

Sacubitril Valsartan 's Antihypertensive Characteristics

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ABSTRACT

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Introduction

Primary hypertension is an important risk factor for the development of cardiovascular disease, cerebrovascular disease and renal disease, and its prevalence is increasing. Previously, angiotensin-II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), calcium channel antagonists (CCBs), and salt corticosteroid receptor antagonists (MRAs) have played an important role in the treatment of hypertension. However, the prevalence of hypertension remains high [1]. Therefore, new antihypertensive drugs need to be developed.

Primary hypertension is the result of the interaction of multiple genetic and environmental factors, and the renin-angiotensin-aldosterone system (RAAS) and natriuretic peptide system (NPs) are involved in the regulation of blood pressure [2], Sacubitril Valsartan, an angiotensin receptor enkephalinase inhibitor (ARNI), has been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency as a first-line treatment for heart failure with reduced ejection fraction. In addition, ARNI is a novel drug that acts on both RAAS and NPs and achieves multi-pathway antihypertension by enhancing the blood pressure regulation of NPs and inhibiting RAAS. Currently, it is mainly used to lower blood pressure by inhibiting the RAAS, suppressing the sympathetic nervous system (SNS), dilating blood vessels, and reducing volume load. This review aims to summarize the antihypertensive characteristics of ARNI and provide a relevant basis for its treatment of hypertension.

Dual Mechanism of Action of Sacubitril Valsartan

Sacubitril Valsartan simultaneously enhances the action of NPs and inhibits RAAS activity, exerting a comprehensive antihypertensive effect. Valsartan can directly prevent Ang II from binding to the receptor, thus antagonizing RAAS to achieve the hypotensive effect. One of the metabolic pathways of natriuretic peptide (NP) in the body is its degradation by enkephalinase (NEP), which is broken down in the body into LBQ657 (the active form of Sacubitril Valsartan), which acts on NEP and inhibits its degradation of NP, resulting in an increase in NP content [3]. NP exerts physiological effects such as vasodilatation, diuretic sodium excretion, antimitotic and anti-sympathetic excitation mainly by acting on NP receptors. In addition, NP can also counteract the vasoconstrictive effect of RAAS and the water and sodium retention effect of vasopressin system. In conclusion, ARNI can both inhibit RAAS and increase NP levels by inhibiting NEP, and this dual mechanism of neuroendocrine system inhibition provides theoretical support for the clinical application of Sacubitril Valsartan.

Safety and Efficacy of Sacubitril Valsartan in the Treatment of Essential Hypertension

Cheung et al. [4] found that sakubitril valsartan was more effective than olmesartan in reducing ambulatory and office blood pressure values with a comparable safety profile. An 8-week trial

by Huo et al. [5] confirmed that Sacubitril Valsartan was more effective than olmesartan in reducing blood pressure values in patients with mild to moderate hypertension with a good safety and tolerability profile. In a 52-week safety and efficacy study by Supasynndh et al. [6], long-term Sacubitril Valsartan treatment was shown to be safe and effective tolerable. Both Sacubitril Valsartan with/without amlodipine showed a stronger antihypertensive effect compared to amlodipine alone, with an effectiveness of 90.6% in reducing systolic blood pressure [7]. Both 12-week and 52-week studies by Schmieder et al. [8] showed that sakubatrtil valsartan was safe, well tolerated, and sustained in lowering blood pressure. In conclusion, Sacubitril Valsartan is safe and effective in the treatment of hypertension, with significant improvements in a number of relevant indicators, including sitting systolic/diastolic blood pressure, 24-h ambulatory blood pressure, nocturnal blood pressure, pulse pressure, central aortic systolic blood pressure and blood pressure compliance, and it is easy to see that Sacubitril Valsartan has a definite efficacy and relatively high safety profile.

Sacubitril Valsartan is More Effective in Lowering Systolic Blood Pressure

A reduction in systolic blood pressure to 120 mmHg reduces the risk of death and reduces nonfatal cardiovascular events in patients with mild to moderate hypertension. In the PARAGON-HF study [9], in which 4795 patients were analyzed, Sacubitril Valsartan resulted in a significant reduction in systolic blood pressure (SBP) from baseline of 5.2 mmHg after 4 weeks of randomization compared with valsartan. This suggests that Sacubitril Valsartan compared with single agent valsartan in the treatment of hypertension in terms of SBP reduction. Multivariate analysis of correction revealed that changes in SBP may be associated with changes in N-terminal brain natriuretic peptide precursors.

Sacubitril Valsartan for Hypertension in the Elderly

The treatment of hypertension in the elderly remains a challenge with high prevalence and recalcitrance. The PARAMETER study [10] focused specifically on elderly patients with atherosclerosis, who are at highest risk for cardiovascular events, stroke and heart failure, and whose central aortic pressure is greatly increased relative to brachial artery pressure. The results showed that from baseline to week 12, the systolic and pulse pressure reductions were more pronounced in the Sacubitril Valsartan group compared to olmesartan, and the mean ambulatory blood pressure reductions were more pronounced and nocturnal blood pressure reductions were more mechanical and functional, with Sacubitril Valsartan contributing more to improve hemodynamics in elderly patients with high systolic blood pressure and providing benefits beyond those of RAAS inhibitor monotherapy.

Sacubitril Valsartan for Salt-Sensitive Hypertension

Salt-sensitive hypertension (SSH) accounts for the majority of hypertensive patients, and in a study by Wang [11] et al. showed that Sacubitril Valsartan was more significant than valsartan in diuretic sodium excretion in the short term, which may be related to its alteration of N-terminal brain natriuretic peptide precursor levels in SSH patients. Therefore, Sacubitril Valsartan has some advantages in the treatment of SSH.

Sacubitril Valsartan for the Treatment of Hypertension in Patients with Combined Renal Insufficiency

Sacubitril valsartan acts directly on smooth muscle cells to cause vasodilation and on renal tubules to increase renal medullary blood flow and increase urinary sodium. In the CKD subgroup analysis of the PARADIGM-HF study and PARAGON-HF study, sakubatrtil valsartan significantly reduced the risk of renal composite endpoints and delayed the decline in eGFR compared to enalapril and valsartan [12]. Sacubitril valsartan promotes water and electrolyte balance through renal regulation of diuretic sodium excretion, decreases intra-glomerular pressure, results in lower proteinuria, and slows the decline in glomerular filtration rate. This protects the kidneys and at the same time provides a good antihypertensive effect.

Discussion

Sacubitril valsartan has emerged as a first-line agent for the treatment of heart failure with reduced ejection fraction, but its ability to replace a particular antihypertensive agent as a starting treatment for hypertension remains controversial. Sacubitril valsartan, a co-crystal compound of ARB and NEP inhibitors, acts as a synergistic effect of the two drug mechanisms of action. This drug has a significant effect in enhancing NPs that can inhibit RAAS pressure and has a target organ protective effect, which is expected to take its place in the treatment of intractable hypertension and refractory systolic hypertension and can be recommended as the first choice in the treatment of hypertension combined with heart failure. Of course, whether Sacubitril Valsartan can be included in the first line use of hypertension still needs to accumulate more research evidence, and it is believed that in the near future for become the guideline recommended antihypertensive drugs.

Conflict of Interest

The authors declare no conflict of interest.

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