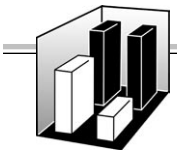

Itzhak Brook MD, MSc

Safety and Immunogenicity of 26-valent Group A Streptococcus Vaccine

McNeil SA, Halperin SA, Langley JM, et al.:
Safety and immunogenicity of 26-valent group A streptococcus vaccine in healthy adult volunteers.
Clin Infect Dis 2005, **41:**1114–1122.

Rating: •Of importance.

Introduction: Group A *Streptococcus* (GAS) causes illnesses ranging from uncomplicated pharyngo-tonsillitis to life-threatening necrotizing fasciitis, toxic shock, glomerulonephritis, and rheumatic fever. The development of an M protein-based vaccine has been complicated by the fact that some M proteins elicit both protective antibodies and antibodies that cross-react with human tissues. However, new molecular techniques have made it possible to overcome these obstacles.

Aims: The goal of this study was to conduct a phase I study of the safety and immunogenicity of a 26-valent plus streptococcal protective antigen (Spa) M protein-based recombinant vaccine. The multivalent vaccine used in this study was designed to include protective epitopes from serotypes responsible for 85% to 90% of cases of uncomplicated pharyngitis and serious, invasive disease.

Methods: The vaccine is comprised of four recombinant proteins adsorbed to aluminum hydroxide that contain N-terminal peptides from streptococcal protective antigen and M proteins of 26 common pharyngitis, invasive, and/or rheumatogenic serotypes. Thirty healthy adult subjects received intramuscular 26-valent GAS vaccine (400 µg) at 0, 1, and 4 months, with clinical and laboratory follow-up for safety and immunogenicity using assays for tissue cross-reactive antibodies, type-specific M antibodies to 27 vaccine antigens, and functional (opsonization) activity of M protein antibodies.

Results: The incidence of local reactogenicity was similar to that noted for other aluminum hydroxide adsorbed vaccines in adults. No subject developed evidence of rheumatogenicity or nephritogenicity, and no induction of human tissue reactive antibodies was detected. Overall, 26 of 27 antigenic peptides evoked a greater than four-fold increase in the geometric mean antibody titer over baseline. The mean $\log_2$ fold-increase in serum antibody titer (± standard error of the mean) for all 27 antigens was 3.67 ± 0.21. A significant mean $\log_2$ reduction in streptococcal bacterial counts in serum samples obtained after immunization was seen in opsonization assays for all M serotypes.

Discussion: The results of this phase I trial illustrated that the 26-valent M protein-based recombinant vaccine was well tolerated and immunogenic. M protein is a filamentous molecule that is expressed on the surface of GAS as a coiled-coil dimer. The carboxy-terminus, on the cell wall, contains conserved epitopes, whereas the more distal amino terminus exhibits the characteristic type-specificity. There are over 100 recognized immunologically distinct M proteins, and their prevalence varies at different times and locations [1]. In the non-immunized host, the M proteins prevents phagocytic cells from killing GAS by binding to plasma proteins that inhibit the activation of the complement cascade. Type-specific immunity against a given M protein is acquired by colonization or infection with GAS that harbors that M protein. This immunity enables the host to eradicate the susceptible strains making the individual with immunity to a specific M protein protected from infection with GAS of the same M protein type.

M protein immunity is not just protective in nature but also has the potential for producing autoimmunity, and these cross-reactive antibodies were implicated in the post-infectious sequelae of GAS infection. The risk of such a consequence was evident in a clinical trial of a partially purified M3 protein vaccine given to 23 healthy children that was conducted 40 years ago, where three cases of proven or suspected rheumatic fever occurred [2]. Naturally acquired and vaccine-induced immunity to native M protein has, therefore, the potential of providing serotype-specific immunity as well as autoimmune sequelae in a small number of individuals.

Two approaches were used to develop protective immunity to M proteins without eliciting molecular mimicry and autoimmune diseases. One utilized a conserved, non–cross-reactive C-repeat region of the protein, found in the carboxy-terminal of the protein proximal to the cell wall [3]. This approach elicits immunity to multiple serotypes, and produced mucosal immunity in animal models. However, these vaccines have not yet advanced to the stage of clinical trials. The other approach is described in the above study by McNeil et al. who reported the use of a 26-valent vaccine that is based on the more cell-wall distal, type-specific regions of the M proteins. The vaccine is made of four fusion polypeptides (each with six or seven N-terminal M protein peptides) and does not contain epitopes that evoke tissue cross-reactive antibodies.

McNeil et al. immunized 30 healthy adults with three doses of the 26-valent vaccine along with alum as an adjuvant. Most of the recipients experienced mild-to-moderate adverse events, such as injection-site reactions, headache, and fatigue, which are typical for alum-adjuvanted protein vaccines [4,5] However, none developed tissue cross-reactive antibodies, echocardiographic or electrocardiographic abnormalities (suggestive of acute rheumatic fever), proteinuria, hematuria, or casts (suggestive of glomerulonephritis).

The implications of the study by McNeil et al. is the feasibility of producing a vaccine-induced protective antibody to the clinically significant serotypes of GAS, without the attendant risk for autoimmune sequelae. The vaccine elicited significant increases in type-specific opsonic antibody in the recipients. Antibody titer remained significantly elevated 1 year after immunization for nearly 60% of the M proteins included in the vaccine. More than 80% of the vaccinated individuals experienced seroconversion to 22 of the 26 M types.

Based on recently published epidemiologic data, immunization with this 26-valent M protein based vaccine elicited seroresponse to 84.5% of isolates causing pharyngo-tonsillitis, 92.5% of isolates associated with rheumatic fever, and 87.6% of invasive disease isolates, including 100% of GAS strains associated with necrotizing fasciitis in the United States [6–8]. Since most cases of these streptococcal infections are caused by a limited number of serotypes this vaccine could significantly reduce these infections.

Editor's comments

Many obstacles have yet to be overcome before this or similar vaccines become clinically useful. There is a need for large-scale clinical trials that will also include children to assess the safety and efficacy of GAS vaccines. It will be difficult to define the study population and the recipients of the vaccine. Since in vitro correlates of GAS immunity are not well defined, carefully selected clinical end points are needed. The variability in prevalence of M protein serotypes over time and geography further complicates the design of vaccine trials. Because different M proteins predominate in developing countries, a vaccine containing the serotypes prevalent in the United States may be less effective in these locations. Furthermore, this type of vaccine may be less affordable in developing countries where the rate of post-infectious complications is much higher. The threat of GAS serotype replacement also exists. The existence of numerous M proteins in GAS reflects the potential of substantial mutability of the genetic loci encoding the protective epitopes. Because of the high rates of carriage of GAS by children and the ability of an individual virulent strain to spread rapidly within a community, the utility of a serotype-specific vaccine may be time limited. Periodic adjustments to the serotypes included in the vaccine, as well as timely reimmunization, may be needed to maintain the effectiveness of protection.

References

1. Kotloff KL, Dale JB: **Progress in group A streptococcal vaccine development.** *Pediatr Infect Dis J* 2004, **23:**765–766.
2. Massell BF, Honikman LH, Amezcua J: **Rheumatic fever following streptococcal vaccination: report of three cases.** *JAMA* 1969, **207:**1115–1159.
3. Batzloff MR, Hayman WA, Davies MR, et al.: **Protection against group A streptococcus by immunization with J8-diphtheria toxoid: contribution of J8- and diphtheria toxoid specific antibodies to protection**. *J Infect Dis* 2003, **187:**1598–1608.
4. Halperin SA, Smith B, Russell M, et al.: **An adult formulation of a five-component acellular pertussis vaccine combined with diphtheria and tetanus toxoids is safe and immunogenic in adolescents and adults**. *Vaccine* 2000, **18:**1312–1319.
5. Halperin SA, Scheifele D, Mills E, et al.: **Nature, evolution, and appraisal of adverse events and antibody response associated with the fifth consecutive dose of a five-component acellular pertussis-based combination vaccine.** *Vaccine* 2003, **21:**2298–2306.
6. Shulman ST, Tanz RR, Kabat W, et al.: **Group A streptococcal pharyngitis serotype surveillance in North America**. *Clin Infect Dis* 2004, **39:**325–332.
7. Schuchat A, Hilger T, Zell E, et al.: **Active bacterial core surveillance of the emerging infections program network**. *Emerg Infect Dis* 2001, **7:**92–99.
8. Stollerman GH: **Rheumatic fever.** Lancet 1997, **349:**935–942.