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Spironolactone for resistant hypertension in advanced chronic kidney disease—red, AMBER or green?

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Resistant hypertension (RHTN) is defined as blood pressure (BP) that remains uncontrolled (> 140/90 mmHg by European guidelines and >130/80 mmHg by US guidelines), despite the use of 3 antihypertensive drugs in optimal doses that include a diuretic ¹. Using 24-hour ambulatory BP monitoring to exclude white coat hypertension, a 2018 meta-analysis ascertained the prevalence of RHTN to be 10.8% in the general population ².

Current guidelines recommend that among patients with RHTN, spironolactone should be the first line therapy added to the 3 antihypertensive therapies that have failed to control the blood pressure ¹. The PATHWAY-2 study was a multiway cross-over trial that demonstrated that spironolactone is more effective than placebo and an alpha- or beta-blocker in improving BP control among patients with RHTN ³. However, the PATHWAY-2 study excluded patients with eGFR <45 mL/min/1.73m² as well as patients with hyperkalemia. These patients are often seen by nephrologists and may benefit from the addition of a mineralocorticoid receptor antagonist to their antihypertensive regimen. The European Society of Hypertension guideline discourages the use of spironolactone unless the eGFR is >45 mL/min/1.73m² or serum K is <4.5 mEq/L. Thus, patients with chronic kidney disease are often denied spironolactone; furthermore, in a worldwide survey, the use of spironolactone among hypertensive patients with CKD was <1% ⁴. This is unfortunate as the prevalence of RHTN is several-fold higher in patients with advanced CKD ⁵. Furthermore, cohort studies indicate that RHTN is associated with increased morbidity and mortality in this population ^{5;6}. The use of drugs that block the mineralocorticoid receptor has been associated with nearly 2 fold increase in the risk of hyperkalemia ⁷.

The development of new drugs that bind potassium (K) in the gut can potentially allow the use of spironolactone in higher risk patients. Recently, the Patiromer to Enable Spironolactone Use in the Treatment of Patients with Resistant Hypertension and Chronic Kidney Disease (AMBER) trial tested the hypothesis that the use of a K-binding drug, patiromer will allow the more persistent use of spironolactone among patients with advanced CKD (eGFR 25-45 mL/min/1.73m²) and resistant hypertension (unattended automated office BP 130-160 mmHg despite using 3 drugs including a diuretic and an ACE inhibitor or an angiotensin receptor blocker) ⁸. Spironolactone was given in a dose of 25 mg once daily in all patients at randomization to patients randomized to either patiromer (8.4 g/d) or placebo (methyl cellulose) in a double-blind manner. Patiromer could be titrated up 1 week after randomization and spironolactone at 3 weeks to 50 mg once daily if home systolic BPs remained >120 mmHg. Participants were seen weekly for the first 4 weeks and then every 2 weeks for a subsequent 8 weeks. At the end of the 12-week treatment period, study drug and spironolactone were withdrawn and a final visit occurred 2 weeks later for another BP measurement and lab evaluation. The primary end-point was the between group difference in the proportion of patients remaining on spironolactone at 12 weeks. A key secondary end-point was the between group difference in change in systolic BP to the end of the trial or escalation of antihypertensive medication.

Key findings

The primary end-point of AMBER was met with a very small probability (<1:10,000) that this could happen by chance alone in nearly 300 patients randomized equally to patiromer or placebo groups ⁹. Retention of subjects in the clinical trial was excellent in both groups with fewer than 10% of study participants prematurely discontinuing the study. In the placebo group, 66% of the patients remained on spironolactone compared to 86% of the patients in the patiromer group at study end. The absolute difference of 20% in the proportion of patients who were treated with patiromer to remain on

spironolactone clinically translates to 1 patient persisting to be on spironolactone over 12 weeks with every 5 being treated (number needed to treat (NNT) = 5). Cumulative dose of spironolactone was 385 mg greater in patients randomized to patiromer than to placebo during the 12 week trial. In each of the two groups there was 11-12 mmHg systolic BP reduction and no statistical difference between groups in the reduction in BP. Thus, spironolactone was associated with a significant and clinically meaningful reduction in systolic BP in patients with advanced CKD, albeit in the absence of a placebo control. The adverse events were balanced between groups. Spironolactone use alone, provoked hyperkalemia defined as serum K of 5.5 mEq/L or more, in about 2 of 3 patients when patiromer was not used. Patiromer reduced this risk by half.

Key learnings

There have been very few studies examining the effectiveness of different BP-lowering drugs in patients with RHTN and advanced CKD. The reduction in systolic BP after starting spironolactone in the AMBER study, a trial composed of patients with RHTN and CKD 3B and 4 was of a magnitude similar to that seen in PATHWAY-2, a RHTN trial with substantially better kidney function (mean eGFR 91 ml/min/1.73m² at baseline in PATHWAY-2, vs. 35-36 ml/min/1.73m² in AMBER, which included 23% of patients with CKD4). The magnitude of reduction in systolic BP after starting spironolactone in AMBER was also similar to results seen in a parallel group, catheter-based renal denervation trial¹⁰, an invasive intervention of interest in patients with RHTN and kidney disease -but patients with an eGFR below 40-45 ml/min/1.73 m² are systematically excluded from renal denervation trials owing to the safety concerns with regard to contrast-induced nephropathy). Therefore, spironolactone offers an effective means to treat resistant hypertension in those with advanced CKD as long as it is being used with patiromer, and potassium is properly monitored the risk of hyperkalemia is mitigated but not removed.

Although patiromer enabled the persistent use of spironolactone, we did not see an additional benefit on systolic BP control. We believe that this was due to two reasons: first, discontinuations in the placebo group started to accumulate midway through the trial with only 6 weeks remaining for most patients prior to the conclusion of the study; secondly, spironolactone is a prodrug and its active metabolites, canrenone and 7 alpha methylspironolactone are long-acting and had persistent effects on BP levels⁸. For example, 36% of the patients who discontinued spironolactone had detectable spironolactone metabolites 3 weeks later⁸. At the end of the trial, all patients discontinued spironolactone and these patients returned 2 weeks later for BP measurement. Remarkably, 54% of the systolic BP lowering effect of spironolactone remained at the post-treatment trial visit despite discontinuing the spironolactone 2 weeks earlier. Thus, long-acting metabolites of spironolactone were the likely cause of a persistently lower systolic BP. Given these pharmacologic effects and relatively small number of discontinuations (51 (34%) in placebo group, 22 (14%) in the patiromer group) the trial was not sufficiently long or large enough to detect a meaningful difference in systolic BP between groups.

Red, Amber or Green?

The AMBER study provided us the cautions (red), uncertainties (amber) and findings that are clinically relevant (green).

In the context of this study, spironolactone use provoked hyperkalemia defined as serum K of 5.5 mEq/L or more in about 2 of 3 patients when patiromer was not used. This observation is clearly a red signal

due to the high rate of hyperkalemia when patients with advanced CKD are exposed to spironolactone and concomitant use of ACE inhibitors or angiotensin receptor blocker.

The amber (or uncertainty) lies in the inability of this trial to demonstrate that despite the persisting use of spironolactone, it was not able to demonstrate more effective BP lowering in the patiromer treated group. Given the long half-lives of spironolactone metabolites, future studies of spironolactone withdrawal should be several weeks longer to determine if a difference in BP between groups emerges as a consequence of the patiromer-enablement of more persistent use of spironolactone.

Patiromer reduced the risk of hyperkalemia by half as only 1 in 3 patients experienced serum K⁺ in excess of 5.5 meq/L in contrast to 2 in 3 in the placebo group. It enabled the use of spironolactone in 1 more out of every 5 patients who was treated with this drug, a finding that was the very unlikely to happen by chance alone. This novel finding gives us a green signal to use patiromer to enable the use of spironolactone in high-risk CKD patients with resistant hypertension. Although not specifically the subject of the AMBER study, 45% of the patients had a history of heart failure. Among patients with heart failure with reduced ejection fraction where spironolactone is a lifesaving drug, patiromer use may be particularly valuable to enable the long-term use of spironolactone.

CONFLICT OF INTEREST STATEMENT

RA reports personal fees from Abbvie, Akebia, Amgen, AstraZeneca, Bayer, Birdrock Bio, Boehringer Ingelheim, Celgene, Daiichi Sankyo, Eli Lilly, GlaxoSmithKline, Ironwood Pharmaceuticals, Johnson & Johnson, Merck, Novartis, Opko, Otsuka, Reata, Relypsa, Sandoz, Sanofi, Takeda, ZS Pharma; has served as associate editor of the *American Journal of Nephrology*, *Nephrology Dialysis and Transplantation*; and an author on *UpToDate*; and received research grants from the US Veterans Administration and the National Institutes of Health.

PR reports consulting for G3P and Idorsia; honoraria from Ablative Solutions, AstraZeneca, Bayer, CVRx, Fresenius, Grunenthal, Novartis, NovoNordisk, Relypsa, Servier, Stealth Peptides, Vifor and Vifor Fresenius Medical Care Renal Pharma; and travel grants from AstraZeneca, Bayer, CVRx, Novartis, and Vifor Fresenius Medical Care Renal Pharma; Cofounder: CardioRenal.

WBW reports serving as a consultant to Relypsa, Inc., a Vifor Pharma Group Company (AMBER Steering Committee).

BW reports honoraria for lectures on hypertension from Daichii Sankyo, Pfizer, Novartis, Servier, and Boehringer Ingelheim, and consulting for Novartis, Relypsa, Inc., a Vifor Pharma Group Company, and Vascular Dynamics Inc.

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