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1. Kalra S, et al. Indian Journal of Clinical Practice. 2022; 32 (12): 2 - 6. **HCTZ** = Hydrochlorothiazide.

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REVIEW ARTICLE

Losartan: Benefits Beyond Hypertension

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ABSTRACT

Losartan was the first angiotensin AT1 receptor blocker (ARB) approved by US Food and Drug Administration (FDA) for the treatment of hypertension. In addition to its established antihypertensive and end organ effects, several benefits of losartan beyond its antihypertensive effect have been demonstrated in clinical trials. Apart from its class effects of ARBs, losartan has pharmacokinetic and pharmacodynamic properties that are unique to it. It has shown considerable benefits as uricosuric agent, in erectile dysfunction and in prevention of stroke in hypertension patients with left ventricular hypertrophy. This review presents the benefits of losartan beyond being a hypertensive agent and associated clinical outcomes.

Keywords: Losartan, ARB, erectile dysfunction, uricosuric agent, hypertensive

The first angiotensin receptor blocker (ARB) approved by Food and Drug Administration (FDA) in 1995 as an antihypertensive drug was losartan. It is one of the most studied ARBs supported by over 1,000 clinical trials. It was the first clinically used drug and has made significant contributions to the understanding of angiotensin II in the kidney and the advantages of inhibiting angiotensin II at the AT1 receptor. Current evidence support its usage beyond the class effects of losartan, which are unique including its effect on uricosuria, thrombosis and erectile dysfunction (ED).[1]

This review will present an overview of these benefits of losartan and its place in hypertension therapy.

PHARMACOKINETICS

Losartan is a nonpeptide molecule, a competitive antagonist with selective binding to AT1 receptors. With an oral bioavailability of 33%, it has significant first-pass metabolism using the cytochrome P450 enzymes. The active metabolites are 10 to 40 times more potent by weight than the parent molecule and are reversible, noncompetitive inhibitors of the AT1 receptor. Forty percent of losartan is eliminated in urine and 60% in feces. The half-life of losartan is 2 hours, while the terminal half-life of the metabolites is longer, 6 to 9 hours.[1] Losartan is primarily metabolized by P450 in the liver. Few side effects of losartan have been reported in clinical trials, and it has a low risk of interaction with other drugs.[2-5]

MECHANISM OF ACTION

Losartan is a selective and competitive angiotensin II receptor inhibitor at the AT1 receptor site, leading to a compensatory rise of renin and angiotensin I levels. It binds with high affinity to the AT1 receptor and is more than 10,000 times more selective for the AT1 receptor than the AT2 receptor.[6]

It blocks angiotensin II-induced vasopressin release (reduces the excretion and absorption process of the kidney), adrenal catecholamine release (reduces the response to physical and emotional stress) and in turn, affects the rapid and slow-pressor response (reflex for a hike or dropping of blood pressure [BP]) by vasodilation or vasoconstriction, thirst, cell growth and multiplication (cellular hypertrophy and hyperplasia), reduces reaction time in case of stimuli (noradrenergic neurotransmission) and decrease the pumping speed of heart muscles (sympathetic tone increase) further lowering BP and reducing supply of oxygenated blood to different parts of the body.[6]

It also blocks the angiotensin II-induced vasoconstriction and action of aldosterone, which eventually reduces BP.

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Compared to angiotensin-converting enzyme (ACE) inhibitors, angiotensin II-receptor inhibitors effectively inhibit the renin-angiotensin system, not affecting the response to bradykinin.[6]

LOSARTAN INDICATIONS

Losartan received FDA approval for hypertension treatment either as monotherapy or in combination with other antihypertensive agents. Patients, who had both hypertension and left ventricular hypertrophy (LVH), are given losartan to reduce the risk of stroke. It is also indicated in patient with hypertension and coexisting type 2 diabetes with diabetic nephropathy and increased serum creatinine and proteinuria to reduce the occurrence of doubling of serum creatinine or end-stage renal disease (ESRD). However, losartan has shown a multitude of benefits beyond these FDA-approved indications.[1]

The LOAT (LOsartan vs ATenolol) study conducted on patients with Marfan syndrome demonstrated losartan to be a useful, low-risk alternative to beta-blockers in the long-term management of these patients.[7] The PREVER-treatment study showed that treatment with losartan as a first-drug regimen was equivalent to diuretics in reducing BP and resulted in a favorable left ventricular (LV) remodeling.[8] The COMPAS-BPV study showed that the BP-lowering effect of the office visit-to-visit standard deviation of systolic BP was similar between losartan and amlodipine.[9]

Results of Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial showed that when compared with atenolol, losartan is superior to atenolol for treatment of patients with isolated systolic hypertension and electrocardiographically documented left ventricular hypertrophy (ECG-LVH).[10] Losartan prevents more cardiovascular (CV) morbidity and death for a similar reduction in BP and is better tolerated. Losartan also confers benefits beyond reduction in BP.[11] Losartan was more effective than atenolol in reducing CV morbidity and mortality from all causes in patients with hypertension, diabetes and LVH.[12]

In the LIFE study, it was seen that losartan-based therapy led to significant cerebrovascular benefit compared with conventional therapy among hypertensive patients with LVH across the spectrum of CV risk. There were fewer strokes in the losartan groups for almost all levels of stroke severity and the effect was consistently seen in all clinical subgroups except for those delineated by age and ethnicity.[13,14]

Losartan along with valsartan and candesartan are indicated for the second-line treatment of heart failure in those cases where ACE inhibitors are not tolerated. The results of the Evaluation of Losartan In The Elderly (ELITE) I and II trials have demonstrated that treatment with losartan was similar to that with captopril in terms of all-cause mortality, sudden death or resuscitated arrests as well as New York Heart Association (NYHA) class improvement.[15]

BENEFITS BEYOND HYPERTENSION

Uricosuric Benefits of Losartan

High serum uric acid levels and chronic kidney disease (CKD) are risk factors for CV events.[16] Hypertension and proteinuria have been constant factors in progressive CKD and the use of drugs such as ACE inhibitors and/or ARBs with or without diuretics or low-sodium diets lead to an improvement in kidney outcome in adults and children, and adolescents with CKD. In this context, the uricosuric effects of losartan in adults and children, and adolescents with CKD become important. Studies have shown that losartan is the only drug amongst other ARBs and ACE inhibitors that lowers serum uric acid in adults.[17,18]

Uric acid has demonstrated a critical role in the pathogenesis of hypertension and kidney disease progression. The pathophysiological mechanisms involved in the pathogenesis include renin-angiotensin-aldosterone system (RAAS) upregulation, kidney afferent arteriopathy, endothelial dysfunction, oxidative stress and systemic inflammation. It has been seen in several cross-sectional studies that hyperuricemia is present in many individuals with untreated essential hypertension, and serum uric acid are associated with prehypertension.[19]

Uricosuric agents increase the urinary excretion of uric acid, thus reducing serum uric acid levels. ARBs have been studied for their potential to inhibit urate transporter 1 (URAT1) and residual uricosuric effects.[20,21] However, there is lack of inhibitory effect of candesartan, olmesartan and valsartan on URAT1. Telmisartan has no clinically evident uricosuric effect.[15]

Whereas in a double-blind study comparing losartan with placebo, it was shown that losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy and it was generally well-tolerated. It reduced the occurrence of a doubling of the serum creatinine concentration and ESRD but did not affect the rate of death. These benefits exceeded those attributable to changes in BP.[22]

The results of the Japan Hypertension Evaluation with Angiotensin II Antagonist Losartan Therapy (J-HEALTH)

study have shown that losartan-based antihypertensive treatment increases the estimated glomerular filtration rate (eGFR) and decreases BP, proteinuria and serum uric acid. It is known that hyperuricemia is a major contributor to increased CV risks in early-stage CKD. Thus, an early reduction of proteinuria and serum uric acid is predictive of future improvement of renal function which in turn has a considerable effect on the occurrence of CV events, especially in CKD patients.[16] Losartan has been known to increase the excretion of uric acid and reduce the serum uric acid levels in both healthy and hypertensive individuals an effect not seen by other ARBs.[15]

Studies have shown that losartan exhibits statistically significant lowering of serum uric acid levels or increase in fractional excretion of uric acid; however, no other ARB showed statistical benefit. Losartan is the only ARB that has consistently demonstrated a significant reduction in serum uric acid levels, and appears to be a safe and efficacious agent to reduce serum uric acid levels in patients with hyperuricemia.[21] Compared with irbesartan and candesartan, losartan significantly reduced serum uric acid levels in hypertensive patients with hyperuricemia and gout.[21,23] Another study comparing candesartan with losartan showed that while both the drugs reduced BP, only losartan showed an effect in reducing uric acid.[24]

Combination therapy of losartan with antihyperuricemic agents significantly decreased serum uric acid and increased uric acid clearance and 24-hour urinary uric acid excretion.[25]

It is shown that increased serum uric acid concentration is an independent risk factor for ESRD. Treatment with losartan reduces serum uric acid compared with placebo treatment in patients with type 2 diabetes mellitus and nephropathy. In a post hoc analysis of 1,342 patients with type 2 diabetes mellitus and nephropathy, it was seen that the degree of reduction in serum uric acid is eventually associated with the degree in long-term renal risk reduction and explains part of losartan's renoprotective effect.[26]

In a post hoc analysis of a prospective study conducted in children with proteinuria, it was seen that losartan provided long-term beneficial effects on serum uric acid and eGFR.[17]

In a double-blind randomized placebo-controlled trial in anuric or oliguric patients with calcular obstruction of a solitary kidney, losartan treatment contributed to renal function recoverability after relief of calcular obstruction of the solitary kidney.[27]

Losartan in CKD

Hyperuricemia has been related to hypertension, diabetes, CV and kidney disease in adults. Increased serum uric acid is commonly seen in patients with CKD due to declining GFR and resultant uric acid retention. Recent years have demonstrated that hyperuricemia is also a contributing factor for both the development and progression of CKD in adults.[17]

The results of Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study showed that losartan was more effective compared to placebo in protecting against the progression of nephropathy due to type 2 diabetes, despite the presence of hypertension in the study participants. The study showed that losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy and was well-tolerated in the patients. When compared with a placebo, losartan given as adjunct to conventional antihypertensive treatment reduced the risk of the ESRD by 28% and reduced the level of urinary protein excretion by 35% in patients with coexistent diabetic nephropathy in RENAAL study.[22]

Effect on Erectile Dysfunction

Impaired erectile function in men occurs as a part of metabolic disturbance and as a sequela of chronic use of few antihypertensive therapies. Results of a prospective interventional study have shown that in men with uncontrolled hypertension (BP ≥140/90 mmHg), losartan improved erectile function and both satisfaction and frequency of sexual activity. Since side effects impact the management of hypertension, an additional benefit of losartan therapy is its positive influence on the quality of life.[28]

A clinical trial conducted on diabetic patients with ED showed that losartan is effective and well-tolerated in diabetic ED, particularly in mild-to-moderate ones. Losartan use led to a significant improvement in the mean International Index of Erectile Function (IIEF-5) score, the percentage of successful penetration, and the successful intercourse completions. Treatment with losartan is related to improved erectile function, sexual satisfaction and frequency of sexual activity in hypertensive patients.[29]

Another study showed that angiotensin II activation may be the causative link in apoptosis and fibrosis of the corpus cavernosum through Smad and non-Smad pathways, leading to corporal fibrosis and corporal veno-occlusive dysfunction (CVOD) and ED. Losartan treatment greatly improved the histological and

molecular changes and CVOD compared with sildenafil with a modest effect on ED.[30]

However, telmisartan did not show any improvement or worsening of ED as seen in the ONTARGET/TRANSCENDT studies.[31]

Effect on Sleep

It is known that sleep disturbance is a common issue at high altitudes, caused due to abnormal ventilatory responses whilst sleeping. The results of a study suggested that peripheral chemoreceptor hypersensitivity is mostly driven by AT1 receptors. It was observed that angiotensin II blockade by losartan reduced the impact of high-altitude exposure on sleep physiology measured by actigraphy. Losartan can thus offer additional benefits in providing protection for high-altitude sleep disturbance.[32]

PLACE OF THERAPY OF LOSARTAN IN HYPERTENSION

- **Hypertension:** First-line therapy with thiazide diuretics.
- **Diabetic nephropathy:** First-line therapy in patients with type 2 diabetes mellitus and hypertension.
- **Patients with higher uric acid levels:** ARB of choice.
- **Hypertension with LVH:** Losartan reduces the risk of stroke.
- **Hypertension in patients with ED:** First choice drug.

CONCLUSION

Losartan is the first ARB to be approved by FDA for use in several conditions including hypertension and diabetic nephropathy. It is renoprotective, reduces increased serum uric acid and improves ED. It is the first-line of therapy in hypertension and has renoprotective benefits in patients with diabetic nephropathy.

As seen in the results of several trials, losartan has been indicated for the treatment of diabetic nephropathy and should be considered as the ARB of choice in these patients. Losartan also has an additional benefit of reducing the risk of ESRD when given with traditional antihypertensive treatment. In patients with higher uric acid levels, losartan should be considered as the ARB of choice. Owing to its exclusive action on uric acid as compared with other ARBs, it can be the choice of therapy in patients with high uric acid levels.

Losartan is one of the most investigated ARBs in patients with ED along with valsartan and irbesartan. Treatment with losartan has established effects on improving ED, sexual satisfaction and frequency of sexual activity in hypertensive patients. Losartan given alone or in combination with tadalafil is known to have a significant improvement in ED in diabetic patients, those with mild-to-moderate ED benefiting the most from losartan use. On the other hand, telmisartan did not have any significant effect on ED. Based on the existing clinical evidence, losartan is preferred as the first-choice antihypertensive agent in hypertension patients with ED, hyperuricemia, CKD and LVH.

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