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New insights in treatment of primary aldosteronism: A narrative review

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Abstract

For the last two decades, we are observing an evolution in our understanding of primary aldosteronism (PA). It is now established that PA has remarkably more adverse cardiovascular and renal impact as compared to essential hypertension because of blood pressure independent deleterious effect of aldosterone. But still it is frequently under-recognized and under-treated. When diagnosed, PA can be adequately managed with widely available mineralocorticoid receptor antagonists (MRAs) and/or unilateral adrenalectomy. Steroidal MRAs are highly effective but often under prescribed and can be poorly tolerated because of adverse effects. New generation non-steroidal MRAs like finerenone and esaxerenone have shown promising results on adverse cardiovascular and renal sequelae among patients with diabetic kidney disease and heart failure. They also have favourable safety profile than steroidal MRAs. Though their efficacy regarding blood pressure control and renin normalization remain unclear, non-steroidal MRAs specially finerenone might fulfill the unmet needs of optimum management of PA. In this article we discuss an up-to-date overview on existing treatment of PA and new therapeutic approach, paying attention to its practical implementation into our day-to-day practice. *[J Assoc Clin Endocrinol Diabetol Bangladesh, January 2024; 3 (1): 22-30]*

Keywords: Primary aldosteronism, aldosterone, mineralocorticoid receptor antagonist, spironolactone, finerenone, eplerenone

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Introduction

For the last two decades, we have witnessed an expansion in our understanding of primary aldosteronism (PA). PA is an endocrine cause of secondary arterial hypertension (HTN) that is characterized by renin and angiotensin-II independent plasma aldosterone concentration (PAC) and this unregulated aldosterone production results in inappropriate activation of mineralocorticoid receptor (MR), excess sodium, and water resorption, intravascular volume expansion and hypertension.[1] This pathophysiology of PA can manifest across a broad continuum. Thus, PA is best considered as a syndrome rather than a single disease.[2]

Long-time exposure to excess aldosterone has a markedly increased risk for end-organ damage.[3] PA has a substantial burden of cardiovascular events compared with non-PA hypertension, namely coronary artery disease (2.1-20%), heart failure (4.1%), stroke (6.1-12.9%) and atrial fibrillation (2.8-7.3%) along with poorer health-related quality of life (QoL).[3,4] The mechanism of adverse cardiovascular events in PA involves several factors related to the excessive production of aldosterone like arterial hypertension, inflammation, oxidative stress, endothelial dysfunction, thrombus formation, myocardial fibrosis, and remodeling. Aldosterone-induced hypokalaemia can lead to cardiac arrhythmias, including ventricular fibrillation.[3,4,5]

Though the prevalence of categorically classified and

overt PA ranges from 10% to 25% in the hypertensive population, epidemiologic data suggest that the vast majority (probably >99%) of PA patients worldwide remain undiagnosed. This occurs largely due to a lack of awareness and testing and constitutes an unrecognized public health crisis since PA pathophysiology can be effectively treated, even reversed with targeted therapies.[3,5]

Current management of patients screened and confirmed positive for PA involves imaging, and with very few exceptions adrenal venous sampling (AVS) to lateralized aldosteronism.[6] The overall approach to treating PA depends upon whether the aldosteronism is unilateral, and therefore amenable to a curative intervention, or bilateral, and therefore more responsive to long-term medical therapy. The vast majority of PA is likely to be caused by diffuse and heterogeneous progressions that occur bilaterally in the adrenal glands, whereas a minority is likely to represent entirely unilateral disease amenable to surgical intervention, particularly in younger individuals.[3]

Laparoscopic adrenalectomy (ADX) is now the gold standard of care for unilateral PA. Many patients with PA who are not eligible or willing to undergo surgery or having bilateral disease are treated by mineralocorticoid receptor antagonists (MRAs). Till date, the steroidal MRA spironolactone represents the first line medical therapy for PA, but its use is limited due to various endocrine dysfunctions, risk of hyperkalemia, and worsening renal function.[3] Finerenone is a potent antagonist of the MR receptor, with minimal affinity for progesterone, androgen, estrogen, and glucocorticoid receptors, so it could be a possible treatment option for PA without the risk of side effects of traditional MRAs.[3] It may be that non-steroidal MRA treatment is better tolerated and thus better facilitates renin normalization, as a surrogate for adequate MR blockade in patients with PA.[3] Esaxerenone is being studied in a Japanese PA population in a recent phase III trial and could be a potentially useful therapeutic option in PA.[7] In this review, we present an up-to-date overview of existing treatment of PA and a new therapeutic approach, paying attention to its practical implementation into our day-to-day practice.

Database search

Google Scholar, PubMed, and MEDLINE were searched for clinical trials and review articles related to the treatment of PA. The results were limited to full-text articles published in English, without restrictions for publication time.

Current treatment

For patients with recognized unilateral PA, laparoscopic ADX is the recommended treatment. If a patient is reluctant or unable to undergo surgery, medical therapy is proposed, including a MRA. If an aldosterone renin ratio (ARR) positive patient is unwilling or incapable of undergoing further investigation, medical therapy including an MRA is similarly recommended (Figure-1).[8]

A) Surgical therapy and radiofrequency ablation for lateralizing PA

For patients with unilateral PA who are healthy enough and willing to undergo surgery, it is recommended to perform unilateral ADX. Adrenalectomy is now chiefly performed via a laparoscopic or retroperitoneoscopic approach. Routinely, complete ADX should be performed as availability AVS is limited for determining the side of excessive aldosterone production and whether a specific adrenal nodule is the source of aldosterone excess. Moreover, even when AVS indicates strong lateralization that might benefit from ADX, there is a chance of remaining or emergent PA from the contralateral gland [owing to aldosterone-producing nodule (APN)/aldosterone-producing micronodule (APM)]. While some lateralizing PAs represent truly unilateral disease, there is fairly a large chance of asymmetric bilateral disease.[2]

The Primary Aldosteronism Surgery Outcomes (PASO) study has set forth the specific criteria for biochemical and clinical success following ADX. Complete biochemical success is defined as the normalization of the aldosterone renin ratio (ARR), along with the resolution of potential hypokalemia, and was achieved in the majority of cases (94%) in the PASO study.[2] This study demonstrated that 37% of patients achieved complete clinical success (defined by normalization of blood pressure without any antihypertensive medication) while an additional 47% of patients achieved partial clinical success (defined by a reduction in the number of antihypertensive medications required or a reduction in blood pressure with the same number of antihypertensive medications).[2] Pre-operative factors predictive of some degree of persistent hypertension

after ADX include older age, use of more than two antihypertensive agents, longer duration of hypertension, increased serum creatinine, and more than one first-degree relative with hypertension.[9]

Several case reports and small cohort studies reported on the successful use of radiofrequency ablation (RFA) for the treatment of unilateral PA.[5] Existing evidence comparing RFA with unilateral ADX is limited. One randomized controlled trial comparing RFA vs. medical therapy in the treatment of unilateral PA demonstrated that 81% of patients treated with ablation achieved complete or partial remission from hypertension along with improvement in biochemical parameters. RFA can be considered a promising new treatment approach, at least for selected patients, as it is less invasive than laparoscopic surgery and thus requires lower postoperative analgesia, reduced length of hospital stay, and promotes earlier return to work. Future clinical trials of RFA vs. ADX are required to compare their efficacy and cost-effectiveness and further define patient populations that are likely to benefit from each approach.[2,10]

B) Medical therapy in PA

In PA patients with bilateral adrenal disease or lateralized PA patients with no desire for surgical intervention, medical therapy is recommended with an MRA.[11] These agents are administered to block the effect of excessive aldosterone to stop either hypertension or hypokalemia and to attenuate organ damages such as atherosclerosis, myocardial injury, vascular stiffness, endothelial dysfunction, and glomerular proteinuria.[2] For more than five decades, the MRA spironolactone has been the drug of choice in the medical management of PA. Eplerenone can be an alternative in cases of side effects from spironolactone or in pregnancy.[12] Currently recommended pharmacological agents are discussed in Table-1.

In general, medical therapy for PA should be accompanied by dietary sodium restriction (<1500 mg/day). Effective dietary sodium restriction can result in volume contraction, a rise in renin, and normalization of blood pressure and ARR. However, sustaining this degree of sodium restriction for a long time can be challenging.[2,5]

i. Spironolactone

Spironolactone is a potent, first-generation, steroidal, non-selective antagonist of the MR. It acts in the distal convoluted renal tubule through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site.[13,14] After oral administration, spironolactone is rapidly metabolized in liver to a number of biologically active metabolites.[15] Plasma half-life is 1.3- 1.4 hours for spironolactone and >12 hours for its active metabolites. Due to the long half-lives of its metabolites, spironolactone can only be administered once daily. Its maximal antihypertensive effect is attained after 3-4 weeks of treatment.[11]

The classic medical treatment of PA is spironolactone. In a recent data summary of spironolactone treatment on 122 patients with bilateral adrenal hyperplasia, with doses varying from 50 to 400 mg/day, reported reductions in patients' systolic and diastolic blood pressures were 25% and 22%, respectively.[12] In another study of 28 PA patients with no detectable adenomas on adrenal CT scan, low-dose spironolactone therapy (25-50 mg/d) reduced Systolic blood pressure (SBP) by 15 mmHg and diastolic blood pressure (DBP) by 8 mmHg. About half of the patients received spironolactone monotherapy and 48% of patients were able to achieve a blood pressure (BP) <140/90 mm Hg[16].

Spironolactone is also effective in most cases of essential hypertension. A mean dose of 96.5mg of spironolactone declined SBP and DBP by 18 and 10 mmHg, respectively, below pre-therapeutic levels. The BP decrease was greater with doses of 75 to 100 mg (12.4% and 12.2% respectively) than with doses of 25 to 50 mg (5.3 to 6.5% respectively), but no further BP decrease was observed for doses of 150 mg or higher.[17] Though according to current guidelines, MRAs are recommended as fourth-line treatment in patients with resistant hypertension, they might be very useful for attaining target BP regardless of the diagnosis of PA[5].

Several guidelines recommend that the starting dose of spironolactone should be 25 mg daily (sometimes, 12.5 mg daily) in PA. The lowest effective dose should be found by gradually titrating upward to a maximum dose of 100 mg/day.[1,12,18] Higher doses may be required for some PA patients but also there is an increased risk of adverse effects. Therefore, it is not recommended to exceed a daily dose of 100 mg.[5] There is no clear recommendation on how to titrate dose of spironolactone in PA and how to diminish concomitant use other antihypertensive drugs in this

setting. However, measurements of serum creatinine and potassium 7-10 days after starting spironolactone and dose titration in steps of 25mg in 4-week intervals, along with simultaneous measurements of creatinine and potassium have been proposed.[5]

The use of spironolactone is limited by its numerous adverse effects like gynaecomastia, breast pain, impotence, and menstrual abnormalities.[11] Gynaecomastia is usually dose-related and reversible. It has been reported that the incidence of gynaecomastia after 6 months of therapy was 6.9% for a dose <50 mg/day and 52.2% for a dose >150 mg/day.[17] Fear of inducing hyperkalemia and worsening renal function are the leading causes of suboptimal use of spironolactone in clinical practice.[19] In previous studies, spironolactone increased the mean serum potassium level by 1.0 mEq/L (pretreatment vs. post-treatment: 3.4±0.1 vs. 4.4±0.1 mEq/L; p<0.001) in PA patients[20] and the overall incidence of hyperkalemia was 10%.[21] Increment of plasma potassium by spironolactone is dose-dependent and markedly influenced by its initial level.[5] Trevisan et al[22] revealed that among 13726 new users of MRA in general population (99.2% spironolactone and 0.2% eplerenone), 18.5% experienced at least one detected hyperkalemia (K^+ >5.0mmol/L) within one year of starting therapy, the majority within the first 3 months of therapy. Hyperkalemia very often leads to down titration or discontinuation of therapy, especially in patients with compromised renal function.[2] In another retrospective study[23], the estimated glomerular filtration rate (eGFR) decreased by 15.3±14.2 (range 19-63) ml/min/m^2 in PA patients following treatment with either ADX or spironolactone. Determinants of eGFR after treatment include older age, female sex, longer duration of HTN, bilateral adrenal hyperplasia, and lower eGFR before treatment.[23]

ii. Eplerenone

Eplerenone a selective MRA without anti-androgen and progesterone agonist effects, having reduced rate of adverse endocrine side effects. It has an efficacy roughly half of that reported for spironolactone (i.e. 50mg spironolactone equals about 100mg eplerenone daily). Eplerenone is a decent alternative in case of side effects of spironolactone. Its superior safety profile necessities to be balanced against its higher cost.[8]

iii. Amiloride

Amiloride is a potassium-sparing diuretic that can ameliorate HTN and hypokalemia in PA. It is generally well tolerated and lacks the sex steroid-related side effects of spironolactone. But it is not capable of blocking several of the MR mediated blood pressure independent adverse effects in PA.[8] In mild cases or when the patient cannot tolerate spironolactone or eplerenone due to adverse effects, epithelial sodium channel blockers (amiloride and triamterene) may be added to MRAs in adjunct in order to decrease the dosage and thus the side effects of these drugs.[5]

iv. Calcium-channel blockers (CCB), angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB)

In general, they are antihypertensive agents without a major effect on MR activation. They are, nevertheless, commonly used to lower BP (in combination with MRAs) if BP remains above normal.

New pharmacological modulators of renin-angiotensin-aldosterone system

i. Esaxerenone

Given its site of action, esaxerenone can be regarded as a third generation MRA (non-steroidal, as selective as eplerenone, as or more potent than spironolactone).[6] Its precise clinical significance is claimed to be as a safe and effective antihypertensive in patients with moderate renal dysfunction and/or type 2 diabetes and albuminuria. Esaxerenone has recently shown favorable and safety and efficacy profile in PA in a multicenter, open label study; though it is currently available only in Japan.[7] The major drug-related adverse events were hyperkalaemia and decreased eGFR (both 4.5%); no gynecomastia or breast pain was observed.[7]

ii. Finerenone

Finerenone, a novel non-steroidal MRA, blocks MR over-activation and MR mediated sodium reabsorption in both non-epithelial (i.e. heart and blood vessels) and epithelial (i.e. kidney) tissues.[24] Finerenone would appear to be a fourth generation MRA (non-steroidal, as selective as eplerenone, as or more potent than spironolactone and in addition have cardiac preferring properties).[6] Besides having a direct inhibitory role on MR signaling cascade,

finerenone also prevents recruitment of downstream transcriptional cofactors and gene expression (SGK1) involved in hypertrophic, pro-inflammatory and pro-fibrotic effects.[25] It decreases cardiac and renal hypertrophy, plasma B-type natriuretic peptide (BNP) and albuminuria more than the steroidal MRAs.[19] As a surrogate marker for adequate MR blockade, finerenone also facilitates better renin normalization.[3] Because of intrinsic ability of PA to exhibit cardiac remodeling, enhancing the incidence of cardiovascular events (CVEs), glomerular hyperfiltration, microalbuminuria and overt proteinuria (prevalence 10.3%); finerenone by virtue of its mechanism of action can be a potential treatment option in PA.[3,5] Finerenone has minimal affinity for androgen, progesterone, estrogen and glucocorticoid receptors, so it would have better safety profile without having the side effects of traditional MRAs.[3]

Based on a number of large clinical trials, finerenone is now indicated to reduce the risk of sustained eGFR decline, end stage kidney disease, non-fatal myocardial infarction, heart failure, cardiovascular death in patients with CKD associated with type 2 diabetes.[13] In Mineralocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy (ARTS-DN) trial, SBP was significantly reduced from baseline with finerenone compared to placebo in 24h ambulatory blood pressure monitoring (ABPM).[26] In multicenter phase III trials in adults with CKD and type 2 DM [Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes (FIDELIO-DKD) and Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes (FIGARO-DKD)] the placebo-corrected relative reduction in urinary albumin-to-creatinine ratio (UACR) in patients with finerenone at month 4 was 31% and 32%, respectively and UACR remained stable for the duration of both of the studies.[27]

Hyperkalemia and decrease in eGFR are two of the most common adverse effects associated with finerenone. Finerenone should be withheld in patients whose potassium level is >5.5 mmol/L.[25] However, hyperkalemia related permanent treatment discontinuation was in only 1.7% of patients receiving finerenone vs. 0.6% with placebo over a median follow-up of 3.0 years in FIDELITY pools (combined FIDELIO-DKD and FIGARO-DKD trial programme analysis)[28]. In phase 2a clinical trial (MinerAlocorticoid Receptor Antagonist Tolerability Study: ARTS), in patients with CKD and HF, receiving finerenone had a lower incidence of hyperkalemia (finerenone vs. spironolactone: 5.3% vs. 12.7%; P=0.048) compared with those receiving spironolactone.[27] In a comparative post hoc analysis of finerenone and spironolactone in CKD, proportion of treatment discontinuation due to hyperkalemia for finerenone group was 0.3% and for spironolactone group was 23%.29 In FIDELIO-DKD and FIGARO-DKD trials, hospitalization due to acute kidney injury and trial discontinuation was similar in both finerenone and placebo.[27]

Because of better tolerability, availability and sufficient protection against end-organ damages in various population[3], finerenone might address current unmet medical needs and could be a potential therapeutic strategy for management of PA in our country. However, its clinical efficacy, renal protection, and safety in PA still need to be proven formally, further research can elucidate this arena in future.

iii. Aldosterone synthase inhibitors (ASIs)

The crucial enzyme in aldosterone production is aldosterone synthase (CYP11B2). CYP11B2 is mostly expressed in the adrenal gland, but it is also expressed in the cardiovascular system and brain. In recent years, ASIs have shown potential in treating hypertension by decreasing aldosterone production. Baxdrostat (CIN107), a highly potent ASI developed by CinCor, has demonstrated excellent antihypertensive effects in recent trials in treatment resistant hypertension.[30]

Goal of Medical therapy

The general treatment goals are to normalize BP and serum potassium (i.e. aim for a level of 4-5 mmol/l) along with a rise in renin level and a decline in the ARR. Several observational studies revealed that, achieving an unsuppressed renin level with MRA treatment in PA patients might reduce the cardiovascular risk to the level of essential hypertension. But this effect was not found in the PA patients under MRA therapy with remaining renin suppression. Based on the existing evidence, Vaidya et al.[2] proposed that an increase in plasma renin activity greater than 1 ng/ml/hour (which approximates direct renin concentrations >10 mIU/l) might be an ideal target for MRA treatment of PA patients. However, upper limit for renin

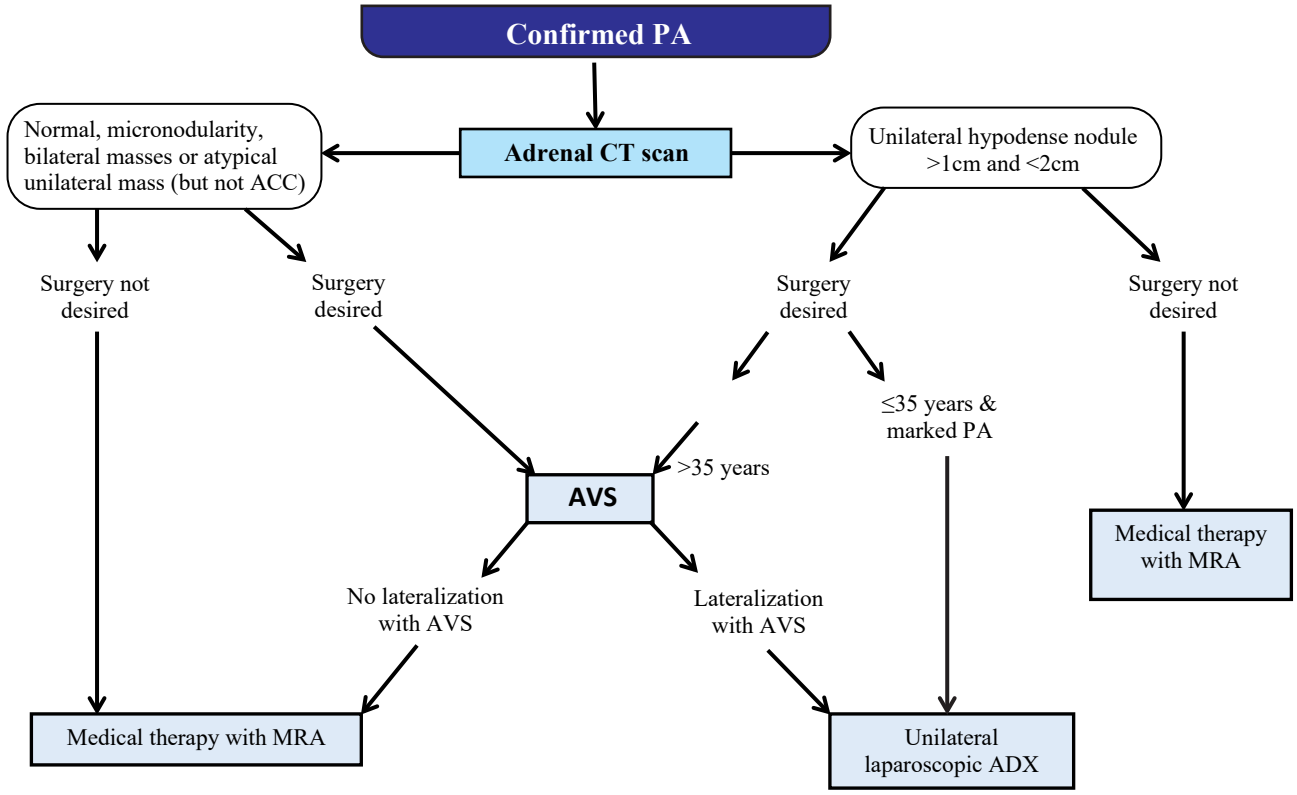

Figure 1: Current treatment algorithm for PA. ACC: Adrenocortical cancer, ADX: Adrenalectomy; AVS: Adrenal venous sampling; CT: Computed tomography; MRA: Mineralocorticoid receptor antagonist. Adopted from Young Jr et al.[9]

normalization is still unclear (levels above the reference range might indicate overtreatment having increased risk of hypovolaemia and hyperkalaemia).[2,5] [Figure-2]

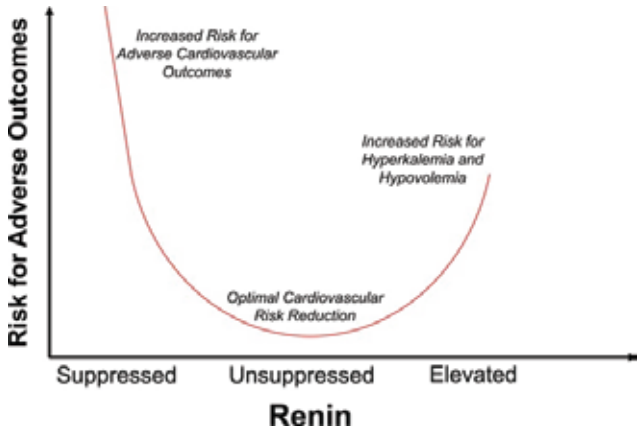

Figure 2: Targeting renin levels during MRA therapy in PA. The aim is to normalize blood pressure and potassium. However, it is likely that any increase in renin from its initial suppressed state is indicative of beneficial MR blockade. Excessive up titration of MRAs results in higher renin levels that might have increased risk for hyperkalemia, hypovolemia and renal hypoperfusion. MRA: mineralocorticoid receptor antagonist; PA: primary aldosteronism Adopted from Vaidya et al.[2]

Debate on long term outcome: Adrenalectomy vs. medical therapy

Whether unilateral ADX improves long-term outcomes beyond medical therapy alone in the treatment of lateralizing PA? It is a common question that arises in everybody's mind. There is no randomized controlled trial addressing this research question. Several observational and cohort studies have demonstrated that ADX in unilateral PA significantly reduced the risk for cardiovascular events, kidney injury, type 2 DM and mortality while improving QoL in comparison to medical therapy.[2,31,32] It should be kept in mind that studies that have compared surgical (in almost entirely lateralized PA) vs. medical (in predominantly bilateral PA or PA with unconfirmed lateralization) therapy are confounded by intrinsic differences in the underlying pathophysiology, clinical presentation and severity between unilateral and bilateral PA. Moreover, it is tempting to speculate that when renin concentration increases to the levels suggested above, there may be no significant additional benefit of ADX in terms of clinical outcomes. Nevertheless, successful ADX may obviate the need for lifelong MRA treatment and may

Table 1: Currently recommended pharmacological treatment of PA [5,8,14]

Drug	Mechanism of action	Dosage	Side effects
Spironolactone	Competitive antagonist of aldosterone and androgen receptors, behaves as a weak agonist of the progesterone receptor	Start with 25 mg/day in a single dose (occasionally, 12.5 mg daily) Maximum dose of 100 mg/day	a. Metabolic: Hyperkalemia b. Reproductive system and breast disorders: • Gynecomastia: • Inability to achieve or maintain erection • Abnormal semen (decreased motility and sperm count) • Irregular menses or amenorrhea, postmenopausal bleeding • Breast pain c. Renal: Renal dysfunction (including acute renal failure). d. Respiratory: Cough, dyspnea. e. Blood and lymphatic system disorders: Leukopenia (including agranulocytosis), thrombocytopenia, anemia. f. Gastrointestinal disorders: Diarrhea and cramping, gastric bleeding, gastritis, nausea, ulceration, vomiting. g. General disorders: Malaise. h. Immune system disorders: Drug fever, urticaria, maculopapular or erythematous cutaneous eruptions, anaphylactic reactions, vasculitis, pruritus, rash. i. Musculoskeletal: Leg cramps. j. Nervous system/psychiatric disorders: Headache, drowsiness, lethargy, dizziness, change in libido.
Eplerenone	Selective MR antagonist, without anti-androgen and progesterone agonist effects	Start with 25 mg twice daily Maximum dose of 100 mg/day	Same side effects of spironolactone, although less frequent and less intense
Amiloride	Epithelial sodium channel blocker (ENac-blocker)	2.5–20 mg/day	Hyperkalemia, gynecomastia, hyperchloremic metabolic acidosis, hyponatremia, cough, dyspnea, dizziness

definitely cure the disease.[2,5]

Another uncertainty in regard to the treatment of bilateral PA is whether unilateral ADX should be considered in particular cases where clinical optimization with MRAs cannot be achieved. In this scenario, unilateral ADX can be considered to attenuate disease severity rather than biochemical cure. As shown in several case series, non-curative unilateral ADX can be a safe and effective option to improve biochemical and clinical sequelae associated with bilateral PA.[2,33]

Conclusions

Over the past few years, there have been rapid advances at all levels of management of PA. One of the novel nonsteroidal MRAs has been shown to be safe and effective at lowering blood pressure in PA. Nonsteroidal MRAs, with much more tolerable side effect profile, have demonstrated substantial risk reduction of adverse cardiovascular and renal events in chronic kidney disease. Whether they can provide durable and long-term risk reduction in PA remains to be elucidated, that warrants further research in this area.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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