19 *Direct Renin Inhibition in Hypertension: A Novel Option*

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Abstract: It is observed in the Joint National Committee (USA), British Hypertension Society (UK) and the World Health Organization, hypertension in most patients who are treated is not controlled adequately, leading to increased (JNC VII) cardiovascular morbidity and mortality.

The renin-angiotensin-aldosterone system (RAAS) is an important pharmacologic target in hypertension and prevention of related target organ damage. Research has shown that compensatory increase in plasma renin levels poses a limitation to therapy with renin-angiotensin-aldosterone system inhibitors. A new agent ***(Aliskiren)***, belonging to a novel group of drugs (renin inhibitor) has shown promising results in clinical trials and is a major way forward in hypertension management. This is the only breakthrough in the last decade.

INTRODUCTION

There are about one billion individuals with hypertension worldwide, with approximately 7.1 million deaths per year. India has more than 100 million hypertension patients. The WHO estimates that poor BP control is largely responsible for two-thirds of strokes and half of ischemic heart disease. A recent European review of essential hypertension drew a similar picture. Current therapeutic strategies include volume regulation with diuretics, sympathetic nervous system activity suppression by means of peripheral adrenergic receptor blockers or centrally acting drugs, vascular smooth muscle cell tone reduction by means of ion channel manipulation, and inhibition of the renin-angiotensin-aldosterone system (RAAS).

RAAS INHIBITION

RAAS activity is initiated by the conversion of angiotensinogen to the angiotensin I (Ang I) by the enzyme renin; the key product of the renin system is the hormone angiotensin II (Ang II), which is formed from Ang I by the angiotensin-converting enzyme (ACE; Fig. 19.1). RAAS regulates blood volume and helps in maintenance of BP. However, excessive RAAS activity causes hypertension and target organ damage, mediated largely through the actions of Ang II on the angiotensin AT_1 receptor. Hence, ACE inhibitor therapy is targeted at hypertension, heart failure, and renal failure.

The renin-angiotensin-aldosterone system (RAAS). RAAS activity is normally regulated by compensatory feedback inhibition by the angiotensin AT_1 receptor on the release of renin, the rate-limiting step of the system. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) disrupt this feedback loop, stimulating increased renin activity, and thus increase angiotensin I (Ang I) generation. Only a renin inhibitor can effectively block this cycle.

Patients who receive ACE inhibitors initially have lower circulating Ang II levels; however, the levels commonly increase to earlier baseline concentrations, due to a phenomenon called

"escape." Angiotensin receptor blockers (ARB) can block the Ang II AT_1 receptor directly, but still may not block the RAAS satisfactorily. Suppression of the RAAS after treatment with either ACE inhibitors or ARB remains incomplete due to a reactive increase in renin activity (Figs 19.1 and 19.2). Also, ACE/ARB may not provide effective inhibition of tissue RAAS activity.

High plasma renin activity is considered to be a significant cardiovascular risk factor and associated with target organ damage, including renal failure and left ventricular hypertrophy.

DIRECT RENIN INHIBITION

Renin represents the rate-limiting step in Ang II production (Fig. 19.3) and appears to be the most logical target for inhibition of the RAAS. Historically, the earlier studies of renin inhibitors include the peptide inhibitors, isovaleryl-His-Pro-Phe-His-Sta-Leu-Phe-NH_2 (SCRIP), which was as effective as the ACE inhibitor enalaprilat in acute LVF. Others agents include a synthetic peptide renin inhibitor, an antirenin antibody, and enalapril, with all three causing increased renal blood flow to a similar degree. The renin inhibitors lead to a greater increase in renal blood flow compared to ACE inhibitors due to a greater suppression of intrarenal RAAS activity and thereby reflects the inability of ACE inhibitors to block ACE-independent pathways for the generation of Ang II**.**

Aliskiren is the latest orally active, nonpeptide, low-molecular-weight renin inhibitor. It is orally well tolerated and induces a dose-dependent decrease in plasma renin activity and active angiotensin peptide concentrations as well as providing a dose-dependent reduction in ambulatory blood pressure of patients with essential hypertension (aliskiren, 37.5 to 300 mg). In a comparative study in 652 hypertensive subjects, aliskiren 150 mg per day was as effective as Irbesartan (150 mg) in lowering blood pressure with similar safety and tolerability over the short term. In another study it was found that aliskiren is effective at lowering blood pressure in diabetic patients with hypertension both as monotherapy and in co-administration with ramipril. Combination therapy with aliskiren and ramipril provided significant additional antihypertensive benefit over either agent alone, and aliskiren alone appeared to reduce systolic pressure more than ramipril alone. In addition there was a suggestion that the cough associated with ramipril may be reduced if aliskiren is added.

These findings suggest that renin inhibitors appear a good alternative to ACE inhibitors and ARBs in treatment of hypertension. At this stage it is not very clear whether direct renin inhibitors will also provide superior organ protection as mono/combination therapy for RAAS blockade.

Preliminary studies of renin inhibitor and ARB combination suggest synergistic effects on RAAS blockade. Results of two new studies with Aliskerin and diuretic in patients with hypertension show that blood-pressure control was continuous over the 24-hour dosing period by ambulatory monitoring, even through high-risk early-morning hours and that the drug was as effective in lowering BP as the diuretic hydrochlorothiazide and may actually have effects additive to that drug when used in combination therapy.

Aliskiren is a well tolerated agent with low incidence of adverse effects, comparable to the ARB (irbesartan 150 mg per day). The most common side effects were headache, dizziness, and diarrhea.

SUMMARY

RAAS is still an intriguing and exciting target for BP reduction. Complete and adequate RAAS blockade cannot be achieved with ACE inhibitors or ARB due to escape and counter-regulatory mechanisms. Direct renin inhibition using new and novel agents like ***Aliskerin*** may offer better and additive BP control and protection of target organs. As most patients will need multi-drug therapy, RAAS inhibition will be an option in almost every patient, achieved by one or more agent(s).

Also, Renin inhibition could be combined with ACE inhibition or AT_1 receptor blockade to inhibit both Ang II and aldosterone generation. It could also be added to other anti-hypertensives like diuretics. Studies in humans till date are promising with aliskerin, as far as safety and tolerability are concerned. Animal studies of target organ damage (TOD) prevention with these agents also hold great promise for future.

FURTHER READING

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