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THERAPEUTIC ADVANTAGES OF BLOCKING ANGIOTENSIN II (AT1) RECEPTOR: LVH MASS REGRESSION, ACTIVATION OF PPAR GAMMA RECEPTOR INFLUENCED GENE AND ANTI-AGEING EFFECTS

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ABSTRACT

The objective of this review is to critically analyse the therapeutic advantages of Angiotensin II receptor (AT1) blockers. While different classes of anti-hypertensive drugs are effective in keeping the systolic and diastolic blood pressure within normal range, the blocking of Angiotensin II AT 1 receptors by ARBs provides additional therapeutic advantages. These beneficial effects are regression of left ventricular hypertrophy (LVH), activation of genes influenced by Peroxisome proliferator activator receptor gamma (PPAR gamma). and anti-ageing effects. Moreover it has been also observed that those essential hypertension (E-HTN) patients who were on ARBs recorded lowest incidence of T2DM compared to those who were on other classes of anti-hypertensive medications. The aforementioned therapeutic advantages of ARBs in specific clinical conditions have been discussed briefly, highlighting their potential therapeutic advantages.

KEYWORDS: Angiotensin II receptor, Anti-hypertensives, LVH mass, PPAR gamma receptors, Anti-ageing effects.

INTRODUCTION

This review aims at critical analysis of the therapeutic advantages of Angiotensin II receptor blockers (ARBs) not only as anti-hypertensives but also because of their beneficial effects beyond blood pressure control, in patients with essential hypertension and particularly in T2DM cases with hypertension. By binding to Angiotensin II AT1 receptor these ARBs not only cause reduction in glomerular intra-arteriolar blood pressure but also reduces GFR rate as well as reduction in proteinuria.[1,2] Because of these beneficial effects the ARBs are also referred to as renoprotective. Hypertension is found to be a frequently observed co-morbid factor in T2DM patients affecting approximately about 60% of the patients (Paulose RM).[3] The role of hypertension in macro and micro-vascular angiopathies is well documented (Gupta R).[4] Diabetic retinopathy, nephropathy and peripheral neuropathy are the important microvascular complications associated with T2DM. The important macrovascular complications include coronary artery disease (CAD), as well as cerebrovascular disease (CVD) and peripheral vascular disease. Essential hypertension is another important clinical entity where a considerable number of patients are kept on ARBs either as monotherapy or in combination with other classes of anti-hypertensive drugs viz., calcium channel blockers or beta blockers etc.

The rational behind anti-hypertensive therapy in T2DM patients with associated vascular complications is to normalize SBP and DBP in order to reduce the risk of such vascular complications. The various classes of anti-hypertensive drugs available are ACE inhibitors, Angiotensin II receptor blockers (ARBs), calcium channel blockers, alpha and beta receptor blockers and diuretics.

The objective of the present review is to critically analyse the therapeutic advantage of ARBs. A recent review of literature concerning pharmacological aspects of ARBs revealed that, besides their effectiveness as anti-hypertensive drugs, these angiotensin II receptor blockers have additional beneficial therapeutic advantages' these include their ability to reduce left ventricular hypertrophy (mass)[5,6] also activate the genes whose expression is targeted by PPAR gamma receptor.[7] Scientific reviews have also convincingly delineated the various molecular mechanisms to emphasize anti-ageing effects of Angiotensin II AT1 receptor.[8-9] Each of these advantages of ARBs have been discussed at length.

ARBs REDUCE LEFT VENTRICULAR HYPERTROPHY (MASS)

Treatment with Angiotensin II receptor blockers has been shown to substantially reduce the LV hypertrophy (mass) thereby reducing the risk of fatal and non-fatal cardiovascular complications including new onset atrial fibrillations (AF).[5-6] It is well established that LVH and AF are important risk factors of cardiovascular morbidity and mortality.[10-11] Comparative studies have also shown that ARB therapy has been found to be more effective than beta blockers in this regard.[5-6] Moreover experimental studies have revealed the effectiveness of these drugs in preventing new or recurrent AF. In view of their beneficial effects ARBs are considered as first line of therapy in LVH patients with HTN (LVH is considered as a very high risk phenotype predisposing to AF), and as adjunctive therapy to anti-arrythmic agents in patients undergoing pharmacological cardioversion of AF. The effectiveness of ARBs in conditions like LVH and AF is understandable in view of the fact that Renin Angiotensin Aldosterone system (RAAS) plays an important role not only in haemodynamic load but also plays an important role in myocardial hypertrophy.

ACTIVATION OF GENES INFLUENCED BY PPAR-GAMMA RECEPTORS

Anti-hypertensive Drugs that can activate genes influenced by PPAR-gamma receptor receptors are considered as effective in cases suffering from metabolic syndrome. The metabolic syndrome which is considered to be a common precursor of cardiovascular diseases and T2DM, is characterised by insulin resistance, dyslipidemia and increased blood pressure.[14] Mutations in the gene coding for peroxisome proliferator-activated receptor (PPAR gamma) are implicated in the causation of full blown form of the metabolic syndrome. Interestingly drugs that can activate PPAR gamma have been shown to be effective for the prevention and treatment of insulin resistance and T2DM.[7] It is interesting to note that one of the commonly used ARB drug, telmisartan prescribed for treatment of hypertension, is structurally unique because it not only acts an effective Angiotensin II receptor blocker but also functions as a partial agonist of PPAR gamma receptor and causes activation of genes which are involved in the metabolism of lipids and carbohydrates. In experimental studies in rats fed on high carbohydrate diet, telmisartan has also been shown to reduce blood glucose levels, insulin, carbohydrates and triglyceride levels.

In contrast to other anti-hypertensive drugs and anti-diabetic agents, molecules that can simultaneously block Angiotensin II receptors and activate the genes targeted by PPAR gamma receptors appear to be more effective in the treatment of hypertension in T2DM.[7]

ARBs ACT AS ANTI-AGEING AGENTS

Reports available in literature have added a repertoire of beneficial pleiotropic effects caused by ARBs. Angiotensin II (AT1) receptor blockade appears to contribute to age retarding phenomenon. Elena et al (2010) have reported that Angiotensin II enhances reactive oxygen species production by activating NAD(P)H oxidase but also enhances additional ROS production by uncoupling endothelial nitric oxide synthase (e-NOS). Apart from these, Angiotensin II also stimulates production of mitochondrial ROS, a process that reduces mitochondrial energy metabolism, thus contributing to ageing process by prompting mitochondrial dysfunction.

Thus the RAAS blockade strategy (Ang II AT1 receptor) appears to result in not only anti-ageing effects as it increases mitochondrial content and function but at the same time it reverses the oxidative stress by reducing mitochondrial ROS production. The other anti- ageing effect described by the authors are; calorie retention, an age retarding intervention in humans and rodents; delay in the manifestations of hypertension, Diabetes mellitus, Nephropathy, Cardiovascular disease (CVD) and Cancer (Elana et al 2010).[7] In another study Benegini et al (2010)[12] reported that disruption of Angiotensin II type 1 receptor promotes longevity in mice.

LOW INCIDENCE OF TYPE 2 DM IN PATIENTS WITH ESSENTIAL HYPERTENSION WHO WERE ON ARB TREATMENT

Low incidence of T2DM was reported in Essential Hypertension (E-HTN) patients who were on ARB treatment (Elliot).[13] These E-HTN patients were on different anti-hypertensive medications and were followed-up for a period upto 2 years. It is reported that effect of different classes of anti-hypertensive medications on the incidence of diabetes varied. The lowest association has been demonstrated in the patients who were on ARBs/ACE inhibitors, followed by those who were on calcium channel blockers / beta blockers and diuretics.[13] (Elliot W and Meyer P M et al 2007). These inferences were drawn by Noto et al (2013)[14] who carried out a meta-analysis of reports available on the incidence of T2DM in E-HTN cases who were followed-up to see as to what proportion of these cases develop T2DM.

The objective of meta-analysis was based on the observation that in experimental studies on human islet cells and murine type 1 and type 2 diabetes have revealed that a calcium channel blocker, verapamil, may inhibit the expression of pro-apoptotic beta-call thioredoxin interacting protein (TXNIP) in INS-1 cells and human islets and are thus responsible for extending beta-cell survival and function thus preventing diabetes in BTBR ob/ob mice Xu G et al,[15] The outcome of the analysis was that in overt diabetes and hypertension ARBs and ACE inhibitors are generally preferred in the light of lower risk of diabetes progression as suggested by their meta-analysis and the nephroprotective effects of ARBs.

CONCLUSION

It is concluded that while different classes of anti-hypertensive drugs have been reported to be effective in the treatment of cases with hypertension, the ARBs in view of some additional therapeutic advantages may be considered especially in cases with LV hypertrophy and also because of their renoprotective effects. Further clinical and experimental studies are required to establish the beneficial effects of ARBs outlined in this review.

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