Mineralocorticoid Receptor Antagonists

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Abstract

The role and adverse effects of mineralocorticoid receptor overactivation in the pathophysiology of heart failure (HF) is well-recognised. MR antagonists (MRAs) have been tested in HF and shown to be effective in improving outcomes. Steroid-type MRAs spironolactone and eplerenone, have been proven to reduce mortality in HFrEF. In patients with HFpEF, the TOPCAT trial found no significant benefits of spironolactone on cardiovascular outcomes. In order to overcome the limitations of existing steroidal MRAs, novel MRAs have been recently developed, finerenone and PF-03882845. These newer agents aim to optimise the benefits of MRA's and reduce their side-effects, especially hyperkalaemia.

Keywords: heart failure; mineralocorticoid receptor antagonists

Citation: Spoletini I, Rosano GMC. Mineralocorticoid Receptor Antagonists. International Cardiovascular Forum Journal. 2019;17:34-36. DOI: 10.17987/icfj.v17i0.603

Introduction

The role of mineralocorticoid receptor (MR) overactivation in the pathophysiology of heart failure (HF) is well-recognised.[1] Chronically elevated aldosterone levels have been described in the failing heart[2], and these are thought to contribute both towards structural and functional changes in the heart such as coronary endothelial dysfunction, myocardial apoptosis, increased arrhythmogenicity, and reactive myocardial fibrosis as well as systemically promoting promote water and sodium retention.[3,4] Clinically MR overactivation leads to arterial hypertension, ventricular hypertrophy and increased vascular stiffness, all of which exacerbate the progression of HF, as shown in Figure 1.[1] Accordingly, high plasma levels of aldosterone in HF are associated with adverse outcomes, such as increased risk of mortality, impaired functional capacity, and adverse renal and extra-renal effects.[2]

In addition to these adverse affects of exaggerated MR activation, clinically MR antagonists (MRAs) have been tested in HF syndromes and shown to be effective in improving outcomes. Steroid-type MRAs spironolactone and eplerenone, which block receptors that bind aldosterone and to a lesser extent other corticosteroids, have been proven to reduce mortality in HF with reduced ejection fraction (HFrEF). The Randomized ALdactone Evaluation Study (RALES)[5] demonstrated the therapeutic benefits of 25 mg/day spironolactone in 1663 patients with severe heart failure of HFrEF type, showing a 30% reduction in all-cause mortality (HR 0.70; 95 % CI, 0.60 to 0.82; P<0.001).

There was also a 35% lower risk of hospitalization for worsening heart failure (HR, 0.65; 95 % CI, 0.54 to 0.77; P<0.001). Side effects of note included gynaecomastia or breast pain in 10 percent of men on spironolactone, compared with 1% with placebo (P<0.001). The incidence of serious hyperkalemia was however minimal in both groups of patients in the trial, although an increased incidence of this was seen after the resultant increased use of spironolactone clinically in the years that followed the reporting of this landmark trial. Following this, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF), in 2737 patients with NYHA class II HFrEF, found a significant reduction in mortality from any cause or hospitalisation for HF in patients treated with eplerenone compared to placebo (HR, 0.63; 95% CI, 0.54 to 0.74; P<0.001). [6] There was also a 24% reduction in the risk of death (HR, 0.76; 95% CI, 0.62 to 0.93; P=0.008). Potassium levels exceeding 5.5 mmol per liter occurred in 11.8% of patients in the eplerenone group and 7.2% of those in the placebo group (P<0.001). The EPHEsus trial tested eplerenone in 3313 patients with acute myocardial infarction (MI) complicated by left ventricular dysfunction and heart failure.[7] It showed a significant reduction in the risk of death (HR, 0.85; 95 %CI, 0.75 to 0.96; P=0.008). In addition death from cardiovascular causes or hospitalization for cardiovascular events, was reduced by eplerenone (HR 0.87; 95 %CI, 0.79 to 0.95; P=0.002). The rate of serious hyperkalemia was 5.5 percent in the eplerenone group and 3.9 percent in the placebo group (P=0.002).

The Failing Heart

Figure 1. MR overactivation in the failing heart

Legend: Effects of MR overactivation on HF symptoms and progression.

HF= heart failure; HFrEF= heart failure with reduced ejection fraction; MR= Mineralocorticoid Receptor; MRAs= Mineralocorticoid Receptor Antagonists

In patients with preserved ejection fraction (HFpEF), the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial found no significant benefits of spironolactone on cardiovascular outcomes. [8] Although, a meta-analysis of randomised clinical trials of MRA's in HFpEF patients [9] have suggested that MRAs may reduce hospitalisations, improve quality of life, and improve echocardiographic measurements of diastolic function, no effect has been seen on all-cause mortality, and as result guidelines have recommended MRA's with a Class 1A recommendation for chronic HFrEF patients [10] and similarly for post-MI HFrE, but have not made a recommendation in the HFpEF setting. The trials to date have demonstrated the effectiveness of "classic" steroidal MRAs but efforts continue to develop better tolerated agents which are non-steroidal in structure.

Limitations of steroidal MRAs

Steroidal MRAs remain underused in clinical practice. [11,12] Hyperkalaemia is one of the major reasons for the low use of steroidal MRAs in routine practice. Increased potassium levels are more often observed in HFpEF patients than HFrEF [3], and appears to be more commonly observed with spironolactone compared to eplerenone, especially in at-risk patients [5]. Spironolactone is also associated with greater rates of impotence, gynaecomastia or breast pain, than eplerenone [5,7]. This is probably due to the more prolonged half-life of spironolactone. On the other hand, due to such a longer duration of its pharmacodynamic effect, spironolactone has also a greater effect in reducing blood pressure than eplerenone. [13] For both adugs, the optimal dose and frequency of dosing should be defined taking into account the pre-therapy serum potassium levels and renal function. [13] Beyond hyperkalaemia and gynecomastia, other common reasons for discontinuing steroidal MRAs are kidney dysfunction and menstrual disorders. [14,15] Hyperkalaemia and renal function deterioration are particularly severe when steroidal MRAs are given on top of angiotensin converting enzyme inhibitors or angiotensin receptor blockers in "real life" settings. [16,12]

Novel MRAs for HF

In order to overcome the limitations of existing steroidal MRAs, novel MRAs have been recently developed for targeting cardiac fibrosis. [4] Two selective non-steroidal inhibitors of MR, finerenone (or BAY-94-8862 from Bayer) and PF-03882845 (from Pfizer) have been investigated. Both these drugs have been shown to have beneficial effects on renal and cardiac fibrosis, with protective effects that are comparable to those obtained with eplerenone. [1,4] Finerenone has a low affinity for androgen, glucocorticoid, and progesterone receptors [17], but a higher selectivity towards MR. For this reason, finerenone may have a more favourable risk/benefit profile compared to spironolactone and eplerenone, with fewer adverse effects on serum potassium levels or renal function [17], especially in patients with diminished kidney function who are more susceptible to electrolyte disturbances. Murine models have demonstrated finerenone to reduce cardiac hypertrophy, plasma prohormone of brain natriuretic peptide, and proteinuria more efficiently than eplerenone. [18] A recent meta-analysis in patients with chronic HF found that finerenone decreased N-terminal pro-B-type natriuretic peptide, urinary albumin/creatinine ratio and other biochemical indicators, in a dose-dependent manner. [19] The study also compared the efficacy and safety of finerenone versus steroidal MRAs, finding that finerenone at 10mg/d was as effective as 20 to 50mg/d of steroidal MRAs in improving anti-ventricular remodeling, with a lower incidence of adverse events. [19] Thus, finerenone may offer end-organ protection in HF patients with a reduced risk of hyperkalaemia. [18] Other approaches include the possible co-administration of potassium lowering agents, although the long-term clinical effects of this approach remain to be proven in adequately sized clinical trials. [20-23]

Limitations of novel MRAs

The clinical use of finerenone is still limited by its inadequately defined clinical dose, ranging from 1.25 to 20mg/d according to the reviewed studies. [19] Further progress is therefore needed to reach a consensus regarding its optimal dosage. Clinical trials are also needed to confirm its theoretical advantages clinically and demonstrate clinical efficacy and safety in HF patients. New combination therapies with novel MRAs are also under investigation, such as optimizing the anti-fibrotic effects of MRAs by combining with other therapies (e.g. metformin) in order to reduce fibrosis allowing the MRA to be used at a dose that reduces the risk of hyperkalaemia. reviewed elsewhere. [4]. The development of these novel targets is in the very early stages and requires further research. [4]

Conclusions

Impressive trial data confirm the importance of MR signaling as a therapeutic target for HF, and one that remains an active area of novel drug development. Newer agents and newer approaches will aim to optimise the benefits of MRA's and reduce their side-effects, especially hyperkalaemia.

Declarations of interest

The authors declare no conflict of interest.

Acknowledgements

The authors state that they abide by the authors' responsibilities and ethical publishing guidelines of the International Cardiovascular Forum Journal. [24]

References

- Kolkhof P, Jaisser F, Kim SY, Filippatos G, Nowack C, Pitt B (2017). Steroidal and Novel Non-steroidal Mineralocorticoid Receptor Antagonists in Heart Failure and Cardiorenal Diseases: Comparison at Bench and Bedside. *Handb Exp Pharmacol* 243: 271-305.
- Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen L (1990). Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. *Circulation* 82: 1730-6.
- Berbenetz NM, Mrkobrada M (2016). Mineralocorticoid receptor antagonists for heart failure: systematic review and meta-analysis. *BMC Cardiovasc Disord* 16: 246.
- Tesch GH, Young MJ (2017). Mineralocorticoid Receptor Signaling as a Therapeutic Target for Renal and Cardiac Fibrosis. *Front Pharmacol* 8: 313.
- Pitt B, Zannad F, Remme WJ et al (1999). The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 341: 709-17.
- Zannad F, McMurray JJ, Krum H et al (2011). Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 364: 11-21.
- Pitt B, Remme W, Zannad F et al (2003). Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 348: 1309-21.
- Pitt B, Pfeffer MA, Assmann SF et al (2014). Spironolactone for heart failure with preserved ejection fraction. *N Engl J Med* 370: 1383-92.
- Chen MD, Dong SS, Cai NY et al (2016). Efficacy and safety of mineralocorticoid receptor antagonists for patients with heart failure and diabetes mellitus: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 16: 28.
- Ponikowski P, Voors AA, Anker SD et al (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 18: 891-975.
- Maggioni AP, Anker SD, Dahlstrom U et al (2013). Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12,440 patients of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 15: 1173-84.
- Rosano GMC, Tamargo J, Kjeldsen KP et al (2018). Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J Cardiovasc Pharmacother* 4: 180-8.
- Lainscak M, Vitale C, Seferovic P, Spoletini I, Cvan Trobec K, Rosano GM (2016). Pharmacokinetics and pharmacodynamics of cardiovascular drugs in chronic heart failure. *Int J Cardiol* 224: 191-8.
- Parthasarathy HK, Menard J, White WB et al (2011). A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism. *J Hypertens* 29: 980-90.
- Savarese G, Carrero JJ, Pitt B et al (2018). Factors associated with underuse of mineralocorticoid receptor antagonists in heart failure with reduced ejection fraction: an analysis of 11 215 patients from the Swedish Heart Failure Registry. *Eur J Heart Fail* 20: 1326-34.
- Katayama S, Yamada D, Nakayama M et al (2017). A randomized controlled study of finerenone versus placebo in Japanese patients with type 2 diabetes mellitus and diabetic nephropathy. *J Diabetes Complications* 31: 758-65.
- Bramlage P, Swift SL, Thoenes M, Minguet J, Ferrero C, Schmieder RE (2017). Non-steroidal mineralocorticoid receptor antagonism for the treatment of cardiovascular and renal disease. *Eur J Heart Fail* 19: 811.
- Kolkhof P, Delbeck M, Kretschmer A et al (2014). Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. *J Cardiovasc Pharmacol* 64: 69-78.
- Pei H, Wang W, Zhao D, Wang L, Su GH, Zhao Z (2018). The use of a novel non-steroidal mineralocorticoid receptor antagonist finerenone for the treatment of chronic heart failure: A systematic review and meta-analysis. *Medicine (Baltimore)* 97: e0254.
- Kosiborod M, Rasmussen HS, Lavin P, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *Jama*. 2014;21:2223-2233
- Bakris GL, Pitt B, Weir MR, et al. Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial. *Jama*. 2015;2:151-161
- Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors. *New England Journal of Medicine*. 2015;3:211-221.
- Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia. *The New England journal of medicine*. 2015;3:222-231.
- Shewan LG, Coats AJS, Henein MY. Authors' Responsibilities and Ethical Publishing. *International Cardiovascular Forum Journal* 2018;13:3-4, DOI: 10.17987/icfj.v13i0.525