

Renovascular and renoprotective properties of telmisartan: clinical utility

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Abstract: Chronic kidney disease (CKD) affects approximately 26 million adults in the United States and millions of others are at increased risk. Type 2 diabetes and hypertension are the two main causes of CKD. Blood pressure control is critical to slow the progression of CKD. Despite adequate control, however, patients continue to progress to end-stage renal disease. Angiotensin receptor blockers (ARBs) are commonly used in the management of hypertension and CKD and have been shown to exert renoprotective effects that are in addition to, but independent of, blood pressure lowering. Telmisartan is a long-acting ARB with pharmacological properties beyond blockade of the angiotensin II type 1 receptor, including activation of the peroxisome proliferator activated receptor- γ (PPAR- γ). This article reviews the beneficial renal and vascular protective effects of telmisartan.

Keywords: kidney diseases, hypertension, vascular diseases, angiotensin II receptor, PPAR- γ

Introduction

The incidence and prevalence of essential hypertension continues to rise worldwide. Changes in diet, daily physical activity, environment, and lifestyle have made hypertension a more common and difficult to control disease. Of greatest concern are the diseases that arise as a consequence of undetected and/or uncontrolled hypertension, including cerebro-vascular, coronary artery, peripheral vascular, and chronic kidney diseases (CKD).

Many classes of medications are currently used to treat hypertension, such as diuretics, beta-blockers, calcium channel blockers, renin inhibitors, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs). Among the ARBs there is one medication that has special pharmacological properties in addition to blocking the angiotensin II type 1 receptor; this medication is telmisartan. It has been shown to lower blood pressure as well as exert cardiovascular and renoprotective effects independently of blood pressure reduction.

In the present review we will discuss the pharmacology and the beneficial properties of telmisartan in the management of hypertension.

Pharmacology

Angiotensin II is the most studied effector peptide of the renin-angiotensin system. It is produced from angiotensin I by ACE and has effects in multiple organs of the human body. There are 4 types of angiotensin receptors (AT1, AT2, AT3, AT4). AT1 is the receptor that enables most of the hemodynamic changes in the body that are

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related to angiotensin II, these include vasoconstriction and stimulation of aldosterone release (Figure 1). In response to angiotensin II, there is an increase in glomerular pressure and glomerular permselectivity as well as activation of fibrosis and cellular growth in the kidney.

Telmisartan is a non-peptide angiotensin II type 1 receptor (AT1) antagonist with high lipophilicity and the longest half-life compared with other ARBs.^{1,2} Available in oral preparation, it is highly bound to plasma proteins (>99.5%), mainly albumin. It is metabolized by conjugation, is not metabolized by the cytochrome P450 system, and is eliminated in feces. It has a greater affinity for the AT1 receptor than angiotensin II (>3000 fold).

Like ACE inhibitors and other ARBs, telmisartan should be avoided in pregnant and nursing patients. The side effects are similar to those of other ARBs, including hyperkalemia, hypotension, and creatinine elevation due to decrease of the glomerular filtration rate. These parameters should be

monitor closely after the medication is started. It has minimal drug interactions, namely digoxin and lithium levels may increase and these should be monitored regularly. After administration of telmisartan, levels of angiotensin II, angiotensin I, and plasma renin activity are elevated, as reported with other ARBs and most likely secondary to blockade of the AT1 receptor.

Dosage and tolerability

Dose ranges from 20 to 80 mg per day with an onset of action of 1–2 hours. Telmisartan has been shown to have a low discontinuation rate among patients. Side effects are less when compared to ACE inhibitors and it is an option when ACE inhibitors are not tolerated.^{3,4}

Clinical properties

Telmisartan is used in the management of hypertension as monotherapy or in combination with other types of

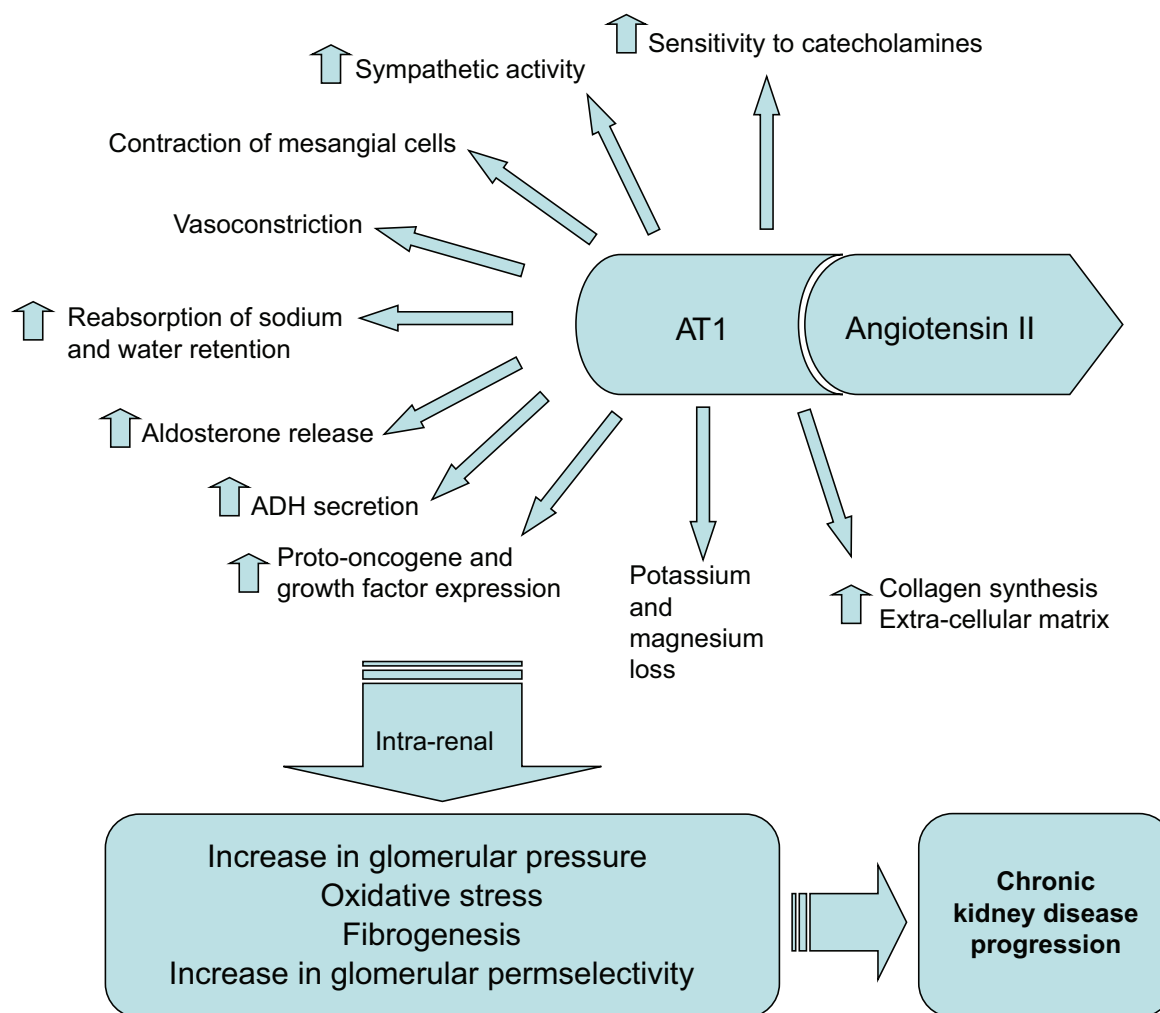


Figure 1 Effects of angiotensin II on the AT1 receptor.

antihypertensive medications. It is well known that ARBs are effective in reducing blood pressure as well as target organ damage, including left ventricular hypertrophy, stroke, proteinuria, and progression of CKD. Moreover, there are intrinsic properties that make this group of antihypertensives unique. It is known that in addition to ACE, the enzyme chymase influences the production of angiotensin II.⁵ Chymase is produced and stored in mast cells, endothelial cells, and mesenchymal cells. It is found in the heart, blood vessels, and the kidney.^{5,6} ACE inhibitors do not inhibit chymase, thus angiotensin II can still be produced. ARBs block ACE and chymase-derived angiotensin II from activating the AT1 receptor.⁵

Metabolic effects

There is evidence that in nondiabetic patients with CKD, a syndrome of insulin resistance is present even at the early stages of renal dysfunction.⁷ This renal insulin resistance syndrome may contribute to the increased incidence of cardiovascular events in CKD patients.

The peroxisome proliferator activated receptor (PPAR) plays an important role in the metabolism of lipids and carbohydrates and has been implicated in insulin resistance, metabolic syndrome, and atherosclerosis. Of the available ARBs, telmisartan has the greatest stimulating effect on PPAR- γ and this effect decreases insulin resistance, increases insulin sensitivity, and reduces dyslipidemia, thereby providing greater target-organ protection.^{8,9} A recent study demonstrated that telmisartan not only increased insulin sensitivity but also decreased blood levels of triglyceride and free fatty acids; this action on lipid metabolism has been attributed to modulation of hepatic PPAR- γ activity.¹⁰

Vascular effects

ARBs inhibit the growth of vascular smooth muscle cells and there is evidence that telmisartan does this to a greater extent.^{11,12} This effect is related to the blockade of the AT1 receptor and the activation of PPAR- γ , but there are other mechanisms that participate.^{11,12} Protein kinase B (AKT) is a proto-oncogene involved in signaling pathways that control cellular growth and differentiation. It has been reported that telmisartan inhibits vascular smooth muscle cell proliferation by inhibiting AKT activation.¹²

Renal effects

Although blood pressure reduction directly contributes to renoprotection, including reduction in proteinuria and slowing of CKD progression, ARBs and ACE inhibitors exert

additional blood pressure-independent renoprotective effects via inhibition of the renin-angiotensin-aldosterone system (RAAS).^{1,13} It has been shown that RAAS blockade prevents fibrosis. Aldosterone per se stimulates fibrosis by stimulating the production of plasminogen activator inhibitor (PAI-1) and transforming growth factor- β (TGF- β) and promoting inflammation and fibroblast growth and proliferation.^{14–19} PAI is an inhibitor of fibrinolysis and a regulator of extracellular matrix turnover.¹⁴ There are two types of PAI; PAI-2 is present in the placenta and PAI-1 is produced in the endothelium. On the other hand, TGF- β induces the production of extracellular matrix, stimulates fibroblast proliferation, and inhibits collagenase production, resulting in accumulation of extracellular matrix proteins, collagen, and fibrosis.^{17,18}

Angiotensin II also plays an important role in the development of fibrosis.^{1,20} Guo et al showed in a mice model that the ARB losartan and the ACE inhibitor enalapril decreased the levels of PAI-1 and reduced glomerular matrix deposition and glomerular mesangial cell activation.²⁰ These effects are also evident with telmisartan. Yao et al and Tsunenari et al showed that telmisartan inhibited TGF- β and that this inhibition was related to the activation of PPAR- γ .^{21,22} Another study has recently demonstrated that telmisartan inhibits the activation of the pro-inflammatory nuclear transcription factor NF- κ B independently of PPAR- γ .²³

In an experimental study that was not related to blood pressure control or proteinuria, it was demonstrated that telmisartan protected the kidneys of rats from iodine contrast-induced tubular damage. Because angiotensin II was elevated after tubular damage, the beneficial effect was attributed to angiotensin II blockade.²⁴

In summary, the beneficial effects on vascular growth and fibrosis in the kidney via blockade of the AT1 receptor as well as the stimulation of PPAR- γ make telmisartan useful in the prevention of hypertensive renal disease.

Combination with other RAAS inhibitors

Accumulating evidence from several recent clinical trials indicates that the combination of an ARB and an ACE inhibitor could produce more harm than benefit. The ONTARGET Study showed that telmisartan combined with ramipril decreased proteinuria but was associated with a decrease in the glomerular filtration rate.^{25,26} Other adverse effects were more common with the combination, such as hypotension and hyperkalemia.^{25,26} Acute renal failure is also more common with dual therapy.²⁶ However, some have noted that combination therapy (dual ACE and AT1 receptor inhibition)

is important in proteinuric glomerulopathies.^{27,28,29} In general, it is recommended to closely monitor patients that are started on combination therapy.

It was recently reported that the combination of an ACE inhibitor with telmisartan in patients with type 2 diabetes was beneficial in reducing the amount of albuminuria and associated with less side effects like hyperkalemia and hypotension.³⁰ The dose of telmisartan used in this study was 40 mg daily compared with 80 mg daily in the ONTARGET study, which may have contributed to the decreased development of side effects.

Combination treatment with the direct renin inhibitor aliskiren seems promising, but there are few studies currently available and it is recommended to be cautious until outcome studies become available.³¹

Use of telmisartan with the calcium channel blocker amlodipine has been shown to provide a notable improvement

in blood pressure control in patients with stage 1 or 2 hypertension.³² In addition, combination therapy was associated with a reduced rate of peripheral edema compared with amlodipine monotherapy. Patients were reported to have tolerated well the combination therapy. Regarding combination therapy with diuretics, Neldam et al prospectively studied telmisartan in combination with hydrochlorothiazide versus amlodipine plus hydrochlorothiazide in older patients ($> \text{ or } = 60$ years of age) with predominantly systolic hypertension.³³ The study showed that telmisartan plus hydrochlorothiazide provided higher systolic blood pressure control rates and lower adverse events and discontinuation of therapy, particularly due to significantly less peripheral edema.

Telmisartan, like other ARBs, has been shown to be beneficial in diabetic nephropathy. Several studies have demonstrated a slowing in the progression of diabetic kidney disease and a decrease in the amount of proteinuria.^{34–36}

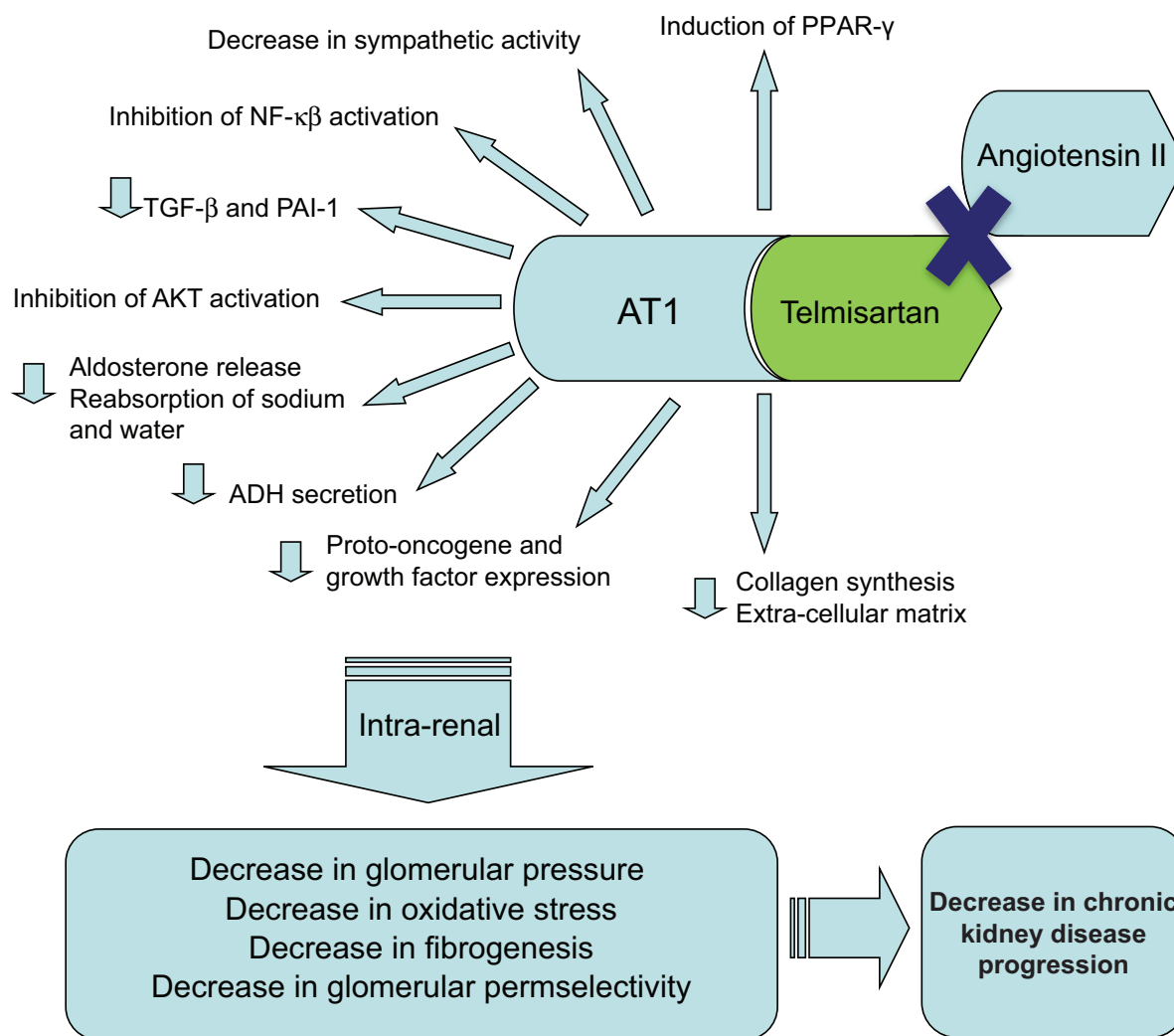


Figure 2 Effects of telmisartan via blockade of the AT1 receptor.

It has been reported that telmisartan is more effective in lowering proteinuria in hypertensive patients with overt diabetic nephropathy.³⁵ This effect may be due, at least in part, to the inhibitory effects on ambulatory blood pressure variability and sympathetic nerve activity. In addition, telmisartan has a longer duration of action on nighttime blood pressure reduction.³⁵ Furthermore, recent studies have indicated that telmisartan may be better in reducing proteinuria when compared to losartan, another commonly used ARB.^{35,36}

Conclusions

The importance of blood pressure control as a means to prevent development or reduce progression of cardiovascular and kidney diseases has been firmly established. Like other blockers of the AT1 receptor, telmisartan is effective in reducing blood pressure when used alone or in combination with other antihypertensives.¹³ Its longer half-life, lipophilicity, and ability to stimulate PPAR- γ seem to provide additional cardiovascular and renal protective properties that make it an attractive agent for global cardiovascular risk reduction (Figure 2).

Disclosures

The authors report no conflicts of interest.

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