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Renin-angiotensin system blockade

Renin–angiotensin system blockade: Finerenone

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ABSTRACT

Finerenone is a novel selective nonsteroidal mineralocorticoid receptor antagonist. Results in preclinical studies showed that lower doses of finerenone were needed to achieve similar cardiorenal protective effects compared to both spironolactone and eplerenone and phase II studies in finerenone in patients with heart failure, type-2 diabetes mellitus and/or chronic kidney disease are encouraging as the drug is effective and safe in patients on renin–angiotensin system inhibitors (significant reduction in albuminuria and a low rate of hyperkalemia), but the primary end points were "soft" end points (serum potassium, estimated glomerular filtration rate, albuminuria, N-terminal prohormone B-type natriuretic peptide levels). Thus, further, large-scale, long-term phase III trials are needed to confirm whether the greater affinity and selectivity is translated into improved clinical outcomes.

1. Introduction

Aldosterone, a mineralocorticoid secreted by the glomerulosa cells of the adrenal cortex, participates in the regulation of blood pressure and water-electrolyte balance through the activation of mineralocorticoid receptors, a member of the steroid receptor family of ligand activated transcription factors [1–3]. Mineralocorticoid receptors are present in multiple tissues, including endothelial and vascular smooth muscle cells, cardiomyocytes, fibroblasts, kidney (mesangial cells and podocytes), adipocytes, macrophages and brain (hipothalamus) [1–4]. This wide distribution explains why aldosterone exerts multiple cardiac, vascular and renal effects including endothelial dysfunction, vasoconstriction, natriuresis, K^+ retention, sympathetic activation, adverse cardiovascular (hypertrophy, fibrosis) and renal (glomerular and tubular sclerosis) remodeling and oxidative stress, increases vascular stiffness and exerts proarrhythmic, proinflammatory and prothrombotic effects [4–7]. In the cytosol, mineralocorticoid receptors are kept transcriptionally inactive by several chaperone proteins. Aldosterone binding to the ligand-binding domain of the mineralocorticoid receptors promotes a conformation change that allows the dissociation of the complex from chaperones which is associated with a rapid translocation to the nucleus where the mineralocorticoid receptor binds to hormone response elements and recruits specific coactivator proteins, allowing the transcription or repression of target genes [5–7]. However, aldosterone also exerts mineralocorticoid receptor-independent effects and in both mineralocorticoid receptor-dependent/independent effects, genomic and non-genomic effects have been described [4,6–10]. The relative contribution of mineralocorticoid receptor-dependent/independent and genomic/non-genomic effects of aldosterone to the pathogenesis of cardiovascular and renal diseases is uncertain [4,7,10].

Elevated aldosterone plasma levels are found in patients with hypertension (particularly resistant hypertension), heart failure, left ventricular remodeling post-MI, coronary artery disease, atrial fibrillation, sudden cardiac death and insulin resistance or metabolic syndrome [2,6,11–16]. The key role of aldosterone in the pathogenesis of cardiovascular and renal diseases is the basis for the use of mineralocorticoid receptor antagonists [2,5,7,17–19].

2. Mineralocorticoid receptor antagonists

First and second generation of mineralocorticoid receptor antagonists were steroidal antagonists (Table 1). Spironolactone

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Table 1
Disadvantages of steroidal mineralocorticoid receptor antagonists.

Spironolactone exhibits a poor selectivity for mineralocorticoid receptor and presents progestogenic and antiandrogenic activities
- Produces sexual adverse effects, such as painful gynecomastia, painful enlargement of the breasts, loss of libido, impotence, and menstrual irregularities

Eplerenone presents higher selectivity, but ~20–40-fold lower affinity for the mineralocorticoid receptor than spironolactone
- It presents up to a 500-fold lower affinity for androgen and progesterone receptors than spironolactone, leading to a negligible sexual adverse-effect profile
- Less efficient in patients with hypertension or with primary hyperaldosteronism

Both drugs present higher accumulation in the kidney than in the heart
- Plasma renin and angiotensin II levels and both plasma and tissular aldosterone levels remain elevated after long-term treatment ("aldosterone scape". This increase:
  - can potentially limit their efficacy
  - produces rapid non-genomic, mineralocorticoid receptor-independent effects, insensitive to mineralocorticoid receptor antagonists

Their clinical use is limited by hyperkalemia and kidney dysfunction, particularly in patients treated with renin–angiotensin–aldosterone system inhibitors or with impaired kidney function

and eplerenone when combined with background therapy, are effective for the treatment of resistant hypertension, metabolic syndrome, chronic kidney disease and diabetic nephropathy; they also exert antiarrhythmic properties (reduce atrial fibrillation in patients with hypertension or heart failure and sudden cardiac death in the early postmyocardial infarction period) and prevent myocardial remodeling and reduce hospitalizations and total mortality in patients with chronic heart failure or postmyocardial infarction [2,5,6,17,20–28].

Spironolactone is a potent, but non-selective mineralocorticoid receptor antagonist, with progestagenic and antiandrogenic effects responsible for frequent sexual adverse effects (gynecomastia, impotence and menstrual irregularities) [6,25]. Eplerenone presents higher selectivity for the mineralocorticoid receptors, but is 20- to 40-fold less potent than spironolactone [6,29,30].

Both drugs are competitive antagonists that bind to the ligand-binding domain of the, prevent that the mineralocorticoid receptors adopt the active conformation and render it transcriptionally inactive, i.e. produce a "passive" antagonism [31]. However, spironolactone and eplerenone are unable to stabilize an important helix (H12) in the C-terminal activation function 2 domain of mineralocorticoid receptor and cannot prevent the H12 helix from adopting the agonist conformation; this might explain the reported partial agonistic activity of steroidal mineralocorticoid receptor antagonists [32].

Unfortunately, and inspite their cardiovascular and renal benefits, spironolactone and eplerenone present several disadvantages and produces adverse events, including hyperkalemia and worsening of renal function, that limit their clinical use (Table 1). These disadvantages stimulated the development of new non-steroidal, highly potent and tissue-selective mineralocorticoid receptor antagonists, i.e. with higher cardiovascular/renal accumulation ratio than available steroidal mineralocorticoid receptor antagonists to avoid the risk hyperkalemia in patients at risk, i.e. with chronic kidney disease, diabetes or elderly people [4,6,25,33,34]. However, they should not completely spare renal effects as this might lead to hypokalemia and Na^+ retention among patients with aldosteronism [4]. Thus, a combined renal Na^+ excretion and a mild K^+ retention are clearly beneficial and demanded characteristics [33,34].

3. Finerenone

In 2004, researchers from Bayer reported that some 1,4-dihydropyridines with L-type calcium channel antagonists can act as mineralocorticoid receptor antagonists *in vitro* [35]. Further, chemical optimization of dihydropyridines led to the identification of a dihydronaphthyridine compound called finerenone (BAY 94-8862) [26,31,37].

Finerenone is a potent (IC_{50} 17.8 nM) and highly selective non-steroidal mineralocorticoid receptor antagonist (over 500-fold more selective for the mineralocorticoid receptor than for other steroid receptors) [31,33,34,37,38] (Table 2). Indeed, finerenone showed no L-type Ca^{2+} channel activity ($IC_{50} > 10\ \mu M$) and no significant effects on 65 different enzymes and ion channels [31,38,39]. This selectivity is predominantly mediated through a hydrogen bond donor interaction with the unique mineralocorticoid receptor-specific residues, Ala^{773} and Ser^{810} [32]. Interestingly, finerenone is a full antagonist in different cell types, including the gain-of function S810L mineralocorticoid receptor mutant, responsible for early-onset hypertension in men and gestational hypertension in women [31–33,37,40]. However, spironolactone or eplerenone display significant agonist activity on the mineralocorticoid receptor mutant [40,41].

Recent evidence showed that finerenone exhibits a different mechanism of action as ccompared steroidal mineralocorticoid

Table 2
Pharmacodynamic and pharmacokinetic characteristics of mineralocorticoid receptor antagonists [6,30,37,47].

	Spironolactone	Eplerenone	Finerenone
Class	Steroidal	Steroidal	Dihydropyridine
Mineralocorticoid receptor IC_{50}	24 nM	990 nM	17.8 nM
Androgenic receptor IC_{50}	77 nM	≥21,240 nM	≥10,000 nM
Glucocorticoid receptor IC_{50}	2410 nM	≥21,980 nM	≥10,000 nM
Progesterone receptor EC_{50}	740 nM	≥31,210 nM	≥10,000 nM
Tissue (cardiac/renal distribution)	6-fold higher in kidney	3-fold higher in kidney	Blanced between both tissues
Oral bioavailability	80–90%	69%	86.5%
C_{max}		1.8 h	0.5–1 h
Protein binding	88% (albumin and alpha-1-acid glycoprotein)	33–60%	8–12% (albumin)
Vd	10 L/kg	0.3–1.3 L/kg	
Metabolism	Deacetylation, dethiolation, tiomethylation	CYP3A4	CYP3A4 90% 2C8 10%
$t_{1/2}$	Spironolactone 1.4 h metabolites 13–15 h	4–6 h	1.7–2.8 h
Excretion	<1%	67% renal, 31% biliar	0.8% renal (unchanged)

IC_{50}: concentration of antagonist required to inhibit 50% activation of the receptor.