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Developing a Vaccine for Rheumatic Fever and Rheumatic Heart Disease: A Review of Current Research Strategies and Challenges

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ABSTRACT

Background: Rheumatic heart disease (RHD) is an auto immune sequelae of rheumatic fever (RF) caused by Group A Streptococcal (GAS) pharyngitis, rather than the direct bacterial infection of the heart, which leads to chronic heart valve damage. Although antibiotics like penicillin are effective against GAS infection, improper medical care such as poor patient compliance, overcrowding, poverty, and repeated exposure to GAS, leads to acute rheumatic fever and RHD. Thus, effort to design a vaccine based on emm gene identification of GAS, M-protein going on for more than 40 years, is unlikely to succeed. M-protein is strain specific. Infection with one strain does not provide immunity from infection with another strain. Based on the emm gene identification, of 250 or more identified strains of GAS, the distribution is heterogenous and keeps changing. The M-protein gene sequence of the organism tends to mutate. A vaccine prepared from available strains may not be effective against a strain following mutation.

Keywords: Group A Streptococcus (GAS); Rheumatic Heart Disease (RHD); Vaccine.

INTRODUCTION

It is generally accepted that rheumatic fever (RF) follows group A beta hemolytic streptococcal (GAS) infection. Since GAS infection spreads through droplets, overcrowding causes an increased transmission from person to person. Under nutrition or malnutrition can increase the susceptibility to infection. Poor socio-economic status results in an inability to obtain optimal medical care. Hence a higher prevalence in developing countries is predominantly related to low socioeconomic status.

The resurgence of RF in the Utah area in USA occurred in middle class families with a healthy lifestyle without overcrowding, a suburban population with facilities for good medical care indicates that improvement in socio- economic status alone cannot control RF.[1] Virulence of RF is related to its capacity to cause more or less permanent cardiac damage. In Utah epidemic, carditis based on clinical combined with echocardiogram findings, occurred in almost 90 percent patients.[1] Hence prevention of rheumatic heart disease requires preventing RF.

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Prevention of RF can be considered under two approaches-primary prevention and secondary prevention.[2]

1. **Secondary prevention**
   Secondary prevention consists in giving injections of intramuscular benzathine penicillin every three to four weeks depending on age and muscle mass to patients who have suffered from acute RF to prevent recurrences and Secondary prophylaxis is ethically mandatory. However, secondary prophylaxis cannot reduce the burden of disease. If given properly, it reduces overall heart damage from subsequent attacks.
2. **Primary prevention**
   Primary prophylaxis consists in identifying that the patient has a sore throat, that it is GAS infection and giving penicillin to eradicate the GAS infection. Primary prophylaxis has too many loopholes and is almost impossible to practice even for individual patients.

   Sore throat is a frequent trigger of antibiotic use, both in children and adults. While only a fraction of sore throats are related to GAS pharyngitis, the justification for antibiotic prescription is, in the great

majority of cases, related to the perceived need to prevent GAS-related complications.[3]

Primary prophylaxis is possible if an anti-GAS vaccine becomes available. Although a number of components of GAS organism are being studied in order to make a vaccine.

A 2018 World Health Assembly resolution calls for better control and prevention. Providing guidance on global health research needs is an important WHO activity, influencing prioritization of investments. Here, the role, status and directions in GAS vaccines research are discussed. WHO preferred product characteristics and a research and development technology roadmap, briefly presented, offer an actionable framework for vaccine development to regulatory and policy decision-making, availability and use. GAS vaccines should be considered for global prevention of the range of clinical manifestations and associated antibiotic use. Impediments related to antigen diversity, safety concerns, and the difficulty to establish vaccine efficacy against rheumatic heart disease are discussed. WHO developed a vision for vaccine development, highlighting strategic targets, product preferences and priority research and development activities.[4]

Vaccine Development For RHD

Development of a vaccine for RHD started in the early 1960s with crude cell wall topurified M proteins.[5] In general, selection of vaccine candidates for any pathogen isbased on few characteristics such as;

i) sub-cellular localization of the target protein,
ii) ability to induce immune responses,
iii) no molecular mimicry between target and host tissue proteins,
iv) conservation of target protein among all the available genomes of the species, and
v) possibility of cloning the target protein (e.g., proteins with no or one trans membranehelix) [Figure 1].[6-11]

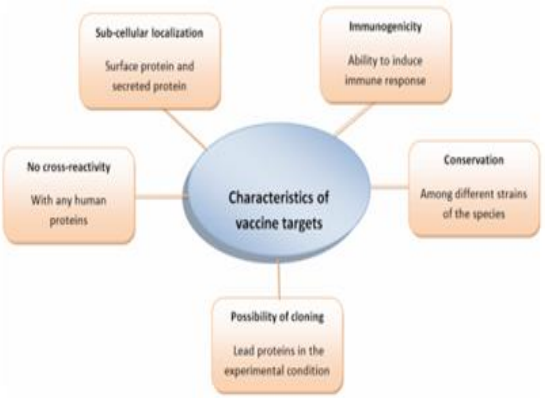

Figure 1: Common characteristics of a potential vaccine candidate.

To be a vaccine candidate, other than virulence factors, proteins with an essential role in the pathogenesis or survival can also be used as a vaccine target. Vaccine targets for Streptococcus pyogenes can be classified into three major types:[12]

i) Vaccines based on cell surface proteins.
ii) Vaccines based on secreted proteins.
iii) Vaccines based on carbohydrates.

Adhesion proteins which help in the pathogen colonization could be used for vaccine design, since the antibodies produced against this protein will prevent colonization of pathogen on the host and further progression of the disease in the host tissue.[13] In order to develop a vaccine, surface and secreted proteins are considered to be thesuitable vaccine candidates in eliciting the antibody response, but when compared to the cytosolic proteins of S. pyogenes, they fail to meet some of the essential characteristicsthat are required for development of vaccine. For instance, limited coverage of somevaccine candidates (serum opacity factor and R28) can provide protection against onlya certain number of serotypes while other antigens (group A carbohydrate) are noteffective in eliciting high concentrations of antibodies,[14,15] which are required to be used asa vaccine target.[14,16] Hence, it is necessary to identify a novel vaccine candidate, whichis highly immunogenic and also capable of giving protection against wide spectrum of Mserotypes.

Vaccines Based On Cell Surface Proteins

There are several cell surface protein like M protein, C5a peptidase (SCPA), C5a peptidase (SCPA), S. pyogenes cell envelope protein (SpyCEP), R28, Streptococcus protective antigen (Spa), Streptococcal immunoglobulin binding protein (Sib35).[12]

M protein

Among the cell surface proteins, M protein of S. pyogenes has been studied extensively. Especially, the hyper variable amino terminal and the highly-conserved carboxylregions have long been the target for vaccine development against RHD due to it simmunogenicity and no cross-reactivity properties.[17] However, the main limitation of using hyper variable N-terminal of M protein is the strain-specific immunity, thusmultivalent vaccines have been developed by combining hyper variable N-terminalregions from different GAS serotypes.

Recently, Dale and colleagues constructed a new 30-valent M protein-based vaccine.[18] This vaccine construct consists of N-terminal fragments (first 50 residues) of M protein from 30 different M serotypes that are predominant in North America and Europe andfurther they have shown to be immunogenic in rabbits. Interestingly, they have further foundthat this multivalent vaccine is protective against another

24 non-vaccine M serotypes,which are not included in the 30 valent vaccine construct.[18] The reason for this cross-protection may be due to the amino acid sequence similarity present in the N-terminl a or high sequence similarity across the whole M protein found within the same emm-cluster.[19]

Although some studies suggested that the level of bactericidal antibodies producedby C-terminal region of M protein may not be adequate to give complete protection against GAS infection,[20] vaccine candidates such as Streptlncor and J,[14] peptide which are derived from the C-terminal of M protein shown to be protective in animal models against RHD.[21]

Vaccine Pipeline

Only two candidate vaccines are actively under evaluation in human trials. A phase I clinical trial of the MJ8VAX vaccine candidate developed by the Queensland Institute of Medical Research, Australia, were recently reported. The vaccine antigen is a 29-amino acid long peptide (J8) from the conserved carboxyl terminus region of the M protein,[22] conjugated with diphtheria toxoid and adsorbed onto aluminium hydroxide. More investigations are planned to further optimise immunogenicity. The 30-valent StreptAnova, developed at the University of Tennessee, USA and Dalhousie University, Canada, is a M protein-based vaccine with 4 recombinant subunits, each containing seven or eight N-terminal fragments of 30 different emm types linked in tandem.[23] The N-terminal fragment of the Spa antigen is also included in the construct.[18]

The peptides were selected from acute and invasive isolates most prevalent in North America and Europe. A phase I clinical trial of the vaccine adjuvanted with alum was recently completed. This program builds on favourable safety and immunogenicity evaluation of previous related constructs including a lower number of emm-type sequences.[23] In preclinical development, the StreptIncor vaccine candidate construct developed by the University of São Paulo, Brazil, is based on the conserved region of the M5 protein, which comprises a 55-amino acidpolypeptide containing conserved B- and T-cell epitopes. A phase I/IIa clinical trial of the vaccine candidate antigen formulated with alum is expected to start in 2018/2019.[24] Investments in GAS vaccine R&D by major vaccine manufacturers have been limited. One candidate based on the conserved antigens streptolysin O, SpyAD, SpyCEP and group A carbohydrate conjugated with a carrier protein is being developed by GSK.[25] The antigens selected are highly conserved and prevalent, either surfaceexposed or secreted, expressed during human infection, soluble and immunogenic in animals. Altogether, the scarcity of products in development as presented above underscore the need to expand and diversify the vaccine pipeline.

Safety Considerations

Safety concerns have constituted an important impediment to past vaccine development efforts. In 1969, the occurrence of ARF following streptococcal vaccination in 3 out of 21 volunteers vaccinated with a partially purified M3 protein was reported.[26] This raised concerns about the safety of GAS vaccines and a theoretical risk of autoimmunity. In 1979, the United States Food and Drug Administration (FDA) prohibited the use of GAS organisms and its derivatives in any bacterial vaccine.[27] However, the validity of such concerns raised by this single study were subsequently questioned. All three children had documented GAS infection before the onset of ARF, and all were siblings of ARF patients. They were exposed to very high and repeated dosing of a crude M-protein vaccine formulation. These factors may have influenced their risk of developing ARF. The FDA resolution was revoked in 2006, when the agency recognized the previous understanding as "both obsolete and a perceived impediment to the development of a GAS vaccine".[27] There had not been a GAS vaccine trial reported during a period of 25 years. Vaccine research resumed, with no similar adverse safety signal identified. Nonetheless, the field would benefit from consensus building on safety risk management strategies appropriately adapted to vaccine development status. Studies have often used serum auto-immunity panel screening, tissue cross-reactive immunofluorescence antibody assays and echocardiography to monitor for potential auto-immune events occurring post vaccination.[23] While due diligence is needed, there is a strong perception that auto-antibody panels and echocardiographic monitoring are poor screening tools and of limited value as adequate safety monitoring requires sufficient endpoint sensitivity and specificity, especially when the number of trial participants is limited, as in early vaccine development. In clinical practice these tests are seldom used in isolation, as their contribution to diagnosis is strongly driven by pre-test probability determined by the clinical context. Borderline results and non-specific findings make interpretation difficult.[28] Screening panels and echocardiographic evaluation may best be reserved for screening out subjects at increased risk of abnormalities detected before entering into investigational vaccine studies.

CONCLUSION

Recent 30-valent vaccines based on M protein, which are shown to be protective against RHD in the US and European population,[18] are undergoing clinical trials. A global vaccine that covers other regions of the world, especially low-income countries, would be extremely helpful to eradicate RHD completely. With the recent computational advancements in the field of vaccinology,[29] we hope that a protective vaccine against RHD is within

reach, either through identification of novel antigens or throughstructure-based design of known antigens of GAS.

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