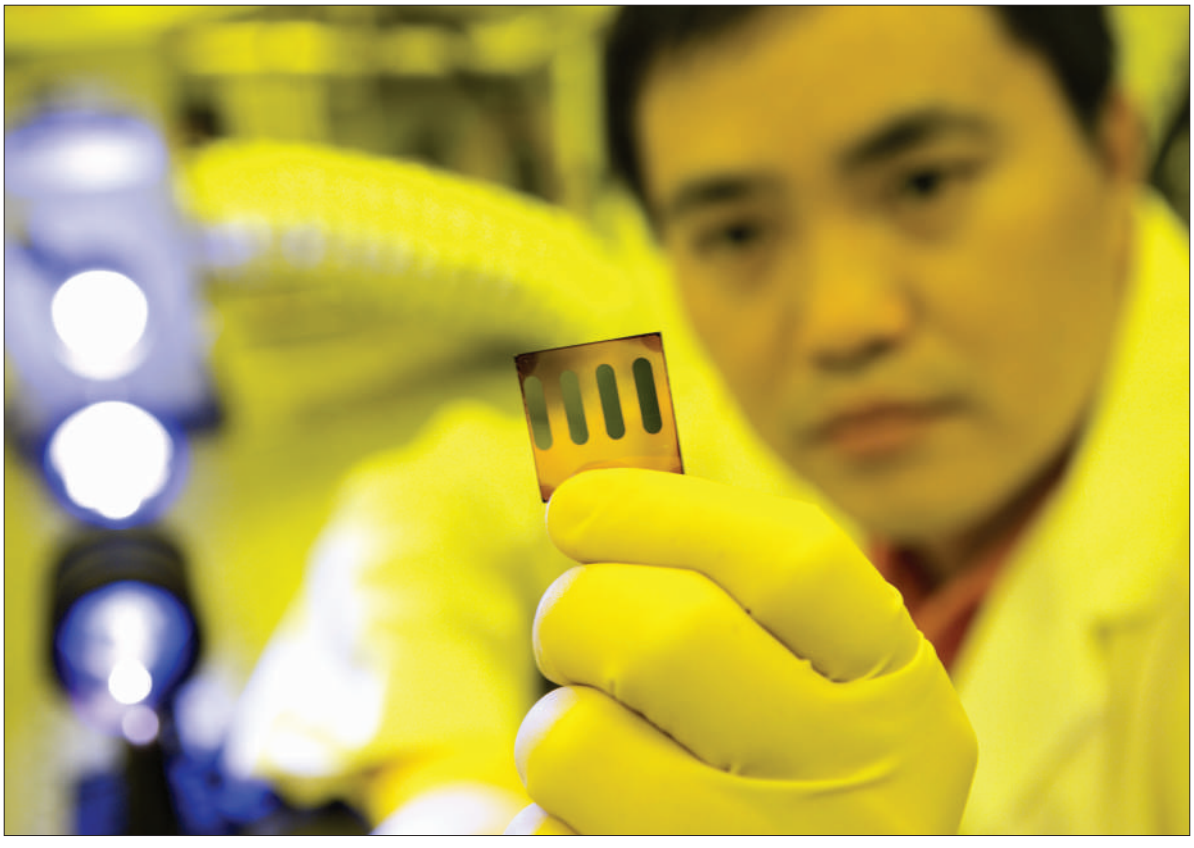

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Vaccines for Hypertension Disorder: Beneficial or Detrimental

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ABSTRACT

The prevalence of hypertension in the adult population was estimated to be 26.4% in 2000 and is projected to be 29.2% by 2025. Hypertension significantly increases the risk of developing disorders such as coronary artery disease, stroke, arrhythmia, heart failure, abnormal renal function and many other complications associated with structural damage to the cardiovascular system, hence the management of hypertension is very essential. Management of hypertension involves different approaches like life style modification and antihypertensive therapy. Life style modifications like weight reduction, discontinue smoking, limiting alcohol intake, increasing physical activity, reducing salt intake, increasing fruit vegetable intake, decreasing saturated and total fat intakes helps in managing hypertension. Antihypertensive therapy without co-morbidities involves administration of different classes of drugs like diuretics, angiotensin convertase enzyme, angiotensin receptor blockers, β blockers, calcium channel blockers, aldosterone antagonist and rennin inhibitors to achieve desired blood pressure intiating treatment with two drug combination may allow blood pressure targets to be reached earlier than monotherapy. This may lead to various adverse effects. Both the approaches requires patient adherence, which is a major problem in management of hypertension. To overcome the problem of patient compliance, research is going on the development of vaccines for hypertension, which produces antibodies against endogenous renin/angiotensin I and II. Vaccines for treatment of hypertension unlike other conventional, vaccine which is used for prevention of various diseases. Although, the concept is intriguing because excessive stimulation of immune system against endogenous substance may lead to autoimmune disorder like nephritis and also renin angiotensin system involved in the maintaining of homeostasis will be hampered. It's better to use many excellent therapeutic options that are already available to inhibit the RAS, until efficient vaccine is developed.

Key words: Hypertension, renin, angiotensin I, angiotensin II, vaccine

INTRODUCTION

Hypertension is defined as a sustained increase in systolic blood pressure (SBP) of 140 mmHg or greater and/or diastolic blood pressure (DBP) of 90 mmHg or greater. Hypertension is classified into two types, i.e., Primary or essential hypertension (no underlying cause) and secondary hypertension (hypertension due to other disorders like kidney disease, vascular or endocrine disorders).

Management of hypertension

Lifestyle modification: Healthy lifestyles by an individual are important for the prevention of high BP and which is also essential for management of those with hypertension (Whelton *et al.*,

Table 1: Classes of drugs nsed for hypertension

Class of drugs	Example
Diuretics	Hydrochlorothiazide
β-Blockers	Metoprolol extended release
	Nebivolol
Calcium channel blockers	Amlodipine
Angiotensin converting enzyme inhibitors	Ramipril, Lisinopril
Angiotensin receptor blocker	Telmisartan, Losartan
α-Blockers	Doxazoxin
Aldosterone antagonist	Eplerenone

Table 2: Recommended fixed-dose combinations by Chobanian *et al.* (2003) and Mancia *et al.* (2007)

No.	Recommended dose
1	Calcium channel blocker and Beta blocker (e.g., Amlodipine and Nebivolol)
2	Calcium channel blocker and Angiotensin converting enzyme inhibitor (e.g., Amlodipine and Lisinopril)
3	Calcium channel blocker and Angiotensin receptor blocker (e.g., Amlodipine and Telmisartan)
4	Calcium channel blocker and Thiazide diuretic (e.g., Amlodipine and hydrochlorothiazide)
5	Angiotensin converting enzyme inhibitor and Thiazide diuretic (e.g., Ramipril and hydrochlorothiazide)
6	Angiotensin receptor blocker and Thiazide diuretic (e.g., Telmisartan&hydrochlorothiazide)
7	Angiotensin converting enzyme inhibitor and Angiotensin receptor blocker (e.g., Ramipril and Telmisartan)
8	Beta blocker and diuretic (e.g., Nebivolol and Hydrochlorothiazide)
9	Thiazide diuretic and potassium-sparing diuretic (e.g., Frusemide and Amiloride)

2002). Reducing weight if overweight (Weight loss of as little as 10 lb reduces BP and/or prevents hypertension in a large proportion of overweight persons) and maintaining the ideal body weight (He *et al.*, 2000), stop smoking, limiting alcohol intake, increasing physical activity, reducing salt intake, increasing fruit-vegetable intake, decreasing saturated and total fat intakes helps in managing hypertension (Chobanian *et al.*, 2003).

Antihypertensive therapy: The ultimate goal of antihypertensive therapy is to reduce cardiovascular mortality and renal morbidities. The decision to start antihypertensive treatment should be based on two criteria, i.e., the level of systolic and diastolic BP and the level of cardiovascular risk. Most persons with hypertension especially those >50 years of age, will reach the DBP goal once the SBP goal is achieved, the primary focus should be on attaining the SBP goal (Franklin *et al.*, 2001).

The Blood Pressure (BP) goal (SBP/DBP) for hypertension associated with cardiovascular disease complication and renal disease is <140/90 and <130/80 mmHg, respectively. Hypertension without co-morbidities can be treated by selecting any of these 5 classes of drugs include diuretics, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers (Table 1) (Chobanian *et al.*, 2003).

Combination therapy: Initiating therapy with two drug combination may allow BP targets to be reached earlier than monotherapy. In high-risk hypertensives, 9 out of 10 patients require two or more antihypertensives to reduce their BP to <140/90 mmHg. When BP is more than 20/10 mmHg above the goal, consideration should be given to initiate therapy with two drugs (Sica, 2002). There are various fixed dose combinations for treatment of hypertension among them very few is recommended (Table 2).

Table 3: Various steps can be used to improve the patient compliance as per (Chobanian *et al.*, 2003)

No.	Step
1	Informing the patient on the risk of hypertension and the benefit of effective treatment
2	Providing clear written and oral instructions about treatment
3	Tailoring the treatment regimen to the patient's lifestyle and needs
4	Simplifing treatment by reducing, if possible the number of daily medicaments
5	Involving the patient's partner or family in information on disease and treatment plans
6	Making use of behavioural strategies such as reminder systems
7	Paying great attention to side effects (even if subtle) and be prepared to timely change drug doses or types if needed
8	Dialogue with patient regarding adherence and be informed of his/her problems

In present days, the number of patients suffering from disorders like diabetes and associated comorbidities, i.e., atherosclerosis, dyslipidemia, hypertension and other disorders is increasing world wide (Sathyanaryana *et al.*, 2008). In such cases there is a need of administration of more than one drug for the treatment of these disorders, hence there is possibility of drug-drug interactions.

A study of the mechanisms of drug interactions is of much value in selecting the drug combinations to provide rational therapy. The drug interaction studies assume much importance, especially for drugs that have a narrow margin of safety and where the drugs are used for a prolonged period of time (Sultanpur *et al.*, 2010). Hypertension is one such disorder that needs treatment for prolonged periods and maintenance of normal blood pressure is very important in this condition because both hypertension and hypotension are unwanted phenomena.

Newer approach

Renin inhibitors: Aliskiren is the first renin inhibitor, binds competitively to the active site of the enzyme. They interrupt the negative feedback effects of angiotensin II on renin secretion; this increases renin concentrations, which may attenuate the inhibition of the renin-angiotensin system by these therapies (Duncan, 2009). Whether renin inhibitors offer therapeutic benefits beyond those provided by ACE inhibitor and angiotensin receptor antagonist therapies will require their direct comparison in clinical outcome studies.

Compliance to treatment: Non-compliance to treatment is the major problem involved in the treatment of hypertension. Various steps have been taken to over come the compliance (Table 3) to some extent these steps have been found to be useful.

Today we have drugs that are highly effective at lowering blood pressure with minimal side effects. However, above approaches lifestyle modification and antihypertensive therapy require patient adherence to be effective. Poor compliance is common for both approaches and is the main reason for inadequate blood-pressure control.

VACCINES FOR HYPERTENSION

Vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease causing microorganism and is often made from weakened or killed forms of the microbes or its toxins. The agent stimulates the body's immune system to recognize the agent as foreign, destroys it and recognize it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters. Unlike conventional, vaccine for hypertension is not used for prevention but it is used for treatment of disease. it is named because they stimulate the immune system by acts on the renin angiotensin system.

Vaccine stimulates immune system and release antibodies against endogenous renin/angiotensin I/angiotensin II. If vaccination for high blood pressure were safe and effective in the long run, it might solve many problems. Besides resolving the compliance problem, the patients will not have to encounter the undesirable side effects of the drugs, would gain smooth, prolonged and progressive onset of action, increased diurnal control of blood pressure and reduction in drug interaction associated with conventional polypharmacy.

Therapeutic active vaccination targeting components of the RAS is a potential option. It offers the possibility for reduction of blood pressure with two to three immunizations per year. Such an approach could circumvent the need for daily medication and substantially reduce the issue of patient compliance (Maurer and Bachmann, 2010).

ROLE OF RENIN-ANGIOTENSIN SYSTEM

The Renin-Angiotensin System (RAS) is a well coordinated hormonal cascade in the control of cardiovascular, renal and adrenal function that maintain homeostasis and plays an imminent role in the regulation of arterial blood pressure (Akiyoshi *et al.*, 1993). Prof. Robert Tigerstedt and a noted Finnish physiologist discovered the renin system in 1898 at the Karolinska Institute in Sweden (Ulfendahl and Aurell, 1998).

Renin: Renin is an aspartyl proteolytic enzyme (Suh *et al.*, 2005) in juxtaglomerular cells of the afferent arteriole of the kidney and is the locus for renin synthesis, storage and release. Translation of renin mRNA in these cells produces pre prorenin, which in turn is then converted to prorenin by the removal of a single peptide and glycosylation. Some of the prorenin to renin conversion takes place in the juxtaglomerular cells, both renin and prorenin are secreted from these cells. Prorenin is the more abundant circulating form of renin (Beierwaltes, 2003).

The primary stimulatory intracellular second messenger for renin release is the cyclic nucleotide c-AMP, which is probably the second messenger for stimulation via beta-adrenergic nerves and prostaglandins. Active renin is secreted in response to regulatory mechanisms: renal baroreceptor, macula densa and β_1-receptor stimulation via renal nerves and humoral factors (Duff *et al.*, 1995).

Renin catalyzes the cleavage of leucine valine bond in the N-terminal region of human angiotensinogen (large globular protein mainly derived from the pericentral zone of liver lobules) or it cleaves a leucine bond in the angiotensinogen of other species to produce the decapeptide angiotensin I (Suh *et al.,* 2005).

Angiotensins: Angiotensins are peptide hormones obtained by cleavage of angiotensinogen by renin, which takes place in series of proteolytic reactions. Angiotensin I doesn't have any biologic role, it serves as the precursor of angiotensin II and III (Berk and Corson, 1997).

Angiotensin II is produced both systematically and locally in the vessel wall by the actions of ACE, which cleaves angiotensin I to form angiotensin II. It is the key effector hormone of the RAS, through the activation of small G proteins such as Ras, Rho and Rac. It causes vasoconstriction, increases afterload, retention of sodium and fluid, all of these actions affect the cardiovascular system and increase the blood pressure (Duff *et al.*, 1995). It induces Vascular Smooth Muscle Cell (VSMC) remodeling, including proliferation, migration and hypertrophy of the smooth muscle cells. Well-documented studies on RAS's role in the development and maintenance of arterial hypertension have been implicated and also angiotensin II in cardiovascular and renal pathologies (Unger *et al.*, 1998).

Angiotensin II stimulate VSMC growth, increase expression of enzymes that produce mediators of inflammation such as phospholipase A_2, NAD(P)H oxidase, stimulate the JAK/STAT pathway and activate gene transcription of such proto oncogenes as c-fos (Schmieder *et al.*, 2007).

Angio-tensin III is more lipid-soluble than angiotensin II, hence abundantly found in the brain and cerebrospinal fluid. It has lower affinity for the angiotensin II binding sites and also degrades more rapidly. Hence elicits less potency than angiotensin II. Angiotensin has effects on the brain that suggest it has a role in memory. It also stimulates the release of plasminogen activator inhibitor from endothelial cells (Schmieder *et al.*, 2007).

Angiotensin convertase enzyme: Angiotensin Converting Enzyme (ACE) is a zinc metallopeptidase widely distributed on the surface of endothelial cells and epithelial cells. It has role in regulating the levels of angiotensin II and bradykinin (Brown and Vaughan, 1998).

Angiotensin II receptors: Angiotensin II have high affinity to receptor AT_1, AT_2 and AT_4 and produce cellular response via signal transduction. The AT_1 and AT_2 receptors may be having similar affinities for angiotensin II bit they have different effects (Duprez, 2006). Angiotensin II binds to the AT_1 receptor and this activates G protein-coupled phospholipase C (PL_C). The PL_C is an essential enzyme for transmembrane signal transduction by generating second messenger molecules like inositol triphosphate (IP_3) and diacylglycerol (DAG). The IP_3 induces the release of Ca^{2+} from internal stores and DAG is the physiological activator of protein kinase. Distribution of the AT_1 receptor in the adult is ubiquitous, including the vasculature, kidney, adrenal gland, heart, liver and brain. With some exceptions, most of the pathologic cardiovascular effects of angiotensin II are mediated through the AT_1 receptor: hypertension, coagulation, inflammation and vascular smooth muscle cell growth (Duff *et al.*, 1995).

Angiotensin II binding to the AT_2 receptor activates a counter regulatory pathway to induce vasorelaxation via activation of the kinin/No/cGMP system. The AT_2 receptor is abundant in the fetal brain, kidney mostly involved in developmental processes in the fetus. The AT_2 receptor reappears in adults, it generally acts as a counterweight to the pathologic effects of AT_1, which inhibits angiotensin II induced growth and pro inflammatory activity and also decreases arterial blood pressure (Duff et *al.*, 1995).

The AT_1 and AT_2 receptors share only 34% homology and they have distinct signal transduction pathways. Evidence suggests that AT_4 receptor produce its effects via angiotensin IV and is an important mediator of the expression of plasminogen activator inhibitor-1 (Burnier, 2001).

Renin immunization (Table 4): Renin immunization is active immunization against human rennin which was first attempted by Goldblatt (1951). The administration of heterologous (hog) renin in man produced anti renin antibody. These antibodies were ineffective against human renin and no fall in blood pressure observed in hypertensive patients (Goldblatt, 1951).

In early studies, the active immunization against renin was the target in several species, particularly hog renin in dogs and human renin in primates have been studied with successful results. But interpretation of these studies was limited by the impurity of the immunogen, absence of hormonal assays throughout the experiment and problems of species specificity (Michel *et al.*, 1989).

High titre of renin antibodies were found by active immunization with pure human renin and Freund's adjuvant in normotensive marmosets. There was a complete inhibition of endogenous

Table 4: Types of vaccine for hypertension

Author	Immunization against	Study subject	BP Response
Johnston *et al.* (1970)	Ang II	Hypertensive rats and rabbits	Nil
Macdonald *et al.* (1970)	Ang II	Rabbits	Nil
Oates *et al.* (1974)	Ang I and /or Ang II	Rats	Nil
Reade *et al.* (1989)	Ang I	SHRs	Nil
Smits *et al.* (1999)	Ang I	SHRs	Not significant
Gardiner *et al.* (2000)	Ang I (PMD 2850)	Male, Sprague-Dawley rats	Reduced response to AngIbut not with AngII
Downham *et al.* (2003)	Ang I (PMD-2850, PMD-3117)	Rats, Human (healthy)	Pressor effects decreased to Ang I but not with Ang II. No response in human
Brown *et al.* (2004)	Ang I (PMD 3117)	Human	No response
Zhu *et al.* (2006)	AngII-type1A receptor (ATR12181)	SHRs	Decrease in BP
Ambuhl *et al.* (2007)	Ang II (AngQb)	SHRs, human	BP decrease in Rats. No significant changes in human
Tissot *et al.* (2008)	Ang II (AngQb)	Human	Decrease in MBP
Hong *et al.* (2009)	Ang I	SHRs	100% response rate

plasma renin activity and decrease in blood pressure. But all marmosets presented an autoimmune disease with specificity to the kidney (cellular inflammatory proliferation around the intrarenal arterial tree and an interstitial nephritis) (Michel *et al.*, 1990).

Later similar studies were performed in Spontaneously Hypertensive Rats (SHRs) using pure mouse submandibular gland renin, which shares 80% homology with the rat renin. Immunization with mouse submandibular gland renin in SHR, with Freund's adjuvant, induced a normalization of blood pressure associated with a high titre of antirenin antibodies. The total inhibition of the plasma renin activity associated with significant decrease in aldosterone secretion. Unfortunately, these animals also presented an autoimmune disease of the kidney (Pandey *et al.*, 2009).

Angiotensin-II immunization (Table 4): The first active immunization against angiotensin II in rats and rabbits was attempted in 1970. Synthetic Ang II was coupled to Bovine serum albumin and emulsified in Freund's adjuvant for better immunization. Although, immunization against Ang II was showed a greater extent in reduction of response to exogenous Ang II, which played no direct role in the production or maintenance of experimental renal hypertension (Johnston *et al.*, 1970).

Macdonald *et al.* (1970) used rabbits for study and were immunized against Ang II. He was confirmed the specific absence of pressor response to high doses of renin and Ang II after immunization. But there was no evidence of modification in established hypertension.

Immunization against Ang II and combined Ang I and Ang II in rats was studied by Oates *et al.* (1974) and he was confirmed that those immunized equal parts Ang I and Ang II were found to develop antibodies titre 6-15 times greater for Ang I than for Ang II. The sustained Ang I and /or Ang II immunity did not alter blood pressure.

Angiotensin-I immunization (Table 4): Immunization against Ang I in SHRs resulting in presence of high levels of antibodies against Ang I, but still it is failed to reveal any fall in blood pressure during the first 6 months time of immunization (Reade *et al.*, 1989).

Smits *et al.* (1999) showed no significant decrease in mean blood pressure in immunized SHRs and the maintenance of the response to Ang II antagonism. The only significant effect was an 11 mmHg decrease in diastolic blood pressure during the sleeping period in immunized animals. Rats were immunized against Ang I with an effective vaccine PMD-2850, which consists of an Ang I analogue conjugated with a Tetanus Toxoid (TT) carrier protein adjuvant with aluminum hydroxide. Anti-angiotensin antibody titre increased by 32,100 fold and these antibodies cross reacted with angiotensinogen and suppress the ability of endogenous Ang I, then it would be expected to be more effective than previous active immunizations. It had limited application due to epitopic suppression (Gardiner *et al.*, 2000).

The efficacy of keyhole limpet haemocyanin (KLH) (an alternative peptide carrier protein) conjugated with Ang I vaccine (PMD-3117) to the earlier TT conjugated vaccine (PMD-2850) is used to immunize rats and healthy human volunteers. Active immunization of rats with immunogen containing Ang I conjugated with either TT or KLH produced equivalent anti-Ang I-IgG titres and change in the dose response to exogenous Ang I. Anti Ang I - IgG induction was not detected in humans with given single doses of Ang I–TT or Ang I-KLH conjugated vaccine but caused production of anti-Ang I-IgG molecules when given in two doses of immunization with AngI-KLH (Downham *et al.*, 2003).

Phase IIa clinical trial was carried out in hypertensive subjects with anti-Ang I vaccine (PMD-3117). One group of 8 patients received three doses of 100 μg of vaccine at 21 days intervals, whereas a second group of 8 patients received the same (100 μg) dose of vaccine on four occasions at 14 day intervals. Twenty four patients completed all scheduled injections. Significant antibody induction was detectable after the second injection with both regimes and were not significantly different. It had no effect on blood pressure and it was assumed that the titre generated by the formulation of the vaccine was too small to provide sufficient AngI inhibition (Brown *et al.*, 2004)

In preclinical studies 6 SHRs were immunized against the peptide from rat AT1A receptor by repeated subcutaneous injections of ATR12181 and observed for 64 weeks to assess its long-term efficacy, safety and its blood pressure lowering ability. Repeated vaccinations resulted in the induction of anti-ATR12181 antibodies. A 17 mmHg reduction of systolic blood pressure was observed in vaccinated SHRs at the 64th week. However, the level of BP did not reach target level (140/90 mmHg). The long term results of vaccine ATR12181 in SHRs seemed to be encouraging in all aspects like BP lowering, target organ remodeling, proving its efficacy and safety (Zhu *et al.*, 2006).

Vaccination against a self-antigen in which a peptide derived from AngII was covalently conjugated to VLP (virus like particles) termed CYT006- AngQb (AngQb), used to immunize SHRs and also human volunteers. Rats were injected subcutaneously on days 0, 14 and 28 with 400 μg AngQb, immunization yielded a consistent reduction in blood pressure lasting more than 35 days after the last boost. In particular, no signs of inflammation were detected in the kidney, indicating no inflammatory immune complex deposition. Human volunteers receiving single dose subcutaneous injection of AngQb (100 μg) responded with high IgG titres against AngII within 2 weeks of immunization but there was no significant changes occurred in blood pressure. Fourteen out of 16 subjects showed local adverse events such erythema, edema, pain and indurations at the injection site, all of mild intensity. This clinical study was successful to show that AngQb vaccine was highly immunogenic, induced no signs of inflammation or immune complex formation and was tolerable (Ambuhl *et al.*, 2007).

Multicenter, double-blind, randomized and placebo-controlled phase IIa trial was conducted on 72 patients with mild-to-moderate hypertension, they were assigned to receive injections of either AngQb 100 μg or 300 μg or placebo in week 0, 4 and 12. All volunteers receiving AngQb responded with high IgG titres against AngII after only one injection and the antibody response was strongly boosted after the second injection. The 300 μg dose induced a significantly higher AngII specific IgG response than 100 μg dose and the average half-life after the third injection was 17 weeks. There was a significant reduction of the early-morning BP surge compared with placebo in the 300 μg group, postural hypertension was not seen. The vaccine was not associated with any serious adverse effects. Interestingly, the drop in BP was pronounced in the early morning, when the RAS is most active and when most stroke and cardiovascular events occur (Tissot *et al*., 2008).

Ang I-R is an aluminum hydroxide adjuvant vaccine fprmulation targeted to Ang I/II and administration of one dose of this results in production of strong antibody response in SHRs. It has demonstrated sustained lowering of blood pressure in SHRs (Hong *et al*., 2009).

Blockade of Rennin Angiotensin System (RAS): The RAS contributes to maintenance of blood pressure during volume depletion (Adams, 2008). It has been argued that, it could cause problems after severe blood loss from anti angiotensin antibody production and reduction of half-lives in the range of several months.

CONCLUSION

Hypertension cannot be cured. It has to be managed throughout the life to avoid cardiovascular and renal complications. Management of hypertension with antihypertensive therapy requires a patient's adherence to lifestyle modifications and medication. In most of the cases it requires polypharmacy, i.e., more than one drug to achieve desired goal, which may lead to various adverse effects. Hence immunization with vaccine would be a better alternative for antihypertensive drugs to overcome the problems related to compliance of the patient. Immunization against endogenous renin, angiotensin I and II could be an advantageous than antihypertensive therapy. Whereas there is also an incidence of autoimmune disorder due to excessive stimulation of immune system against endogenous substance released for maintaining homeostasis of body and undesired effects due to blockade of renin angiotensin system and it could be a major problem with vaccine for hypertension. It is better to use many excellent therapeutic options, which are already available to inhibit the RAS until efficient vaccine is developed.

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