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Review

Glycoconjugate vaccines and immune interference: A review

Ron Dagan[a,*], Jan Poolman[b], Claire-Anne Siegrist[c]

[a] The Pediatric Infectious Disease Unit, The Faculty of Health Sciences, Ben Gurion University of the Negev and Soroka University Medical Center, Beer-Sheva, Israel
[b] GlaxoSmithKline Biologicals, Rue de l'Institut 89, Rixensart 1330, Belgium
[c] Center for Vaccinology and Neonatal Immunology, CMU 1, 1 Rue Michel Servet, 1211, Geneva, Switzerland

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ABSTRACT

Bacterial polysaccharide–protein conjugate vaccines (*Haemophilus influenzae* type b [Hib], pneumococcal and meningococcal conjugates) have revolutionized pediatric vaccination strategies. The widely used carrier proteins are tetanus toxoid (TT), diphtheria toxoid (DT) and diphtheria toxoid variant CRM197 protein, DT conjugates being in general less immunogenic. Multivalent conjugates using TT were found to be at risk for reduced polysaccharide responses, whilst multivalent CRM197 conjugates are at lower risk for this, but may be at higher risk of inducing bystander interference, particularly affecting Hib and hepatitis B immune responses. Novel carriers avoiding these issues could enable the further development of pediatric schedules and combinations.

Contents

1. Background

The development of polysaccharide–protein conjugate vaccines (CV) has been instrumental in preventing potentially fatal disease due to *Haemophilus influenzae* (Hib), *Neisseria meningitidis* and *Streptococcus pneumoniae* in infants and young children. It has become evident that as the number of glycoconjugates (valencies) and dosage of carrier protein (CP) included in CVs increase, so does the likelihood of interference with the immune response to conjugated and/or co-administered antigens. Attempts to explain disparate clinical observations between different co-administered CVs by the administered dose of CP or classical carrier-induced epitopic suppression mechanisms alone have proven unsuccessful [1], indicating other mechanisms at play. This review considers the history and nature of the immune interference phenomena that continue to influence the development of new CVs.

* Corresponding author at: The Pediatric Infectious Disease Unit, The Faculty of Health Sciences, Ben Gurion University of the Negev and Soroka University Medical Center, Itzhak Rager Avenue, P.O. Box 151, 84101 Beer-Sheva, Israel.
Tel.: +972 8 6400547; fax: +972 8 6232334.
E-mail address: rdagan@bgu.ac.il (R. Dagan).

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2. Mechanisms of interference on responses to conjugate vaccines

2.1. Carrier-specific enhancement of T-cell help

Previously or simultaneously elicited T-cell responses to a CP may enhance responses to haptens conjugated to the same carrier (Fig. 1). For example, monovalent meningococcal serogroup C polysaccharide-Tetanus toxoid (MenC–TT) CVs enhanced the immunogenicity of Hib–TT given concomitantly in infants [2–8] and increases in anti-polyribosyl-ribitol-phosphate (PRP) geometric mean antibody concentrations (GMCs) were also observed when the combination of MenC–TT and Hib–TT was administered in the same vaccine (Table 1). The enhancing effect on Hib–TT from co-administration or combination with one or two additional polysaccharide–TT conjugates is assumed to result from an increase of carrier-driven T-helper frequency and T-cell-mediated co-stimulatory signals. A Hib–MenCY–TT combination of 5 μg PRP–10 μg MenC–10 μg MenY polysaccharide dosages resulted in satisfactory Hib, MenC and MenY antibody seroprotection rates and GMCs (Table 1) [3]. Co-administration or combination with diphtheria–tetanus–whole-cell pertussis (DTPw) but not DTPa (acellular pertussis components) resulted in enhanced TT, Hib–TT and MenC–TT responses, suggesting an adjuvant influence of Pw (discussed in Section 4), but did not enhance DT and MenC–CRM197 responses (Table 2). Table 2 also illustrates reduced anti-Hib responses following DTPa–Hib combinations, an interference which is generally believed to be of physicochemical nature and mostly due to the interaction between aluminium hydroxide and poly-riboseribitol-phosphate [12–14].

2.2. Carrier-induced-epitopic suppression (CIES)

The classically described CIES mechanisms relate to pre-existing immunity to a CP that may suppress the immune response to a hapten or saccharide linked to the same carrier, thus jeopardizing the hapten or (poly)saccharide immune responses [15–19]. In pre-clinical and clinical studies, CIES related to hapten–TT conjugates has been encountered [20–22]. Several mechanisms can be involved, alone or simultaneously. Pre-existing antibodies to the carrier may prevent the access of hapten-specific B-cells to their epitopes by steric hindrance and/or facilitate the uptake of the antigen–antibody complex by antigen-presenting-cells, favoring anti-carrier B-cell responses to the detriment of anti-hapten B-cell responses (Fig. 2A and B). Dominant carrier-specific memory B-cells may deprive hapten-specific B-cells of necessary resources such as T-cell help through competitive mechanisms (Fig. 2C, see also [23]), and carrier generated regulatory T-cells may interfere with anti-hapten responses (Fig. 2D). Each of these processes leads to suboptimal anti-hapten antibody and memory B-cell responses. These CIES mechanisms are of general importance for hapten conjugates and of particular importance for bacterial capsular polysaccharide CVs.

There are marked differences in the CIES potential of CPs used in human vaccines, most notably between TT and diphtheria toxoid (DT). In clinical and pre-clinical studies with human chorionic gonadotrophin (hCG) conjugated to TT or DT, pre-existing immunity to TT but not to DT suppressed the antibody response to hCG. Boosting with hCG-DT was able to overcome hCG-TT related suppression [22]. Similar pre-clinical observations were made with pneumococcal serotype 4 polysaccharide–TT and meningococcal serogroup C polysaccharide–TT (Men C–TT) conjugates, but not with MenC–CRM197 (point-mutated diphtheria toxin protein) conjugates and pre-existing carrier immunity [25].

2.3. Bystander interference

Tetanus toxoid, DT and CRM197 are widely used as CPs. CRM197 is a mutated form of DT that differs in one amino acid residue in the 'fragment A' region [26]. Alteration of fragment A removes its enzymatic activity, making CRM197 non-toxic. It is thought that the conformation of CRM197 differs from DT, leading to lower B-cell responses. Since CRM197 is not treated with formaldehyde, the T-helper epitopes appear to be better preserved, explaining the better carrier effect of CRM197 versus DT. Co-administration of DT- and TT-containing vaccines may induce additional antigen-specific interference mechanisms, such as bystander interference [23,28,29].

Bystander interference may influence responses to non-conjugated antigens administered simultaneously, or even sequentially [30]. Possible mechanisms may include competition for

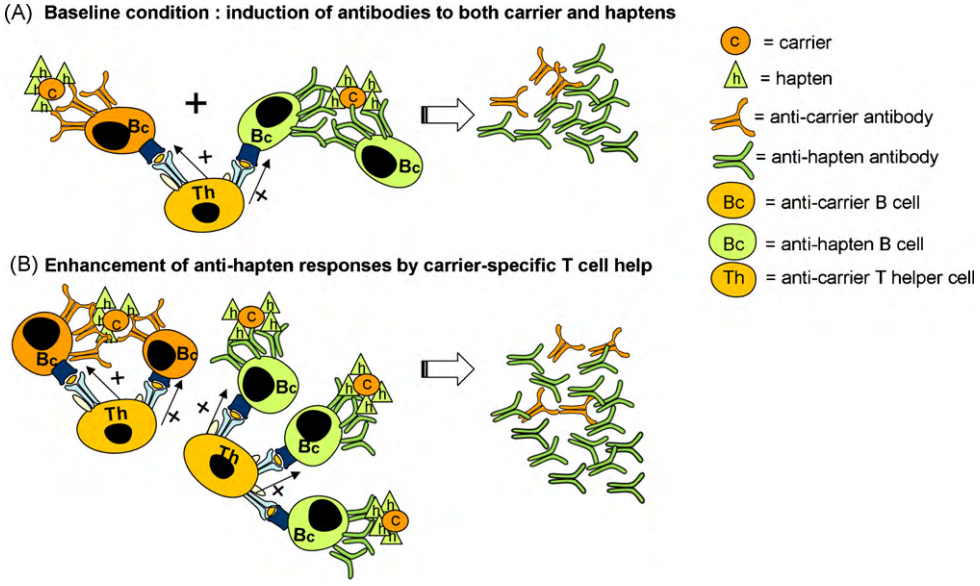

Fig. 1. Schematic representation of carrier-specific enhancement of T-cell help.