Renal and metabolic effects of valsartan

Tevfik Ecder

Department of Internal Medicine, Division of Nephrology, Faculty of Medicine, İstanbul Bilim University; İstanbul-*Turkey*

Abstract

It is known that the drugs which suppress the renin-angiotensin-aldosterone system can prevent target organ damage, independent of their blood pressure lowering effects. Besides, it has been reported that this group of drugs has positive metabolic effects. There are many studies showing that valsartan, being an angiotensin receptor blocker and widely used in hypertension treatment, has cardioprotective and renoprotective effects in high risk patients. It has been seen in these studies that, valsartan treatment has a decreasing effect on proteinuria, independent of its blood pressure lowering effects in the patients having either diabetic and non-diabetic nephropathy. In this review, the studies investigating the renal effects of valsartan will be mentioned. Additionally, the studies about the metabolic effects of valsartan will be reported *(Anadolu Kardiyol Derg 2014; 14(Suppl 2): S14-S9)*

Key words: angiotensin receptor blocker, chronic kidney disease, metabolic, renal, valsartan

Introduction

At present, chronic kidney disease is an increasing public health concern (1, 2). It is an important cause of morbidity and mortality and is an economic burden worldwide because of its high treatment cost. According to the records of the Turkish Society of Nephrology, more than 60,000 patients have been undergoing renal replacement therapy due to end-stage renal failure (ESRF) by the end of 2012 (3).

Diabetes and hypertension are the primary causes of chronic renal failure, in addition to increasing the risk of cardiovascular events. In patients with chronic renal failure, the most common cause of death is cardiovascular diseases (3, 4). As chronic renal failure progresses, the risk of cardiovascular morbidity and mortality apparently increases (2-4). Accordingly, therapies that slow the progression of chronic renal failure also have the advantage of decreasing the risk of cardiovascular events and delaying progression toward ESRF. Therefore, "cardiac protection" and "renal protection" are the targets that are parallel to each other, and "cardiorenal protection" is a frequently used concept nowadays.

The role of the renin-angiotensin-aldosterone system in the pathogenesis of renal damage

In patients with chronic renal failure, hemodynamic changes occur as the remaining nephrons adapt to nephron loss that develops over time. As a result, intraglomerular hyperperfusion, hypertension, and hyperfiltration develop in the remaining nephrons, regardless of the etiology of chronic kidney disease (5, 6). In rats in which 5/6 of the kidney mass was surgically exposed to ablation, hypertension, proteinuria, and rapidly progressing renal failure were observed (7, 8). It was observed that the development of renal failure could be delayed by decreasing intraglomerular hypertension using angiotensin-converting enzyme (ACE) inhibitor therapy in these rats (9).

Because the vasoconstrictor effect of angiotensin II on efferent arterioles of the glomeruli is more apparent than that on the afferent arterioles, stimulation of the renin-angiotensin-aldosterone system increases intraglomerular pressure. Elevated intraglomerular pressure is unfavorable because it leads to both capillary damage and increased proteinuria. Various experimental and clinical studies have revealed that proteinuria is a risk factor for the progression of kidney disease (7). Proteinuria leads to interstitial inflammation and fibrosis by stimulation of the synthesis and release of proinflammatory cytokines from tubular epithelial cells (7, 8, 10).

Angiotensin II exerts both nonhemodynamic effects and hemodynamic effects to increase intraglomerular pressure. It has been revealed that there are a high number of angiotensin II receptors in the glomeruli, arterioles, proximal tubular cells, mesangial cells, and interstitial medullary cells (11). Angiotensin

Address for Correspondence: Dr. Tevfik Ecder, Department of Internal Medicine, Division of Nephrology, Faculty of Medicine, İstanbul Bilim University; İstanbul-*Turkey* Phone: +90 212 375 61 64 E-mail: tevfikecder@yahoo.com

Accepted Date: 09.09.2014

DOI: 10.5152/akd.2014.00003

II stimulates the proliferation of glomerular endothelial and mesangial cells (12, 14). Transforming growth factor-beta (TGF-β), which is one of the growth factors stimulated by angiotensin II, exerts an effect on the production and destruction of the extracellular matrix. TGF-β stimulates the synthesis of matrix proteins, such as fibronectin, collagen, and proteoglycans; suppresses matrix destruction by increasing the synthesis of protease inhibitors; and stimulates the synthesis of matrix protein receptors such as integrins (15). Moreover, TGF-β increases fibroblast proliferation. Therefore, fibrosis develops in the kidneys (16, 17). As a consequence of all these effects, renal function decreases, gradually resulting in ESRF.

Suppressing the renin-angiotensin-aldosterone system for renal protection

Because the renin-angiotensin-aldosterone system has several negative effects that can damage target organs, therapies that suppress this system are beneficial in patients with hypertension. Therefore, based on evidence obtained from large randomized controlled trials, suppression of the renin-angiotensin-aldosterone system using ACE inhibitors or angiotensin receptor blockers is recommended in patients both with a high cardiovascular risk and chronic kidney disease in the Hypertension Guidelines of the European Society of Hypertension and European Society of Cardiology, published in 2013 (18). In addition, the eighth report of Joint National Committee in the United States, published in 2014, recommends the use of primarily ACE inhibitors or angiotensin receptor blockers in diabetic patients with hypertension and individuals with chronic kidney disease (19).

Renal effects of valsartan

Various studies have investigated the renal effects of valsartan therapy in patients with diabetic and nondiabetic nephropathy (Table 1). These studies investigated various parameters such as decreased albuminuria/proteinuria, decreased renal functions, and progression toward ESRF.

Some studies have reported the beneficial effects of valsartan therapy in patients with diabetic nephropathy. These benefits are primarily associated with the fact that valsartan decreases albuminuria or proteinuria. In diabetes, which is the most common cause of chronic renal failure, the occurrence of microalbuminuria following a normoalbuminuric period suggests the development of nephropathy. Furthermore, an apparent increase in the risk of cardiovascular mortality is observed in patients with microalbuminuria (20). Following a microalbuminuric period, a progressive decrease in renal function occurs in patients, leading to the development of macroalbuminuria over time. This condition is also associated with a concurrent increase in cardiovascular risk. If patients do not experience cardiovascular event-related mortality, they will progress toward ESRF. Therefore, delaying the progression of microalbuminuria is important for cardiorenal protection.

Several studies investigating the renal effects of valsartan have been conducted in type 2 diabetic patients. In the MicroAlbuminuria Reduction with VALsartan (MARVAL) study, a multicenter, randomized, and double-blinded study, the effects of 80 mg/day valsartan and 5 mg/day amlodipine treatment in 332 patients with type 2 diabetes and microalbuminuria were assessed over 24 weeks. The target blood pressure was identified as 135/85 mm Hg. Data revealed that valsartan was superior to amlodipine in decreasing microalbuminuria, despite similar blood pressure control (21). In addition, 29.9% of patients treated with valsartan showed regression from microalbuminuria to normoalbuminuria, compared with 14.5% of patients treated with amlodipine ($p<0,001$). Valsartan treatment led to an apparent decrease in albuminuria even in normotensive patients in the MARVAL study. Based on the data reported in the MARVAL study, Smith et al. (22) performed Markov model analysis to assess how the disease course and costs differ over an 8-year follow-up period in patients receiving valsartan or amlodipine. This analysis found that the cost of using valsartan rather than amlodipine would decrease by approximately US$32,412 per person and also lower the risk of progression to ESRF and death.

In the randomized, double-blinded, parallel group study conducted by Karalliedde et al. (23), the effects of valsartan and amlodipine on arterial resistance and albuminuria were investigated in 131 patients with type 2 diabetes. In this study, treatment was initiated with 160 mg/day valsartan or 5 mg/day amlodipine. At the end of week 4, 25 mg hydrochlorothiazide was added to the valsartan group, and the dose of amlodipine was increased to 10 mg/day. After a 24-week follow-up period, a significantly higher decrease in the aortic pulse wave velocity was observed in the valsartan group compared with that in the amlodipine group. In addition, significantly decreased albuminuria was found only in the valsartan group. This study also supports the hypothesis that valsartan has cardiorenal protective features.

The SaiTama Medical School, Albuminuria Reduction in Diabetics with Valsartan (STAR) study was conducted in 28 patients with microalbuminuria and type 2 diabetes (24). In this study, 80 mg/day valsartan was added to the treatment of individuals in the patient group whose blood pressure did not decrease to below 130/85 mm Hg using calcium channel blockers. In contrast, the treatment of patients whose blood pressure levels decreased to below 130/85 mm Hg using calcium channel blocker treatment was switched to 80 mg/day valsartan alone. Both groups were followed-up with these therapies for 1 year. An apparent decrease in blood pressure and albuminuria was observed in the group receiving the combination of valsartan and calcium channel blocker. In addition, although no further decrease was observed in the blood pressure of patients whose blood pressure was under control and in whom the calcium channel blocker was switched to valsartan, a significant decrease in albuminuria was observed. These findings suggest that valsartan treatment is renoprotective, independent of its effects in decreasing blood pressure.

Table 1. Studies performed using valsartan with a renal endpoint

Study	Patient population	Study design	Treatment	Follow-up duration	Findings
MARVAL (21)	332 type 2 diabetic patients with microalbuminuria	Randomized, double-blinded, parallel groups	80-160 mg valsartan or 5-10 mg amlodipine	24 weeks	Albuminuria was decreased by 44% in the valsartan group, and 8% in the amlodipine group. In valsartan group, 29.9% of patients returned to normoalbuminuria, compared with 14.5% in the amlodipine group (p<0.001)
Karalliedde (23)	131 type 2 diabetic patients with albuminuria	Randomized, double-blinded, parallel groups	160 mg valsartan+25 mg hydrochlorothiazide or 10 mg amlodipine	24 weeks	Albuminuria was decreased significantly in the group receiving valsartan
STAR (24)	28 type 2 diabetic patients with microalbuminuria	Randomized, open-label	Calcium channel blocker or calcium channel blocker + 80 mg valsartan	1 year	Apparent decrease in albuminuria in the group receiving the combination treatment
ABCD-2V (25)	129 type 2 diabetic patients with normoalbuminuria or microalbuminuria	Randomized, single-blinded, placebo-controlled	Intense BP control with valsartan (target diastolic BP of 75 mm Hg) or moderate BP control with placebo	2 years	Apparent decrease in albuminuria and intense BP control with valsartan
DROP (26)	391 type 2 diabetic patients with micro- or macroalbuminuria and hypertension	Randomized, double-blinded	160 mg, 320 mg, or 640 mg valsartan	30 weeks	More prominent decrease in albuminuria in patients who received 640 mg valsartan independent of BP control
VIVALDI (27)	885 type 2 diabetic patients with macroalbuminuria and hypertension	Randomized, double-blinded	160 mg valsartan or 80 mg telmisartan	1 year	Similar decreases in proteinuria in both groups
Hermida (28)	200 patients with microalbuminuria and essential hypertension	Randomized, open-label	160 mg valsartan after getting up in the morning or before going to bed in the evening	3 months	Apparent decrease in albuminuria in patients taking valsartan before going to bed
Kanagawa valsartan trial (29)	303 patients with chronic renal failure	Randomized, open-label	Valsartan or conventional antihypertensive drugs	3 years	Decreased renal outcome in the valsartan group (a two-fold increase in serum creatinine or development of ESRF)
Suzuki (30)	34 patients undergoing chronic ambulatory peritoneal dialysis	Randomized, open-label	40-80 mg valsartan or conventional antihypertensive drugs	2 years	Better protection of residual renal function in patients taking valsartan

BP - blood pressure; ESRF - end-stage renal failure

In the Appropriate Blood pressure Control in Diabetes Part 2 with Valsartan (ABCD-2V) study, 129 patients with type 2 diabetes whose blood pressure was <140/80 mm Hg and who did not have macroalbuminuria were randomized into valsartan and placebo treatment groups (25). The target in the valsartan group was intensive blood pressure control (target diastolic blood pressure, 75 mm Hg) compared with mild blood pressure control (diastolic blood pressure, 80-90 mm Hg) in the placebo group. The effects of these therapies on urinary albumin excretion were then examined in patients who were followed-up for 2 years. The data from this study revealed significant regression in albuminuria in patients whose blood pressure was decreased <120/80 mm Hg by valsartan.

Based on the above-mentioned studies, which revealed that valsartan decreased albuminuria, the DROP (Diovan Reduction of Proteinuria) study investigated whether a higher dose of valsartan decreased albuminuria further (26). In this study, 391 patients with type 2 diabetes, hypertension, and albuminuria (20-700 µg/min) were randomized into three groups in which valsartan was given at doses of 160 mg, 320 mg, or 640 mg per day. In week 30 of the study, regression toward normoalbuminuria was observed in 12% of patients treated with 160 mg/day valsartan, compared with 24% of patients treated with 640 mg/day valsartan (p<0.01). These high doses were well tolerated, and no increase in undesirable effects, such as hypotension and

hyperkalemia, was observed. Remarkably, this study revealed that increasing the dose of valsartan from 160 mg to 320 mg and 640 mg decreased albumin levels significantly without causing any further decrease in blood pressure. This suggests that valsartan exerts a protective effect at the tissue level, independent of its effect of decreasing blood pressure.

The inVestIgate the efficacy of telmisartan vs. VALsartan in hypertensive type 2 DIabetic patients with overt nephropathy (VIVALDI) study compared valsartan with telmisartan, another angiotensin receptor blocker. It randomized 885 patients with type 2 diabetes, hypertension, and proteinuria into groups that received 160 mg/day valsartan or 80 mg/day telmisartan in a double-blinded manner (27). The serum creatinine concentrations were <3.0 mg/dL in all patients. After a 12-month follow-up period using these treatments, a similar decrease was observed in the daily amount of proteinuria in both groups. Furthermore, there was no significant difference between groups in either serum creatinine concentrations or the glomerular filtration rate.

Another study using valsartan investigated the effects of receiving the drug at different times of the day on albuminuria in patients with essential hypertension (28). In this prospective, randomized, open-label study, 200 patients with stage 1 and 2 essential hypertension were randomized into two groups: 160 mg/day valsartan administered after getting up in the morning, and 160 mg/day valsartan before going to bed in the evening. At the end of the 3-month follow-up period, a similar decrease in blood pressure was observed in both groups. There was also no change in the diurnal/nocturnal blood pressure ratio in patients who received the drug after getting up in the morning. However, it was remarkable that a significant increase in this ratio occurred in patients who received the drug before going to bed in the evening because of the reduced nocturnal blood pressure. In addition, the decrease in urinary albumin excretion was higher in patients who received the drug before going to bed.

In the multicenter, randomized, open-label Kanagawa Valsartan Trial (KVT) performed by Yasuda et al. (29), 303 patients with chronic renal failure associated both diabetic and nondiabetic causes were enrolled. Patients were randomized into a control group (144 patients) that received antihypertensive drugs but not angiotensin receptor blockers and a valsartan group (149 patients) that received valsartan and the conventional therapy. Serum creatinine concentrations were >2 mg/dL in all patients, and the mean estimated glomerular filtration rate (eGFR) was 17 mL/min/1.73 m^2. Following a 3-year follow-up period, the number of patients whose serum creatinine concentrations had increased 2-fold or who developed ESRF was significantly lower in the valsartan group compared with the control group (p=0.007). In addition, the mean daily dose of valsartan given to patients in the valsartan group was 75.6 mg.

In a study performed in 34 patients undergoing treatment with chronic ambulatory peritoneal dialysis, the effect of valsartan therapy on residual renal function was investigated (30). These patients were randomized into a valsartan therapy group and a control group that received conventional antihypertensive treatment within a period from 3 months to 2 years after the initiation of chronic peritoneal dialysis therapy. Patients were followed-up until their target blood pressure reached 130/80 mm Hg. Despite similar blood pressure control in both groups, it was remarkable that the residual renal function was better protected in the valsartan group. Because the survival rate was higher in chronic peritoneal dialysis patients in whom residual renal function was protected, these findings in patients treated with valsartan are very important (31).

Metabolic effects of valsartan

One of the important features of drugs that suppress the renin-angiotensin-aldosterone system is the absence of negative metabolic effects. Among antihypertensive drugs, diuretics and beta-blockers enhance insulin resistance. In a meta-analysis of 22 clinical trials that included a total of 143,153 patients, data revealed that the risk of developing diabetes was lower in patients who received ACE inhibitors and angiotensin receptor blockers (32). This meta-analysis revealed that the use of calcium channel blockers and placebo had an equal effect on the risk of developing diabetes, whereas the use of a beta-blocker or diuretic increased the risk of diabetes. These results must be considered when selecting medications because the cardiovascular risk in patients who have recently developed diabetes is as high as those who developed diabetes previously (33). Indeed, current guidelines suggest that the presence of metabolic syndrome is a possible contraindication for the use of a diuretic or beta-blocker (19).

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study examined the effects of valsartan and amlodipine-based treatments on cardiovascular events in hypertensive patients with a high cardiovascular risk. Data revealed that the recent development of diabetes, which was a secondary endpoint of the study, was apparently lower at a rate of 23% in patients using valsartan compared with those using amlodipine (34). This positive effect of valsartan was investigated further in the NAteglinide and Valsartan in Impaired Glucose TolerAnce ouTcOme Research (NAVIGATOR) trial (35). In this study, the effect of ~160 mg/day valsartan on the development of diabetes and lifestyle changes was investigated in 9,306 patients with cardiovascular disease or cardiovascular risk factors and impaired fasting glucose. A significant decrease in the risk of developing diabetes was observed at a rate of 14% in patients using valsartan for 5 years compared with patients not using valsartan (p<0.001). However, there was no reduction in cardiovascular events.

Conclusion

Studies performed using the angiotensin receptor blocker valsartan suggest that it has positive renal and metabolic effects. Most studies investigating the renal effects of valsartan

were performed in patients with type 2 diabetes. These studies suggest that valsartan exhibits an albuminuria-reducing effect, independent of its blood pressure-lowering effect. Moreover, valsartan therapy decreased the risk of developing diabetes in patients at a higher risk of diabetes.

Conflict of Interest: Prof. Tevfik Ecder is a member of Novartis' Advisory Board.

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