REVIEW ARTICLE

Dental Caries Vaccine: A Review

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ABSTRACT

Vaccines have long been attractive for broad-based public health coverage of infectious diseases, of which dental caries is one of the most pervasive. Anti-caries vaccine has long been expected for caries prevention since the early fifties of the 20th century. Many kinds of vaccine immunogens such as protein, recombinant or synthetic peptide, or DNA-based active vaccines and mucosal adjuvants such as heat-labile enterotoxins from Vibrio cholera or Escherichia coli , chitosan have been successful in animal models. However, vaccines have not been brought to market till now mainly due to the low ability to induce and maintain protective antibody in oral fluids. Ultimately, the clinical trials of immunologically superior dental caries vaccine formulations will determine their usefulness for public health applications.

KEYWORDS: Dental caries, caries vaccine, streptococcus mutans

INTRODUCTION

Dental caries is one of the most prevalent diseases in humans, second only to the common cold. According to WHO, caries is defined as "localized post-eruptive, a pathological process of external origin involving softening of hard tooth tissue and proceeding to the formation of a cavity."

Is dental caries conquered? walk into a day care center in Brazil, and the chances are that at least 25% of the three years age or over children will have active caries lesions. Go to china where epidemiologists report that three-quarters of five–year-old children experience significant dental decay.[1] In India, the dental caries prevalence is 35-44-year olds was reported to be 80-95% in a National oral health survey. The National oral health survey reported that among the elderly in the 65-74 years age group, the caries prevalence to be about 70%, while the present survey in various states reported it to be 51-95%.Caries prevalence of approximately 58% was showed in Surveys which were done on school children in India. In the united states, dental caries was found to be in 90% of late adolescents and young adults, while 94% of all dentate adults had evidence of treated or untreated coronal caries. In the united states, $70 billion is spent annually for dental services, a significant portion of which pays for dental caries treatment.[3]

Currently, various caries preventive strategies are in use like oral health education, chemical and mechanical control of plaque, application of pit and fissure sealants, use of fluorides, etc. Many of these approaches can be effective. However, economic, behavioral or cultural barriers to their use have continued the epidemic of dental disease of many children globally.[1]

The latest approach for combating dental caries is through the development of an effective vaccine that will be well suited for public health applications especially in the environments that do not lend themselves to regular oral health care.

VACCINES

Vaccines are an immuno-biological substance designed to produce specific protection against a given disease. It stimulates the production of a protective antibody and other immune mechanisms. Vaccines are prepared from live, inactivated or killed organisms, modified organisms extracted cellular fractions, toxoids, or a combination thereof.[3]

STUDIES

Animal studies: Rats and monkeys have been largely used in immunization studies. The ability to arrive at an accurate diagnosis of caries by examination of the tooth surface and to establish large experimental groups makes rodents a good choice for laboratory animals. Numerous studies have shown that mutant streptococci (MS) can bring about caries in pits and fissures as well as on smooth, approximal and root surfaces of the teeth of both gnotobiotic and conventional animals. Further evidence for MS involvement in the etiology of caries has been shown from immunization studies. In one such study, the oral administration of *S.mutans* cells to gnotobiotic rats induced the production of secretory antibodies in the saliva and has been correlated with the reduction of caries incidence in these animals. The Tonsillar application of rabbits by formalin-killed cells of S. sobrinus reduced the caries areas in the rabbits decreased to a level one-fifth of that in nonimmune rabbits.[4]

Human studies: As dental caries fulfills the infectious disease criteria, the possibility of preventing it by

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vaccination has been taken up by the investigators. The rationale is that immunization with S. mutans should induce an immune response, which might prevent the organism from colonizing the tooth surface, and thereby prevent the tooth decay.[3] A study in humans showed that the immunization of glucosyltransferase-enriched preparation (E-GTF) administered by nasal or tonsillar topical spray showed a Significantly higher anti- E-GTF responses in nasal wash samples and indicating that nasal immunization was more effective in inducing mucosal responses in adults.[5]

ROUTES OF ADMINISTRATION

Oral: A mice orally immunized with a recombinant Streptococcus lactic strain which carries the structural gene for a surface protein antigen (PAc)from streptococcus mutans serotype c ,resulted in significant salivary immunoglobulin A and serum immunoglobulin G responses.[6] Oral immunization with S. mutans did not induce significant secretory IgA in monkeys. Immunological memory in secretory IgA responses is limited and this may curtail the value of oral immunization.[7] Tthough the oral route was not ideal for reasons including the detrimental effects of stomach acidity on antigen, or because inductive sites were relatively distant, experiments with oral route established that induction of mucosal immunity alone was sufficient enough to change the course of infection with S. mutans and disease process in animal models and in humans.[1,2,8]

Intranasal: In the recent times, attempts have been made to induce protective immunity in mucosal inductive sites that are in closer anatomical relationship to the oral cavity. The intranasal immunization primes the immune system for a secondary localized responses to s.mutans antigens by immunizing with enriched-glucosyltransferase (E-GTF).[10] A study showed that intranasal immunization of rats with S. mutans antigen I/II coupled to the B subunit of cholera toxin-induced a protective salivary immune response associated with a reduction in S. mutans colonization and dental caries.[9] The Protection could also be demonstrated with S.mutans Ag I/II, the SBR of Ag I/II, the glucan binding domain of S. mutans, fimbrial preparations from S. mutans with antigen alone or combined with mucosal adjuvants and GBP-B.[3]

Tonsillar: The ability of tonsillar application of antigen to induce immune responses in the oral cavity is of great interest. A study showed that the Tonsillar application of rabbits by formalin-killed cells of S. sobrinus reduced the caries areas in the rabbits.[4] The repeated tonsillar application of a particulate antigen can induce the IgA antibodies producing cells in both the major and minor salivary glands of the rabbit.[1]

Intragastric: A mice immunized intragastrically with chimeric proteins constructed from (saliva binding region) SBR and the type II enterotoxins of Escherichia coli or cholera toxin (CT) showed an increase in the number of B cells and macrophages in Peyer's patches (PP) and diminished B cell numbers in mesenteric lymph nodes (MLN) providing a molecular basis for the enhanced immune responses induced by chimeric proteins compared with uncoupled antigen.[11]

Salivary Gland: A study was conducted by immunizing groups of Sprague-Dawley rats subcutaneously in the salivary gland vicinity with the CAT-GLU (diepitopic construct of catalytic and glucan binding domains of glucosyltransferases), Suggesting that it can be a potentially important antigen for a caries vaccine.[12]

Subcutaneous: Subcutaneous administration of S. mutans was successfully used in monkeys and elicited predominantly serum IgG, IgA, and IgG antibodies. These antibodies find their way into the oral cavity via gingival crevicular fluid and are protective against dental caries. However, Protection against caries was associated predominantly with increased serum IgG antibodies.[7]

EFFECTIVE MOLECULAR TARGETS FOR DENTAL CARIES VACCINES

Although over the years numerous surface or secreted products of mutans streptococci have been proposed as vaccine antigen candidates ,attention has become focussed on three protein antigens :the surface fibrillar Adhesins known as AgI/II (Synonyms :antigen B,P1,SpaP,PAc,SpaA,PAg), the glucosyltransferases and the glucan binding proteins. [2]

Adhesins: From the two principal human pathogens, *Streptococcus mutans* (variously identified as antigen I/II, PAc, or P1) and *Streptococcus sobrinus* (SpaA or PAg), adhesins have been purified.[8] Rats immunized orally with recombinant Salmonella typhimurium mutant, expressing the surface protein antigen A (SpaA) of Streptococcus sobrinus resulted in the production of antigen-specific mucosal antibody and provides protection against dental caries.[13] Antibody directed to the intact antigen I/II molecule or to its salivary-binding domain blocked adherence of *S. mutans* to saliva-coated hydroxyapatite.[14] Furthermore, numerous immunization approaches have shown that active immunization with intact antigen I/II [9] or passive immunization with monoclonal or transgenic antibody to putative salivary-binding domain epitopes within this component can protect humans from dental caries caused by *S. mutans*.[15]

Glucosyltransferases (gtfs): S. mutans and S. sobrinus each synthesize several glucosyltransferases. The deduced sequences of glucosyltransferases enzymes vary from 1400 to nearly 1600 amino acid residues and contain considerable sequence homology, despite the differences in water-solubility and linkages among the glucans which are synthesized. Genes which are responsible for glucan synthesis in S. mutans are gtfB , which synthesizes an α-1,3-linked insoluble glucan , gtfC, which synthesizes glucan with both α-1,3 and α-1,6

linkages, and gtfD , which synthesizes a soluble α-1,6-linked glucan.[1] Antibody directed to native GTF or sequences associated with its catalytic or glucan-binding function interfere with the synthetic activity of the enzyme and also with the in vitro plaque formation.[16] Thus, the presence of antibody to glucosyltransferase in the oral cavity prior to infection can significantly influence the disease outcome, presumably by interfering with one or more of the functional activities of the enzyme.[1]

Glucan binding proteins: The ability of mutans streptococci to bind to glucans is mediated, at least in part, by cell-wall-associated glucan-binding proteins (Gbp) S. mutans secretes at least three distinct proteins with glucan-binding activity: GbpA , GbpB , and GbpC.1 Of the three S. mutans glucan-binding proteins, only GbpB has been shown to produce a protective immune response to experimental dental caries .[16] Protection can be either achieved by subcutaneous injection of GbpB in the salivary gland region or by mucosal application through intranasal route. [1]

SUBUNIT VACCINES

Synthetic peptide vaccines: Intranasal immunization with PAcA, coupled to cholera toxin B subunit, suppressed the colonization by *S. mutans* in mouse teeth .[17] Monoclonal antibody, produced by immunization with intact Ag I/II, that reacted with the fragment containing the proline-rich region has also inhibited the formation of experimental dental caries.[7]

Recombinant vaccines/ attenuated expression vectors: Oral immunization with recombinant Salmonella typhimurium, expressing surface protein antigen A of Streptococcus sobrinus, was able to bring about persistent mucosal immune responses which could give protection after a challenge of Fischer rats with cariogenic S. sobrinus.[13]

Conjugate Vaccines: Another vaccine approach which may cut off more than one feature of mutans streptococcal molecular pathogenesis is the chemical conjugation of functionally associated protein/peptide components with bacterial polysaccharides.[1] In separate studies, it was reported that conjugation of either tetanus toxoid or S. sobrinus GTF to the water-soluble glucan synthesized by GTF significantly increaed serum IgG and salivary IgA antibody levels to the water-soluble glucan and to the conjugated protein.,[18]

ADJUVANTS & DELIVERY SYSTEMS FOR DENTAL CARIES VACCINE

A variety of new approaches has been tried out to potentiate aspects of the immune response to induce sufficient antibodies to achieve a protective effect to overcome the existing disadvantages.[3]

Cholera toxin And E. Coli Heat-Labile Enterotoxin: Cholera toxin (CT) is a powerful mucosal immunoadjuvant, used to increase the generation of mucosal immunity to a variety of bacterial and viral pathogens. Mucosal application of a soluble protein or peptide antigen alone rarely results in high or constant IgA responses. However, the addition of small amounts of CT or the closely related E.coli heat-labile enterotoxins (LT) can extensively enhance mucosal immune responses to intragastrically or intranasally applied mutans Streptococcal antigens or to peptides derived from these antigens. The coupling of the protein with the nontoxic unit of the cholera toxin was effective in suppressing the colonization of S. mutans. [3]

Microparticles: The microparticles made up of poly lactide-co-glycolide (PLGA) has been used as a local delivery systems because of their ability to control the rate of release, elude preexistent

antibody clearance mechanisms, and degrade slowly without eliciting an inflammatory response to the polymer.[3,19]

Nanoparticles: An anti-caries DNA vaccine was developed through incorporation of anionic liposomes in chitosan/DNA complexes a nanoparticle system as a effective carrier for nasal mucosal immunization and showed that nanoparticles offer a probable platform for DNA vaccine packaging and delivery for more efficient elicitation of mucosal immunity.[20]

Liposomes: Liposomes are bilayered phospholipids membrane vesicles manufactured to hold and deliver drugs and antigens. Administration of liposomes containing anti-idiotype (anti-id) vaccine provided partial protection against dental caries and also can bring about protective immune responses to pathogens of mucosal surfaces.[21]

PASSIVE IMMUNIZATION

A study suggested that Mc Ab (monoclonal antibodies) which is directed against an essential cell surface antigenic determinant of S. mutans (streptococcal antigen I/II) prevents adherence of S. mutans to the acquired pellicle on the tooth surface.[22] Systemic immunization of cows with a vaccine using whole S. mutans has led to the bovine milk and whey- containing polyclonal IgG antibodies. This was then added to the diet of a rat model. The immune whey brought a drop in the caries level. [23]

RISKS ASSOCIATED WITH CARIES VACCINE USAGE

All vaccines, even if properly manufactured, seems to have risks. Rabbits immunized with killed Streptococcus sanguis or Streptococcus mutans showed that the findings lend no acceptance to the concept that vaccination of human subjects against dental caries might increase their susceptibility to streptococcal endocarditis.

[24] A study was conducted wherein, rats and rabbits immunized peripherally with ribosomal preparations from S.mutans lacked the putative human heart cross-reactive determinant and suggested that S. mutans ribosomal vaccine against dental caries may not be pathogenic to human heart or renal tissues.[25] A study, in which rabbits immunized with some strains of Streptococcus mutans provided an evidence that antigens in S. mutans might elicit antibodies that cross-react with heart tissue, which in turn may induce instances of myocarditis, representing an unacceptable risk to the health of the vaccine recipients.[26] Because of the potential of Streptococcal whole cells to bring about heart reactive antibodies, the development of a sub-unit vaccine for controlling dental caries has been the focus of intense research.[3]

CONCLUSION

Dental caries vaccine has long been expected for caries prevention since the early fifties of the 20th century. Many kinds of vaccine immunogens such as protein, recombinant or synthetic peptide, or DNA-based active vaccines and mucosal adjuvants such as heat-labile enterotoxins from Vibrio cholera or Escherichia coli, chitosan have been successful in animal models .

However, no vaccines have been brought in the market till now mainly due to the low ability to bring about and maintain protective antibody in oral fluids. Another greater challenge faced by the vaccine against caries is the elimination of the one of the commensal oral microorganisms. Before any vaccine is brought in the market, the long-term consequences of disturbing the commensal microflora of the oral cavity that has evolved over many centuries should be determined.

For a dental caries vaccine to be accepted by the dental profession, many questions need to be answered. One of the important questions is: what will be the long-term effect of altering the indigenous oral microflora? Also, can the highest caries activity level of infection caused by the pathogen, streptococcus mutans, be inactivated immunologically? Which entry pathways of S.mutans into the dental biofilm can be controlled by immunization? Can an immune response be brought about by virulence factors associated with s.mutans? How safe are dental caries vaccine comparative to other caries prevention regimens? Will the profession accept vaccination as a caries prevention mechanism provided the decline in caries prevalence over the past several decades?

Even though scientific, regulatory and economic hurdles need to be cleared to reach this goal the potential benefit continues to make the race worth running.

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