabetes and microalbuminuria, which showed a greater reduction in estimated glomerular filtration rate with esaxerenone compared to placebo (-11% vs. -1%). Considering all these results, esaxerenone, when added to ARBs or CCBs, can be considered an effective option for patients with essential HT, including those with type 2 diabetes and chronic kidney disease. Esaxerenone has been approved in Japan for this indication. However, studies evaluating its antihypertensive effectiveness in RHT, particularly in Caucasian populations, are still lacking.

Two other new pharmacological compounds in the nonsteroidal mineral receptor antagonist class are ocedurenone and finerenone. Ocedurenone, a highly selective receptor antagonist, is under development for RHT, particularly in patients with CKD. The BLOCK-CKD (Blood Pressure Lowering With Ocedurenone in Chronic Kidney Disease and Resistant Hypertension) trial,[20] a Phase 2b, multicenter, randomized, double-blind, placebo-controlled study, was conducted in patients with RHT and stage 3b/4 CKD. After 84 days of treatment, systolic BP was significantly reduced with both 0.25 mg and 0.50 mg daily doses of ocedurenone compared to placebo, while diastolic BP did not differ between the groups. In 77.2% of patients with baseline proteinuria, the urinary albumin-to-creatinine ratio remained unchanged. A subsequent subgroup analysis[21] demonstrated that both doses of ocedurenone reduced systolic BP (placebo-corrected) even in patients with type 2 diabetes, stage 4 CKD, and high albuminuria (Table 1). Hyperkalemia (≥ 5.6 to ≤ 6.0 mmol/L) was observed in 9.8% and 13.0% of patients receiving 0.25 mg and 0.5 mg of ocedurenone, respectively. This study, however, had some limitations: a) a small number of patients, b) the lack of a significant difference in diastolic BP between ocedurenone and placebo, c) the absence of 24-hour BP monitoring to confirm the diagnosis of RHT, and d) the short treatment duration (< 3 months). Therefore, the evidence supporting the effectiveness of ocedurenone remains limited. Long-term clinical trials with a larger sample size are needed to confirm its antihypertensive efficacy in routine clinical practice.

The other non-steroidal selective mineralocorticoid receptor antagonist is finerenone. The U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved finerenone for cardiovascular and renal protection in patients with diabetes and CKD. However, in patients with RHT and CKD, finerenone has been associated with a highly variable and lower reduction in office systolic BP compared to spironolactone.[22] Therefore, finerenone cannot be considered an effective antihypertensive drug.

Aldosterone Synthase Inhibitors

Another pharmacological approach to lowering elevated BP, particularly in RHT, is the inhibition of aldosterone synthesis through selective aldosterone synthase inhibitors. Selectivity is a crucial property of these compounds in order to avoid a reduction in plasma cortisol, as aldosterone synthase shares a similar chemical structure with 11β-hydroxylase, involved in cortisol synthesis.[23] Aldosterone plays a key role in the regulation of water and electrolyte homeostasis. Elevated plasma aldosterone levels induce vasoconstriction (through nitric oxide degradation and endothelin-1 release from endothelial cells), increase water and sodium reabsorption in the distal renal tubules, and consequently contribute to elevated BP and RHT.[23] Following the negative results with osilodrostat,[24] another aldosterone synthase inhibitor, baxdrostat, with significantly higher selectivity, has been tested in patients with RHT. The BrigHTN (Blood Pressure Reduction in Resistant Hypertension With Baxdrostat) trial, a Phase 2, multicenter, double-blind, placebo-controlled study,[25] randomized patients with RHT to receive baxdrostat (0.5, 1, or 2 mg/day) added to ACE inhibitors or ARBs and CCBs, or placebo, for 12 weeks. Baxdrostat significantly reduced systolic and diastolic BP at all three doses, with a statistically significant reduction observed at 1 mg and 2 mg. Diastolic BP was reduced only at the highest dose. Therefore, the 2 mg dose appears to be the most effective (Table 1). At this dose, a dose-dependent reduction in plasma and urinary aldosterone levels, along with a compensatory increase in renin activity, was observed, indicating effective aldosterone synthase inhibition. Plasma cortisol concentrations were not affected by any dose of baxdrostat, confirming its minimal effect on 11β-hydroxylase. Overall, the drug was well tolerated, and cases of hyperkalemia (5.5–6.3 mmol/L) were managed with temporary discontinuation of treatment. However, in the HALO (Hypertension and Aldosterone Synthase Inhibition with Lorundrostat) trial, another multicenter, randomized, Phase 2 study,[26,27] there was no statistically significant difference between baxdrostat and placebo in reducing systolic BP or in the proportion of patients achieving systolic BP control. The BrigHTN study also had two notable limitations: a) 24-hour BP monitoring was not performed to confirm the diagnosis of RHT, and b) the proportion of patients achieving BP control was not reported. Given the conflicting results between the BrigHTN and HALO trials, the efficacy and tolerability of baxdrostat require further confirmation.

Lorundrostat, another agent targeting aldosterone synthase, has also been evaluated in patients with RHT. The Target-HTN (Treatment With Lorundrostat in Adults With Uncontrolled Hypertension and Elevated Aldosterone Levels) study, a multicenter, placebo-controlled trial,[28] randomized patients with uncontrolled HT and low or normal plasma renin activity. In the subgroup with plasma renin ≤ 1.0 ng/mL/h and plasma aldosterone ≥ 1 ng/dL, lorundrostat (50 mg and 100 mg once daily for eight weeks) reduced office systolic BP more effectively than placebo. Interestingly, diastolic BP was reduced more with the 50 mg dose than with the 100 mg dose. The change in 24-hour BP monitoring was not statistically significant compared with placebo (Table 1). Office systolic BP reduction was similar in patients with both low and normal plasma renin levels. The percentage of subjects achieving BP control (< 130/80 mmHg) was higher with all doses of lorundrostat (42.9% vs. 30.0%) compared to placebo (23.3%). Aldosterone levels were reduced with all lorundrostat doses. No changes in plasma cortisol were reported, and only 3.6% of patients experienced hyperkalemia (> 6.0 mmol/L). This study had two major limitations: a) a small sample size, and b) the absence of BP monitoring to confirm the diagnosis of RHT. Therefore, further clinical trials are needed to better define the role of lorundrostat in the treatment of uncontrolled HT.

Brain Renin-Angiotensin System Inhibitors

Overactivation of the brain renin-angiotensin system plays a significant role in elevating BP. The enzyme aminopeptidase A (APA) is involved in the conversion of angiotensin II into angiotensin III, which has a high affinity for brain angiotensin 1 (AT 1) and type 2 (AT 2) receptors. This interaction leads to increased vasopressin release, heightened sympathetic neural outflow, and inhibition of the brain baroreflex activity.[29] Pharmacological blockade of APA activity reduces the effects of brain angiotensin III and, consequently, lowers BP. Several aminopeptidase A inhibitors have been synthetized, but only firibastat has been tested in clinical trials.[29] A Phase 2, placebo-controlled, crossover study[30] conducted in patients with uncontrolled HT showed that firibastat (250–500 mg twice daily) had effects on office and 24-hour mean BP; however, the difference compared to placebo was not statistically significant (Table 1). BP reduction was also observed in patients with essential HT, particularly in overweight or obese individuals,[31] where systolic/diastolic BP was significantly reduced by 9.5/4.2 mmHg compared to baseline values. Additionally, firibastat monotherapy lowered mean 24-hour systolic/diastolic BP, although it did not significantly affect nighttime BP. The subsequent FRESH (Firibastat in Resistant Hypertension) trial,[32,27] a randomized, double-blind, placebo-controlled study presented at the 2022 annual meeting of the American Heart Association, confirmed the lack of difference between firibastat and placebo in patients with RHT. These findings led to the discontinuation of firibastat's development.

Hepatic Angiotensinogen Inhibitors

Angiotensinogen, synthesized primarily in the liver, plays a central role in the pathophysiology of HT, serving as the precursor of both angiotensin I and II. Two drugs, IONIS-AGT-LRx and zilebesiran, are currently under evaluation in patients with RHT. The effects of IONIS-AGT-LRx, an antisense oligonucleotide,[33] have been assessed in two small, randomized, double-blind, placebo-controlled clinical trials. In patients with uncontrolled BP, the effect of IONIS-AGT-LRx (80 mg weekly via subcutaneous injection for eight weeks), added to ongoing antihypertensive therapy, was not statistically different from placebo in terms of overall BP reduction. However, a high percentage of subjects treated with IONIS-AGT-LRx achieved a systolic/diastolic BP

reduction of ≥ 10.0/5.0 mmHg. Similar findings were observed in subjects with controlled essential HT treated with IONIS-AGT-LRx as monotherapy (Table 1). Plasma angiotensinogen levels significantly decreased in both trials compared with placebo. The lack of BP reduction is likely due to the small sample sizes in these studies. Therefore, additional studies with different clinical protocols are currently underway.[33]

Zilebesiran is a ribonucleic acid (RNA) interference drug that targets hepatic angiotensinogen synthesis. Following the positive results of a Phase 1 trial,[34] which demonstrated a reduction in 24-hour ambulatory BP and plasma angiotensinogen levels, a Phase 2 multicenter, randomized, double-blind study (Kardia-1 [A Study of Zilebesiran in Adults With Mild to Moderate Hypertension]) was conducted in patients with mild to moderate HT.[35] After a washout period, patients were randomized to receive zilebesiran subcutaneously at 150 mg every six months, 300 mg every three to six months, or 600 mg every six months, or to placebo administered every three months. At three months post-administration, zileberisan at all doses (150 mg, 300 mg every three to six months, and 600 mg every six months) significantly lowered both 24-hour ambulatory and office systolic BP. Similar results were maintained after six months of treatment. However, 26.8% of subjects assigned to zilebesiran required the addition of CCBs and/or diuretics, compared with 52.0% of subjects in the placebo group. Zilebesiran reduced plasma angiotensinogen levels by more than 90%, with an effect lasting up to six months. The ongoing Kardia-2 trial, along with other large-scale studies, will further evaluate the therapeutic role of zilebesiran, particularly in patients with RHT. Zilebesiran is a particularly promising drug, not only because it reduces both office and 24-hour ambulatory BP (Table 1), but also because its long-lasting hypertensive effects may help improve patient adherence to treatment.

Atrial Natriuretic Peptides

Atrial natriuretic peptides (ANP) are secreted by atrial cardiomyocytes in response to plasma volume overload and play a key role in BP and renal homeostasis. Their mechanisms include inhibition of the renin-angiotensin-aldosterone system, reduction of renal sodium reabsorption, and induction of vasodilation. M-atrial natriuretic peptide (MANP) is an analog of ANP with high resistance to enzymatic degradation.[36] A small open-label study conducted in untreated hypertensive patients demonstrated the long-acting antihypertensive efficacy of MANP.[36] Subcutaneous doses of 1.0, 2.5, and 5 μg/kg once daily reduced systolic BP, although no clear dose-response relationship was observed. Diastolic BP responses showed wide variability. MANP increased renal sodium excretion, particularly during the first four hours after administration, and decreased plasma aldosterone levels. Treatment was associated with an increased heart rate, especially at doses of 2.5–5.0 μg/kg. An important limitation of this study was the small number of enrolled patients (n = 12). Another small, double-blind, placebo-controlled trial tested MANP in hypertensive patients with metabolic syndrome37, but found no significant difference between MANP and placebo. Therefore, doubts remain regarding the role of MANP as an antihypertensive agent, and future larger clinical trials are needed to confirm its BP-lowering effects.

Endothelin-1 Receptor Inhibitors

Endothelin-1 (ET-1) is synthetized by vascular endothelial cells and plays a physiological role in BP regulation through ET^A and ET^B receptors, which are primarily expressed on vascular smooth muscle and endothelial cells.[38-40] Some selective ET^A inhibitors, such as bosentan, ambrisentan, and macitentan, are approved for use in patients with pulmonary HT. Other agents (atrasentan, zibotentan, and sparsentan) are currently under clinical development for patients with type 2 diabetes and/or CKD.[39,43] Sitaxentan and avosentan were discontinued during development due to serious drug-related adverse events, particularly edema and heart failure.[39] Other endothelin-1 antagonists have high affinity for both ET^A and ET^B receptors. Among these, aprocitentan has been tested in patients with RHT[44] and essential HT.[45] The PRECISION (Placebo-Controlled Randomized Study of the Selective Endothelin A Receptor Antagonist Aprocitentan in Resistant Hypertension) trial, a Phase 3, multicenter, randomized, international study,[44] was conducted in patients with RHT. After a placebo run-in phase, patients were randomized through three subsequent clinical stages: a) a four-week double-blind period during which patients received aprocitentan (12.5 mg or 25 mg daily) or placebo, b) a 32-week single-blind phase during which all patients were treated with aprocitentan 25 mg daily, and c) a 12-week, double-blind, placebo-controlled, withdrawal phase in which patients were re-randomized to continue aprocitentan 25 mg daily or switch to placebo. This was followed by a 30-day safety observation period. Throughout the study, aprocitentan was used as an add-on to background antihypertensive therapy (valsartan, amlodipine, and hydrochlorothiazide). Unattended office systolic BP decreased from baseline by 15.3 mmHg and 15.2 mmHg with aprocitentan at doses of 12.5 mg/day and 25 mg/day, respectively. Office diastolic BP also decreased compared to placebo (Table 1). During phase (b), office systolic blood pressure (SBP) with aprocitentan continued to decline until the 20^{th} week and then remained stable. In phase (c), office SBP was reduced by an additional 1.5 mmHg in the group that continued aprocitentan. The BP-lowering efficacy of aprocitentan has also been confirmed by 24-hour ambulatory BP monitoring (Table 1). Thus, when used as an add-on to other antihypertensive agents, aprocitentan demonstrates effective antihypertensive activity in patients with RHT. A Phase 2, double-blind, multicenter, dose-finding study[45] compared different doses of aprocitentan monotherapy with placebo and lisinopril (20 mg/day) in patients with essential HT. After an eight-week treatment period, a greater reduction in office BP from baseline was achieved with aprocitentan compared to both placebo and lisinopril. Additionally, aprocitentan reduced 24-hour ambulatory BP. The percentage of patients achieving diastolic blood pressure (DBP) < 90 mmHg at the end of treatment was 52.1%, 64.2%, and 57.4% with aprocitentan at doses of 10 mg, 25 mg, and 50 mg respectively, compared to 33.3% with placebo and 55.1% with lisinopril.

Aprocitentan was generally well tolerated. In the PRECISION study, mild to moderate fluid retention occurred in approximately 9% of subjects receiving 12.5 mg and 18% receiving 25 mg, particularly among patients with CKD. This side effect was reversible with the use of loop diuretics. Therefore, it is recommended to monitor hemoglobin levels and observe for signs of fluid retention or

heart failure. No hepatotoxicity or hyperkalemia was reported. All these findings suggest that aprocitentan at 12.5–25.0 mg/day, when added to conventional antihypertensive agents, can be considered a valid strategy for lowering BP in patients with RHT. In fact, aprocitentan has recently been approved by the U.S. Food and Drug Administration and the European Medicines Agency for the treatment of RHT.[46] Patients with chronic heart failure should be maintained in a euvolemic state, as some patients treated with aprocitentan in the PRECISION study[44] were hospitalized for heart failure.

Conclusion

This review summarizes the main characteristics of emerging drugs for the treatment of RHT, some of which have also been studies in essential HT. Therapeutic strategies involving brain or hepatic angiotensinogen inhibitors, novel natriuretic peptides, aldosterone synthase inhibitors, and certain nonsteroidal mineralocorticoid receptor antagonists (such as esaxerenone and ocedurenone) have demonstrated efficacy in lowering both office and 24-hour ambulatory BP (Table 1). However, only a few preliminary studies have been conducted with these compounds so far. Therefore, their therapeutic efficacy and tolerability need to be confirmed through future long-term, randomized controlled clinical trials, comparing them with placebo and/or currently available antihypertensive drugs. As emphasized by recent guidelines, the goal of these studies is to improve BP control in the population using therapies that also enhance patient adherence to antihypertensive treatment.[47,48]

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