

Vaccine for Dental Caries - An Imminent Target

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Abstract

Cariosity is an inevitable microbial malady primarily induced by pathogens like streptococcus mutans. The hard tissue of the oral cavity is affected by the host agent and environment. Time factor plays an important role for development and progression of dental caries that is observed in all parts of the world with no predilection to gender, socioeconomic strata and age group. However dental caries has overcome the phase of being unrestrained with various scientific advancements. Numerous clinical trials affirm that tooth decay can be interrupted by approaches such as to sustain adequate levels of salivary antibodies and to establish immune memory for greater span. Efforts are being carried about to achieve a definite route of administration and to evaluate the safety of vaccines to overcome the likely uncertainty.

Keywords: *Animal Model, Dental Caries, Immune Memory, Teeth, Salivary Antibodies*

1. INTRODUCTION

Embodiment of caries is an irrevocable microbial ailment which is preliminarily marked by demineralization and destruction of the inorganic and organic constituents of teeth thereby progressing to cavity formation. A high increased incidence of caries has been observed in developing countries due to consumption of highly refined sugar.¹ The event of tooth decay takes place through diverse interplay between anaerobic acid-producing bacteria together with carbohydrates and the host factors namely teeth and saliva within a span of time. Due to tight contact between the tooth surfaces, a disparate distribution of saliva can lead to deficient fluoride exposure, poor oral hygiene and the like.² Among the numerous microorganisms secluded from decayed tooth surfaces, the gram positive anaerobic class of bacteria such as Lactobacillus acidophilus, Streptococcus mutans, Lactobacillus fermentum, Actinomyces viscosus are the predominant pathogens identified; the S. mutans species being the utmost ubiquitous causative organism.³ Latterly, numerous methods like creating awareness of maintaining good oral hygiene, chemical and mechanical methods to

manage formation of plaque, application of pit and fissure sealants, fluorides, restoration of decayed tooth and the like has been promoted to impede caries. Approaches have been introduced to resist dental caries with the advent of potent vaccine that is effective to prevent caries.⁴

Vaccine

“A vaccine is a substance that is introduced into the body to stimulate the body’s immune response. It is given to prevent an infectious disease from developing and the person becoming ill. It is prepared from live modified organisms, inactivated or killed organisms, extracted cellular fractions, toxoids, or a combination.”

Scheduled Mechanism of Action of Dental Vaccine

The main immunoglobulin constituent in the saliva is IgA along with IgM and IgG, being the trivial components that are liberated into the saliva from the gingival crevicular fluid along with inflammatory cells such as lymphocytes, macrophages and neutrophils. The presumed modes of activity of antibodies are as follows



- i. The specific agglutinin activity of salivary immunoglobulin communicates with the superficial receptors on the bacilli that causes hindrance to its array and resists caries. The IgA may also act on glucosyl transferase leading to reduced synthesis of extracellular glucans and minimal plaque deposits.
- ii. Immunising the gut associated lymphoid tissue (GALT) directly can cause production of secretory IgA by salivary glands that prevents the adhesion of streptococcus mutans on the enamel. Formation of dextran may also be inhibited by IgA with suppression of glucosyl transferase.
- iii. The cellular and humoral elements of the immune system detected at the gingival crevices may exhibit its activity on the tooth surface. Following subcutaneous immunization with streptococcus mutans, the macrophages phagocytose and process the antigen. The B and T lymphocytes are sensitized by the macrophages, following blockade of human leucocyte antigen Class II complex and discharging IL1. The CD4 helper and CD8 cytotoxic suppressor response is activated with stimulated activity of IL2 receptors and liberation of IL2. The interplay between the cells is crucial in harmonising the formation of IgA, IgG, IgM and B lymphocytes.^{1,5,6,7,8}

Exploratory Studies

Enormous research work in the past decennium has proven the workability of vigilant immunity in opposition to streptococcus mutans. Studies have been performed on animal models and in vivo on humans.

Animal Trial

Studies have been conducted on animal models like mice, rabbits, rabbits and the like. The commonly approached animal models in

researches are the mice. However, when compared to the time required for humans to develop caries and the short duration of experiments on mice; an ideal assessment of the caries pathogenesis poses a limitation. To overcome this disadvantage, studies are performed on primates. The vaccines against dental caries can be prepared with protein antigens present in the streptococcus mutans that have adequate virulence and colonize tooth surfaces. Glucosyl transferases (GTF), the proteins Antigen I/II, and the glucan-binding proteins are surface fibrillar adhesins.⁹ The initial experiments to develop vaccine against caries were by oral immunization with destroyed microorganisms and purified protein antigens; its effects were minimal on the mucosa. Investigations were attempted on primates (monkeys) by immunizing them with streptococcus mutans through various routes to obtain particularly immunoglobulin A response. Attempts showed that administration of antigens, streptococcus mutans cell structures subcutaneously on rhesus monkeys declined the incidence of fissured and smooth surface caries by 70%. Assay conducted on Macaque monkeys have exhibited successful immunization with substantial antibody formation by subcutaneous infusion of S. mutans and glycosyl transferase (GTF). However an unaltered antibody titre was noticed in the serum and saliva of orally immunized monkeys treated with enterically coated and uncoated capsules.

Human Trial

Possibility of preventing the incidence of dental caries has shown up through different human trials. The levels of S-IgA antibodies can be increased to that of streptococcus mutans and can also interfere with its colonization. The incidence of caries can be managed in the paediatric subjects by administering the preparation simultaneously with vaccines of diphtheria and tetanus prior to the eruption of the primary dentition for utmost effectivity.^{10,11}

Highlights

- Clinical trials by administering Mixture



of glycosyl transferase from streptococcus sobrinus along with aluminium phosphate oral capsules on 14 subjects revealed increase in salivary IgA antibody

- A different study was accomplished where the study subjects were young adults. Glycosyl transferase was extracted from streptococcus sobrinus and administered into the lower lip, which stimulated in production of local antibodies in minor salivary glands causing delayed oral recolonization of S.mutans
- Administering 500 microgram of oral enteric coated capsule which contains GTF from the bacilli S.mutans in adults lead to elevated salivary IgA antibodies to the antigen

Outlook

- Attempts can be made to modify the dose of (GTF) antigen, the frequency of administration, composition, route of administration, to precise antigen-presenting cells can ascertainably upsurge the concentration and action of the antibody
- Administration of glycosyl transferase through intranasal route or topically to the tonsils, by dissolving the solute or consolidating with liposomes lead to advanced salivary IgA antibodies

Intention of Caries Vaccine

The protein components namely glucosyltransferase (GTF), adhesins, dextranases and glucan binding protein (GBP) present on streptococcus mutans has anticariogenic properties which are the key constituents for vaccine preparation.

Adhesin

The proteins primarily the antigens acquired from Streptococcus mutans and sobrinus are individual

polypeptide segments that has roughly 1600 residues within it. Antigens I and II exhibits an enhanced activity due to the centrally placed proline and alanine that is located at the N-terminal third. Researches on various animal models prove that administering vaccine with undamaged proteins namely the Antigens I and II or passively administering monoclonal or transgenic proteins present in the salivary component can prevent cariosity.^{12,13}

Glucosyltransferase

S. mutans that are inefficient to produce GTF have minimal potency to harm animal models. Isoforms of glucosyl transferase the GTF 1, GTF-S-1, GTF-S that correspond to GTF-B, GTF-C and GTF-D respectively are present in S.mutans . Antibodies directed to innate GTF hinder the synthetic activity of enzymes along with plaque formation. The GTFs present in the gram positive anaerobes have analogous series at its functional realms that can protect other species by immunization. This was proven by clinical trials on different animal models, like on the rodents.¹⁴

Routes of Administration

The secreta of major and minor salivary glands obtain the IgA antibody activity which is the prime immune constituent following mucosal application of caries vaccine. Numerous studies prove the protein susceptibility to mucosal associated lymphoid tissue in the nasal, gut, rectal, or bronchial site that can induce immune responses at the respective site and periphery.^{15,16}

Oral Route

Initially conducted studies exhibited protective salivary IgA antibody reaction by oral administration of the soluble protein or combined with liposomes, gastric intubation and the like. Clinical trials were performed on animal models, by preference on germfree rats. Administering aqueous media comprising of killed Streptococcus mutans fetched absolute decline of caries and elevated level of salivary protein IgA antibodies. However, its administration caused adverse effects like stomach acidity.^{1,16}



Intranasal Route

Attempts have been made in recent studies to bring about vigilant immunity within different sites of the oral mucosa. The Nasal-Associated Lymphoid Tissue (NALT) gets targeted in the event of administering the antigen intranasally and aids in the immunization of antigens associated with *S.mutans* aggregation. In animal models, the vaccine could be administered intranasally as an effort of maintaining vigilant immunity following an incidence of caries by the virulent gram positive bacilli.^{15,16}

Tonsillar Route

Surveys conducted have demonstrated that by inducing the antigen via tonsillar route can propagate an immune response within the mouth orifice. Tonsillar tissue can activate secretory IgA responses despite the predominance of IgG. Palatine and nasopharyngeal tonsils are scheduled to provide messenger cells to regions of salivary glands by identifying the mucosal effector sites. Numerous animal trials have exhibited the ability of formalin prepared *S. sobrinus*, a topical applicant that minimises its infection sequale.¹⁵

Minor Salivary Glands

The predominant sites are soft palate, labial and buccal mucosa. Salivary immune response can be optimum by inducing it to the overlying mucosa of the minor salivary glands. The secretory ducts have the ability to decline the course of bacteria and its toxins. Aggregates of lymphatic tissue are observed along with the minor salivary ducts. Studies conducted have proved the topical administration of *S.Sobrinus* GTF in the lower labial mucosa as a potential minor salivary gland route.^{1,15}

Rectal

Investigations on administration of antigens rectally have been done to determine the potential of the mucosae at this vicinity. In the lower intestinal tract, colo-rectal region has maximum lymphoid follicles, which suggests it to be an incipient locale for mucosal immune responses in

humans. Preliminary studies have indicated that rectal immunization with *helicobacter pyroli* and *streptococcus pneumonia* antigens presented itself in different parts of the body; therefore administration of caries vaccine by means of rectal mucosae would be a unique approach.^{4,15}

Systemic Route^{1,4}

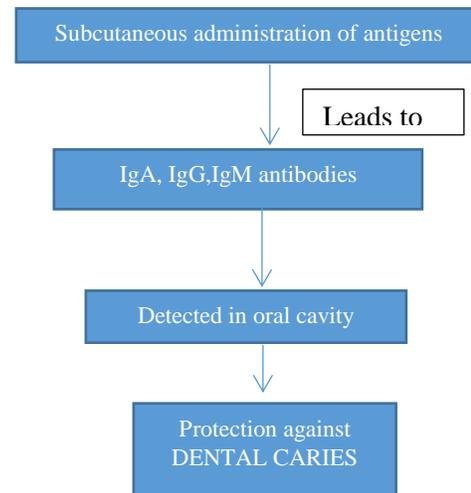


Fig. 1 Systemic route

Gingivosalivary Route

GCF has been used as a favourable route to administer *streptococcus mutans* antigens as it has the potential to localize the immune response and ability to overcome detrimental effects of other routes of administration.¹⁵

Passive Administration/Immunization

A different means to develop antibodies against dental caries is by passive administration of the antigen orally. It is an advantageous task where the risks of active immunization can be overcome. However, its effect persists only for few hours to 3 days within the plaque as no immunological memory is produced. The methods of passive immunization are:

- Use of mouth rinse comprising of bovine milk or egg yolk that succeeded with interim decline of *S. mutans* in saliva/dental plaque
- Passive immunization with transgenic



plants like nicotina tabacum, that can produce antibodies is a current approach as an applicant on the teeth. It is a colourless, tasteless blend of immunoglobulin A-G heavy chain, secretory component, murine and monoclonal antibody kappa chain

- Attempts are being put forth to inject peptide into fruits that can decline the carious potential of S mutans

Cost effective methods like administration of antigen through dentrifice and mouth washes have been introduced by antibody engineering; however, its long-term efficacy is minimally inspected.^{1,17}

2. ADJUVANTS AND DELIVERY SYSTEMS

The response of effective immunization against caries has been accomplished by clinical trials. Application of antigens on the mucosae rarely resulted in sustained release of IgA. New efforts have been attempted to introduce immunomodulators and delivery system that can enhance mucosal response by antigens.^{15,18}

Synthetic Peptides

Studies have proved that protective immunity can be achieved with alanine rich repeat domain of antigen I and II. Administering the synthetic preparation, a derivative of GTF enzyme that comprises of S. mutans antigen I and II subcutaneously, exhibited higher levels of serum IgG antibody that is reactive with recombinant AgI/II when compared to synthetic peptide with a proline-rich zone. Synthetic peptides have the competence to produce antibodies in the gingival crevicular fluid and saliva.⁴

Combination of Protein and Non-Toxin Domains:

Binding the streptococcus mutans antigen with nontoxic excerpt of cholera toxin showed exceptional decline in S. mutans colonization. It plays a potent role by intensifying the mucosal immunity of numerous bacterial and viral

pathogens. Consolidating streptococcus mutans antigen with heat labile strain of E coli and minute cholera toxin enhances the immune response through gastric or intranasal routes.¹⁵

Liposomes

These are bilayered phospholipid membranes in a closed vesicle that aids in the M cell uptake and transfer of antigen to lymphoid elements in the preliminarily exposed tissue which brings about an increased titre of IgA antibody.^{15,18}

Microcapsules and Microparticles

To obtain a favourable mucosal immune response, efforts with mixtures of antigen or combination of different molecules have been attempted. The microparticles prepared from Poly (lactide-co-glycolide) (PLGA) aid in the local drug delivery by omitting the prevailing antibody clearance activities and declining gradually with least inflammatory response.^{4,16}

Conjugate Vaccines

The chemical consolidate comprising of bacterial carbohydrates and essential peptides interrupt the S. mutans. It is an additional anticariogenic approach to reinforce the immunogenicity of the T-cell independent polysaccharides.¹⁵

Uncertainty of Caries Vaccine

Encountering uncertainties are occasional incidents if vaccines are manufactured according to its protocol. Of those, the most probable instances being the reaction within sera of heart tissue antigen and haemolytic streptococci. Immunologically cross-reactive polypeptides with human cardiac tissue and skeletal muscles of rabbit are observed in the cell membrane of S. mutans.¹⁹

3. CONCLUSIONS

Numerous techniques like application of fissure sealants, health talks on dental awareness, systemic application of fluorides have been acquainted. However due to inadequate competence, an impedance to dental caries is not accomplished; further clinical trials with caries



vaccines is essential to identify its efficacy to abstain the aggression of bacterial domain on hard tissues of the oral cavity .

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