JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

RECENT UPDATES ON FENERENONE

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Abstract: Finerenone is a novel, selective, nonsteroidal MRA that is efficacious in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD). Steroidal MR antagonists (MRAS) are included in treatment paradigms for resistant hypertension and heart failure with reduced ejection fraction, while the nonsteroidal MRA finerenone was shown to reduce renal and cardiovascular outcomes in two large phase III trials (FIDELIO-DKD and FIGARO-DKD) in patients with chronic kidney disease and type 2 diabetes, respectively.

Key Words: FIDELIO-DKD (Finerenone),Mineralocorticoid receptor (MRAs), chronic kidney disease (CKD), sodium-glucose cotransporter-2 inhibitor (SGLT-2i), renin-angiotensin system (RAS).

INTRODUCTION

Finerenone (Bayer) is a novel non-steroidal MRA with the most advanced global clinical development programme. Finerenone is a dihydronaphthyridine-based compound with high selectivity for the MR over all other steroid hormone receptors and high binding affinity. Molecular modelling studies revealed that finerenone has a specific binding mode to the MR-LBD[1]. By binding as a bulky antagonist, finerenone changes the positioning of helix 12 in a specific manner, which results in dis tinct MR cofactor-binding profiles compared with other MRAS[2,3]. This molecular binding pattern induces an antagonistic ligand specific target gene programme, which may explain, at least in part, the differential clinical responses observed with finerenone[4]. The non-steroidal chemical structure of finerenone determines not only specific interactions with amino acich in the MR-LED but also the physicochemical properties of the compound, which has a direct impact on plasma protein binding as well as tissue penetration and distribution. Finerenone is 6 to 10-fold less pophilic than

steroidal MRA and does not cross the blood-brain barrier. Finerenone, a third-generation highly selective MRA, can directly and specifically block MR hyperactivation, and promote the anti-inflammatory and anti-fibrotic effects[5]. In this way, finerenone exhibits cardiovascular and renal double-benefits, and is used in the treatment of T2DM-related CKD (diabetic kidney disease, DKD) to reduce the risk of persistent decline in glomerular filtration rate (eGFR) and the progression of end stage renal disease (ESRD). In general, finerenone could reduce the risk of cardiovascular and renal outcomes (3, 6).

A number of large-scaled clinical trials have proved that finerenone can significantly reduce both cardiorenal endpoints and the adverse reactions such as electrolyte disorders and sex hormone-like effects (7). In this review, we discuss the pharmacological characteristic, molecular mechanism, effectiveness and safety of finerenone in the treatment of T2DM with CKD/DKD and CVD, to provide clinical evidence and deep insight for therapeutic strategies.

The available evidence suggests that finerenone offers cardiorenal protection, as observed in patients with HF and mild-to-moderate CKD (phase II study MinerAlocorticoid Receptor antagonist Tolerability Study (ARTS)) and T2D and CKD (phase III studies FIDELIO/FIGARO; phase II study Mineralocorticoid Receptor antagonist Tolerability Study in Diabetic Nephropathy (ARTS-DN)) via a combination of different mechanisms determined in preclinical studies. As an MRA, finerenone acts as a natriuretic to prevent sodium and fluid retention in the body and, thus, the development of hypertension. By blocking the MR, finerenone may also inhibit the generation of reactive oxygen species (ROS), which promote oxidative stress in cells of the kidney, cardiac, and vascular systems, leading to tissue injury. Finerenone also appears to prevent inflammation and fibrosis driven by the MR on inflammatory cells, which further contribute to tissue damage, as well as hypertrophy and tissue remodeling, in the cardiovascular system (alla).

Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

Type 2 diabetes (T2DM) is regarded as the most common cayse of chronic kidney disease (CKD)[8]. As per international Recomendation for the management of type 2 diabetes (T2DM), ACE inhibitor or, angiotensin recertor blocker (ARB) and sodium-glucose cotransporter 2 (SGLT2) are the first line treatment [9-10]. But still

thease drugs are not efficient in controlly CKD. Hence, formed in there is need to explore novel treatment[11-12]. Reseaches indicated that MRA Activation plays an vital role progeression of cardial renal disorder[13-16].Preclinically, nonsteroidal, selective mineralocorticoid receptor antagonist finerenone has been g inflammation and preventing fibrosis than steroidal mineralocorticoid receptor antagonists[17-20]. In CKD patients using a RAS blocker, finerenone has been found to lower the urinary albumin-to-creatinine ratio while having less of an impact on serum potassium (k^+) levels than spironolactone[21-22].

Effect of Finerenone on CVD

Increased levels of aldosterone are linked to higher rates of morbidity and mortality in people with heart failure[23-25]. Experimental overactivation of aldosterone in the heart causes myocardial apoptosis, myocardial fibrosis, and coronary endothelial dysfunction, which all contribute to pathological remodelling of the heart [26].The mineralocorticoid receptor (MR), a nuclear hormone receptor (NRR) specific to aldosterone, is mostly expressed in the kidney, colon, arteries, and the heart[27]. Through MRs that are expressed in cardiomyocytes, fibroblasts, vascular endothelium, and smooth muscle cells, are main key mediator cardiac remodelling and renal tubulointerstitial fibrosis [28].Hence, blockage of the MR has provide benifits clinically in CRD(Chronic renal disease) and heart failure (HF) [29-30]. Endothelial dysfunction, inflammation, and oxidative stress are among the nontraditional CV risk factors that contribute to atherosclerotic CVD in patients with CKD and T2D. In preclinical models, excessive mineralocorticoid receptor (MR) activation raises the risk of cardiovascular disease (CV) by promoting fibrosis and inflammation, which harms the heart, kidneys, and peripheral vasculature[31,32,33]. In addition, primary aldosteronism is common in people with resistant hypertension. High aldosterone can contribute to a number of diseases, including as CKD, heart failure, coronary artery disease (CAD), and stroke[34]. Patients at risk of CKD development or CVD may have MR overactivation due to elevated aldosterone levels; additional potential causes in this population include enhanced MR expression, cortisol-mediated MR activation, and ligand-independent MR activation[35,36,37]. Finerenone, a novel, nonsteroidal, selective MR antagonist (MRA), was linked to a lower incidence of a composite endpoint of all-cause mortality and heart failure outcomes than the steroidal MRA eplerenone[38].

Effect of Finerenone on Albuminuria in Patients with Diabetic Nephropathy

End-stage excretory organ disease is most frequently caused by diabetes mellitus in industrialised countries.[39] Retrospective analyses in outcome trials of diabetic uropathy patients show a significant correlation between the amount of albuminuria reduction and the speed of CKD progression as well as lower rates of vascular events.13-18 It has been proven again and time again that adding endocrine MRAs to RAS blockers can reduce symptoms.[8,9,10] Lack of large-scale outcome research assessing the long-term effects of MRAs on CKD development in diabetic uropathy is mostly due to safety concerns over the risk of symptoms and decreasing urinary organ function.[40,41,42].

A non-steroidal mineralocorticoid receptor antagonist (MRA) with higher receptor affinity than eplerenone in vitro and significant receptor selectivity relative to spironolactone is called finerenone.[5] Equinatriuretic doses of Finerenone are reported to reduce proteinuria and end organ damage more than eplerenone in preclinical investigations.[6] Finerenone reduced simple proteinuria from baseline in patients with CKD and failure in the corticoid receptor antagonist tolerability study (ARTS), with a lower incidence of symptom than Aldactone, at doses of 2.5 to 10 mg/d.[7] Therefore, finerenone may also be able to meet the unmet medical need of controlling proteinuria safely without negatively affecting blood serum atomic number 19 in children with type 2 DMS WHO have a clinical diagnosis of diabetic child Ney illness. Diabetes renal disease associated with ARTS.

In patients with type 2 diabetes mellitus and protracted symptoms (urinary albumin-creatinine quantitative relation [UACR] 30 mg/g) who were taking a RAS blocker, the ARTS-Diabetic Nephrosis (ARTS-DN) study was created to evaluate the effectiveness and safety of various once-daily oral doses of finerenone and placebo.

The use of a novel non-steroidal mineralocorticoid receptor antagonist finerenone for the treatment of chronic heart failure

Chronic heart failure (CHF) is a widespread condition that affects patients' quality of life significantly in the twenty-first century and places a significant financial burden on the healthcare system.[40] A steady reduction in health-related quality of life, as well as a significant risk of hospitalisation and death, are features of people with chronic heart failure. Treatment regimens based on adrenal cortical steroid receptor antagonists (MRAs) are one

of the most promising ways to reduce vascular risk in chronic cardiac failing patients with deteriorating nephritic function.

For chronic heart failure (CHF) patients with heart failure with reduced ejection fraction (HFrEF) and LVEF 35%, the traditional hormone MRAs (spironolactone and eplerenone) have a category 1A recommendation regardless of whether they are being treated with an antihypertensive drug (or hypertensin receptor blocker) and a beta-blocker. [41,42] For patients with persistent coronary failure with HFrEF, MRAs frequently reduce mortality and hospitalisations. However, due to potential hazards of symptoms, nephritic function degradation, male breast growth, and discharge abnormalities, the use of traditional hormone MRAs is restricted [43].

A new non-steroidal selective MRA called finerenone is being tested in clinical studies as a means of overcoming these steroidal MRAs' fundamental limitations. Preclinical investigations revealed that compared to spironolactone, finerenone exhibited better selectivity towards the mineralocorticoid receptor (MR) and less affinity for the androgen, glucocorticoid, and progesterone receptors.[44] In comparison to spironolactone and eplerenone, finerenone is more selective and has higher affinity. Particularly in groups vulnerable to symptoms, such as those with chronic nephrosis or polygenic illness, finerenone exhibits a lot of good balance between and excretory organ facet effects. Finerenone has a consistent propensity in heart and excretory organ tissues, unlike corticoids and eplerenone, which have a tendency to focus on the excretory organ rather than the centre.[45] The most cutting-edge third generation non-steroidal MRAs medication is finerenone. Over the past few years, an increasing number of research have focused on the therapeutic efficacy and safety of finerenone.[45,46] It was necessary to divide the existing clinical analysis into multiple dosage teams, commencing with one.25 to 20mg/d. Its therapeutic efficacy, nephritic protection, and safety are still unknown. In order to compare the efficacy and safety of finerenone vs steroidal MRAs in patients with chronic heart disease, we prefer to intend to do a scientific review and meta-analysis.

REFERENCE

1.US Food and Drug Administration. FDA approves drug to reduce risk of serious kidney and heart complications in adults with chronic kidney disease associated with type 2 diabetes..

2. Pitt B, Anker SD, Böhm M, Gheorghiade M, Køber L, Krum H, Maggioni AP, Ponikowski P, Voors AA, Zannad F, Nowack C. Rationale and design of MinerAlocorticoid Receptor antagonist Tolerability Study-Heart Failure (ARTS-HF): a randomized study of finerenone vs. eplerenone in patients who have worsening chronic heart failure with diabetes and/or chronic kidney disease. European journal of heart failure. 2015 Feb;17(2):224-32.

3. Bärfacker L, Kuhl A, Hillisch A, Grosser R, Figueroa-Pérez S, Heckroth H, Nitsche A, Ergüden JK, Gielen-Haertwig H, Schlemmer KH, Mittendorf J. Discovery of BAY 94-8862: a nonsteroidal antagonist of the mineralocorticoid receptor for the treatment of cardiorenal diseases. ChemMedChem. 2012 Aug;7(8):1385-403..

4. Kolkhof P, Delbeck M, Kretschmer A, Steinke W, Hartmann E, Bärfacker L, Eitner F, Albrecht-Küpper B, Schäfer S. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. Journal of cardiovascular pharmacology. 2014 Jul 1;64(1):69-78..

5.Pitt B, Kober L, Ponikowski P, Gheorghiade M, Filippatos G, Krum H, Nowack C, Kolkhof P, Kim SY, Zannad F. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. European heart journal. 2013 Aug 14;34(31):2453-63.

6. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, De Boer IH, Goldstein-Fuchs J, Hirsch IB, Kalantar-Zadeh K, Narva AS, Navaneethan SD, Neumiller JJ. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes care. 2014 Oct 1;37(10):2864-83.

7.Chung EY, Strippoli GF. Aldosterone antagonists in addition to renin angiotensin system antagonists for preventing the progression of CKD: editorial summary of a Cochrane review. American Journal of Kidney Diseases. 2021 May 1;77(5):810-2.

8. Mavrakanas TA, Gariani K, Martin PY. Mineralocorticoid receptor blockade in addition to angiotensin converting enzyme inhibitor or angiotensin II receptor blocker treatment: an emerging paradigm in diabetic nephropathy: a systematic review. European journal of internal medicine. 2014 Feb 1;25(2):173-6.

9. American Diabetes Association. 11. Microvascular complications and foot care: standards of medical care in diabetes− 2020. Diabetes care. 2020 Jan 1;43(Supplement_1):S135-51.

10.Katsiki N, Ferrannini E, Mantzoros C. New American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guidelines for the pharmacotherapy of type 2 diabetes: Placing them into a practicing physician's perspective. Metabolism-Clinical and Experimental. 2020 Jun 1;107.

11. Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2020;63:221-8.

12. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, Kolkhof P, Nowack C, Schloemer P, Joseph A, Filippatos G. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. New England Journal of Medicine. 2020 Dec 3;383(23):2219-29.

13. Barrera-Chimal J, Girerd S, Jaisser F. Mineralocorticoid receptor antagonists and kidney diseases: pathophysiological basis. Kidney International. 2019 Aug 1;96(2):302-19.

14. Barrera-Chimal J, Estrela GR, Lechner SM, Giraud S, El Moghrabi S, Kaaki S, Kolkhof P, Hauet T, Jaisser F. The myeloid mineralocorticoid receptor controls inflammatory and fibrotic responses after renal injury via macrophage interleukin-4 receptor signaling. Kidney International. 2018 Jun 1;93(6):1344-55.

15. Guo C, Martinez-Vasquez D, Mendez GP, et al. Mineralocorticoid receptor antagonist reduces renal injury in rodent models of types 1 and 2 diabetes mellitus. Endocrinology 2006;147:5363-73.

16. Buonafine M, Bonnard B, Jaisser F. Mineralocorticoid receptor and cardiovascular disease. American Journal of Hypertension. 2018 Oct 15;31(11):1165-74.

17.Grune J, Beyhoff N, Smeir E, Chudek R, Blumrich A, Ban Z, Brix S, Betz IR, Schupp M, Foryst-Ludwig A, Klopfleisch R. Selective mineralocorticoid receptor cofactor modulation as molecular basis for finerenone's antifibrotic activity. Hypertension. 2018 Apr;71(4):599-608.

18. Grune J, Beyhoff N, Smeir E, Chudek R, Blumrich A, Ban Z, Brix S, Betz IR, Schupp M, Foryst-Ludwig A, Klopfleisch R. Selective mineralocorticoid receptor cofactor modulation as molecular basis for finerenone's antifibrotic activity. Hypertension. 2018 Apr;71(4):599-608.

19. Kolkhof P, Jaisser F, Kim SY, Filippatos G, Nowack C, Pitt B. Steroidal and novel non-steroidal mineralocorticoid receptor antagonists in heart failure and cardiorenal diseases: comparison at bench and bedside. Heart failure. 2017:271-305.

20. Agarwal R, Kolkhof P, Bakris G, Bauersachs J, Haller H, Wada T, Zannad F. Steroidal and non-steroidal mineralocorticoid receptor antagonists in cardiorenal medicine. European Heart Journal. 2021 Jan 7;42(2):152-61.

21. Bakris GL, Agarwal R, Chan JC, Cooper ME, Gansevoort RT, Haller H, Remuzzi G, Rossing P, Schmieder RE, Nowack C, Kolkhof P. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. Jama. 2015 Sep 1;314(9):884-94.

22. Pitt B, Kober L, Ponikowski P, Gheorghiade M, Filippatos G, Krum H, Nowack C, Kolkhof P, Kim SY, Zannad F. Safety and tolerability of the novel non-steroidal mineralocorticoid receptor antagonist BAY 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease: a randomized, double-blind trial. European heart journal. 2013 Aug 14;34(31):2453-63.

23. 25. Swedberg K, Eneroth P, Kjekshus J, Wilhelmsen LF. Hormones regulating cardiovascular function in patients with severe congestive heart failure and their relation to mortality. CONSENSUS Trial Study Group. Circulation. 1990 Nov;82(5):1730-6.

24. Vantrimpont P, Rouleau JL, Ciampi A, Harel F, De Champlain J, Bichet D, Moye LA, Pfeffer M. Two-year time course and significance of neurohumoral activation in the Survival and Ventricular Enlargement (SAVE) Study. European heart journal. 1998 Oct 1;19(10):1552-63.

25. Delcayre C, Silvestre JS. Aldosterone and the heart: towards a physiological function?. Cardiovascular research. 1999 Jul 1;43(1):7-12.

26. Funder JW. Mineralocorticoid receptors: distribution and activation. Heart failure reviews. 2005 Jan;10:15-22.

27. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. New England Journal of Medicine. 1999 Sep 2;341(10):709-17.

28. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. New England Journal of Medicine. 2003 Apr 3;348(14):1309-21.

29. van den Meiracker AH, Baggen RG, Pauli S, Lindemans A, Vulto AG, Poldermans D, Boomsma F. Spironolactone in type 2 diabetic nephropathy: Effects on proteinuria, blood pressure and renal function. Journal of hypertension. 2006 Nov 1;24(11):2285-92.

30. Fraccarollo D, Galuppo P, Schraut S, Kneitz S, van Rooijen N, Ertl G, Bauersachs J. Immediate mineralocorticoid receptor blockade improves myocardial infarct healing by modulation of the inflammatory response. Hypertension. 2008 Apr 1;51(4):905-14.

31. López-Andrés N, Martin-Fernandez B, Rossignol P, Zannad F, Lahera V, Fortuno MA, Cachofeiro V, Díez J. A role for cardiotrophin-1 in myocardial remodeling induced by aldosterone. American Journal of Physiology-Heart and Circulatory Physiology. 2011 Dec;301(6):H2372-82.

32. Calhoun DA. Aldosterone and cardiovascular disease: smoke and fire. Circulation. 2006 Dec 12;114(24):2572-4.

33. Kolkhof P, Jaisser F, Kim SY, Filippatos G, Nowack C, Pitt B. Steroidal and novel non-steroidal mineralocorticoid receptor antagonists in heart failure and cardiorenal diseases: comparison at bench and bedside. Heart failure. 2017:271-305.

34. Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Cardiometabolic outcomes and mortality in medically treated primary aldosteronism: a retrospective cohort study. The lancet Diabetes & endocrinology. 2018 Jan 1;6(1):51-9.

35. Monticone S, D'Ascenzo F, Moretti C, Williams TA, Veglio F, Gaita F, Mulatero P. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. The lancet Diabetes & endocrinology. 2018 Jan 1;6(1):41-50.

36. Filippatos G, Anker SD, Böhm M, Gheorghiade M, Køber L, Krum H, Maggioni AP, Ponikowski P, Voors AA, Zannad F, Kim SY. A randomized controlled study of finerenone vs. eplerenone in patients with worsening chronic heart failure and diabetes mellitus and/or chronic kidney disease. European heart journal. 2016 Jul 14;37(27):2105-14.

37. Tuttle KR, Bakris GL, Bilous RW, Chiang JL, De Boer IH, Goldstein-Fuchs J, Hirsch IB, Kalantar-Zadeh K, Narva AS, Navaneethan SD, Neumiller JJ. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes care. 2014 Oct 1;37(10):2864-83.

38. Mehdi UF, Adams-Huet B, Raskin P, Vega GL, Toto RD. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. Journal of the American Society of Nephrology. 2009 Dec 1;20(12):2641-50.

39. Dickstein K. The Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology: Developed in collaboration with the Heart Failure Association of the ESC

(HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J. 2008;29:2388-442.

40. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Kardiologia Polska (Polish Heart Journal). 2016;74(10):1037-147.

41. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. New England Journal of Medicine. 1999 Sep 2;341(10):709-17.

42. Pitt B, Pedro Ferreira J, Zannad F. Mineralocorticoid receptor antagonists in patients with heart failure: current experience and future perspectives. European Heart Journal–Cardiovascular Pharmacotherapy. 2017 Jan 1;3(1):48-57.

43. Bramlage P, Swift SL, Thoenes M, Minguet J, Ferrero C, Schmieder RE. Non-steroidal mineralocorticoid receptor antagonism for the treatment of cardiovascular and renal disease. European journal of heart failure. 2016 Jan;18(1):28-37.

44. Kolkhof P, Delbeck M, Kretschmer A, Steinke W, Hartmann E, Bärfacker L, Eitner F, Albrecht-Küpper B, Schäfer S. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. Journal of cardiovascular pharmacology. 2014 Jul 1;64(1):69-78.

45. Orena S, Maurer TS, She L, Eudy R, Bernardo V, Dash D, Loria P, Banker ME, Tugnait M, Okerberg CV, Qian J. PF-03882845, a non-steroidal mineralocorticoid receptor antagonist, prevents renal injury with reduced risk of hyperkalemia in an animal model of nephropathy. Frontiers in pharmacology. 2013 Oct 14;4:115.

46. Yang C, Balsells J, Chu HD, Cox JM, Crespo A, Ma X, Contino L, Brown P, Gao S, Zamlynny B, Wiltsie J. Discovery of benzimidazole oxazolidinediones as novel and selective nonsteroidal mineralocorticoid receptor antagonists. ACS medicinal chemistry letters. 2015 Apr 9;6(4):461-5.