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Therapeutic Potential of Vaccines in the Management of Hypertension

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Abstract

Therapeutic vaccination is an exciting new development in hypertension, but proof-of-concept in the clinic is not yet clearly established. Effective renin-angiotensin system (RAS) inhibition by a twice-yearly treatment would be attractive in pre-hypertension, maybe even preventing hypertension itself from developing. However, it is hoped that proof-of-concept with a vaccine, the efficacy of which is easy to measure, will encourage development of more adventurous vaccines directed against targets such as aldosterone or completely novel pathways where alternative treatments are scarce or absent.

Two current angiotensin vaccines are in development. PMD3117 is a modified angiotensin I coupled to keyhole limpet haemocyanin. CYT006-AngQb is a conjugate of angiotensin II linked to virus particles. Studies in patients with hypertension demonstrate some efficacy for both vaccines, but far short of what is seen with existing RAS inhibitors. Modification of the immunogen or adjuvant is required to boost the antibody titre.

The treatment of hypertension has been a therapeutic success story, with perhaps a greater genuine choice among drugs with different mechanisms of action than exists for any other common disorder.[1] More patients have also participated in long-term trials to evaluate the benefits of treatment than for other common disorders.[2] Yet, there is a serious debate about whether we need new treatments. The decision of the UK National Institute for Clinical Excellence to drop β-adrenoceptor antagonists (β-blockers) from first-choice therapy was a timely reminder that even older drug classes are not immune to findings that substantially affect practice, and that even in hypertension, the options for an individual patient could become limited if one or two major drug classes became unfashionable.[3] UK prescribing figures show as steep a decline in the use of thiazide diuretics as of β-blockers, presumably because both were used together in the arm of the ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) that showed the combination to be less effective than 'newer' drugs in preventing complications of hypertension.[4]

1. Rationale for a Vaccine

This background already suggests room for new treatments in hypertension, but what about vaccines? There appears to be two reasons why these might be attractive. One is to circumvent the problem of non-compliance with the need for daily oral medication. The other is to provide a means of blocking or inhibiting pathways for which no oral drug exists. The former has appeared the best route for the development of vaccines that are discussed here, which target the renin pathway, because an effective vaccine with a good safety profile can expect to find use in the long-term treatment of

hypertension. However, it is to be hoped that angiotensin vaccines (which do not really fill an unmet need in our current pharmacological approach) will be used mainly as positive controls to encourage vaccine development against targets for which there is a paucity of oral compounds. The most obvious of these is aldosterone, which is the major factor in resistant hypertension.[5,6] Yet, we currently have only spironolactone, which causes gynaecomastia, and eplerenone, which is relatively ineffective. However, the most exciting use of the vaccine approach would be against novel molecules or pathways identified by genomic or other -omic approaches.

Currently, the vaccines in active development are directed against angiotensin. As the most crowded area of the hypertension market, with ACE inhibitors, angiotensin receptor antagonists (angiotensin receptor blockers [ARBs]) and now direct renin inhibitors (available as better tolerated alternatives to β-blockers), an angiotensin vaccine would be of most value to patients unwilling to take daily treatment, in whom renin-angiotensin system (RAS) inhibition is sufficient treatment as sole therapy to achieve good blood pressure control. Because older patients generally required a calcium channel antagonist or diuretic in addition to a RAS inhibitor, it may be that vaccination is most attractive to younger patients – both because their blood pressure is more likely to be controlled by the vaccine alone and because young patients are often keen to avoid starting life-long drug medication. Indeed, the advent of a vaccine could encourage the use of RAS inhibitors at an earlier age, when experimental data suggests that hypertension might be prevented or reset.[7]

Historical approaches to RAS inhibition and possible problems with these have been reviewed.[8] Although it has been argued that the immunization approach is flawed, either because antibodies cannot reach tissue angiotensin or because the RAS will upregulate to overcome the antibodies, the main challenge for an angiotensin vaccine (as for any vaccine) is quite simply to generate an adequate immune response. The evidence for a physiologically important local RAS remains virtually non-existent in humans, and there is no more reason for immunological blockade to be overcome by a reactive rise in renin secretion than is true for any of the small molecule inhibitors. This reactive rise in renin is the best single measure of RAS inhibition, being a result of the removal of the normal negative feedback of angiotensin II. However, it is conceivable that it also attenuates response to RAS inhibitors and, hence, the slightly unexpected benefit of combining an ARB with the new direct renin inhibitor.[9]

2. Vaccines in Development

Two current angiotensin vaccines are in development; PMD3117 and CYT006-AngQb. Of the two vaccines, PMD3117 consists of a 12-amino-acid analogue of angiotensin I in which the decapeptide is extended by acetylcysteine-glycine at the N-terminal and covalently linked to keyhole limpet haemocyanin. The vaccine is formulated as an aqueous suspension by adsorption on to the registered adjuvant aluminium hydroxide (Alhydrogel™)[1]. The website of the manufacturer (Protherics) says that a new formulation with the proprietary adjuvant CoVaccine HT™ has resulted, in pre-clinical study, in a 10-fold higher antibody titre and this will be used in a proof-of-concept phase IIa study in patients. The previous formulation lowered blood pressure in salt-depleted healthy volunteers, but not in patients with hypertension.[10] The primary objective of this latter study was to determine the optimum regimen for generating antibody titre. In order to maximize the sensitivity for detecting pharmacological efficacy, the study incorporated a crossover design to investigate the influence of PMD3117 upon the blood pressure and neurohumoral changes during 2 weeks of withdrawal from a conventional RAS inhibitor. Some evidence of efficacy was deduced from a fall in aldosterone excretion following vaccination, and an attenuation by PMD3117 of the normal fall in plasma renin when the conventional RAS inhibitor (ACE inhibitor or ARB) was discontinued.

1 The use of trade names is for identification purposes only and does not imply endorsement.

Table I. Change from baseline in ambulatory blood pressure for treatment groups in a phase IIa trial of the angiotensin vaccine AngQb (reprinted from The Lancet, Tissot et al.,[11] Copyright 2008, with permission from Elsevier)

Blood pressure (mm Hg)	100 μg		300 μg	
[mean (± SD)]	placebo (n = 12)	AngQb (n = 22)	placebo (n = 12)	AngQb (n = 22)
Systolic daytime	−3.4 (2.3)	−1.5 (1.7)	3.4 (2.8)	−5.5 (2.1)*
Diastolic daytime	−1.6 (1.8)	0.0 (1.3)	1.1 (1.7)	−2.9 (1.2)**
Systolic night-time	−2.6 (3.2)	1.1 (2.3)	−2.5 (4.0)	−1.2 (3.0)
Diastolic night-time	1.7 (2.0)	1.3 (1.5)	−1.8 (2.3)	−0.8 (1.7)

* p = 0.012 vs baseline; ** p = 0.024 vs baseline.

The second vaccine, CYT006-AngQb, is a conjugate vaccine composed of angiotensin II chemically linked to recombinant virus-like particles derived from the RNA phage.[11] In a multicentre, double-blind, randomized, placebo-controlled, phase IIa trial, 72 patients with hypertension received either CYT006-AngQb 100 μg, CYT006-AngQb 300 μg or placebo. In the 300-μg group, there was a reduction in mean daytime blood pressure at week 14 by −9.0/−4.0 mmHg compared with placebo (p = 0.015 for systolic and p = 0.064 for diastolic). The 300-μg dose reduced the early morning blood-pressure surge compared with placebo. However, these apparent dose-related effects seemed to owe as much to the 6.8 mmHg difference between the two placebo groups as to the 4.0 mmHg difference between the two active groups (table I). There was a <25% increase in renin levels after vaccination, with no significant difference between the placebo and active groups in the maximum level of plasma renin. This contrasts with the several-fold increases seen following conventional RAS inhibition with ACE inhibitors, ARBs or direct renin inhibitors.[12] The absence of a clear reactive rise in renin levels should engender doubt about the scale of RAS inhibition achieved by the immunization because only direct interference in renin secretion (e.g. by β-adrenergic inhibition) has been shown to counter the loss of negative feedback by angiotensin II seen during other forms of RAS inhibition.[1]

Reported antibody titres were similar in these two studies of distinct vaccines, but can probably not be directly compared because of differences in immunogen and assay methodology. However, the methodological differences between these studies do not explain the <2-fold increases in titre between the dose regimens within each study. Although immunization appears to achieve pharmacological effects in rats,[13,14] it seems likely that improved immunogenicity is required before vaccines will rival existing RAS inhibitors for their effect upon blood pressure in patients with hypertension.

2.1 Safety

Both vaccines were well tolerated, with no obvious evidence of immune complex formation. In the longer-term, issues to be addressed will include the incidence of any rare consequences of vaccinating against an endogenous molecule, and the risks of semi-permanent RAS inhibition if a patient develops an urgent need for RAS activation (e.g. after trauma or any cause of rapid volume depletion). These concerns are probably theoretical. For instance, use of long-acting oral RAS inhibitors has not been clearly associated with serious hazard during volume depletion. Most ACE inhibitors and ARBs have sufficiently long half-lives that they are eliminated only over many hours after an emergency, and presumably patients simply experience a higher requirement for fluid and pressor agents. Had sustained RAS inhibition been a problem with these widely used drugs, it seems unlikely that Hypertensin™ (the therapeutic formulation of angiotensin II) would have been withdrawn some years ago.

3. Conclusions

In conclusion, therapeutic vaccination is an exciting new development in hypertension, but there is a long way to go before even proof-of-concept is established. Effective RAS inhibition by a twice-yearly treatment would be attractive in pre-hypertension, maybe (like any self-respecting vaccine)

even preventing hypertension itself from developing. However, it is hoped that proof-of-concept with a vaccine whose efficacy is easy to measure will encourage development of more adventurous vaccines, directed against targets where alternative treatments are scarce or absent.

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