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Modern possibilities of angiotensin II receptor antagonists therapy in clinical practice

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Renin-angiotensin aldosterone system hyperactivation is one of the main mechanisms of cardiovascular diseases progression. Nowadays angiotensin II receptor antagonists have a sufficient evidence base as antihypertensive drugs with organoprotective properties. This article presents and substantiates the possibilities of one of angiotensin II receptor antagonist — telmisartan, in various clinical cases from the perspective of evidence-based medicine.

Key words: *angiotensin II receptor antagonists, telmisartan, organoprotective properties, cardiovascular risk.*

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Cardiovascular disease (CVD) is the leading global cause of death. CVD mortality is annually about 31.5% among all-cause mortality and about 45% among noncommunicable diseases mortality [1]. According to 2014 data, half of all-cause mortality in the Russian Federation (44.9% men, 55.4% women) have CVD cause, and over 80% is associated with coronary artery disease (CAD) and brain strokes [2].

Large international studies INTERSTROKE and INTERHEART have shown that arterial hypertension (AH) is one of the main risk factor (RF) for mortality and disability in population. The prevalence of AH among people of working age has recently increased in Russia to 43%, that can be associated with high prevalence of obesity, especially among men [3].

At the same time, it has been shown that high-risk strategies that include identifying patients with high CVD risk with the following RF reduction are effective for primary prevention of cardiovascular disease and its complications [4].

According to the results of many clinical studies, isolated RFs are found only in 10–15% of cases. Therefore, 15% of patients with AH also had lipid metabolism disturbances or obesity, and 64% of patients had a combination of more than three RFs [5]. The results of prospective studies showed that the development or course of CVD is more severe in patients with the combination of, even moderately expressed, RFs compared with one RF. In particular, the RROCAM study showed that a combination of more than two CVD RFs leads to significant increase of sudden death and myocardial infarction (MI) risks (200 among 1000 patients at 8-year follow-up) [6,7].

Today experts agree that RFs should be eliminated as much as possible [8]. Such measures are especially important for people at high and very high CVD risk. According to the Cardiovascular Epidemiology in Russian Federation (ESSE-RF) study, such patients make up about 1/3 of the Russian population [9]. They often require hyperlipidemia, AH, and carbohydrate metabolism disorders management.

The main requirements for modern antihypertensive drugs are:

- solid evidence base;
- achievement of target blood pressure (BP) levels with minimal adverse effects;
- positive or neutral metabolic effect [10].

From this point of view, angiotensin II receptor's antagonists (ARAs II) are of special interest. Nowadays, the drugs affecting renin-angiotensin-aldosterone system (RAAS) are used in AH and chronic heart failure (CHF) treatment, CVD prevention [1, 10, 11]. RAAS hyperactivation is a key mechanism for CVD development and progression according to cardiovascular continuum. The concept of the cardiovascular continuum includes the development of the pathological process from RFs to target organ damage, including heart and blood vessels remodeling and heart failure development [12].

The main RAAS mediator is angiotensin II (AT II). AT II acts on two main subtypes of membrane-bound receptors — AT1 and AT2. AT1 receptors are expressed predominantly in the smooth muscles of blood vessels, heart, liver, adrenal cortex, kidneys, lungs, nerve fibers and some brain areas.

Main AT1 receptors activation effects include:

- blood pressure increase (due to direct vasoconstrictor effect and renal glomerular arterioles spasm, followed by release of renin by juxtaglomerular apparatus cells);
- increased proximal renal tubular sodium reabsorption;
- increased aldosterone, vasopressin and endothelin-1 secretion;
- increased norepinephrine release from sympathetic nerve endings followed by sympathoadrenal system activation;
- stimulation of proliferation of endothelial and vascular smooth muscle cells and cardiomyocytes;
- pro-inflammatory and pro-oxidative effects [13].

Prolonged (or even moderate) increase in AT II concentrations in patients with long-term catecholamine load (sympathetic nervous system activation, stress) and the accumulation of reactive oxygen species in tissues are leading mechanisms for the development of CVD, blood vessels and myocardium remodeling. Experimental studies have shown that AT II causes myocardial hypertrophy even in patients with normal BP [13].

The activation of type 2 receptors, that are mostly expressed in the brain and adrenal glands, causes vasodilation, inhibits smooth muscle and endothelial cells proliferation, reduces cardiomyocyte hypertrophy, suppresses cell apoptosis, and decreases calcium ions concentration inside the cell.

The discovery of specific AT II receptors stimulated the creation of its receptor's selective antagonists. Losartan, first ARA, was synthesized in 1986. Later, other representatives from this group were synthesized. They had class-specific properties and individual characteristics that allowed to use them in

the management of patients with different comorbidities [13]. ARAs became effective agents for the treatment and prevention of CVD with unique properties, including favorable metabolic profile [14]. The so-called "pleiotropic activity" can be explained by AT2 receptors stimulation during selective blockade of AT1 receptors that leads to vasodilation, inhibition of smooth muscle cells proliferation and natriuretic effect, and increases antioxidant defense [15,16].

In addition, some ARAs, for example, telmisartan, stimulate PPAR-γ receptors that activate peroxisome proliferation and reduces inflammation, oxidative stress and smooth muscle cells proliferation, regulates intracellular glucose and lipid metabolism [17].

Pharmacokinetic and pharmacodynamic features of telmisartan

Telmisartan is a potent, long-lasting ARA that selectively and irreversibly blocks AT1 receptors without affecting other receptor's systems involved in the regulation of blood circulation. It is known that the degree of affinity to type 1 angiotensin II receptors is different and has the following decreasing sequence: telmisartan → olmesartan → candesartan → eprosartan → EXP 3174 (active metabolite of losartan) → valsartan → losartan [1, 18–20].

High lipophilicity in combination with a large volume of distribution gives telmisartan the ability to penetrate into tissues and cells, and long half-life provides stable blood pressure in patients with once daily dosage from 40 to 80 mg. Peak plasma concentration of telmisartan (Cmax) is attained within approximately 0.5–1 hour after oral administration. A state plasma concentration is achieved in 5–7 days after administration, and cumulation of the medication after prolonged treatment is unlikely. The bioavailability of telmisartan is 50 %. Plasma protein binding is 99.5 %, mainly with albumin and α1-acid glycoprotein. Telmisartan is metabolized via conjugation with glucuronic acid. Metabolites are pharmacologically inactive. The elimination half-life is over 20 hours. It is excreted through the intestine unchanged, kidneys excretion is less than 2 %. Therefore, it is safe to use telmisartan in patients with renal pathology. The high antihypertensive effectiveness of the drug is combined with its high tolerance [21–23]. One of the new and promising telmisartan mechanisms of action is the ability to stimulate g-receptors, activated by peroxisome proliferator-activated receptor gamma (PPAR-γ). The effects of PPAR-γ receptors stimulation are numerous and diverse. The most well-known is the effect on insulin sensitivity, that is used in patients with type 2 diabetes mellitus (T2DM) with predominant insulin resistance. It is also suggested that, together with other subtypes of PPAR-γ receptors, they regulate the expression of endothelial cell adhesion molecules affecting thrombus formation and the formation of cellular immune response to vasculitis. The production of pro-inflammatory cytokines, including tumor necrosis factor alpha, interleukin-6 and interleukin-1β, is also downregulated by PPAR-γ receptors. Moreover, PPAR-γ receptors can modulate oxidative stress processes by increasing the expression of opposing factors, such as CuZn superoxide dismutase. Another well-known property of PPAR-γ receptors is the ability to reduce macrophage matrix metalloproteinases concentration, that are responsible for atherosclerotic plaque destabilization, as well as the formation and accumulation of glycation end-products. It should be emphasized that the affinity of telmisartan for this receptor is approximately 10–30 times higher compared with other ARAs. Therefore, telmisartan can be called a selective modulator of PPAR-γ receptors [24–26].

The described above effects and strong evidence base allowed to include ARA into the first-line antihypertensive treatment. According to guidelines, ARAs are indicated for primary and secondary CVD prevention in patients with ACE inhibitors intolerance, microalbuminuria, impaired renal function and chronic kidney disease, metabolic syndrome (MS) and diabetes mellitus (DM), myocardial infarction, left ventricular hypertrophy (LVH), atrial fibrillation and CHF. Telmisartan is prescribed to decrease cardiovascular mortality in patients with atherothrombotic CVD (CAD, peripheral artery disease, stroke history) and patients with T2DM with target organ damage [1, 18, 27].

ARAs role in the treatment of patients with CVD is defined, but its use in other clinical situations haven't been clearly established yet. Therefore, we have to rely on the results of multicenter clinical trials.

Antihypertensive effectiveness of telmisartan was evaluated in the MICARDIS Community Access Trial (MICCAT-2) that included 1615 patients with AH. 79 % of patients achieved target BP levels. BP daily monitoring in patients during telmisartan treatment revealed significant BP decrease in the early morning hours, when patients with CVD are the most vulnerable [29]. Multicenter randomized PRISMA I and II trials compared hypotensive effects of once-daily telmisartan of 40–80 mg and ramipril of 2.5–10 mg in

patients with grades I—II AH using daily BP monitoring. After 14 weeks of treatment, the average daily BP reached target levels in telmisartan group that was superior to ramipril group [30, 31]. Patients treated with telmisartan had higher decrease in BP in the last 6 hours of the drug action (early morning hours) compared with ramipril group ($p<0.05$).

Prospective ATHOS study included 1000 elderly patients (aged over 60 years) with predominant systolic blood pressure (SBP) increase and analyzed daily BP profile after 6 weeks of once-daily telmisartan of 40–80 mg with hydrochlorothiazide of 12.5 mg treatment compared with once-daily amlodipine of 5–10 mg with hydrochlorothiazide of 12.5 mg treatment [32]. SBP decrease for the last 6 hours of the dosing interval was comparable between groups of elderly patients. However, the SBP control during 24-hour monitoring in the telmisartan group was significantly higher compared with amlodipine group. Early discontinuation of treatment was observed more often in amlodipine group (11.3%), compared with telmisartan group (5%), mainly due to peripheral edema ($p<0.05$).

Other comparative studies have demonstrated the benefits of telmisartan by the duration and strength of antihypertensive action, especially in the early morning hours, even if the medication was missed, compared with losartan, candesartan and valsartan [29,33].

Many multicenter trials studied the effect of medications on cardiovascular morbidity and mortality, the most significant of them are: ONTARGET, TRANSCEND, PRoFESS.

The ONTARGET study showed the ***effectiveness of telmisartan in reducing cardiovascular mortality***, MI, stroke, or hospitalization for heart failure, similar to ramipril [34].

The TRANSCEND study showed significant decrease in hospitalizations for CVD and MI in patients with AH and high cardiovascular risk and arterial damage of atherosclerotic/diabetic origin during telmisartan treatment. The decrease of LVH severity has also been proven [35]. A combined analysis of the data obtained in PRoFESS study confirmed the effectiveness of telmisartan in cardiovascular mortality, MI and stroke reduction [36]. Comparative retrospective analysis of Lin J.W. et al. (2014) included about 700 thousand patients with high cardiovascular risk and demonstrated potential differences between the most common AT1 receptor blockers in terms of all-cause and cardiovascular mortality reduction [37]. The telmisartan or olmesartan group had 7% lower relative risk of all-cause mortality compared with losartan. A study of the causes of deaths showed that olmesartan reduced relative risk of cardiovascular mortality by 16%, and telmisartan reduced relative risk of cerebrovascular disease mortality by 11% compared with losartan.

ARAs have proven its ***effectiveness in acute cerebrovascular accident frequency reduction, and cerebrovascular complications and cognitive impairment prevention.*** The PRoFESS study showed that telmisartan after 6 months of therapy significantly reduced the risk of recurring stroke compared with placebo [38,39]. A prospective cohort analysis of data obtained from over 800 thousand patients aged over 65 years showed significant decrease in the relative risk of dementia and an improvement in cerebral blood flow in several brain areas according to single-photon emission computed tomography [40,41].

The ability of ARAs to activate PPAR-γ receptors underlies many ***metabolic effects*** of this class of medications. Numerous studies have demonstrated that PPAR-γ receptors contribute to atherogenesis, insulin resistance, oxidative stress, inflammation and fibrosis. Drugs that increase the activity of these receptors can significantly increase insulin sensitivity, reduce the risk atherosclerosis.

Most clinical studies confirmed no effect of telmisartan on plasma lipid levels. However, there are few studies that have shown a significant decrease in total cholesterol (TC), low-density lipoproteins (LDL) and triglycerides (TG) plasma levels compared with baseline in patients with MS during telmisartan treatment [42–44]. One of the studies have shown significant decrease in the amount of visceral fat and increase of high-density lipoproteins (HDL) [43]. This phenomenon is pathogenetically substantiated, but requires further clinical confirmation.

The effect of telmisartan on ***glucose metabolism*** has been studied in randomized controlled trials that included over 1300 patients with AH and T2DM or insulin resistance. During telmisartan treatment, fasting plasma glucose test, fasting plasma insulin level, adiponectin level, and HOMA-IR index — quantitative method for assessing insulin resistance, were identified [45, 46]. Once-daily telmisartan of 80 mg reduced fasting plasma insulin level and peripheral insulin resistance (measured by HOMA-IR index) [47]. The results of meta-analysis showed that 80 mg of telmisartan was superior to other ARAs (including eprosartan, irbesartan, candesartan, valsartan and olmesartan) in fasting plasma glucose level reduc-

tion. Six clinical studies showed adiponectin increase in patients using telmisartan of 80 mg once-daily. PPAR-γ receptors activation increases adiponectin synthesis by adipocytes that is the main protein in the processes of free fatty acids oxidation that enhances insulin sensitivity in skeletal muscles and liver. Thus, adiponectin increase in blood plasma can reduce insulin resistance and inhibit the development of MS and T2DM [45].

It has been shown that ARAs can also reduce the incidence of newly diagnosed diabetes mellitus cases compared with placebo in patients with high cardiovascular risk and / or AH [48,49]. The TRANSCEND and PRoFESS studies revealed that telmisartan reduced the incidence of DM by 16 % reduction compared with placebo [39]. ARAs also showed cardioprotective properties in patients with T2DM. Thus, a population cohort study involved elderly patients with T2DM and showed that telmisartan and valsartan were associated with reduced risk of hospitalization for myocardial infarction, stroke, or heart failure compared with irbesartan [50].

ARAs also have ***nephroprotective effect.*** Many studies have shown that ARAs are the most effective antihypertensive drugs that prevent chronic renal failure [51]. A meta-analysis of twenty randomized controlled trials of telmisartan (including ONTARGET, TRANSCEND, DETAIL, INNOVATION, AMADEO and VIVALDI) that involved a large number of patients with DM showed its effectiveness in proteinuria reduction and prevention. Telmisartan significantly decreased albuminuria and urinary albumin to creatinine ratio compared with other ARAs, angiotensin converting enzyme inhibitors, and other antihypertensive drugs [39]. The ESPRIT study showed antihypertensive effectiveness and high tolerance for telmisartan in patients with difficult-to-control hypertension with chronic kidney disease [52]. Considering the results of above-mentioned studies, as well as the fact that only 2 % of medication is excreted through the kidneys, telmisartan can be used in patients with severe renal impairment on hemodialysis, without dose adjustment according to the glomerular filtration rate.

Thus, nowadays pronounced evidence-based antihypertensive effect and organoprotective properties of ARAs allow us to use them in various clinical situations at all stages of the cardiovascular continuum. Telmisartan has many advantageous pharmacological properties among other representatives of ARAs: the longest half-life (over 20 hours) and the highest lipophilicity and affinity for AT1 receptors. Many clinical studies have shown that telmisartan activates PPAR-γ receptor and, therefore, reduces proteinuria and the progression of kidney and retinal damage in patients with DM, as well as reduces the risk of T2DM in patients with high cardiovascular risk. This medication is indicated to reduce cardiovascular mortality in patients with atherothrombotic diseases (CAD, peripheral arterial damage, stroke history) and in patients with T2DM with target organ damage.

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