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Finerenone in type 1 diabetes and chronic kidney disease

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INTRODUCTION

The recent Finerenone in Type 1 Diabetes and Chronic Kidney Disease (FINE-ONE) trial randomized 242 patients with type 1 diabetes mellitus (T1DM) and chronic kidney disease (CKD) to 10 or 20 mg daily (depending on the glomerular filtration rate) of the nonsteroidal mineralocorticoid receptor antagonist (MRA) finerenone. Finerenone or placebo was given in addition to ongoing therapy including renin-angiotensin system inhibitors (RASi). The patients had an initial estimated glomerular filtration rate (eGFR) of 25 to < 90 mL/min per 1.73 m^2, a urinary albumin-to-creatinine ratio (UACR) of 200 to < 5,000 mg/g, and a serum potassium (Sk) level of 4.8 mmol/L or less. Over a 6-month follow-up period, the median UACR of those randomized to finerenone decreased from 575 to 374 mg/g. This was a 35% greater reduction than those randomized to placebo ($P < 0.001$). The eGFR changed by -5.6 mL/min per 1.73 m^2 with finerenone and -2.7 mL/min per 1.73 m^2 with placebo, but approached baseline in those randomized to finerenone during the washout period, indicating that the fall in GFR was probably hemodynamic. Changes in Sk were modest, although 10.1% of patients on finerenone and 3.3% on placebo developed hyperkalemia[1]. A reduction in UACR in type 2 diabetes mellitus (T2DM) predicts a slower progression of CKD to end-stage renal disease (ESRD)[2], although this association has not yet been studied in T1DM[3]. This important trial suggests that finerenone may be a much-needed novel therapy for CKD in T1DM, which has seen few recent advances and, as yet, no indications for sodium-glucose linked transport 2 inhibitors (SGLT2i) or glucagon-like peptide-1 receptor agonists. Small trials of SGLT2i have produced promising results in patients with T1DM and CKD, although there is an increased risk of diabetic ketoacidosis in those receiving these drugs[4].

RATIONALE FOR USE OF MRAS

A study of 64 patients with T1DM and 58 controls during a controlled sodium and potassium intake found a significant increase in plasma renin activity (PRA), plasma angiotensin II (Ang II), and plasma aldosterone concentration in those with T1DM[5].

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A retrospective cohort study of 78 individuals with primary hyperaldosteronism found that 62% had prediabetes or T2DM[6], suggesting that high levels of aldosterone impair glucose tolerance. High blood glucose and diabetes mellitus (DM) increase reactive oxygen species (ROS) and inflammation that promote hypertension, vascular dysfunction, nephropathy, cardiovascular disease, and aldosterone secretion[7,8]. Indeed, a retrospective study of 21 patients with untreated T2DM found that plasma aldosterone was associated with insulin resistance[9]. If similar associations occur in T1DM, this could create a positive feedback loop in which hyperglycemia increases aldosterone secretion from the adrenal zona glomerulosa, while aldosterone impairs insulin sensitivity and glucose homeostasis, increasing blood glucose levels.

RASi initially reduce aldosterone levels but, within several months, aldosterone escapes inhibition[10]. Thus, RASi use could be accompanied by a persistent increase in insulin resistance, glucose, and ROS driven by aldosterone. Moreover, the increase in ROS with DM increases the renal expression of mineralocorticoid receptors (MRs) and promotes progression of diabetic nephropathy[11].

Both cortisol and aldosterone activate the MR. Its specificity for aldosterone in many tissues is due to co-expression of 11β hydroxysteroid dehydrogenase type 2 (11β-HSD2), which metabolizes cortisol to the inactive cortisone, whereas 11β-HSD1 metabolizes cortisone to cortisol. An experimental study found that hyperglycemia increases 11β-HSD1 activity and cortisol levels in skin or cultured keratinocytes[12]. A study of 6,931 elderly individuals found that the urinary cortisol-to-cortisone ratio (an index of 11β-HSD1 activity) was increased in T2DM especially in those with hypertension[13]. Conversely, *11β-HSD2* gene expression is decreased in the kidneys of a rat model of T1DM[14]. Since cortisol secretion is stimulated by insulin[9,15], cortisol should robustly activate the MR in addition to aldosterone in insulin-treated patients with T1DM.

An increase in renal ROS in animal models of DM increases the renal expression of the small GTPase Rac-1 that enhances post-receptor MR signaling, thereby enhancing the responsiveness of the MR to aldosterone or cortisol[11]. Together, these data indicate that hyperglycemia and ROS in T1DM might enhance aldosterone secretion, MR expression, and cortisol production, which could increase MR signaling even when aldosterone levels are not increased. This provides a strong rationale for using an MRA to prevent CKD progression in patients with T1DM.

CHOICE OF MRA

There is a sharp increase in the risk of ischemic and hemorrhagic stroke as well as dementia and cognitive impairment (CI) in patients with T1DM[16]. While the benefits of finerenone in slowing the loss of renal function or reducing UACR in patients with diabetic nephropathy are now established, finerenone has not been shown to cross the blood-brain barrier (BBB). In contrast, studies in dogs have shown that spironolactone, and especially its active metabolite canrenone, crosses the BBB readily[17]. It is interesting that the FIDELITY analysis of the combined FIDELIO and FIGARO trials of finerenone in CKD did not report a reduced risk of stroke in this high-risk population. In contrast, two recent propensity-matched observational studies have associated spironolactone use with a reduction in stroke. A study of 2,461 patients with hypertension over 2 years reported a significant ($P < 0.001$) and dose-dependent 2% reduction in ischemic and hemorrhagic stroke in spironolactone users that was independent of blood pressure[18]. A hospital-based cohort study of 2,711 patients with CKD stages 3-5 reported a significant ($P < 0.001$) 20% reduction in adjusted risk of ischemic stroke over a median of 3.4 years in non-hypertensive spironolactone users[19]. Similar studies in patients with T1DM are not available. However, the risks of stroke and CI are increased in adults with T1DM, CKD, high glucose levels, uncontrolled blood pressure (BP), macroalbuminuria, and prior stroke or white matter lesions on magnetic resonance imaging (MRI). Presently, data are insufficient to determine whether starting therapy with spironolactone might be beneficial in reducing the risk of stroke and CI in this high-risk group of patients. Head-to-head studies of finerenone and spironolactone in individuals with T1DM and CKD are needed to guide this important clinical choice.

DECLARATIONS

Authors' contributions

Prepared, corrected, and approved the manuscript: Pitt B, Wilcox CS

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

Not applicable.

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Conflicts of interest

Pitt B: Consultant for Bayer, AstraZeneca, Boehringer Ingelheim, Lexicon, SC Pharmaceuticals, SQ Innovations, KBP Biosciences, Cereno Scientific, Sarfez Pharmaceuticals, Prointel, Sea Star Medical, and Anacardio; stock/stock options in SC Pharmaceuticals, SQ Innovations, KBP Biosciences, Cereno Scientific, Sarfez Pharmaceuticals, Prointel, Sea Star Medical, and Anacardio; Data and Safety Monitoring Board (DSMB) member for Mineralys; U.S. Patent No. 9,931,412 ("Site-Specific Delivery of Eplerenone to the Myocardium"); U.S. Patent Application No. 63/045,783 ("Histone Modulating Agents for the Prevention and Treatment of Organ Damage"). Wilcox CS: Stockholder of Sarfez Inc. and consultant for SQ Innovations and BridgeBio.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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