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A COMPREHENSIVE REVIEW ON BALCINORENONE, ITS MECHANISM AND FUNCTIONALITY

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Abstract

Balcinrenone represents a groundbreaking modulator of mineralocorticoid receptors that, as indicated by early studies, maintains cardiovascular and renal benefits without raising the likelihood of hyperkalemia. Its development is paired with dapagliflozin for the management of heart failure in individuals with impaired kidney function and chronic kidney disease. The aim of this research was to employ a population pharmacokinetic approach to define the pharmacokinetics of Balcinrenone and evaluate how both internal and external factors influence its pharmacokinetic behavior. An investigation into absorption, distribution, metabolism, and excretion was carried out to establish essential pharmacokinetic parameters, mass balance, and metabolite profiles of Balcinrenone in human subjects. This study was designed as an open-label, single-center, nonrandomized trial with two distinct periods. In the first period, eight healthy male participants were administered a microtracer intravenous infusion of Balcinrenone immediately after taking an oral dose of unlabeled Balcinrenone in a capsule form. Following a washout period of seven days, the same participants later received an oral suspension of Balcinrenone in the second period. The clearance and absolute bioavailability of Balcinrenone were established at 14. 2 l/h and 52%, respectively. The renal clearance rate was calculated at 5. 4 l/h, which indicates elimination through active tubular secretion potentially facilitated by P-glycoprotein 1 and/or organic anion transporter 3 based on in vitro transporter studies. A total of 94. 1% of the administered oral dose was recovered, with 45. 2% found in urine and 48. 9% in feces. The primary metabolic pathway of Balcinrenone involved oxidation, with in vitro evidence indicating that cytochrome P450 3A4 mainly drives this process. Unchanged Balcinrenone constituted 55% of the drug-related substance in plasma, with four metabolites observed, none exceeding 6% of the overall plasma radioactivity. In summary, this two-period investigation has established the fundamental pharmacokinetic characteristics of Balcinrenone in humans, including absolute bioavailability and its disposition profile. The identified metabolites did not require further investigation due to their minimal presence, and their potential role in influencing pharmacodynamic responses or drug-drug interactions was considered insignificant. Overactive mineralocorticoid receptor function is associated with cardiovascular and renal disorders. Reducing MR activation through mineralocorticoid receptor antagonists has proven effective in slowing the progression of chronic kidney disease and its related cardiovascular complications in both animal research and patient studies. This current investigation looks into the effects of the mineralocorticoid receptor modulator Balcinrenone alongside the mineralocorticoid receptor antagonist eplerenone on kidney injury within a metabolic chronic kidney disease mouse model that combines nephron reduction with a high-fat diet consisting of 60%. Both Balcinrenone and Eplerenone showed similar effectiveness in preventing the advancement of kidney injury, extracellular matrix changes, and inflammation. A novel mechanism was identified that connects MR activation to the deposition of renal proteoglycans and inflammation through the stimulation of the TLR4 pathway. Balcinrenone and eplerenone were both effective in attenuating this pathway activation.

2. Introduction [1-7]

According to preclinical research, the novel, selective mineralocorticoid receptor (MR) modulator balcinrenone (AZD9977) retains cardiorenal benefits while not increasing the chance of hyperkalemia. Presently, it is being created in conjunction with the sodium-glucose cotransporter-2 inhibitor (SGLT2i) dapagliflozin for the treatment of heart failure (HF) in individuals with impaired renal function and chronic kidney disease (CKD). Mineralocorticoids like aldosterone and glucocorticoids activate MR, which is present in both epithelial and nonepithelial tissues, such as the heart and kidneys. The kidneys' MR activation controls electrolyte balance and blood pressure, but excessive activation of MR over time can lead to the progression of cardiorenal disorders such HF and CKD. By lowering mortality rates and minimizing hospital risks, mineralocorticoid receptor antagonists (MRAs), such as spironolactone, eplerenone, and finerenone, have been shown to be effective in the treatment of hypertension and heart failure. The increased risk of hyperkalemia caused by the suppression of aldosterone's effects, which blocks potassium loss, limits their use, however. Balcinrenone works through a different mechanism than current MRAs; studies show that its binding to MR causes a different conformation than that induced by MR antagonists. The distinct interaction with MR is predicted to distinguish organ-protective effects from negative effects on urinary electrolytes, such as the possibility of hyperkalemia. Balcinrenone improved renal function in preclinical research without causing any immediate change in the urinary sodium/potassium ratio. As a result, Balcinrenone is anticipated to provide similar cardiorenal benefits as MRAs, but with a lower chance of hyperkalemia. Dapagliflozin is a very potent SGLT2i that improves glycemic control in people with diabetes mellitus and offers cardiorenal benefits for patients with type 2 diabetes mellitus, HF, and CKD. It is used to prevent cardiorenal complications in CKD and heart failure (HF), especially when standard steroidal MR antagonists are not well tolerated. It belongs to the same mechanistic family as finerenone and esaxerenone, which aim to maintain the positive effects of MR blockade while reducing hyperkalemia in people with compromised kidney function. The steroid-related endocrine side effects seen with spironolactone and, to a lesser extent, Balcinrenone are still being studied and have not yet been authorized by any big regulatory bodies.

Concomitant renal impairment is frequent in individuals with heart failure (HF), and it complicates HF therapy and has a detrimental impact on prognosis.1 Despite being a cornerstone therapy for heart failure with reduced ejection fraction, mineralocorticoid receptor (MR) antagonists are significantly underutilized in individuals with chronic kidney disease (CKD)2 and are not advised in those with an estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73 m2. Balcinrenone (previously AZD9977) is a selective MR modulator that has partial antagonist action due to its unique interaction with the receptor and ability to distinguish between urinary electrolyte excretion and organ-protective effects.5

Balcinrenone may have advantages in patients with HF and CKD who are already receiving standard-of-care treatment with sodium-glucose cotransporter 2 (SGLT2) inhibitors (e.g. dapagliflozin). The findings of MIRACLE (MIneRAlocorticoid reCeptor modulator and sodium–glucosE cotransporter 2 inhibitor in HF and CKD), an international, randomized, double-blind, phase 2b trial of the efficacy and safety of Balcinrenone and dapagliflozin in patients with HF and CKD, are presented here.

3. Methods [8-11]

Balcinrenone was manufactured for AstraZeneca by Eurofins Selcia in Essex, UK. Quotient Sciences (Nottingham, UK) created the oral suspension of Balcinrenone as well as the intravenous solution of the microtracer Balcinrenone, while AstraZeneca (Gothenburg, Sweden) manufactured capsules with pellets of Balcinrenone. AstraZeneca (Gothenburg, Sweden) supplied synthetic standards for six metabolites of Balcinrenone (M2 and M5 9). The final PerkinElmer (Waltham, MA, USA) Ultima Gold LSC-cocktail was purchased. Paracetamol and acetanilide, both purchased from Sigma-Aldrich (Saint Louis, MO, USA), and ANU sucrose-8542, which had a certified 14C/12C ratio and was bought from the National Institute of Standards and Technology (Gaithersburg, MD, USA), were among the specific chemicals used by TNO (Metabolic Health Research, Leiden, Netherlands) for accelerator mass spectrometry (AMS) analysis. All other chemicals and reagents were of analytical or higher grade and were obtained from commercial suppliers.

3.1 Research methodology (12–17)

Between December 21, 2020, and February 4, 2021, Quotient Sciences conducted this non-randomized, open-label, single-center, 2-period study of healthy people (NCT04686591) (Figure 1). The London-Surrey Borders Research Ethics Committee gave the study its blessing after it followed the Helsinki Declaration. Prior to beginning any of the study procedures, each participant gave written informed consent, which was downloaded from dmd.aspetjournals.org at ASPET Journals on August 2, 2023. The absolute bioavailability of a single oral dosage of Balcinrenone and the PK characteristics of Balcinrenone following intravenous injectio n were evaluated during Period 1. After at least a 10-hour overnight fast, participants were given a single oral dosage of 100 mg of Balcinrenone in a capsule; two hours and fifteen minutes later, they received a continuous 15-minute intravenous infusion of 100 µg of Balcinrenone, which included 30.7 kBq (0.8 µCi) of Balcinrenone. Balcinrenone's predicted oral Tmax occurred at the conclusion of the infusion. The participants stayed in the clinical unit for a maximum of 72 hours following the oral dose (up to day 4). The oral Balcinrenone's ADME characteristics were evaluated during Period 2. Subjects were given a single 100 mg oral dose of Balcinrenone, containing 8 MBq [14C] (216 µCi), as an oral suspension after an overnight fast (at least 10 hours). Subjects were housed in the clinical unit until 168 hours after the dose (up to day 8),

and when all discharge requirements were met, they were released as a group. The same individuals were involved in both study periods. The dosing in Periods 1 and 2 were separated by a minimum washout period of seven days.

3.2 Rationale for dose [18-22]

The current study looked at a single oral dose of 100 mg, which falls within the dosage range that has been assessed in prior clinical trials and is still being evaluated in ongoing research (Erlandsson et al., 2018; Whittaker et al., 2020). In the early clinical trials of Balcinrenone, dosage levels up to 1200 mg were examined, and no tolerability or safety issues were discovered, and dose-linear pharmacokinetics were seen up to 200 mg (Erlandsson et al., 2018; Whittaker et al., 2020). The aim was to obtain the primary The study's goals, which were downloaded from dmd.aspetjournals.org at ASPET Journals on August 2, 2023, called for the oral radioactive dosage of Balcinrenone to be kept as low as possible while still being high enough to permit a fair examination of its metabolite profile using radioactivity detection (RAD). The intravenous dosage of 100 µg Balcinrenone is consistent with the International Council for Harmonisation (ICH) M3 definition of a microdose (a dose that is ≤1/100th of the pharmacologically active dose, up to a maximum dose of 100 µg) (European Medicines Agency, 2013). Estimates of the expected total radiation exposure following intravenous and oral doses of Balcinrenone resulted in a committed effective dose equivalent of 1.55 mSv, which fell within International Commission on Radiological Protection (ICRP) risk category IIb (1–10 mSv) for a radioactive dose (ICRP, 1991).

3.3 Patients [23-26]

Patients eligible for inclusion were those aged 21 years or older with New York Heart Association (NYHA) class II–III HF, a left ventricular ejection fraction (LVEF) below 60%, serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels of 300 pg/mL or higher (600 pg/mL or higher in people with atrial fibrillation/flutter), CKD (eGFR between 30 and 60 ml/min/1.73 m2),6 serum potassium levels between 3.5 and 5.0 mmol/L, and a centrally measured UACR be tween 30 and 3000 mg/g (online supplemental Table S2). Every patient gave written informed permission. Participants must be at least 18 years old, have a CKD diagnosis as determined by an estimated glomerular filtration rate (eGFR) of between 25 and 60 mL/min/1.73 m2, a urinary albumin-to-creatinine ratio (UACR) of between 100 and 5000 mg albumin/g creatinine, and serum potassium levels between 3.5 and 5.0 mmol/L. Patients with or without prior therapy with an SGLT2i are eligible for the study. For patients receiving renin–angiotensin–aldosterone system (RAAS) inhibitors—angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB)—dose must have been stable for at least four weeks prior to screening. However, participants with documented ACEi or ARB intolerance or those who are not currently being treated with a RAAS inhibitor are allowed to participate. Key

exclusion criteria include autosomal dominant polycystic kidney disease, type 1 diabetes mellitus, and uncontrolled arterial hypertension [systolic blood pressure (SBP) >160 mmHg or diastolic blood pressure (DBP) >100 mmHg)]. Patients with adrenal insufficiency are excluded to avoid potential confounding factors and taking into account contraindications for MRAs.

3.4 Statistical Methods [27-30]

Assuming a 5% dropout rate, the intended sample size of approximately 500 (125/arm) had 80% power to identify a relative reduction of at least 30% in UACR compared to dapagliflozin plus placebo (α = 0.05). All randomized participants were to be included in the efficacy analyses, according to the planned treatment. All participants who received study medication were to be included in the safety and pharmacodynamic analyses, according to the treatment they got. A mixed model for repeated measures was used in the pre-specified primary efficacy analysis to the change from baseline in log-transformed UACR, with treatment and visit as fixed effects, baseline log-transformed UACR, cohort variable, and stratification variables as covariates, and treatment-by-visit as an interaction term (online supplementary Methods). Exploratory endpoints and post hoc analyses were deemed to be hypothesis-generating.

4. Sample analysis by LC-HRMS-RAD [31-34]

Plasma, urine, and fecal sample extracts were subjected to metabolite profiling of Balcinrenone using a Waters Acquity UPLC system (Waters, UK) coupled with a Synapt G2-Si Q-TOF mass spectrometer and off-line radioactivity assays. MassLynx was the program used to acquire data and manage instruments.

HRMS analysis: An electrospray interface (ESI) was used to introduce the eluent from the UPLC column into a Synapt G2-Si Q-TOF mass spectrometer. Using TOF MSE, data were collected in two parallel functions: the first, low-energy function produced precursor ion spectra, while the second, high-energy function produced product ion spectra. Mass spectra were acquired separately in positive and negative ESI modes. Selected metabolites were subjected to product ion MS/MS to generate fragment ions, which were used to determine the structure. The Supplemental Methods section contains a thorough description of the HRMS instrument settings used to identify metabolites. For data collecting and instrument control, the MassLynx program (version 4.1) was utilized. For metabolite identification, data processing, and analysis, MassLynx and Metabolynx were used.

4.1 Analysis of Balcinrenone and total ^{14}C by AMS [35-40]

Using AMS, TNO (Leiden, Netherlands) examined total 14C radioactivity in plasma after intravenous microtracer injection of Balcinrenone. After sample fractionation using high-performance liquid chromatography, the quantities of Balcinrenone in plasma and urine were also measured using AMS. In summary, plasma samples were placed into tin foil cups, dried, and burned using an elemental

analyzer (vario MICRO; Elementar, Langenselbold, Germany), and total 14C was analyzed using 1 MV multielement AMS (model 4110 Bo, High Voltage Engineering, Amersfoort, Netherlands). Plasma samples were extracted using protein precipitation to identify Balcinrenone, and the supernatant was separated and concentrated under a mild nitrogen stream. The plasma extracts and urine samples were then injected into an ultraperformance liquid chromatography (UPLC) column, and the liquid chromatography (LC) elute of Balcinrenone was fractionally collected in foil cups for AMS analysis. An Acquity UPLC HSS C18 SB column (1.8 µm, 2.1 mm × 150 mm; Waters Corp., Milford, Massachusetts) was used to achieve the LC separation of Balcinrenone from the matrices at 45°C. Acetonitrile and water were the components of mobile phases A and B, respectively, with a formic acid concentration of 0.1%. The flow rate was 0.4 mL/min, with a linear gradient from 15% B to 40% B in 17.5 minutes, then a ramp to 90% B in 1.4 minutes, and a 4 minute hold before returning to 15% B at 23 minutes. The Balcinrenone peak was monitored using a photodiode-array detector. At the retention time between 10.1 and 10.5 minutes, the Balcinrenone eluate fraction was collected. The total 14C in plasma and the Balcinrenone fraction in plasma and urine were quantified using the AMS-specific instrument setup, calibration, and data processing for 14C determination that were previously described (Bauman et al., 2022).

4.2 Metabolite Characterization [41-42]

The retention times of precursor ions ([M+H]+ or [M-H]–) of Balcinrenone and metabolites in LC-HRMS chromatograms coincided with RAD peaks in the matching radio-chromatograms. Molecular compositions were predicted using observed HRMS full-scan precursor ions, and tentative metabolite structures were predicted using product ion spectra (MS/MS). Some of the metabolites were analyzed for unambiguous identification since they were available as synthesized standards.

5. Determination of Blood-Plasma Partitioning [43]

By measuring the ratio of total radioactivity in whole blood to plasma at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 8, 12, and 24 hours following a dosage of 100 mg of Balcinrenone, the extent of distribution of total 14C radioactivity into blood cells was determined.

5.1 Pharmacokinetics [44-47]

Phoenix WinNonlin (Certara Inc., Princeton, NJ, USA), a non-compartmental program, was used to determine the pharmacokinetic characteristics of balcinrenone in plasma and urine. The parameters were the apparent volume of distribution (Vz/F), the half-life of elimination related to the terminal slope of a semi-logarithmic concentration–time curve (t½λz), the time to maximum concentration (tmax), the maximum concentration (Cmax), the area under the concentration-time curve from time zero to infinity (AUC∞) and to the last measurable concentration (AUClast). The difference between total apparent clearance (CL/F) and

CLR was non-renal clearance (CLNR). With the natural logarithm of AUC∞, AUClast, and Cmax as response variables and the renal function cohort as an independent variable, the pharmacokinetic parameters were analyzed using a simple linear regression model. By back-transforming the model estimates of least square mean difference and its CI into the original scale, the ratios of geometric means and their associated two-sided 90% confidence intervals (CIs) were estimated for each of these parameters in the severe renal impairment cohort versus the control cohort. The connection between baseline eGFR values (independent variable) and CL/F (dependent variable) was also examined using a linear regression model.

5.2 Bioanalysis of Unlabeled Balcinrenone and Total Radioactivity [48-51]

High-performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) was used to analyze unlabeled Balcinrenone. Covance Laboratories Limited (Harrogate, UK) used HPLC-MS/MS to determine the concentrations of unlabeled Balcinrenone in plasma and urine, as previously described (Whittaker et al., downloaded from dmd.aspetjournals.org at ASPET Journals on August 2, 2023 & 2020).

Liquid scintillation counting (LSC) was used to measure the total radioactivity. Following oral administration of [14C [Balcinrenone in Period 2, Pharmaron (Northamptonshire, UK) utilized LSC to analyze the total 14C radioactivity in plasma, whole blood, urine, and feces. Before adding scintillation fluid, whole blood samples were first dissolved and decolored, while plasma and urine samples were treated with scintillation cocktail directly. Prior to analysis by LSC, the fecal samples were homogenized, and subsamples of each homogenate were dried and burned. Then, scintillation cocktail was added. In the Supplemental Methods, there is a thorough description of the method used to identify radioactivity.

5.3 In Vitro Drug Transporter Studies [52-54]

In polarized Caco-2 cell monolayers and in polarized Madin-Darby canine kidney (MDCK) cells transfected with the multidrug resistance 1 gene (MDR1), the potential of Balcinrenone to be a substrate of the human efflux transporters P glycoprotein 1 (P-gp) and breast cancer resistance protein (BCRP) was evaluated, respectively. Details of the experimental methods are included in the Supplementary Methods. The efflux ratio for Balcinrenone was calculated in the presence and absence of known inhibitors for P-gp and BCRP (Supplemental Methods).

6. Safety and Tolerability [55-59]

The healthy participants in this trial tolerated well single doses of 100 mg oral Balcinrenone and 100 µg IV Balcinrenone in Period 1, as well as 100 mg oral Balcinrenone in Period 2. Balcinrenone was not thought to be responsible for any of the minor negative occurrences. The physical examination, electrocardiogram, vital signs, and clinical laboratory assessments yielded no clinically significant results. Since balcinrenone is nonsteroidal and extremely

specific to MR Gynecomastia, menstrual abnormalities, and sexual dysfunction, these side effects have not been significant in the early clinical trials. To date, there have been no reports of noteworthy endocrine safety signals off target. After treatment, three participants (16.7%)—two from the severely renal impaired group and one from the control group—reported a total of four minor adverse events (AEs): infusion site erythema, infusion site edema, coronavirus illness 2019 (COVID-19), and a fall. With the exception of the COVID-19 AE, which was not resolved at the conclusion of the study, all the recorded AEs were described as being of mild to moderate severity and as having been resolved prior to the conclusion of the study visit. One participant from the group with severe renal impairment had an adverse event involving a fall, which resulted in the participant's withdrawal from the trial. The investigator did not believe that any of the AEs were linked to Balcinrenone. There were no fatalities or major adverse events. According to laboratory results, vital indicators, and electrocardiographic data, there were no clinically significant trends or changes from baseline.

7. Mass Balance and Excretion [60-64]

94.1% of the radioactivity administered in a single oral dose of Balcinrenone was recovered by the conclusion of the 168-hour sampling period; 45.2% was recovered from the urine and 48.9% was recovered from the feces. In the first 24 hours after the dosage, 42.7% of the total radioactivity was found in the urine, while 4.65% was found in the feces. As expected, the highest concentration of Balcinrenone was observed at the conclusion of the intravenous microtracer infusion during Period 1. Following the conclusion of the infusion, the concentrations showed a quick distribution phase followed by an elimination phase with a geometric mean half-life of 4.2 hours. The geometric mean clearance (CL), steady-state volume of distribution (Vss), and apparent volume of distribution (Vz) of Balcinrenone were found to be 14.2 l/h, 37.8 l, and 86.2 l, respectively. Balcinrenone's geometric mean renal clearance (CLR) was found to be 5.6 liters per hour, which accounts for about 40% of the total clearance. The geometric mean absolute bioavailability of the Balcinrenone capsule was found to be 52%. The geometric mean AUC(0-inf) values for total 14C radioactivity exposure were roughly twice as high as for Balcinrenone exposure, with values of 36 and 17.7 nmol.h/l, respectively.

8. Conclusion

Balcinrenone is a potential, highly selective nonsteroidal MR antagonist with: demonstrated antihypertensive and antiproteinuric effects in CKD; a mechanistic basis for cardiorenal protection in HF-CKD; and a predictable but evident dose-dependent risk of hyperkalemia, especially at higher dosages and in advanced CKD. The data currently available comes from early phase trials and the underpowered MIRACLE trial, which confirmed the expected pharmacodyn

amic and safety profile in HF–CKD but did not show a significant albuminuria advantage over dapagliflozin alone. Balcinrenone should be considered an experimental treatment alternative with possible benefits for certain high-risk individuals, but with an unclear net clinical benefit when compared to proven MR antagonists, until solid phase 3 outcome data are available.

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