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EDITORIAL REVIEW

Conjugate vaccines

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INTRODUCTION

The first glycoconjugate vaccine for use in humans, a *Haemophilus influenzae* type b (Hib) conjugate, was licensed in the USA in 1987 and shortly thereafter was introduced into the US infant immunization schedule. The success of the Hib conjugate vaccines in reducing the incidence of invasive Hib disease in childhood [1–3] has accelerated the development of conjugate vaccines designed to prevent infection by other encapsulated bacteria. The imperative driving the development of such vaccines has been the need to find a vaccine formulation that renders bacterial capsular polysaccharides immunogenic in those most at risk of infection.

Pathogens such as *Neisseria meningitidis* serogroup C, *Streptococcus pneumoniae* and Hib are all major causes of childhood meningitis as well as other infection syndromes and have in common polysaccharide capsules (although of different structure) that act both as virulence determinants and targets for protective antibody. The importance of these pathogens in the young can partly be explained by the poor immunogenicity of some polysaccharides in this age group and the consequent inability of infants and young children to mount protective antibody responses. Vaccines containing Hib or pneumococcal capsular polysaccharides alone have thus failed to consistently protect this high risk group from infection [4,5].

IMMUNOLOGY OF ANTI-POLYSACCHARIDE RESPONSES

Polysaccharide antigens are large molecules consisting of repeating epitopes which are not processed by antigen-presenting cells (APC) but interact directly with B cells, inducing antibody synthesis in the absence of T cells (thus designated T-independent antigens). T cells can influence the antibody response to certain polysaccharides, such as the capsular polysaccharide of *S. pneumoniae* type 3 [6], but an absolute requirement for T cells has not been demonstrated. T-independent responses are restricted in a number of ways. Most importantly, they fail to induce significant and sustained amounts of antibody in young children below the age of 18 months [7,8]. While polysaccharides are immunogenic in older children and adults, the characteristics of the antibody responses are rather restricted. They are dominated by IgM and IgG2, are relatively short lived and a booster response cannot be elicited on repeated exposure [7–9]. This failure to induce immunological memory is also reflected in the absence of demonstrable affinity maturation [10]. In contrast to polysaccharides, antibody responses to protein antigens have an absolute requirement for T cells. The consequence of this T cell help are that antibody responses to protein antigens can be elicited in the very young and immunity is long lived due the generation of immunological memory. Antibody responses to protein antigens are dominated by the IgG1 and IgG3 subclasses and affinity maturation can be demonstrated over time.

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IMMUNOLOGY OF GLYCOCONJUGATE VACCINES

The ability to enhance the immunogenicity of polysaccharide antigens was first noted by Avery & Goebel in 1929, who demonstrated that the poor immunogenicity of purified *S. pneumoniae* type 3 polysaccharide in rabbits could be enhanced by conjugation of the polysaccharide to a protein carrier [11]. Their observations have formed the foundation for the modern development of conjugate vaccines.

Following animal studies, initial human infant studies confirmed the immunogenicity of the Hib capsular polysaccharide (polyribosylribitol phosphate (PRP)) conjugate vaccines [12]. Formulations of Hib conjugates with different protein carriers including tetanus toxoid (TT), diphtheria toxoid (D), mutant diphtheria toxin (CRM_{197}) and outer membrane protein (OMP) have been developed and have been shown to vary both quantitatively and qualitatively in their immunogenicity. For example, the PRP vaccine conjugated to OMP has been shown to be immunogenic following a single dose in infancy, while the other formulations have only demonstrated significant immunogenicity after two, but more strikingly after three doses [13]. Antibody avidity induced by different Hib conjugates has also been shown to vary [14], as has Hib variable region gene usage [15]. Prototypes of the pneumococcal and meningococcal conjugate vaccines have also shown enhanced immunogenicity compared with plain polysaccharide formulations in infants and young children [16–18] and formulations using different carrier proteins have similarly been shown to vary in their avidity [19].

Primary antibody responses to the Hib conjugate vaccines in infancy have been demonstrated to be predominantly IgG1 [20], while boosting with pure PRP in toddlers generates a response that is dominated by IgG1 although IgG2 responses are also seen [21].

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Adult responses to pneumococcal polysaccharides are dominated by IgG2, but both IgG1 and IgG2 are mounted to pneumococcal conjugate vaccines in adults [22,23].

GLYCOCONJUGATES AND IMMUNOLOGIC MEMORY

In addition to being immunogenic in the very young, conjugate vaccines have been shown to prime for memory responses. This has been demonstrated by studying antibody responses to pure polysaccharide antigens at 12–18 months of age in infants who did or did not receive conjugate vaccines in the first year of life [9,24,25]. Significant responses to plain polysaccharide challenge are generally not seen in unprimed toddlers, thus the presence of a response in primed toddlers is considered indicative of the presence of immunological memory. An increase in antibody avidity following primary immunization and boosting has also been demonstrated and has been proposed as a surrogate marker for the successful generation of immunological memory [19,26,27].

The relative importance of memory versus circulating antibody levels for clinical protection by conjugate vaccines is unclear but it is interesting to note that even the least immunogenic of the Hib conjugates, PRP-D, has been shown to be efficacious in reducing the incidence of invasive Hib infection in Finland [1]. The efficacy of such formulations may thus be related to the ability of the conjugate vaccines to prime for memory, even in the face of poor primary immunogenicity [24]. The demonstration of the presence of immunological memory is thus increasingly being used in the phase II evaluation of such formulations [28].

GLYCOCONJUGATES AND CORRELATES OF PROTECTION

While antibody levels have historically provided a robust correlate of vaccine immunogenicity/efficacy for Hib, the importance of demonstrating functional activity of antibodies measured against serotypes of *S. pneumoniae* has recently been highlighted [29,30]. In the December issue of the journal, Anttila and colleagues have studied the relative importance of IgG concentration, IgG subclass composition and antibody avidity to the function of antibodies specific for pneumococcal serotypes 6B, 19F and 23F (see pp. 402–407). They conclude that the serotype-specific IgG titre measured by ELISA in the serum of adult or paediatric vaccinees following pneumococcal conjugate vaccination is a robust correlate of the functional capacity (as measured by opsonophagocytic activity) of the measured antibody. Such data, together with the demonstration of the comparability of assays used to measure pneumococcal antibodies, will be critical for the evaluation of new and modified pneumococcal vaccine formulations in the period following the licensing of the first formulation(s).

PNEUMOCOCCAL CONJUGATE VACCINE EFFICACY

Data from the first pneumococcal efficacy study to be completed have recently been presented [31]. Infants in the Kaiser Permanante Efficacy Study (Northern California, USA) were randomized to receive a seven valent pneumococcal conjugate vaccine or a meningococcal C conjugate vaccine at the same time as their routine infant immunizations (2, 4 and 6 months of age) and a booster dose in the second year of life. Thirty-seven thousand infants were enrolled and when 17 invasive pneumococcal infections had been identified in the study population the randomization code was broken. All the infections at that stage were in the control group, giving the vaccine an efficacy estimate of 100% (95% confidence interval 81·4–100%). Recent data presented by the group have also shown the vaccine to have some efficacy against pneumonia and otitis media (S. Black, personal communication). A formal efficacy study with otitis media as the main endpoint is currently being conducted in Finland and will report in late 1999.

The impressive efficacy of the 7 valent pneumococcal conjugate vaccine is exciting and the results of further efficacy studies conducted in different populations are eagerly awaited. The success of the Hib conjugate vaccines in reducing the incidence of disease in vaccinated populations is partly due to the reduction of the nasopharyngeal carriage of Hib in the vaccinees and the resulting interruption in the person to person spread of the organism. Pneumococcal conjugate vaccines have also been shown to reduce nasopharyngeal carriage of the serotypes contained in the vaccine, but unlike Hib, a large numbers of serotypes of *S. pneumoniae* may be responsible for invasive disease. Increased nasopharyngeal carriage of pneumococcal serotypes not included in the vaccine has been noted [32–34], thus studies with the power to detect an increase in pneumococcal disease caused by non-vaccine serotypes should still be conducted.

CONCLUSION

Despite all the research on conjugate vaccines, the precise nature of the molecular events that permit polysaccharides conjugated to protein carriers to be processed as T-dependent antigens remains unclear and more research is required. Despite our poor understanding of the mechanism, the success of these vaccines in the field is impressive and hence the licensing of *N. meningitidis* serogroup C and multivalent *S. pneumoniae* conjugate vaccines is imminent.

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