REVIEW ARTICLE

CONTENTS

Novel pharmacologic approaches in resistant hypertension

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ABSTRACT

Resistant hypertension (RH) affects 10% to 18% of all patients with hypertension. It is diagnosed when blood pressure cannot be normalized despite the use of 3 classes of antihypertensive drugs (ACE inhibitors or sartans), calcium antagonists and diuretics in maximum doses. If the above-mentioned drugs are ineffective, spironolactone is most often administered. Recently, valsartan/sacubitrol and flozins have been increasingly used in resistant hypertension, which have been introduced for the treatment of diseases other than hypertension but can be a supplement to previously used drugs in resistant hypertension. Pharmaceutical companies are currently working on a dozen or so antihypertensive drugs. The most advanced studies concern aldosterone synthesis inhibitors, an endothelin receptor antagonist, and a drug that inhibits angiotensinogen synthesis. The results to date allow for the consideration of aprocitentan (a drug that inhibits endothelin receptors) or baxdrostat or another new aldosterone synthesis inhibitor in the treatment of resistant hypertension that does not respond to 4 drugs, including spironolactone. Further studies are needed to confirm the efficacy and safety of these new drugs in the treatment of resistant hypertension.

KEY WORDS: resistant hypertension, baxdrostat, aprocitentan, zilebesiran

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INTRODUCTION

Resistant hypertension (RH) is diagnosed when blood pressure cannot be normalized despite the simultaneous use of 3 different antihypertensive drugs, including a diuretic in maximum doses [1]. Diagnosis of true resistant hypertension requires exclusion of non-adherence to an appropriate lifestyle and non-systematic use of drugs. Blood pressure measurements using the ABM method are desirable to exclude white-coat hypertension [1]. Studies indicate that in almost 50% of patients resistant hypertension is diagnosed, which disappears after full-adherence with medical recommendations [2]. Many authors use the term true resistant hypertension (RH) to distinguish it from resistant hypertension caused by non-adherence to medical recommendations (pseudoRH) [3]. So far, the terms resistant and refractory hypertension have been used interchangeably in the literature. Resistant hypertension (RH) is diagnosed when 3 or 4 drugs used simultaneously do not normalize blood pressure. It affects 10-15% of patients with hypertension [1]. On the other hand, refractory hypertension (RfRH) can be diagnosed when treatment is ineffective with the use of five or more antihypertensive drugs listed above, including spironolactone [1]. In recent years, this issue has been discussed more and more often. according to Filippone et al., true resistant hypertension is characterized by volume overload and aldosterone excess, refractory by enhanced sympathetic tone [6]. Refractory hypertension (RfRH) occurs in 0.5% to 4.5% of all patients with hypertension [5,6,7]. Patients with RfRH are usually younger, overweight, and more likely to suffer from type 1 diabetes or obstructive sleep apnea, in contrast to people with resistant hypertension (RH), where usually older people predominate, often black race [6, 7]. RH significantly more often causes heart ischemia (including myocardial infarction), strokes and leads to increased mortality compared to hypertension that responds well to antihypertensive therapy [1]. Even more frequent complications of hypertension occur in RfRH) [7, 8] These patients required more drugs than patients with RH [7]. It is therefore understandable to search for new drugs that would effectively lower blood pressure in patients with resistant or refractory hypertension. Is there any hope that new antihypertensive drugs will be released in the near future that will improve the prognosis in patients with resistant hypertension?

REVIEW AND DISCUSSION

SEARCH FOR NEW ANTIHYPERTENSIVE DRUGS

For many years, the pharmaceutical industry has not produced a new drug dedicated solely to the treatment of hypertension, and the last one was aliskiren introduced to therapy almost 20 years ago. Work is

currently underway on a dozen or so preparations that have the potential to have an effective antihypertensive effect. These include angiotensin 1-7, inhibition of angiotensinogen, aldosterone synthesis, endothelin receptors, mechanisms that increase nitric oxide levels, vaccines, and change intestinal microbiota. Great hopes are currently pinned on a new drug called zilebesiran. It is a new class of siRNA therapeutic that reduces the production of angiotensinogen. The latter compound is synthesized in the adipose tissue in the brain, kidneys, and primarily in the liver [9]. As a result, less angiotensin I and angiotensin II are produced in the body, which translates into a decrease in blood pressure. In subsequent studies, zilebesiran has been shown to prevent the stimulation of the RAS system despite a large increase in renin [9]. Phase I studies of zilebesiran confirmed that a single subcutaneous administration of this drug at a dose of 800 mg reduces the concentration of angiotensinogen by over 90% and this effect is maintained for 6 months, and a drop in blood pressure of over 15 mm Hg lasts for about 8 weeks. These studies also showed that this drug is well tolerated and that adverse effects are rare (local reactions at the site of drug administration in 5 out of 56 patients treated). In particular, no hypotension or liver function damage was observed [10, 11] The next study (KARDIA-1) recruited 107 patients with mild or moderate hypertension. Zilebesiran was administered subcutaneously at doses of 10, 25, 100, 200, 400, and 800 mg or placebo [11]. Finally, some patients were given zilebersan in combination with irbesartan. The reduction in blood pressure correlated with the dose of zilebesiran and was maintained for up to 24 weeks. A single dose of 200 mg or more of zilebesiran caused a reduction in systolic blood pressure of at least 10 mm Hg and diastolic blood pressure of at least 5 mm Hg. The combined administration of zilebesiran with irbesartan caused a greater reduction in blood pressure. The reduction in blood pressure after a single administration of zilebesiran was maintained for 24 weeks [11]. Currently, there are ongoing studies with zilebesiran injections every 3 months or 6 months, as well as studies with the concomitant use of zilebesiran with other antihypertensive drugs. Among others, the Kardia-2 study concerns the addition of zilebesiran to the therapy of patients with uncontrolled hypertension despite the use of standard antihypertensive treatment. Completion of these studies is expected in 2024/2025.

Endothelin is a very strong vasoconstrictor. It could be assumed that endothelin receptor antagonists would be compounds that strongly lower blood pressure. Several types of these antagonists are currently known. These include bosentan and darutensin, but due to numerous serious side effects, they have not found wider therapeutic use. Recently, aprocitentan is a dual ETAR/ETBR receptor antagonist, evaluated in a randomized, double-blind PRESISION study of 730 patients with resistant hypertension [12, 13]. Doses of 12.5 mg or 25 mg of aprocitentan or placebo were administered for over 44 weeks. A significant reduction in systolic blood pressure was observed compared to placebo (P= 0.0042 and P= 0.0046). Blood pressure was measured using unattended automated off-line BP. Aprocitentan caused a greater reduction in blood pressure at night than during the day in the 24-hour ABP study. Fluid retention during aprocitentan treatment was dose-dependent and occurred in 9 to 18% of treated patients and in 2.1% of patients receiving placebo. Mahfooz et al. conducted a meta-analysis of aprocitentan regarding the antihypertensive efficacy of this drug. This meta-analysis shows that this drug, both at a dose of 10 and 25 mg, statistically significantly reduces systolic and diastolic blood pressure [14]. In the third phase of the PRECISION study, the usefulness of aprocitentan in the treatment of resistant hypertension was assessed. The results of aprocitentan treatment allow the use of this drug in elderly patients with renal failure, especially when spironolactone therapy must be discontinued due to its adverse effects. A unique effect of aprocitentan is a significant reduction in proteinuria and nephroprotection properties. There was no difference in the frequency of serious adverse events between the drug and placebo [15, 16]. These beneficial features of this drug resulted in the fact that in March 2024, the United States Food and Drug Administration has been approved under the brand name Tryvio for treatment resistant hypertension in combination with other antihypertensive drugs in adult patients [13].

Hypertension can be caused by excess aldosterone. Spironolactone, which has been used for a long time and effectively reduces resistant blood pressure, is a synthetic analogue of progesterone, which blocks the binding of this drug to the aldosterone receptor [17]. Common side effects of spironolactone include excessive increase in serum potassium concentration. For this reason, it cannot be used in patients with advanced renal failure. Administration of drugs that lower serum potassium concentration may prolong the use of this drug, but does not protect against the development of gynecomastia. Recently, the efficacy and safety of a new aldosterone receptor antagonist called esaxerenone [18,19] was assessed in Japan. The drug proved to be effective and safe, with only a slight decrease in GFR and an increase in serum potassium concentration [19].

Another drug called baxdrostat (inhibiting aldosterone synthesis) has successfully passed the first human

trials. Its half-life is 26-31 hours, which allows it to be administered once daily [20]. In a multicenter placebo-controlled study of 275 patients with therapy-resistant hypertension, baxdrostat was administered at a dose of 0.5 mg, 1 mg or 2 mg for 12 weeks. Patients receiving an aldosterone receptor antagonist, potassium sparing diuretics and patients with GFR <45 ml/min were excluded from the study. At the end of the study, systolic blood pressure decreased by 20.3 mm Hg, 17.7 mm Hg and 12.1 mm Hg in patients receiving 2. mg, 1 mg and 0.5 mg of the study drug/day, respectively. In patients receiving placebo, blood pressure decreased by 9.4 mm Hg. The decrease in blood pressure in patients receiving 1 or 2 mg of the drug was highly statistically significant. No serious side effects were noted during the study; only in two patients the concentration of potassium in the blood exceeded 6 mmol/l.

Sometimes headaches and weakness occurred after using this drug. Hyperkalemia did not cause cardiac arrhythmias. Baxdrostat is therefore well tolerated and does not cause adrenal insufficiency [20]. The HALO study is another evaluation of the efficacy and safety of baxdrostat. The study included 249 patients with hypertension, and the drug was used similarly at a dose of 2 mg, 1 mg and 0.5 mg/day. After 8 weeks of treatment, blood pressure dropped insignificantly compared to placebo. The authors of the study explain the lack of significant decrease in blood pressure by the criteria for qualifying patients for the study. Namely, initial blood pressure was above 180/110 mm Hg, some patients had uncontrolled diabetes and some of the subjects had GFR < 30 ml/min. The study lasted 8 weeks, not 12 weeks as in the previous study [21, 22]. Further evaluations of baxdrostat are currently underway lasting 26 weeks of therapy. The use of baxdrostat in the treatment of hypertension, also resistant, is the subject of further studies [23].

Another drug inhibiting aldosterone synthesis, called lorundrostat, was used at a dose of 50 or 100 mg once daily or at a dose of 12.5 and 25 mg twice daily in 163 patients with uncontrolled hypertension. The decrease in systolic blood pressure was statistically significant. A decrease in serum aldosterone concentration was observed in all patients. In one patient, the treatment was discontinued due to hyponatremia. In 6 patients, the serum potassium concentration exceeded 6 mmol/l. However, the study was not discontinued, only the dose of lorundrostat was reduced [24].

Two drugs (entresto - valsartan/sacubitril and flozyny) recently introduced to the therapy of heart failure and diabetes moderately reduce blood pressure values. The first of these drugs contains valsartan and sacubitril. The latter component inhibits neprilysin, which causes vasodilation and increased natriuresis [25]. According to Rakugi et al., entresto is more effective in lowering blood pressure than olmesartan [26]. Therefore, Wang et al. used entresto alongside the previous drugs in resistant hypertension in hemodialysis patients. The decrease in blood pressure was 20.7/8.3 mm Hg and was statistically significant, the NT-proBNP concentration decreased, and the therapy proved to be safe [27]. Entresto was also successfully used by Jackson AM et al. in the therapy of resistant hypertension and heart failure [28]. Flozins introduced to diabetes therapy have proven effective in the treatment of circulatory failure. It has long been known that these drugs have a diuretic effect [29]. All known flozin preparations slightly but statistically significantly reduce blood pressure. The hypotensive effect of flozins has already been confirmed by meta-analyses [30]. The greatest decrease in blood pressure was observed in the SACRA study. The hypotensive effect of flozins is complex and not fully explained. The diuretic effect of these drugs plays an important role in the hypotensive effect of flozins. Flozins reduce the body weight of patients by an average of 2.2-2.6 kg within 6 months, [31] increase the excretion of uric acid, which leads to a small decrease in this compound in blood serum [32]. Clinical studies also suggest inhibition of sympathetic activity, as well as reduction of vascular stiffness [33]. The first successful trials of using flozins in resistant hypertension have appeared. Ferreira et al. administered empagliflozin or placebo to 7020 patients with hypertension, and among them 22.5% of patients showed hypertension resistant to 3 or 4 antihypertensive drugs, including a diuretic and in 17.2% spronolactone. (34) Adding empagliflozin caused a decrease in blood pressure in the entire study group by 4.5 mm Hg. In 38% of patients with resistant hypertension a decrease in systolic blood pressure below 130 mm Hg was achieved, in the placebo group in 26%. In addition, a decrease in the number of heart attacks and strokes was observed. An interesting report by Obeid et al. is about a 68-year-old man with diabetes and hypertension, despite taking ramipril, bisoprolol, diltiazem, amiloride and furosemide, excluding secondary causes of hypertension and skipping doses of the drug by the patient. Renal artery denervation was also performed. Despite this, the hypertension did not subside. The administration of canagliflozin caused a decrease in blood pressure from 151/87 to 136/83 mm Hg) [35]. The literature reports to date regarding the use of flozins in patients with resistant hypertension encourage the conduct of larger studies assessing the efficacy and safety of such a procedure. It can be assumed that the results of these studies will expand the number of drugs used in resistant hypertension. It can

also be assumed that GLP-1 inhibitors will also be used in the future to treat resistant hypertension. They have a diuretic effect and reduce excess weight more than flozins. However, there are no reports in the literature on this subject so far.

PROPOSALS FOR A NEW TREATMENT REGIMEN FOR RESISTANT HYPERTENSION

According to the current recommendations of experts, in patients with resistant hypertension we use angiotensin-converting enzyme inhibitors or sartans, calcium antagonists and diuretics, usually hydrochlorothiazide or indapamide [1]. If this procedure is ineffective, in light of the studies presented above, now we can optimize the current pharmacological treatment, namely swap sartans for entresto and/or add flozins regardless of the presence of diabetes in the patient with hypertension. The next, fourth drug in the treatment of resistant hypertension depends on the degree of renal function. In patients with glomerular filtration less than 35 ml/min, it is recommended to administer a strong diuretic, e.g. chlorthalidione (but not spironolactone, which will intensify hyperkalemia). In patients with glomerular filtration greater than 35 ml/min, spironolactane (an aldosterone receptor blocker) should be added to the above treatment. Spironolactone lowers blood pressure by a further 8.7 mm Hg after 12 weeks of therapy. Long-term use of this drug can cause dangerous hyperkalemia and gynecomastia in men and menstrual disorders in women. Currently, in the case of contraindications to spironolactone, baxdrostat or aprocitentan can be considered (Table1). Baxdrostat is a drug that inhibits aldosterone synthesis, and at a dose of 2 mg/day it lowers blood pressure by 20 mm Hg. Aprocitentan, a dual endothelin receptor antagonist, lowers blood pressure by about 11 mm Hg and does not increase potassium levels. In patients with GFR lower than 30 ml/min/1.73 m^2 and who do not respond to strong diuretics, aprocitentan should be considered [13]. Many patients with resistant hypertension are overweight and have diabetes. Such patients often have elevated serum endothelin (ET-1) levels. Higher endothelin levels are also often observed in renal failure, as well as in the elderly, hypertensive blacks and especially in women [36-38]. All of the above-mentioned reasons indicate the advisability of administering aprocitentan to the above-mentioned patients with hypertension resistant to therapy with previously used drugs, especially when renin activity is low. It has been shown that there is an inverse relationship between serum endothelin levels and plasma renin activity [39]. Aprocitentan can be used both in patients with spironolactone intolerance and in patients with advanced renal failure and resistant hypertension. In 2021, Sidharta et al conducted a study in patients with severe renal failure (GFR 21 ml/min) who were given aprocitentan at a dose of 50 mg/day. The pharmacokinetics of aprocitentan were similar in patients with severe renal impairment and in healthy subjects, as well as in younger and elderly subjects (the half-life of the drug in patients was slightly longer than in healthy subjects and the maximum drug concentrations in blood were comparable [40].

The next steps in the treatment of resistant hypertension that does not respond to previous treatment are the administration of beta blockers or alpha-1 blockers. Bisoprolol, carvedilol or nebivolol are usually used. These drugs can also be administered to patients with advanced renal failure [1].

Alpha-1 antagonists include Doxazosin (alpha-1 antagonist). In the Treatnent to Prevent Heart Attack study, doxazosin administration was associated with more frequent cardiac complications compared to chlorthalidone therapy, and in the PATHWAY-2 study, the antihypertensive efficacy was lower than that of spironolactone.

After beta and alpha blockers, the next step in treatment is peripheral vasodilators, which strongly lower blood pressure but are burdened with numerous side effects. These include hydralazine (Apresolina). Another drug used in the case of persistent high blood pressure is alpha methyldopa. This drug is used in hypertension during pregnancy but can also be administered in resistant hypertension. In the absence of improvement, some authors recommend the use of clonidine (central sympatholytic agents), which in the ReHOT study significantly lowers systolic and diastolic blood pressure but is burdened with many common side effects.

Moxonidine is an imidazole receptor agonist that works slightly longer than clonidine. The last therapeutic option, according to some authors, is minoxidil. The initial dose of this drug is 5 mg/day and can be gradually increased if no adverse effects occur. This drug causes fluid retention and stimulates the sympathetic system. It often causes hirsutism and for this reason patients discontinue therapy with this drug.

Lack of improvement after the use of the above-mentioned drugs is an indication for renal artery denervation or baroreceptor activation.

The optimal treatment of RfRH is unclear, but sympathetic inhibition (α-β blockade, centrally acting sympathoinhibitors, or both) and aprocitentan seems reasonable. Renal denervation has shown minimal benefit for resistance, but its role in refractory hypertension is probable better [6].

Table 1. Treatment plan of RH

Treatment plan of RH	
ACEi or ARB + CA + Diuretic	
Patients not controlled change	
ARB on valsartan/sacubitrol or/and flozin	
CKD stage 1 to 3	CKD stage 4-5 (not on dialysis)
eGFR> 30 ml/min/1,73 m^2	eGFR < 30 ml/min/1,73 m^2
Patients not controlled	
ADD	ADD
Spironolacton or another MRA	Chlortalidone or anther thiazide-like DD
Patient not controlled	
ADD	ADD
Aprocitentan or baxdrostat	**Aprocitentan**
Patietnt not controlled	ADD
BB or A1-blocker	BB or A1- blocker
Patient not controlled	ADD
Centrally acting drug	Centrally acting drug

Abbreviations:
ACB – angiotensin converting enzyme inhibitor, ARB - sartan, MRA - mineralocorticoid receptor antagonist, BB beta-blockers , CA – calcium, antagonists diuretic (DD) -- ADD. Changes to current recommendations are marked in bold letters.

CONCLUSIONS

True resistant hypertension (RH) affects over 10% of all patients with hypertension. It causes 44% more ischemic heart disease, 57% more strokes. We hope that after the break caused by the Covid-19 pandemic, when almost 80% of pharmaceutical companies were busy searching for a cure for this epidemic, the pharmaceutical industry will now accelerate research on new drugs for hypertension. The most promising trials concern baxdrostat, aprocitentan and zilebesiran. It is already possible to modify the recommendations of the Hypertension Societies from 2023 by adding enresto and flozins to the treatment of resistant hypertension. In the event of lack of effectiveness, it is worth considering the use of endothelin receptor antagonists and aldosterone synthesis blockers, which have not been included in the recommended treatment regimens for resistant hypertension so far. However, they require further studies assessing their effectiveness and safety in these patients.

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CONFLICT OF INTEREST

The Author declare no conflict of interest

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