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REVIEW

Resistant Hypertension: Which Agent?

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Resistant hypertension is commonly defined as office blood pressure above recommended target despite the use of optimal doses of at least three antihypertensive drugs including a diuretic. Australian guidelines recommend combination of blockers of the renin-angiotensin system, either ACE inhibitors or angiotensin receptor blockers, with calcium channel blockers and diuretics as the preferred triple therapy. A substantial proportion of hypertensive patient will require additional pharmacotherapy to achieve or get close to target blood pressure levels. Here we briefly review the evidence currently available to provide guidance on the most appropriate choice for additional antihypertensive pharmacotherapy and touch on interventional approaches that may be considered in some patients.

Keywords Resistant hypertension • Pharmacotherapy • Devices • Sympathetic • Aldosterone antagonists • Antihypertensive medication

Introduction

Patients with resistant hypertension (RH) are at higher risk of cardiovascular and renal diseases compared to hypertension, necessitating its identification and differentiation from essential and secondary forms of hypertension [1]. In line with the generally accepted definition [2], the 2016 National Heart Foundation Guidelines on the diagnosis and management of hypertension in adults define RH as office blood pressure (BP) that cannot be maintained below 140/90 mmHg with at least three antihypertensive medications given at maximally tolerated doses including a diuretic; or require >4 antihypertensive medications to maintain BP control. Of note, the very recently published updated ACC/AHA US Clinical Practice Guidelines introduced a lower threshold of >130/80 mmHg for the definition of hypertension including resistant hypertension if this BP level is exceeded with concomitant prescription of three or more antihypertensive drugs at optimal doses including a diuretic. The recommended new BP target, aimed at achieving BP below 130/80 mmHg, if adopted by treating physicians, will inevitably result in prescription of fourth and fifth line antihypertensive therapies and potentially interventional approaches in many more patients, rendering the considerations regarding the current evidence for most appropriate choices summarised in this article a timely update.

The prevalence of RH is estimated to be 3–30% of hypertensive patients [1],with the wide variation due to difficulties in obtaining reliable BP measures, poor patient adherence to antihypertensive medications and suboptimal prescribing practices [3]. Increased use of out-of-office BP measurements, particularly 24-hour ambulatory blood pressure monitoring (ABPM) is crucial in obtaining more reliable BP measures and is increasingly being recognised to provide additional prognostic value and guidance for adequate treatment. Similarly, there is increasing evidence for additional benefit for home BP monitoring. Major international hypertension guidelines agree that, in conjunction with lifestyle modifications, cumulative prescription of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), a calcium channel blocker (CCB), and thiazide diuretic at maximally-tolerated doses represents the preferred combination of pharmacotherapy for hypertension. To date, no clear recommendation for a preferred fourth-line

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pharmacotherapy for RH exists. Mineralocorticoid receptor (MR) antagonism, peripheral or central blockade of the sympathetic nervous system and direct peripheral vasodilators have been investigated. Furthermore, a number of device-based approaches to lower BP are emerging and may be particularly useful in patients with intolerance to pharmacotherapy. In this brief overview, we summarise the latest evidence relating to the most useful fourth-line approach in the context of RH. A number of additional aspects including non-pharmacologic interventions such a weight loss, salt reduction and others, as well as measures to improve patient compliance and adherence with prescribed pharmacotherapy, multi-disciplinary team-based approaches and telehealth and app-based approaches are clearly relevant in the management of patients with resistant hypertension but cannot be covered in adequate detail in this brief overview.

In patients with RH, pharmacological agents interfering with the major pathophysiological pathways believed to contribute to uncontrolled BP including volume homeostasis, renin-angiotensin-aldosterone system and sympathetic nervous system activation are currently proposed to be the most suitable targets for further pharmacologic intervention. Options include the addition of a mineralocorticoid receptor (MR) antagonist, β-blockers, α1-adrenergic receptor blockers, Imidazoline I1 receptor/α2-adrenergic receptor (AR) agonists, or peripheral vasodilators.

Options for Fourth-Line Pharmacotherapy

Mineralocorticoid Receptor Antagonists

Based on trial evidence available to date, MR antagonists are currently emerging as a preferred fourth-line therapy, with spironolactone the most commonly used MR antagonist as it retains potassium and avoids hypokalaemia from existing diuretic therapy. Eplerenone, a newer agent with lower affinity but higher selectivity for the mineralocorticoid receptor has been shown to exert similar BP lowering efficacy with less side effects, specifically antiandrogenic and oestrogenic side effects such as gynaecomastia. In an 8-week, double-blind, placebo-controlled trial in 417 patients with mild to moderate hypertension, eplerenone significantly decreased seated systolic and diastolic blood pressure in a dose-dependent manner over a dose range of 50, 100, and 400 mg/d. The dose of 400 mg/d eplerenone was equivalent to 50 mg BID spironolactone [4]. Eplerenone is often used as an alternative to spironolactone, particularly if side effects limit its utility.

A significant body of evidence now exists to support the use of spironolactone as initial fourth-line therapy for RH. The vast majority of data comes from retrospective evidence of randomised trials such as ASCOT, and placebo-controlled trials including ASPIRANT; however the recently published prospective PATHWAY-2 trial has provided most convincing support for spironolactone to date. In this double-blinded, randomised, cross-over trial spironolactone was compared to the α1-adrenergic blocker doxazosin, the β1-selective AR bisoprolol and placebo in 285 patients with RH. Spironolactone 25–50 mg/d was found to significantly lower home SBP compared to placebo (12.8 vs 4.1 mmHg, $p < 0.0001$) after 12 weeks [5]. More importantly, spironolactone was also found to be superior to 5–10 mg/d bisoprolol(a) and 4–8 mg/d doxazosin, reducing home average SBP by 12.8 vs 8.3 and 8.7 mmHg, respectively (both $p < 0.0001$) (Figure 1a) [5]. Spironolactone has also proved superior over the loop diuretic frusemide, reducing 24-hour ABP by 24/11 vs 14/5 mmHg after 6 months in 30 RH patients, and is associated with reducing proteinuria and improving survival in congestive heart failure [6,7]. Caution must be given to prescribing spironolactone due to its potassium-sparing activity. Spironolactone has to be used with substantial caution in patients with serum potassium >4.5 mmol/L as hyperkalaemia is a common serious adverse effect occurring in 2% of PATHWAY-2 and ASCOT participants, and other studies reporting even higher proportions [5,8]. Gynaecomastia and breast tenderness are also not uncommon (6% in PATHWAY-2 and ASCOT trials) due to spironolactone's partial actions on sex hormone receptors [5,8]. The comparative efficacy and safety profile of spironolactone in patients with an eGFR < 45 is also largely unknown as patients with CKD 3b or worse were excluded from the PATHWAY-2 trial [5]. Given the common occurrence of hypertension with diabetes and renal disease, spironolactone must be prescribed with vigilance and electrolytes and glomerular filtration rate closely monitored in all patients prior to, and after initiating therapy. Further investigations into the safety profile of spironolactone in severe renal disease and diabetes are required due to the increasing prevalence of these common co-morbidities. While the blood pressure lowering effects that can be achieved with spironolactone as a fourth-line agent are impressive, no data are available on the long-term persistence with the drug and its long-term safety profile in the context of RH. Particularly in male subjects, the anti-androgenic actions may prove to be an important hindrance for longer term adherence and BP control. In this context, eplerenone can be used as an alternative mineralocorticoid receptor antagonist as it is typically associated with a more favourable side effect profile. Another alternative often used in clinical practice for longer term treatment is the potassium-sparing diuretic amiloride, often in combination with a thiazide or loop diuretic, however, long-term data for amiloride are lacking.

Imidazoline I1 Receptor (I1R) Agonists

Moxonidine is another antihypertensive medication commonly prescribed as fourth-line therapy that acts centrally to reduce sympathetic outflow to the periphery. Given that guideline-recommended triple therapy does not target the sympathetic nervous system, which has been demonstrated to be positively correlated with the patient's degree of hypertension severity [9], moxonidine appears as a reasonable fourth-line medication to counteract increased sympathetic drive frequently observed in RH. It is important to note that moxonidine acts on central receptors that are different to

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