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Opinion Article

Immunogenicity and Protective Efficacy of a Lead Streptococcal Vaccine

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DESCRIPTION

Infections with streptococcus pyogenes (Group A S treptococcus; GAS) continue to be a major public health issue in resource-limited settings, causing significant morbidity and mortality. GAS is a versatile pathogen capable of causing a wide range of human diseases, from minor infections like pharyngitis and impetigo to more serious infections like cellulitis, toxic shock syndrome, and necrotizing fasciitis. The annual burden of invasive GAS disease is concerning, with at least 663,000 new cases and 163,000 deaths. Furthermore, repeated streptococcal infection can result in the post-infection sequelae of rheumatic fever, rheumatic heart disease, and acute post streptococcal glomerulonephritis. In addition, autoimmune reactions can cause a variety of neuropsychiatric disorders such as Sydenham's chorea, obsessive-compulsive disorder, and syndrome 2. Globally, GAS causes over 500,000 deaths per year, and treatment for GAS disease costs several billion dollars in the United States alone1. To prevent primary GAS infections and reduce mortality and morbidity, an effective GAS vaccine is therefore highly desirable.

A variety of approaches have been taken in order to develop a GAS vaccine. Others are based on non-M-protein antigens and include streptococcal C5a peptidase, streptococcal carbohydrate, streptococcal fibronectin binding proteins, cysteine proteases, streptococcal pyrogenic exotoxins, and streptococcal pilli. The vaccine, which is based on peptides derived from the M-N-terminal protein's domain, was found to be immunogenic and safe in clinical trials; however, the vaccine is expected to have limited coverage in developing countries, and there are concerns that it may cause a shift in serotype prevalence.

In parallel with a rabbit toxicology study, another lead vaccine based on an M-protein conserved region minimal epitope (J8) was tested for safety in the Lewis Rat (LR) model for valvulitis. These studies found that the J8-DT vaccine (J8 conjugated to diphtheria toxoid) did not result in abnormal pathology. The vaccine was also tested in a pilot study and found to be immunogenic in humans, with no serious side effects reported (manuscript in preparation). The vaccine epitope's high sequence conservation suggests that it has the potential for broad coverage.

We have shown in a number of preclinical studies that J8 conjugated to diphtheria toxoid (J8-DT) is effective in protecting animal models against multiple GAS strains. However, we found that the vaccine has a lower efficacy against hypervirulent CovR/S mutant GAS strains because of their enhanced ability to degrade IL-8, preventing neutrophil chemotaxis. To address this, a 20-mer B-cell epitope (S2) derived from the streptococcal IL-8 protease SpyCEP was combined with J8-DT. As a result, a combination vaccine (J8-DT+S2-DT) was developed that provided excellent protection against CovR/S mutant GAS strains. Following infection, we found that both J8 and S2 were poorly immunogenic (cryptic) to humans and mice. However, as peptide vaccines, they were highly immunogenic and capable of inducing protective responses.

This vaccine is now being prepared for human clinical trials. However, in order to create a consistent product, the vaccine has been modified. CRM197 is a chemically defined genetically modified analogue of the carrier protein Diphtheria toxoid (DT) (henceforth referred to as CRM). CRM is a nontoxic, enzymatically inactive form of diphtheria toxin with a single amino acid substitution (G52E). CRM is a well-defined protein that is consistent from batch to batch. It is approved for human use in several highly effective conjugate vaccines. The S2 peptide has also been reformed with lysine residues (K4S2) to improve its solubility in water. The current study compares CRM to DT for the preparation of the peptide conjugate vaccine J8-CRM + K4S2-CRM (henceforth referred to as MJ8CombiVax), as well as its characterization, immunogenicity, and protective efficacy in a murine challenge model. Finally, the study addresses critical aspects of human vaccine efficacy, such as the effect of prior DT exposure and the effect of human plasma (which is known to contain proteins capable of binding to the M-protein) on vaccine efficacy.

CRM197, which improves immunogenicity and is commonly used in licenced human vaccines. The new vaccine was compared to the DT conjugate vaccine to ensure that the

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modifications had no effect on the vaccine's physicochemical properties. When tested in an animal model of GAS infection, this vaccine demonstrated significant reductions in systemic and local GAS burden, with efficacy comparable to the DT conjugate vaccine. The vaccine was shown to be equally effective in the presence of both human plasma and pre-existing DT-specific antibodies, reducing concerns about its potential efficacy in humans.