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RESISTANT HYPERTENSION (L DRAGER, SECTION EDITOR)

New Molecules for Treating Resistant Hypertension: a Clinical Perspective

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Abstract

Purpose of Review To review the findings of trials evaluating pharmacological treatment approaches for hypertension in general, and resistant hypertension (RH) in particular, and propose future research and clinical directions.

Recent Findings RH is defined as blood pressure (BP) that remains above target levels despite adherence to at least three antihypertensive medications, including a diuretic. Thus far, clinical trials of pharmacological approaches in RH have focused on older molecules, with spironolactone being demonstrated as the most efficacious fourth-line agent. However, the use of spironolactone in clinical practice is hampered by its side effect profile and the risk of hyperkalaemia in important RH subgroups, such as patients with moderate-severe chronic kidney disease (CKD). Clinical trials of new molecules targeting both well-established and more recently elucidated pathophysiologic mechanisms of hypertension offer a multitude of potential treatment avenues that warrant further evaluation in the context of RH. These include selective mineralocorticoid receptor antagonists (MRAs), aldosterone synthase inhibitors (ASIs), activators of the counterregulatory renin-angiotensin-system (RAS), vaccines, neprilysin inhibitors alone and in combined formulations, natriuretic peptide receptor agonists A (NPRA-A) agonists, vasoactive intestinal peptide (VIP) agonists, centrally acting aminopeptidase A (APA|) inhibitors, antimicrobial suppression of central sympathetic outflow (minocycline), dopamine β-hydroxylase (DβH) inhibitors and Na+/H+ Exchanger 3 (NHE3) inhibitors.

Summary There is a paucity of data from trials evaluating newer molecules for the treatment of RH. Emergent novel molecules for non-resistant forms of hypertension heighten the prospects of identifying new, effective and well-tolerated pharmacological approaches to RH. There is a glaring need to undertake RH-focused trials evaluating their efficacy and clinical applicability.

Keywords Blood pressure · Hypertension · Resistant hypertension · Treatment · Sympathetic nervous system · Chronic kidney disease

Introduction

Resistant hypertension (RH) is defined as office blood pressure (BP) that remains uncontrolled (≥ 140 mmHg systolic BP (SBP) or ≥ 90 mmHg diastolic BP (DBP)) despite adherence to three or more different antihypertensive drug classes, including a diuretic, at maximally tolerated doses [1–3]. Its true prevalence significantly varies between reports due mainly to variability in measurement methods, patient adherence, and prescribing practices [4–6]. Patients with RH are at higher risk of cardiovascular and renal diseases compared to those with uncomplicated hypertension, necessitating its reliable and timely identification, and its differentiation from essential and secondary forms [6–9]. The pathophysiology of RH is rather complex and involves multiple regulatory biological systems, at the forefront of which are the renin-angiotensin-aldosterone-system (RAAS) and sympathetic nervous system (SNS) [10, 11].

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Moreover, several large cross-sectional analyses consistently show that chronic kidney disease (CKD), diabetes mellitus, heart disease, and left ventricular hypertrophy are comorbidities commonly associated with RH, with CKD being especially common [8, 12–15]. International hypertension guidelines recommend lifestyle modifications in addition to the cumulative prescription of first-line agents such as a renin angiotensin system inhibitor (angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB]), a long-acting calcium channel blocker (CCB), and thiazide diuretic at maximally-tolerated doses until target blood pressure (< 140/90 mmHg) is attained [16]. Thus far, studies of novel anti-hypertensive molecules have largely been undertaken either in preclinical or early clinical phases, or were limited to a non-RH context [17, 18]. The latest available Pharmaceutical Research and Manufacturers of America (PhRMA) report lists 12 new drugs for hypertension in clinical development for 2018, of which only two specifically deal with RH [19]. Nevertheless, any potential new molecule targeting pathophysiologic mechanisms yet unopposed by currently available drugs has potential and likely utility in RH. Considering the complex genesis of RH, and the comorbidities commonly associated with RH, we reflect on the progress and outcomes of studies to date of new molecules under development and propose future research directions that might influence guideline development and clinical practice.

Anti-aldosterone Agents

Mineralocorticoid Receptor Antagonists (MRA)

Aldosterone excess is a common feature of RH even in the absence of primary aldosteronism. Furthermore, a phenomenon described as 'aldosterone escape', where aldosterone levels rise after an initial decline in patients treated with ACE inhibitors or ARBs usually prescribed in patients with RH, underpins the important role for MRA in this patient population [20, 21].

The steroidal MRA spironolactone has been in clinical use since the 1960s [22]. Although spironolactone monotherapy has modest BP-lowering effects, it has thus far been shown to be the most efficacious add-on therapy in the context of RH as clearly demonstrated in the PATHWAY-2 trial; spironolactone achieved mean home systolic BP reductions of − 8.7 [95% CI − 9.72 to − 7.69], − 4.03 [95% CI− 5.04 to − 3.02], and − 4.48 [95% CI− 5.50 to − 3.46] mmHg versus placebo, doxazosin, and bisoprolol, respectively [23]. More recently, spironolactone was comparable to clonidine in achieving treatment target BP (20.8% versus 20.5%) and promoted greater absolute BP reductions in 24-h systolic and diastolic BP and diastolic daytime ambulatory BP. Considering the latter outcome and easier posology, spironolactone may be preferable over clonidine in clinical practice [24].

The appeal for MRAs in RH is offset by the relatively commonly encountered steroidogenic side effects, in particular with spironolactone (approximately 2–9% of patients). These include gynaecomastia, breast tenderness, erectile dysfunction, and menstrual irregularities [25, 26]. The greatest deterrent for treating clinicians is the risk of hyperkalaemia, rates of which significantly increased following the publication of the RALES trial [27–29]. Furthermore, RH is prevalent among the CKD population, affecting 24–36% of those referred to a CKD clinic, [30] with prevalence steadily increasing with progressively declining eGFR strata [31]. Therefore, experts rightly recommend careful monitoring of serum potassium if spironolactone is chosen as add-on therapy in RH, particularly if baseline potassium levels are above 4.5 mmol/L [32].

The less favourable side effect profile of spironolactone led to the development and study of dihydropyridine-based nonsteroidal MRA, BAY 94-8862 (fineronone), which has an affinity for MR that is comparable to spironolactone, while, like eplerenone, desirably maintaining low affinity for androgen, glucocorticoid and progesterone receptors, hence theoretically achieving a better balance between mechanistic benefit and undesirable steroidogenic side effects [33, 34]. Although promisingly reducing proteinuria in a preclinical [35], a safety and tolerability (ARTS) [36], and the phase 3 ARTS-DN trials [37] and demonstrating a favourable safety profile, there was only a modest reduction in BP at even the highest studied doses of finerenone [36, 37]. Finerenone was superior to eplerenone in lowering the cumulative rate of the composite clinical endpoint of death from any cause, cardiovascular hospitalizations or emergency presentation for worsening HF in the ARTS-HF trial [38]. Again, reductions in BP were rather modest; mean systolic BP decreased by < 3 mmHg in all finerenone dose arms. This rather modest antihypertensive effect is likely because finerenone, unlike its steroidal counterparts, does not cross the blood-brain barrier to act on centrally located MRs [39].

Another highly selective nonsteroidal MRA, KBP-5074, which demonstrated a favourable safety profile in preclinical studies [40, 41], was also found to be safe and well-tolerated in a phase I study which enrolled haemodialysis and non-haemodialysis patients with severe CKD [42•]. Two other clinical trials, a phase 1 study in healthy subjects and a phase II trial comparing safety and efficacy in healthy subjects vs. those with mild to moderate renal impairment, have completed recruitment but not yet reported results (ClinicalTrials.gov NCT02228733 and NCT02653014). A phase II b placebo-controlled trial in subjects with uncontrolled hypertension and advanced CKD (stages 3b and 4) is currently recruiting (ClinicalTrials.gov NCT03574363). If these trials show clinically meaningful reductions in office and ambulatory BP measures, it would justify a phase III trial in RH with

coexistent CKD, a cohort without robust therapeutic pharmacological recommendations, the current approaches being empirical and limited to alpha blockade, beta blockade, direct vasodilators and centrally acting drugs [43••].

Aldosterone Synthase Inhibitors

The BP-lowering effects of MRAs are blunted by the reactive upregulation of RAAS system resulting in increased stimulation of cardiac and vascular contractility, and increasing central sympathetic outflow [44, 45]. In an attempt to circumvent this, attention turned to reducing the production of aldosterone, and a new class of anti-aldosterone agents, an aldosterone synthase inhibitor (ASI), LCI699 was developed [46]. LCI699 produced non-inferior reductions compared to eplerenone in office systolic BP in a randomized controlled trial of 524 patients with primary hypertension [47]. Conversely, when studied as add-on therapy in RH, reductions in BP were inferior to eplerenone and statistically insignificant compared to placebo [48]. This could be explained by co-inhibition of the almost homologous encoding genes for aldosterone synthase (CYP11B2) and 11 β-hydroxylase (CYP11B1) which causes a near tenfold increase in MR-activating 11-deoxycorticosterone, consequently offsetting the benefit of reduction in aldosterone synthesis [17].

The search for a selective ASI has further led to the development of RO6836191 and LY3045697, both demonstrating selectivity for CYP11B2 over CYP11B2 [49•, 50•]. Addition of a selective ASI alone, or in combination with an MRA, would be worth evaluating in a prospective study of patients with RH [48].

Renin Angiotensin System (Targeting the Old with New Technology)

ACE inhibitors and ARBs are well-established first-line agents in the treatment of hypertension that almost universally feature in the multi-drug antihypertensive regimen of patients with RH [16, 43••]. Their benefits extend beyond simple BP lowering, conferring renal and cardiovascular benefits in high-risk patient populations, most notably, patients with diabetes [51–53]. At one point, combining these agents was fashionable, encouraged mainly by the quest to achieve BP control and amplify their individual cardiovascular and renal benefits. However, as the ON TARGET and VA NEPHRON-D trials demonstrated, this combination is associated with more adverse events without benefit [54, 55]. Similarly, combining a renin inhibitor with either of these agents led to an increase in all cardiovascular and renal endpoints as demonstrated by the ALTITUDE trial, possibly by abrogating the renin feedback-driven activation of the counter regulatory RAS (described below) [56].

Another potential option to achieve more complete RAS inhibition may be targeting inhibition upstream from renin, ACE and angiotensin components, namely angiotensinogen, thereby potentially preserving renal compensatory mechanisms while causing less side effects. IONIS-AGT-L_{Rx} is a Generation 2+ ligand-conjugated antisense (LICA) drug designed to reduce the production of angiotensinogen. This is one of the several pipeline antisense technology molecules designed to target and destroy mRNA that are under evaluation across several medical disciplines including cancer, cardiovascular, neurological, infectious and pulmonary diseases [57•]. Having gone through a phase I safety and tolerability study in 64 healthy volunteers, it is now undergoing a phase II trial in which hypertensive subjects are randomized to once weekly subcutaneous IONIS-AGT-L_{Rx} or placebo (ClinicalTrials.gov: NCT03101878 and NCT03714776). Results from this study will indicate whether or not dual targeting of RAS in any form may still yield some potential benefit.

Counter Regulatory Renin Angiotensin System

It is well established that the classical RAS plays a pivotal role in the pathophysiology of cardiovascular disorders, including hypertension [11, 58]. Angiotensin II (Ang II) is the main effector molecule in this system, exerting its effects through its actions on type-1 angiotensin II (AT1) and type-2 angiotensin II (AT2) receptors [11]. Over the past two decades, there has been a growing understanding of and research interest in the "protective" counter regulatory RAS, namely the angiotensin-converting enzyme2/angiotensin(1–7)MAS receptor axis [ACE2/Ang(1-7)/Mas-R]. ACE2 converts angiotensin 1 to Ang(1–9) and Ang II to Ang(1–7), both of which promote BP lowering [59, 60]. Activation of the ACE2/Ang(1-7)/Mas-R axis and the AT_2 receptor antagonizes the prohypertensive effects of Ang II and hence present attractive therapeutic targets to counteract the detrimental effects of an overactivated RAS in pathological states, including hypertension [61].

Recombinant ACE2 and ACE2 Activators

ACE2, a homologue of ACE, is an exopeptidase that catalyses the conversion of Ang II to cardioprotective Ang(1-7) which counteracts the pro-hypertensive effects of Ang II [61]. The antihypertensive effect of ACE2 has been established in various preclinical models of hypertension [62, 63]. Systemic infusion of recombinant ACE2 (rhACE2) induces sustained reduction in BP in both Ang II–induced and spontaneously hypertensive rat (SHR) models [64, 65, 66•]. However, the latter two compounds are not currently undergoing human

clinical trials. Conversely, rhACE2 (GSK2586881) has undergone a phase I and a phase IIa trial both of which demonstrated sustained reductions in Ang II levels with no effect on BP, and good safety profile [67, 68]. Recently, it was found to have promising therapeutic prospects in the context of pulmonary arterial hypertension [69].

Ang(1-7) Analogue and Mas-R Agonists

Ang(1-7) is subject to enzymatic degradation, giving it a short half-life in vivo. To overcome this limitation, an orally active formulation incorporating hydroxypropyl-β-cyclodextrin with a cyclic Ang(1-7) analogue was developed, abbreviated HP-β-CD/Ang1-7 [70]. It had been shown to be cardioprotective in a preclinical model of myocardial infarction [71]. A phase 1 study showed adequate absorption and tolerability of this formulation [72].

Studied Mas-R agonists, the nonpeptide imidazole compound AVE0991, and peptide G protein-coupled receptor activator CGEN-856S, have been shown to lower BP in DOCA-salt-induced hypertensive rats and attenuate isoproterenol-induced cardiac remodelling and myocardial infarction rat model, respectively [73, 74].

Alamandine is a heptapeptide generated from decarboxylation of the N-terminal Asp residue of Ang II followed by hydrolysis by ACE2. It is both structurally and functionally similar to Ang(1-7), however, acting through the Mas-related G protein-coupled receptor [75]. It exerts sustained antihypertensive effects when orally administered to SHRs in the inclusion compound of alamandine/beta-hydroxypropyl cyclodextrin (alamandine/HP-β-CD) [76]. It was also shown to attenuate hypertension, ameliorate cardiac hypertrophy and improve left ventricular function when administered subcutaneously to SHRs [77•]. More recently, it was also shown to attenuate arterial (ascending aorta) remodelling in a transverse aortic mouse model [78]. Human studies of the aforementioned molecules have not yet been performed.

AT2 Receptor Agonists

The action of the AT2 receptor is to oppose the AT1 receptor–mediated effects, promoting antiproliferation, regression of cardiovascular remodelling and vasodilation [79, 80]. Mimicking the antihypertensive effects of endogenous Ang(1-9) through activation of AT2R stimulated the development of the nonpeptide AT2R agonist, compound 21 (C21). Unlike its predecessor peptide AT2R agonists, CGP42112A and LP2, C21 is orally available, specific and selective for ATR2 [81].

A preclinical study showed that C21 prevented salt-induced blood pressure rise in obese Zucker rats [82]. More recently, a phase I study in healthy volunteers showed C21 was safe and well-tolerated, and has favourable pharmacokinetic properties for further clinical development [83•]. However, AT2 receptor agonism does not produce vasodilation or blood pressure reduction, unless the AT1 receptor is simultaneously blocked [84]. Therefore, C21 has potential for additive BP-lowering effects when prescribed with traditional RAS blocking agents and might, therefore, one day find its place as add-on therapy in RH patients who are already on RAS inhibitors.

Vaccines

Considering that medication non-adherence is a pervasive problem in patients with hypertension, the concept of inducing long-lasting effects with vaccines that modulate components of RAS stimulated preclinical and clinical studies in this area [85, 86]. AngQb (also named CYT006-AngQb), an Ang II-derived vaccine, reduced mean ambulatory daytime (but not nighttime) BP by 9/4 mmHg and significantly attenuated the morning BP surge compared to placebo in patients with mild-moderate hypertension, essentially reflecting diurnal RAS activity [87]. However, a subsequent study which used CYT006-AngQb in an accelerated immunization schedule resulted in smaller BP reductions, because, in spite of the augmented anti-Ang II antibody titre, this came at the expense of its affinity for Ang II [88, 89]. Shortly after, a trial using the angiotensin therapeutic vaccine with adjuvant CoVaccine HT™ was terminated due to dose-limiting side effects (ClinicalTrials.gov NCT00702221).

More recently, the AT1 receptor vaccine ATRQβ-001 reduced systolic BP in Ang II–induced hypertensive mice and SHR models by as much as 35 and 19 mmHg, respectively [90]. Likewise, SHRs immunized with another AT1 receptor vaccine, ATR12181, had reductions in blood pressure similar to losartan [91]. There does not appear to have been human follow through as yet, although this remains a future prospect given the results of preclinical studies. An effective and sustained BP-lowering effect through vaccination seems an attractive approach, in particular, were adherence and long-term costs associated with guideline and marketed pharmacotherapies pose a challenge.

Neprilysin Inhibitors Alone and in Combinations

Neprilysin (NEP), also known as membrane metalloendopeptidase (MME) is a metalloprotease that hydrolyses several peptide hormones. Among these are the pro-hypertensive vasoconstrictive peptides Ang 1, Ang II and endothelin-1 (ET-1). It also hydrolyses the vasodilative peptide, bradykinin, in addition to the natriuretic peptides, namely atrial natriuretic peptide (ANP), brain natriuretic peptide

(BNP) and urodilatin [85, 92]. Considering the opposing downstream sequelae, one can appreciate why NEP alone only results in small reductions in BP [93, 94]. Considering this, using a two-pronged approach which incorporates NEP inhibitors with either RAS inhibitor or an anti-ET-1 agent presented an attractive treatment strategy and hence been under intensive investigation since around turn of the century [95, 96].

Neprilysin Inhibitor Alone as Add-on Therapy

A phase 2 placebo-controlled safety and efficacy study in 64 patients with resistant hypertension uncontrolled on three or more antihypertensive drugs including an angiotensin receptor blocker and diuretic recently showed statistically significant reductions in BP. After 4 weeks, the mean reductions in 24-h ambulatory BP was 8.95/3.25 mmHg in the LHW090 100 mg group and 14.5/6.74 in the LHW090 200 mg group. Mean NT-proBNP trended lower in LHW090 treated groups compared to placebo [97••]. Simultaneously, a phase 2 trial to evaluate the renal safety, tolerability and pharmacokinetics of LHW090 in patients with moderately impaired renal function has completed, but the results are not reported yet (ClinicalTrials.gov NCT02678000). Phase III trials evaluating its efficacy in the RH subgroup with coexistent CKD, and also against currently popular fourth line agents such as spironolactone would be of great interest.

Dual Neprilysin – Angiotensin-Converting Enzyme Inhibition

Omapatrilat was the earliest trialled dual vasopeptidase molecule, combining NEP inhibitor prodrug, AHU377 (sacubitril), with an ACEi. It showed some promise in the OCTAVE trial which randomized three groups of hypertensive patients (untreated, treated uncontrolled stage 1 and treated uncontrolled stage 2) to omapatrilat, or enalapril alone. Overall, omapatrilat lowered mean SBP and DBP by a mere 3.6 and 3 mmHg more than Enalapril. Notwithstanding the modest comparative BP reduction, it was superior to enalapril at achieving target BP regardless of demographics or comorbid conditions, and whether used as initial, replacement or add-on therapy (overall rate 58.2 vs 49.6%) [94].

Omapatrilat achieved prespecified noninferiority, but not superiority, criteria compared to Enalapril in reducing risk of death and hospitalization in a study of chronic heart failure patients (OVERTURE trial). Hypotension occurred more frequently in the omapatrilat arm, which could be interpreted as a more profound anti-hypertensive effect, however, notably the average baseline SBP and DBP were ~ 124 and 74 mmHg, hence the inability to draw any firm conclusions about its utility in hypertensive individuals [98]. The alarmingly higher rates of angioedema in the omapatrilat arm of the OCTAVE trial prompted suspension of further development [99]. A phase III trial employing the newer generation ilepatril (AVE-7688) was planned but never undertaken, an online search suggests.

Dual Neprilysin Inhibition – Angiotensin Receptor Blockade

The first-in-class compound angiotensin receptor neprilysin inhibitor (ARNI) LCZ696 (Entresto®) has shown remarkable clinical outcome benefits not only in the context of heart failure but also in the hypertension realm. LCZ696 produced significantly greater reductions than valsartan in office and 24-h ambulatory BP in patients with mild-to-moderate hypertension in a large trial that compared LCZ696, AHU377, valsartan and placebo [100]. Similarly, in a double blind, placebo-controlled study of Asian patients with mild-moderate hypertension LCZ696 showed significant reductions in office 24-h, daytime and nighttime ambulatory systolic and diastolic BP compared with placebo in all of the 100, 200 and 300 mg doses. Importantly, no cases of angioedema were reported in this population known to be at higher risk of this side effect when treated with the dual NEP-ACE inhibition [101].

In the landmark phase III trial PARADIGM-HF, LCZ696 achieved a risk reduction of 20% for cardiac mortality, 16% for total mortality and 21% for heart failure hospitalizations compared to Enalapril in patients with heart failure and reduced ejection fraction. It was associated with a non-significant difference in occurrence of angioedema [102]. BP reduction with LCZ696 was modest compared to Enalapril at 8 months (3.2 ± 0.4 mmHg), notwithstanding the fact that participants mostly had controlled or at most mildly uncontrolled hypertension at enrolment.

Likewise, LCZ696 resulted in modestly greater reduction in BP compared to Valsartan alone (9.3 vs 2.9 mmHg at 12 weeks, and 7.5 versus 1.5 mmHg at 36 weeks) in the PARAMOUNT trial which enrolled 149 patients with heart failure with preserved ejection fraction and primarily examined the effect on the cardiac wall stress biomarker, NT-proBNP. Notably, however, although 95% enrolled had hypertension — all having been on a diuretic and most (93%) on a RAS inhibitors at study entry — BP was controlled (median sitting pressure 136/79 mmHg) at baseline; hence, a conclusion cannot be drawn regarding its potential antihypertensive role [103].

More recently, LCZ696 was evaluated for the first time in an 8-week open-label study in Japanese patients with severe hypertension (SBP ≥ 190 mmHg and/or DBP ≥ 110 mmHg). Reductions in office SBP/DBP (baseline 173.4 mmHg/112.4 mmHg) and pulse pressure (baseline 61.0 mmHg) at week 8 were 35.3/22.1 mmHg and 13.2 mmHg, respectively, with no report of angioedema or drug discontinuation [104].

Given their antihypertensive effects versus ARB alone, and their apparent tolerability, further trials which assess the potential role of this combination molecule in the context of RH for patients established on a RAS inhibitor are warranted.

Dual Neprilysin and Endothelin Converting Enzyme (ECE) Inhibition

Established understanding of the role Edothelin-1 plays in the genesis of hypertension has led to studying its antagonism as a proposed treatment approach [105]. Daglutril (SLV-306), an orally administered prodrug of its active metabolite KC-12615, is a combined inhibitor of NEP and ECE. It has been shown to reduce BP and proteinuria and exert reno-protective effects in diabetic rat model as effectively as captopril [106]. A phase II placebo-controlled crossover study showed that daglutril reduced both ambulatory and office BP and proteinuria in humans with albuminuric diabetic nephropathy treated with an ARB, losartan. It did not show added albuminuria lowering benefit, notwithstanding, this suggested a super-added anti-hypertensive benefit on top of any conferred by RAS inhibiting agents in the diabetic sub-population of hypertensive patients. It is worth noting the population studied essentially had preserved renal function (mean eGFR of 89 and 72 mL/min per 1·73 m^2) in the crossover arms [107]. An avenue worth exploring is their potential BP lowering and reno-protective benefits in patients with RH and proteinuric mild-moderate stages of CKD that are established on maximally tolerated RAS inhibiting agents.

Endothelin Receptor Antagonists

Endothelin-1, (ET-1) via its receptors (ET_A and/or ET_B) triggers arterial vasoconstriction, promotes inflammation, oxidative damage, fibrinogenesis and atherosclerosis, and is involved in salt and water regulation [108]. The selective endothelin receptor antagonist, darusentan, achieved a placebo corrected reduction in BP of ~ 11/6 and ~ 18/11 mmHg in phase II and III trials in participants with RH [109, 110]. However, this was at the expense of a significant rate of oedema and fluid retention compared to placebo (27 vs 14%) [110].

Very recently, the SONAR study assessed the effect of selective ET_A receptor antagonist, atrosentan, on the composite renal outcome (doubling of serum creatinine or end-stage kidney disease) in 2648 patients with proteinuria and CKD (eGFR ranged 25–75 mL/min per 1·73 m^2) and showed a relative risk reduction of 35% (hazard ratio 0.65 [95% CI 0·49–0·88]). Importantly, those randomized had to have passed an 'enrichment period' during which they had demonstrated meaningful reduction of albuminuria with no substantial fluid retention. All patients were established on an ACEi or ARB and ~ 75 had been on a diuretic at study entry. There was a 52% reduction in albuminuria, and 6 mmHg placebo-corrected reduction in SBP during the 6 week enrichment period, and a further 1.6 mmHg over a median follow-up of 2.2 years [111].

Considering these findings, selective ET receptor antagonists might find their place in certain subsets of the RH population, in particular with coexisting diabetic CKD. A phase III placebo-controlled trial evaluating the efficacy of newer generation selective ET_A receptor antagonist aprocitentan (ACT-132577; active metabolite of macitentan) at doses of 12.5 and 25 mg in the treatment of RH (PRECISION study) is currently recruiting (ClinicalTrials.gov NCT03541174).

Natriuretic Peptide Receptor Agonists

Given the potential off-target effect of neprilysin inhibition, a logical alternative approach would be to augment or amplify the effects of its anti-hypertensive substrates, such as ANP. As such, the synthetic natriuretic peptide receptor A (NPR-A) agonist PL-3994 was developed. An important pharmacokinetic characteristic of this synthetic molecule is its resistance to degradation by neprilysin, rendering a long half-life when administered subcutaneously. A phase IIa placebo-controlled trial of 21 patients with treated hypertension, of which 12 were taking a single antihypertensive, 3 were taking 2 and 6 were taking 3, showed a reduction in SBP [112]. Importantly, PL-3994 appeared to augment the BP-lowering effects in the group receiving a RAS inhibitor (14/21 participants). Since then, a planned phase 2 placebo-controlled crossover study was withdrawn by the study sponsor (ClinicalTrials.gov NCT01304628). Of interest, a similar molecule named ZD100 has been shown in preclinical study to exhibit marked in vitro resistance to NEP degradation and hence could potentially enter the clinical trial phase in the not so distant future [113].

Vasoactive Intestinal Peptide Receptor Agonists

BP-lowering effects of vasoactive intestinal peptide (VIP) in humans were first observed as early as 1987 [114]. To overcome its gastrointestinal side effects and excessively short half-life, a more selective and longer-acting analogue of VIP (PB1046) was developed and has shown a dose-dependent effect on BP [115]. An ongoing dose-finding double-blind controlled phase II study assessing the safety and efficacy of once weekly PB1046 is recruiting patients with symptomatic pulmonary hypertension (ClinicalTrials.gov NCT03556020). There are no active trials of VIP agonists in systemic arterial hypertension at this point in time.

Centrally Acting Aminopeptidase Inhibitors

Aminopeptidases are involved in the metabolism of Ang II into shorter Angiotensin peptide fragments. Aminopeptidase A (APA) converts Ang II into Angiotensin III (Ang III) by removing N-terminal aspartate. Both Ang II and Ang III can activate the ubiquitous AT_1 receptors, stimulating the sympathetic nervous system, promoting peripheral vasoconstriction and consequently elevating BP [116]. APA inhibitor, RB150 (renamed QGC001) was shown to be safe and well-tolerated in 56 healthy normotensive volunteers [117].

There was concern that its centrally mediated Ang III suppressing benefits would be offset by peripheral upregulation of Ang II [18]. Encouragingly, in a recent phase II open-label uncontrolled multicentre study which enrolled 256 ethnically diverse overweight hypertensive patients (54% Hispanic or black), QGC001 (renamed Firibastat) lowered ambulatory SBP and DBP by 9.5 and 4.3 mmHg, respectively. Ambulatory SBP decreased by 10.2 mmHg in the obese subgroup of patients. No angioedema was reported [118].

Furthermore, in phase IIa double-blind placebo-controlled proof-of-concept study, 4-week treatment with Firibastat as monotherapy for hypertensives with ambulatory BP > 135/85 and < 170/105 mmHg, ambulatory daytime SBP was lowered by 2.7 mmHg versus placebo [119••].

These findings justify further investigations of brain APA inhibitors to improve blood pressure control in high-risk diverse populations with difficult-to-treat or resistant hypertension.

Suppressing Central Neuroinflammation

Mounting evidence implicates a key role for peripheral and neuroinflammation in the pathophysiology of hypertension in both humans and animal models [120–122]. It has been shown that increased sympathetic drive can mediate hypertension by norepinephrine-mediated T cell activation. As a meeting point for the CNS and immune system and the site of leukocyte and progenitor cell production, the bone marrow (BM) serves as an ideal link between the inflammatory system and hypertension [123–125]. Prohypertensive signals such as Ang II activate paraventricular nucleus (PVN) pre-autonomic neurons to increase sympathetic nerve activity (SNA) and cause release of C-C chemokine ligand 2 (CCL2). The increased SNA induces an inflammatory phenotype in BM, generating inflammatory cells (IC), and is associated with vascular pathology and a rise in BP. In addition, some of these IC progenitors migrate to the PVN as a result of an increased neuronal release of CCL2 where they differentiate into BM-derived microglia/macrophages, which along with the resting microglia are activated to release an array of cytokines and chemokines which further increase pre-autonomic neuronal activity and results in a state of sustained sympatho-excitation, thereby perpetuation of high BP and ultimately established hypertension. This view is further supported by observational studies wherein chronic treatment of hypertension with minocycline, an anti-inflammatory, small molecule antibiotic that freely passes the blood brain barrier and inhibits microglial activation, produced BP-lowering effects [126].

As a therapeutic agent, minocycline has also been shown to decrease total sympathetic nerve activity, as measured by plasma norepinephrine concentration and spectral analysis of systolic BP in two different models of hypertension [123, 127]. In an Ang II–induced hypertension rat model, intracerebroventricular minocycline resulted in a decrease of MAP from 156 ± 7.2 to 104 ± 4.2 mmHg further supporting the involvement of microglial activation in neurogenic hypertension.

Minocycline is currently under evaluation in drug-resistant neurogenic hypertensive individuals in a parallel-design phase 1 dose-finding trial (ClinicalTrials.gov NCT02133872). Concurrently, a double-blind, placebo-controlled, cross-over phase II trial is also recruiting patients with resistant hypertension (ClinicalTrials.gov NCT02133885).

Dopamine β-Hydroxylase Inhibitors

The final step of noradrenaline biosynthesis from its immediate precursor dopamine is mediated by Dopamine β-Hydroxylase (DβH). Given the role of the SNS in the pathophysiology of hypertension, and importantly, resistant hypertension, a logical therapeutic approach would be inhibiting conversion of dopamine to noradrenaline in sympathetic nerves. Earlier generation DβH-inhibiting molecules were nonselective and/or crossed the blood brain barrier, inducing undesirable side effects which stimulated the development of novel, peripherally selective DβH inhibitor, BIA 5-453, later renamed Etamicastat [128]. Etamicastat has been shown to reduce BP as monotherapy and in combination with other classes of antihypertensive agents in the SHR model [129•]. In another SHR model, Etamicastat produced greater and more sustained reductions in SBP and DBP compared to renal denervation [130]. It was found to be safe and well-tolerated in two phase 1 trials, one in healthy males and the other in males with mild hypertension [131, 132]. There were dose-dependent decreases in SBP and DBP, the greatest of which was a reduction in nighttime SBP of 15 mmHg in the 100 mg arm [132]. No further clinical trials of Etamicastat are listed on clinicaltrials.gov at this point. This approach might be worth investigating as add-on therapy in RH.

Intestinal Na+/H+ Exchanger 3 (NHE3) Inhibitor

It is well-established that excessive sodium intake plays an important role I the pathogenesis of hypertension, and that restriction of sodium intake affects BP reduction [133]. Inhibition of the intestinal Na+/H+ Exchanger 3, the most essential member of NHE family for absorption of dietary sodium, has been shown to reduce sodium absorption and BP in SHRs [134]. This led to the development of highly selective NHE3 inhibitor, Tenapanor, which has been shown to be well-tolerated and to reduce intestinal sodium absorption in two phase I studies that recruited healthy volunteers [135]. A search on ClinicalTrials.gov reveals it is currently being studied in hyperphosphatemia of CKD, albuminuric diabetic kidney disease, and irritable bowel syndrome, but not actively in hypertension. Given that reduction in sodium intake synergistically lowers BP in patients treated with ACE inhibitors and diuretics, alternatively reducing its absorption using a NEH3 inhibitor could be worth evaluating in RH patients established on these agents [136].

Molecules Listed as Under Development

B244, under development by AOBione Therapeutics, is a first-in-class live single-strain ammonia-oxidizing bacteria (*Nitrosomonas eutropha*) that is undergoing a phase II study in patients with elevated blood pressure (ClinicalTrials.gov NCT02998840), following the observation of dose-dependent reduction in BP in normotensive subjects in a phase IB/IIA acne study (ClinicalTrials.gov NCT02656485).

RMJH-111b (magnesium citrate), has undergone a phase I/II safety and tolerability in subjects with essential hypertension, but results have not been reported (ClinicalTrials.gov NCT02822222).

SP20203, BAY sGCstim and IT-103 are listed as being in the development pipeline as of 2018 [88]. No clinical trials concerning these molecules are listed on ClinicalTrials.gov at present time.

Summary

Despite the significant leaps in unravelling the complex and multi-faceted pathophysiology of human hypertension, and the ongoing efforts to address pro-hypertensive mechanisms unopposed by conventional first-line anti-hypertensive agents, the identification of an effective fourth-line molecule remains elusive. The results of recent studies favour spironolactone, however, this approach might exclude significant subgroups of patients with RH, leaving treating clinicians with no option but to turn to older very modestly effective and less well-tolerated agents. The great breadth of potential therapeutic targets undergoing preclinical and early clinical research provides a glimmer of hope that we may arrive at our desired goal in the not-so-distant future.

In the meantime, research into device-based approaches is accelerating at great speed and showing promising results. These approaches include renal denervation (ClinicalTrials.gov NCT02444442), carotid body ablation (ClinicalTrials.gov NCT03314012) and the creation of a central iliac arteriovenous fistula using the ROX coupler system [137–139]. The interventional approaches might indeed serve to bridge the potentially protracted molecular time gap.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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