

# ***INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES***

**Pharmaceutical Sciences**

**Review Article.....!!!**

Received: 26-03-2012; Accepted: 28-03-2012

## **HYPERTENSIVE VACCINES: A REVIEW**

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### **Keywords:**

Hypertension, angiotensin-II with CYT006-AngQb vaccine, PMD-3117

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### **ABSTRACT**

Hypertension remains an important public health challenge. High BP is associated with an increased risk of mortality and morbidity from stroke, coronary heart disease, congestive heart failure, and end-stage renal disease; it also has a negative impact on the quality of life. Hypertension cannot be eliminated because there are no vaccines to prevent the development of hypertension, but, its incidence can be decreased by reducing the risk factors for its development, which include obesity, high dietary intake of fat and sodium and low intake of potassium, physical inactivity, smoking, and excessive alcohol intake. More recently, immunization against angiotensin-I with PMD-3117 vaccine, angiotensin-II with CYT006-AngQb vaccine and targeting angiotensin-II type 1A receptor with ATR12181 vaccine have provided optimism in the development of a hypertension vaccine. AngQb vaccine has proved to become the first vaccine ever to lower ( $-9/-4$  mm Hg) blood pressure in human beings. Vaccine could induce long lasting effects with a dosing interval of months, increasing patient acceptability and compliance and thus a better control of high blood pressure. Our objective will be to focus on the importance of the RAS and to explore the extent of safety, efficacy and the future implications of vaccine against the RAS.

## INTRODUCTION

New classes of antihypertensive drugs and new compounds in the established drug classes are likely to widen the armamentarium available to combat hypertension. These include the aldosterone receptor blockers, vasodilator beta-blockers, renin inhibitors, endothelin receptor antagonists, and dual endopeptidase inhibitors. There is a conceptual possibility that gene therapy may yield long-lasting antihypertensive effects by influencing the genes associated with hypertension. But, the treatment of human essential hypertension requires sustained over-expression of genes. Some of the challenging tasks for successful gene therapy that need to be mastered include identification of target genes, ideal gene transfer vector, precise delivery of genes into the required site (target), efficient transfer of genes into the cells of the target, and prompt assessment of gene expression over time. Targeting the RAS by antisense gene therapy appears to be a viable strategy for the long-term control of hyper.(1,3) In animal models, vaccination against renin was effective but resulted in fatal autoimmune renal disease. In humans, angiotensin I vaccination did not reduce BP. More promising is the AngQb vaccine, which uses an immunization technology involving angiotensin II to virus-like particles tension. (3)

### **CYT-006-AngQb Hypertensive vaccine**

CYT-006-AngQb, under development by Cytos Biotechnology AG, is a vaccine in which a peptide derived from the angiotensin II molecule is conjugated to the surface of the highly repetitive structure of virus-like particles. CYT-006-AngQb was designed to treat hypertension with the benefit of relatively long-lasting effects that do not require daily dosing. In spontaneously hypertensive rat models, CYT-006-AngQb induced strong angiotensin-II-specific antibodies and reduced systolic blood pressure. In a phase I clinical trial, single doses of CYT-006-AngQb were well tolerated in healthy males. In a phase II trial, multiple doses of CYT-006-AngQb administered to patients with mild-to-moderate hypertension reduced blood pressure; the average half-life was longer than all currently available oral hypertension medications. There were no significant side effects except for local skin reactions at the injection site. Given the novel mechanism of CYT-006-AngQb, and the potential to complement other hypertension treatments, success in ongoing phase II trials in patients with hypertension would potentially make this therapy a valuable addition to the therapeutic armamentarium for hypertension.(4)

Immunization against angiotensin II may offer a valuable alternative to conventional drugs for the treatment of hypertension, because vaccines induce relatively long-lasting effects and do not require daily dosing. Here we describe the preclinical development and the phase I clinical trial testing of a virus-like particle (VLP)-based antihypertensive vaccine. Methods and results: An angiotensin II-derived peptide was conjugated to the VLP Q $\beta$  (AngQ $\beta$ ). Conclusions: AngQ $\beta$  reduces blood pressure in SHR to levels obtained with an ACE inhibitor, and is immunogenic and well tolerated in humans. Therefore, vaccination against angiotensin II has the potential to become a useful antihypertensive treatment providing long-lasting effects and improving patient compliance. (5)

Worldwide, the prevalence of noncommunicable chronic diseases is increasing. The use of vaccines to induce autoantibodies that neutralize disease-related proteins offers a means to effectively and affordably treat such diseases. Twenty vaccines designed to induce therapeutic autoantibodies were clinically tested in the past 12 years. Immunodrugs are therapeutic vaccines comprising virus-like particles (VLPs) covalently conjugated with self-antigens that induce neutralizing autoantibody responses. Four such VLP-based vaccines have been clinically tested and one has achieved proof of principle: a reduction of blood pressure in hypertensive patients. To facilitate preliminary clinical testing, novel nonclinical study programs have been developed. Safety study designs have considered the underlying B and T cell immunology and have examined potential toxicities of vaccine components and primary and secondary pharmacodynamic action of the vaccines. (6)

### **ATR12181 Antihypertensive Vaccine**

Vaccines, which induce relatively long-lasting effects and do not require daily dosing, could provide a solution for patients who have difficulties in adhering to antihypertensive medication regimens. Researchers began experimenting with vaccines against the renin-angiotensin system over 50 years ago. The first candidate vaccine targeted renin, but autoimmune disease developed in the animals that received it. A later vaccine that targeted angiotensin I generated antibodies and was well tolerated, but it did not significantly modify blood pressure. Recent peptide vaccines have been directed against angiotensin II, and several that showed efficacy in improving blood pressure in preclinical studies are currently in early clinical trials. (7)

Hypertension produces pathophysiological changes that are often responsible for the mortality associated with the disease. It is evident that overactive renin-angiotensin systems play a central role in the development of hypertension and target organ damage associated with hypertension. We have previously found that a novel angiotensin II receptor (AT<sub>1</sub>) vaccine-ATR12181 attenuated the development of high blood pressure (BP) in spontaneously hypertensive rat (SHR) model of human essential hypertension. Our objective was to determine whether this attenuation of high BP is associated with prevention of target organ damage induced by hypertensive state. SHRs were immunized against a peptide (coded ATR12181) from the extracellular portion of the AT<sub>1A</sub> receptor by repeated subcutaneous injections of peptide-tetanus-toxoid complex in combination with Freund's adjuvant. A 64 weeks long-term observation was performed. Repeated vaccinations resulted in the induction of anti-ATR12181 antibodies. At the end of observation, vaccinated SHRs manifested lower BP, decreased cardiac hypertrophy and attenuation of kidney injuries. mRNA levels of c-fos and c-jun in heart and kidneys were decreased in vaccinated SHRs. Since a self antigen was used, safety of vaccine was concerned. However, the signs of autoimmune diseases were not observed in the sections of heart and kidney. These data demonstrated that repeated immunization against a domain of the extracellular portion of the AT<sub>1</sub> receptor was able to cause a target organ protection against hypertension. Active immunization against the AT<sub>1</sub> receptor may be considered as a promising new strategy in the treatment of hypertension. (8)

Immunologic approaches to renin-angiotensin-aldosterone system (RAAS) inhibition have been studied for more than 50 years. In animal models, vaccination against renin was effective but resulted in fatal autoimmune renal disease; vaccines directed at small peptides including angiotensin I and II and a segment of the AT<sub>1</sub> receptor reduced blood pressure (BP) without causing autoimmune disease. In humans, angiotensin I vaccination did not reduce BP. More promising is the AngQb vaccine, which uses an immunization technology involving conjugation of angiotensin II to virus-like particles.

### **PMD3117 Antihypertensive vaccine**

Immunization against a component of the renin–angiotensin system might obviate the need for daily drug administration in patients with hypertension or other indications for chronic treatment

with drugs that block the renin system. The PMD3117 vaccine consists of a 12-amino-acid analogue of Ang I (angiotensin I) in which the decapeptide is extended by acetylcysteine–glycine at the N-terminal and covalently linked to KLH (keyhole limpet haemocyanin). The vaccine is formulated as an aqueous suspension by adsorption on to the registered adjuvant aluminium hydroxide (Alhydrogel™). In laboratory animals, an earlier formulation of the vaccine decreased the BP (blood pressure) response to infused Ang I, and the 24 h BP was lower in spontaneously hypertensive rats immunized with PMD3117 than in sham immunized rats.(9) A similar antihypertensive vaccine under development by Protherics (London, UK, and Brentwood, Tennessee) is scheduled to be the focus of a phase 2a proof of concept study starting in the first half of 2008. Angiotensin Therapeutic Vaccine (ATV) is a conjugate of a 12-amino acid analogue of angiotensin I (PMD3117) crosslinked to keyhole limpet hemocyanin (KLH). An earlier version of the vaccine was evaluated in phase 1 and was well tolerated and generated a prolonged antibody response, but did not affect blood pressure. Protherics now have a new formulation of ATV containing a novel adjuvant, *CoVaccine HT*, an oil-in-water emulsion that acts by stimulating the B-cell immune response against the antigen component of the vaccine it is combined with. This results in an increase in the amount of circulating IgG synthesized against the antigen. The double-blind, placebo-controlled phase 2a study with ATV will enroll approximately 120 patients with mild-to-moderate hypertension. Patients will be given 3 intramuscular injections 21 days apart and both antibody response and effects on blood pressure will be assessed. The goal of this study will be to confirm that the new formulation increases levels of anti-angiotensin antibodies in hypertensive patients and to establish whether this results in a reduction in blood pressure. The results are expected during the first half of 2009. If they are positive, Protherics plans for further development and commercialization of the vaccine.

Research into antihypertensive vaccines is also continuing in China, at Huazhong University of Science and Technology in Wuhan. Preclinical studies with a vaccine that uses a peptide from the extracellular portion of rat angiotensin II type 1A (AT1A) receptor have been reported. The vaccine, ATR12181, was shown to be effective in reducing blood pressure and ameliorating remodeling of target organs in spontaneously hypertensive rats.(10)

Antihypertensive vaccination; exploratory study says immunization safe, well tolerated, and experimental vaccine may control morning blood pressure.(11,12,13)

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