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NEW ANTIHYPERTENSION DRUG ESAXERENONE AS A NON-STEROIDAL MINERALOCORTICOID RECEPTOR ANTAGONISTS

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Hypertension is the leading modifiable risk factor for cardiovascular disease, which represents the top cause of death in China and worldwide. Esaxerenone (CS-3150) is non-steroidal, selective mineralocorticoid receptor drug which is currently approved in Japan for the treatment of hypertension . Its selection of antagonist of the mineral receptor (MR) is greater than 1,000 times compared to steroid hormone receptors, and 4-fold and 76-fold higher affinity for the MR relative to the current aldosterone antagonist spironolactone and eplerenone. In this review, we summarize pharmacological and clinical trial of esaxerenone and its possible use in essential hypertension.

Keywords: Esaxerenone (CS-3150), Hypertension , selective mineralocorticoid receptor antagonists, aldosterone

1.INTRODUCTION

Hypertension is defined as a systolic blood pressure ≥140 mmHg and/or a diastolic pressure ≥90 mmHg [Rodriguez et al(2014), Kanegae et al (2017)], which represents the top cause of deaths worldwide [Chockalingam et al(2006)]. Uncontrolled hypertension is related to coronary heart disease/myocardial infarction, heart failure[Iyer et al(2010)], and nephropathy[Nazar C.M.(2014)], all of which are classic manifestation of hypertensive end-organ damage[Schmieder R.E. (2010).]. Although monotherapy may be effective in 10-20% of patients with mild or mild-to-moderate hypertension[Morgan T. (1983)], failure to obtain the desired antihypertensive effect requires the concurrent use of a combination of antihypertensive agents as part of a multifactor strategy[Guerrero-García C. and Rubio-Guerra A.F. (2018)]. In addition, long-term research showed that most hypertensive patients require three or more antihypertensive drugs for adequate control [Mazza et al (2017)]. Triple drug therapy combinations usually include a renin–angiotensin system inhibitor (angiotensin converting enzyme inhibitors or angiotensin II-receptor blockers), a calcium channel blocker, and a diuretic[Mizuno et al (2008)]. The Japanese Guidelines for the Management of Hypertension (2014) recommend adding an aldosterone antagonist to the treatment regimen of patients with poorly controlled blood pressure or resistant hypertension[Shimamoto et al (2014)]. MR antagonists attribute blood pressure reduction through renal and extrarenal pathways. Treatment with MR antagonists indicated in decreased end-organ damage because aldosterone/ MR are involved in activation of a variety of pathologic processes including inflammation, remodeling, and fibrosis in several target organs. Spironolactone and eplerenone are both mineralocorticoid receptor antagonist drugs which are currently available for clinical treatment. Clinical evidence indicated that spironolactone and eplerenone have an effective strategy for the prevention and treatment for not only hypertension, but also heart failure and chronic kidney disease [Sun et al (2017)]. However, these agents may be associated with adverse events such as hyperkalaemia (spironolactone and eplerenone) and gynaecomastia (spironolactone)[Holaj et al (2015)]. Spironolactone,however, is a potent competitive MR antagonist but showed poor selective mineralocorticoidal receptance because it not only inhibits aldosterone but also inhibits the androgen and progesterone receptors. It is the reason of spironolactone has side effects such as gynecomastia, impotence, and menstrual irregularities. Moreover at high concentrations it may also interfere with the glucocorticoid receptor. Eplerenone, a second generation MR antagonist, was used for the treatment of hypertension and heart failure. This MR antagonist is much more selective for MR than spironolactone, which reduces sex hormone-related adverse effects. But its potency is less than to that of spironolactone, and requires higher doses in clinical treatment.

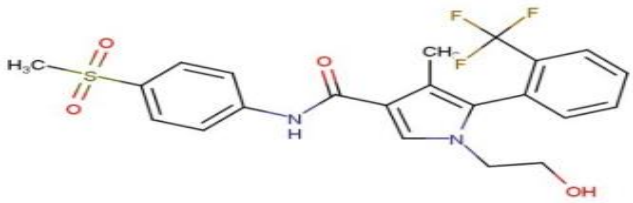
Esaxerenone (CS-3150) is a non-steroidal antimineralocorticoid drug currently developed for the treatment of hypertension, essential hypertension, hyperaldosteronism, and diabetic nephropathies[Duggan S.(2019)]. Esaxerenone selected the antagonist of the mineral receptor (MR) with higher potency than spironolactone and eplerenone. The selection of antagonist of the mineral receptor (MR) is greater than 1,000 times for this receptor compared to steroid hormone receptors [Arai et al (2015)]. In this review, we summarize the pharmacological and clinical trial of esaxerenone and its possible treatment in essential hypertension.

2.THE ROLE OF ALDOSTERONE AND THE MINERALOCORTICOID RECEPTOR IN BLOOD PRESSURE, CARDIOVASCULAR AND RENAL DISEASE

The kidney fluid system is a predominant regulator of blood pressure, and reduced kidney function constitutes a major cause of hypertension [Judd E. and Calhoun D.A.(2015)]. Long term hypertension treatment is closely associated with an overlapping and intermingled cause and effect relationship. Declines in kidney function are typically associated with rises in blood pressure (BP), and sustained elevations in BP hasten the progression of kidney function decline [Judd E. and Calhoun D.A.(2015), Zhang et al (2013)]. Aldosterone is the most important mineralocorticoid hormone with a well-known effect on regulator of the potassium reabsorption and water balance of the body which plays an important role in blood pressure control [1 Muñoz-Durango et al (2016)]. Aldosterone binds to mineralocorticoid receptors (MR) through a ligand-activated transcription factor for acting physiological function[Shibata S. and Fujita T.(2011)] . Especially an increase in aldosterone combination with inappropriate salt and redox status can damage multiple tissues such as heart and kidneys that express the MR. Blockade of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has become a leading strategy in slowing the progression of chronic heart and kidney disease[Brewster et al (2003)]. Indeed, aldosterone mineralocorticoid receptor binding promotes cardiac and renal remodeling by inducing myocardial fibrosis and glomerular and tubular sclerosis[Leopold J.A.(2011)][Wright J.and Hutchison A.(2009)]. Glomerular and tubular sclerosis represent the mainstays of chronic disease progression[Woroniecki R.P., Schnaper H.W.(2009)]. Previous research indicated that aldosterone and MR activation play an important role in the pathophysiology of cardiovascular and renal disease. Thus use of MR antagonists is a new therapeutic strategy in controlling blood pressure, chronic renal disease progression [Shavit et al (2012)] and cardiovascular remodeling [Kapelios et al (2019)]. Indeed, spironolactone and eplerenone, given in combination with ACE inhibitors or ARBs, are now standard treatments in managing congestive heart failure [Hargovan M. and Ferro A.(2014).] and have become increasingly used in the care of proteinuric chronic kidney disease (CKD) patients [Bolignano et al (2014)]. However, the clinical use of these mineralocorticoid receptor antagonists is limited by their safety and efficacy profiles, especially in CKD patients due to the high incidence of hyperkalemia [Montford J.R. and Linas S.(2017)]. Esaxerenone as a non-steroidal antimineralocorticoid drug has recently been developed to obtain a greater selective receptor block and fewer side-effects for hyperkalemia and thereby making the drugs suitable for administration to CKD patients [Ito et al (2018)]. This ‘aldosterone breakthrough’ may contribute to the progression of renal and cardiovascular dysfunction. Patients experiencing aldosterone breakthrough during treatment with RAAS inhibiting agents may therefore benefit from treatment with MR antagonists Box 1.

Box 1. Drug summary

Drug name: Esaxerenone
Code name:CS-3150
Stage of development: Phase III
Indication: Hypertension
Mechanism: Mineralocorticoid receptor antagonists
Route of administration: oral
Molecular Formula: C22H21F3N2O4S
Molecular Weight: 466.481
Storage: Room temperature
Chemical structure:



3.PHARMACODYNAMICS

Esaxerenone is a new nonsteroidal mineralocorticoid receptor antagonist. In the radioligand-binding assay,CS-3150 exerted admirable binding to MR with an IC50 value of 9.4 nM, and its efficacy was better to that of spironolactone and eplerenone, whose IC50s were 36 and 713 nM, respectively (Table. 1)[Yamada et al (2019)]. Its selection of mineralocorticoid is at least 1000-fold higher than other steroid hormone receptors, glucocorticoid receptor, androgen receptor and progesterone receptor (Table. 1) [aria et al(2015),yamada et al (2019)]. The gene assay indicated that CS-3150 was 18 and 260 times more effective than spironolactone and eplerenone [aria et al(2015),yamada et al (2019)]. Furthermore, at high concentration (5 μM) esaxerenone also exerts no agonistic effect or agonistic effect on mineralocorticoid receptors, glucocorticoid receptors, androgen receptors and progesterone receptors [Arai et al (2015)]. CS-3150 treatment abolished aldosterone-induced decrease in urinary Na+/K+ ratio, and this suppressive potency was stronger and longer-lasting than that of spironolactone and eplerenone in adrenalectomized rats [Arai et al (2015)].Chronic treatment with CS-3150 (3 mg/kg) inhibited blood pressure elevation induced by deoxycorticosterone acetate (DOCA)/salt loading in rats with an additional protective effect on the heart and kidneys, and this antihypertensive effect was more potent than that of spironolactone (30 mg/kg) and eplerenone (30 mg/kg) (Table. 2) [Arai et al (2015)]. These results showed that this agent could be useful for the treatment of hypertension, cardiovascular and renal disorders.

Table 1. In vitro potency of spironolactone, eplerenone and esaxeranone vs different MR agonists

	Spironolactone	**Eplerenone**	**Esaxeranone**
Trade name	Aldactone	Inspra	Minnebro
Class	Steroidal	Steroidal	None Steroidal
Human Mineralocorticoid Receptor IC50 (nM)	66	970	3.7
Androgen Receptor IC50 (nM)	133	≥100000	>10000
Glucocorticoid Receptor IC50 (nM)	764	3060	>10000
Progesterone Receptor IC50 (nM)	1200	≥100000	>10000
Half-life (h)	1.4	4–6	6.5-6.9

IC50, concentration of antagonist required to inhibit 50% activation of receptor.

Table 2. Effects of CS-3150, spironolactone and eplerenone on heart rate and systolic blood pressure in DOCA/salt-loading rats

	Control	**vehicle**	**CS-3150**	**SPL30**	**EPL30**
HR pre	363±9	366±4	358±10	370±15	387±9
HR 2wks	354±9	370±18	355±4	354±12	378±19
SPB pre	121±2	119±3	117±2	121±3	119±4
SPB 2wks	145±4	187±6##	131±4**	181±8	191±5

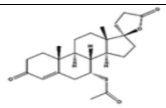
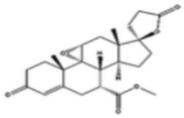
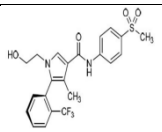
CS-3150 (3 mg/kg)-treated group; **SPL30**: spironolactone (30 mg/kg)-treated group. **EPL30:** eplerenone (30 mg/kg)-treated group.
HR pre: heart rate before compound administration, **HR 2wks**: heart rate 2 weeks after compound administration.
SPB Pre: systolic blood pressure before compound administration. **SPB 2wks**: systolic blood pressure 2 weeks after compound administration.
$p < 0.01$ vs. Control by a Student's t-test; ** $p < 0.01$ vs. Vehicle by a Student's t-test

4.PHARMACOKINETICS

The pharmacokinetic (PK) profile of esaxerenone has been examined in healthy Japanese subjects . In the healthy subject Esaxerenone (5mg) is absorbed rapidly following oral doses with Tmax (maximal plasma concentrations) reached between 2.5 - 3.5 hours after dosing. The absolute bioavailability is high, with approximately 90% of the dose being absorbed, ingestion of food didn't have influence on esaxerenone PK [Kurata et al (2019)]. After oral the administration of [14C]-esaxerenone, most of the radioactivity recovery was eliminated 54.0% by the fecal route and 38.5% was recovered in the urine. Low urinary excretion of esaxerenone suggested that PK of esaxerenone would not be affected by renal dysfunction. Because one of the aims of esaxerenone is diabetic nephropathy treatment, this feature is considered favorable. The estimated elimination half-life was 30 hours which is higher than the half-lives of the active metabolites of spironolactone and eplerenone respectively 12 h and 3 - 5 h (Table 3). The T1/2 appears to be suitable for once-daily dosing because efficacy is expected to be sustained throughout the day(Table 3) [kato et al (2018)]. The total apparent clearance of drug is 4.0-5.2 l h and apparent volume of distribution also remained constant.
The radioactivity was widely distributed to whole body, with the exception of a low distribution to the central nervous

system . It has been demonstrated that activation of MR localized in kidney or heart is directly involved in the pathogenesis of renal or cardiac damage [yamada et al (2017)]. The tissue/blood radioactivity ratios in kidney and heart at 2 h post-dose of [14C]esaxerenone in rats were 7.14 and 6.12, respectively. While spironolactone and eplerenone typically build up to higher concentrations in the kidney vs. the heart (table 3) [yamada et al (2017), Bramlage et al (2016)], a property that may contribute to seriously hyperkalaemic adverse event, exaserenone achieves an equivalent distribution between cardiac and renal compartments [yamada et al (2017)].

Table 3. Pharmacokinetic parameters of spironolactone, eplerenone and esaxeranone to rat Spironolactone Eplerenone Esaxeranone

	Spironolactone	**Eplerenone**	**Esaxeranone**
Structure			
Tissue distribution kidney vs heart	x 6 higher in kidney	x 4 higher in kidney	equal
T max	66	970	3.7
Half-life ($T_{1/2}$)(h)	>12	3-5	30

Tmax: the time to reach the maximum plasma concentration
T1/2 : the time required for a radioactive element to reduce half of its initial mass

5. CLINICAL EFFICACY

5.1 **Essential hypertension**

Essential hypertension and end-organ damage are the leading risk factors for morbidity and mortality throughout the world[Bolívar J.J.(2013)]. Esaxerenone demonstrated antihypertensive effects and safety compared to eplerenone as active control in patients with essential hypertension in a pivotal randomised, double-blind, parallel-group [Ito et al (2019a)]. The present findings indicated that 2.5 and 5 mg/day esaxerenone are optimal dosages based on the efficacy and safety for essential hypertension. Esaxerenone 2.5mg/day showed a non-inferior antihypertensive effect to eplerenone 50mg/day in essential hypertension[Ito et al (2019a)]. Previous non-clinical studies have shown that esaxerenone has no agonistic or antagonistic effects on glucocorticoid, progesterone, or androgen receptors. The clinical study therefore supports this conclusion as evidenced by the absence of sex hormone-related adverse effects. [Ito et al (2019a)]. The study also indicated that the risk of increased serum K+ levels were not clear differences as compared with placebo. However, the concentration of K+ in serum generally increased in proportion with esaxerenone dose and reached a maximum value at week 1 or week 2 of treatment, this increase did not continue through to week 12 [Ito et al (2019a)]. Hyperkalemia was only detected in one patient in the esaxerenone 5 mg/day group, however, this was transient and this patient recovered without further treatment. The perceived limitations of this study include the small sample size, short observation period (12 weeks), and open-label nature of the comparator eplerenone. However, a randomized, double-blind, long-term phase 3 study has been completed recently to further investigate the safety and efficacy of esaxerenone therapy in essential hypertension patients [Ito et al (2019)]. In addition, the safety and efficacy profiles of esaxerenone therapy in other patient populations, such as those affected by chronic kidney disease and type 2 diabetes mellitus with albuminuria, have been assessed in several phase 3 studies that have been completed recently.

5.2 Diabetic nephropathy

The preventive effect of the molecule on hypertension and cardiorenal injury was tested in Dahl salt-sensitive hypertensive rats where the administration of 0.5 mg/kg and higher doses suppressed the elevation of systolic blood pressure [Arai et al (2015)]. Moreover, the same dose was able to inhibit the increase in urinary protein excretion which appeared after 7 weeks of salt loading [Arai et al (2015)]. Esaxerenone, a non-steroidal mineralocorticoid receptor antagonist, showed renal protective effects in clinical studies for DN in Type2 diabetic patients. Phase 2 study evaluated the efficacy and safety of esaxerenone indicated that adding esaxeranone at 1.25, 2.5 and 5 mg/day for 12 weeks to renin-angiotensin system inhibitor significantly decreased urinary albumin-to-creatinine ratio in patients with type 2 diabetes mellitus and microalbuminuria[Ito et al (2019b)]. Esaxerenone is also being tested in humans in phase III Diabetic nephropathies but no significant results have been published to date.

5.2. Adverse events

The serious side effects with esaxerenone are very rare, the most common adverse events indicated were hyperkalemia

,nasopharyngitis, bruises, dizziness on standing up, and kidney dysfunction [Ito et al (2019b)]. Among these adverse events, hyperkalemia was reported to be dose dependent. In the treatment with 5mg esaxerenone group, dizziness on standing up and kidney dysfunction were only observed in the treatment 5mg esaxerenone group. There are no side effects related to sexual hormones. Serious adverse events in patients included one case each of intestinal obstruction (esaxerenone 1.25-mg/d group), cerebral infarction (esaxerenone 2.5-mg/d group), and carotid stenosis (esaxerenone 5-mg/d group) [Ito et al (2019b)]. No deaths were observed in these studies [Ito et al(2019a),Ito et al (2019b)]. Incidence of hyperkalemia (esaxerenone ≤2.5 mg/d) had similar to those in the placebo group. All side effects were slight, and patients got over without any treatment.

CONCLUSION

Esaxerenone showed good efficacy and safety profiles in Japanese essential hypertensive patients. Moreover, supplementing esaxerenone to renin-angiotensin system inhibitor significantly decreases urinary albumin-to-creatinine ratio in patients with type 2 diabetes mellitus and microalbuminuria. CS-3150 exerted strong antihypertensive and cardiorenal protective effects in DS rats, and these effects were much greater than those observed with spironolactone and eplerenone. Therefore, CS-3150 could be a promising mineralocorticoid receptor antagonist with an improved profile for the treatment of hypertension and cardiorenal disorders.

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REFERENCES

Arai K., Homma T., Morikawa Y., Ubukata N., Tsuruoka H., Aoki K., Ishikawa H. , Mizuno M. , Sada T. (2015).Pharmacological profile of CS-3150, a novel, highly potent and selective non-steroidal mineralocorticoid receptor antagonist, European journal of pharmacology 761 (2015) 226-34.

Arai K., Tsuruoka H., Homma T.(2015) CS-3150, a novel non-steroidal mineralocorticoid receptor antagonist, prevents hypertension and cardiorenal injury in Dahl salt-sensitive hypertensive rats, European journal of pharmacology 769 (2015) 266-273.

Bolignano D., Palmer S.C., Navaneethan S.D., Strippoli G.F.(2014) Aldosterone antagonists for preventing the progression of chronic kidney disease, The Cochrane database of systematic reviews (4) (2014) Cd007004.

Bolívar J.J.(2013) Essential hypertension: an approach to its etiology and neurogenic pathophysiology, International journal of hypertension 2013 (2013) 547809.

Bramlage P., Swift S.L., Thoenes M., Minguet J., Ferrero C., Schmieder R.E.(2016) Non-steroidal mineralocorticoid receptor antagonism for the treatment of cardiovascular and renal disease, European Journal of Heart Failure 18(1) (2016) 28-37.

Brewster U.C, Setaro J.F., Perazella MA.(2003). The renin-angiotensin-aldosterone system: cardiorenal effects and implications for renal and cardiovascular disease states, The American journal of the medical sciences 326(1) (2003) 15-24.

Chockalingam A. , Campbell N.R. , Fodor J.G.(2006) Worldwide epidemic of hypertension, The Canadian journal of cardiology 22(7) (2006) 553-5.

Duggan S.(2019). Esaxerenone: First Global Approval, Drugs 79(4) (2019) 477-481.

Guerrero-García C. , Rubio-Guerra A.F. (2018). Combination therapy in the treatment of hypertension, Drugs in context 7 (2018) 212531.

Hargovan M., Ferro A.(2014). Aldosterone synthase inhibitors in hypertension: current status and future possibilities, JRSM cardiovascular disease 3 (2014) 2048004014522440.

Holaj R., Rosa J., Zelinka T., Štrauch B., Petrák O., Indra T., Šomlóová Z., Michalský D., Novák K, Wichterle D., Widimský J., Jr.(2015). Long-term effect of specific treatment of primary aldosteronism on carotid intima-media thickness, Journal of hypertension 33(4) (2015) 874-82; discussion 882.

Ito S., Ito H., Rakugi H., Okuda Y., Yoshimura M., Yamakawa S.(2018). A DOUBLE BLIND PHASE III STUDY OF ESAXERENONE (CS-3150) COMPARED TO EPLERENONE IN PATIENTS WITH ESSENTIAL HYPERTENSION (ESAX-HTN STUDY), Journal of hypertension 36 (2018) e239.

Ito S., Itoh H., Rakugi H., Okuda Y., Yamakawa S.(2019). Efficacy and safety of esaxerenone (CS-3150) for the treatment of essential hypertension: a phase 2 randomized, placebo-controlled, double-blind study, Journal of Human Hypertension (2019a).

Ito S., Shikata K., Nangaku M., Okuda Y., Sawanobori T.(2019b). Efficacy and Safety of Esaxerenone (CS-3150) for the Treatment of Type 2 Diabetes with Microalbuminuria A Randomized, Double-Blind, Placebo-Controlled, Phase II Trial. Journal of Clinical Journal of American Society Nephrology,2019

Iyer A.S., Ahmed M.I. , Filippatos G.S., Ekundayo O.J., Aban I.B., Love T.E., Nanda N.C., Bakris G.L., Fonarow G.C., Aronow W.S., Ahmed V.(2010).Uncontrolled hypertension and increased risk for incident heart failure in older adults with hypertension: findings from a propensity-matched prospective population study, Journal of the American Society of Hypertension : JASH 4(1) (2010) 22-31.

Judd E. , Calhoun D.A.(2015). Management of hypertension in CKD: beyond the guidelines, Advances in chronic kidney disease 22(2) (2015) 116-22.

Kanegae H., Oikawa T., Okawara Y., Hoshide S., Kario K.(2017). Which blood pressure measurement, systolic or diastolic, better predicts future hypertension in normotensive young adults?, Journal of clinical hypertension (Greenwich, Conn.) 19(6) (2017) 603-610.

Kapelios C.J., Murrow J.R., Nuhrenberg T.G., Montoro Lopez M.N.(2019)Effect of mineralocorticoid receptor antagonists on cardiac function in patients with heart failure and preserved ejection fraction: a systematic review and meta-analysis of randomized controlled trials, Heart failure reviews 24(3) (2019) 367-377.

Kato M., Furuie H., Shimizu T. , Miyazaki A., Kobayashi F., Ishizuka H.(2018).Single- and multiple-dose escalation study to assess pharmacokinetics, pharmacodynamics and safety of oral esaxerenone in healthy Japanese subjects, British journal of clinical pharmacology 84(8) (2018) 1821-1829.

Kurata A., Furuie H., Ishizuka T., Nakatsu T., Shimizu T., Kato M., Nishikawa Y., Ishizuka H.(2019). Absolute Bioavailability of Esaxerenone and Food Effects on its Pharmacokinetics After a Single Oral Dose in Healthy Japanese Subjects: An Open-Label Crossover Study, Advances in therapy (2019).

Leopold J.A.(2011). Aldosterone, mineralocorticoid receptor activation, and cardiovascular remodeling, Circulation 124(18) (2011) e466-8.

Mazza A. , Lenti S., Schiavon L., Sacco A.P., Dell'Avvocata F. , Rigatelli G., Ramazzina E. (2017).Fixed-Dose Triple Combination of Antihypertensive Drugs Improves Blood Pressure Control: From Clinical Trials to Clinical Practice, Advances in therapy 34(4) (2017) 975-985.

Mizuno Y., Jacob R.F. , Mason R.P. (2008). Effects of Calcium Channel and Renin–Angiotensin System Blockade on Intravascular and Neurohormonal Mechanisms of Hypertensive Vascular Disease, American Journal of Hypertension 21(10) (2008) 1076-1085.

Montford J.R., Linas S.(2017). How Dangerous Is Hyperkalemia?, Journal of the American Society of Nephrology : JASN 28(11) (2017) 3155-3165.

Morgan T. (1983). Monotherapy in the treatment of hypertension, Chest 83(2 Suppl) (1983) 419-22.

Muñoz-Durango N., Fuentes C.A., Castillo A.E., González-Gómez L.M., VecchiolaA., Fardella C.E., KalergisA.M.(2016) Role of the Renin-Angiotensin-Aldosterone System beyond Blood Pressure Regulation: Molecular and Cellular Mechanisms Involved in End-Organ Damage during Arterial Hypertension, International journal of molecular sciences 17(7) (2016).

Nazar C.M.(2014).Mechanism of hypertension in diabetic nephropathy, Journal of nephropharmacology 3(2) (2014) 49-55.

Rodriguez C.J. , Swett K., Agarwal S.K., Folsom A.R., Fox E.R., Loehr L.R., Ni H., Rosamond W.D., Chang P.P.(2014). Systolic blood pressure levels among adults with hypertension and incident cardiovascular events: the atherosclerosis risk in communities study, JAMA internal medicine 174(8) (2014) 1252-61.

Schmieder R.E. (2010). End organ damage in hypertension, Deutsches Arzteblatt international 107(49) (2010) 866-73.

Shavit L., Lifschitz M.D., Epstein M.(2012). Aldosterone blockade and the mineralocorticoid receptor in the management of chronic kidney disease: current concepts and emerging treatment paradigms, Kidney International 81(10) (2012) 955-968.

Shibata S., Fujita T.(2011). The kidneys and aldosterone/mineralocorticoid receptor system in salt-sensitive hypertension, Current hypertension reports 13(2) (2011) 109-15.

Shimamoto K., Ando K., Fujita T., Hasebe N., Higaki J., Horiuchi M., Imai Y., Imaizumi T., Ishimitsu T., Ito M., Ito S., Itoh H., Iwao H., Kai H., Kario K., Kashihara N., Kawano Y., Kim-Mitsuyama S., Kimura G., Kohara K., Komuro I., Kumagai H., Matsuura H., Miura K., Morishita R., Naruse M., Node K., Ohya Y., Rakugi H., Saito I., Saitoh S., Shimada K., Shimosawa T., Suzuki H., Tamura K., Tanahashi N., Tsuchihashi T., Uchiyama M., Ueda S., Umemura S. (2014). The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014), Hypertension research : official journal of the Japanese Society of Hypertension 37(4) (2014) 253-390.

Sun L.J. , Sun Y.N. , Shan J.P., Jiang G.R (2017). Effects of mineralocorticoid receptor antagonists on the progression of diabetic nephropathy, Journal of diabetes investigation 8(4) (2017) 609-618.

Woroniecki R.P., Schnaper H.W.(2009). Progression of glomerular and tubular disease in pediatrics, Seminars in nephrology 29(4) (2009) 412-24.

Wright J., Hutchison A.(2009) Cardiovascular disease in patients with chronic kidney disease, Vascular health and risk management 5 (2009) 713-22.

Yamada M., Mendell J., Takakusa H., Shimizu T., Ando O.(2019) Pharmacokinetics, Metabolism, and Excretion of [(14)C]Esaxerenone, a Novel Mineralocorticoid Receptor Blocker in Humans, Drug metabolism and disposition: the biological fate of chemicals 47(3) (2019) 340-349.

Yamada M., Takei M., Suzuki E., Takakusa H., Kotsuma M., Washio T., Murayama N., Inoue S.I., Izumi T.(2017), Pharmacokinetics, distribution, and disposition of esaxerenone, a novel, highly potent and selective non-steroidal mineralocorticoid receptor antagonist, in rats and monkeys, Xenobiotica; the fate of foreign compounds in biological systems 47(12) (2017) 1090-1103.

Zhang Y.P., Zuo X.C., Huang Z.J., Kuang Z.M., Lu M.G., Duan D.D., Yuan H.(2013).The impact of blood pressure on kidney function in the elderly: a cross-sectional study, Kidney & blood pressure research 38(2-3) (2013) 205-16.