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The Veracity of Periodontal Vaccine: An Insight

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Review Article

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ABSTRACT

In today's era, periodontal diseases with their polymicrobial etiology, are a major cause of tooth mortality, among various other systemic problems. Current treatment modalities have resulted only in arresting the disease progression but have not succeeded in curing the disease completely and preventing its recurrence. Hence there is a need for more sophisticated therapeutic modalities which may include vaccines targeting the putative periodontal pathogens. No periodontal vaccine trials have been successful, to date in fulfilling all the requirements of an ideal periodontal vaccine.

Periodontal vaccines could emerge as an adjunct to mechanical therapy in the future. To date, no preventive modality exists for periodontal disease, and treatment rendered is palliative. The availability of periodontal vaccine would not only change and modify the course of periodontal diseases and their treatment but also enhance and improve the quality of life of people for whom periodontal treatment cannot be easily obtained.

Keywords: Immunization, Periodontitis, Plantibodies, Probiotics, Vaccine.

Introduction

The study of periodontal disease in human beings has been of immense interest throughout the last few decades. A lot of progress has been made in the understanding of the disease etiology and pathogenesis along with the intricate interrelationships between the host and periodontal pathogens. Periodontitis is defined as 'an inflammatory disease of the supporting tissues of teeth caused by specific microorganisms or group of microorganisms resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession or both.[1]

Periodontal infections are caused by bacteria in dental plaque. Most subgingival pathogens are strictly anaerobic and Gram-negative microorganisms, but Gram-positive strict anaerobic pathogens have also been discovered. Spirochetes comprise a major part of the motile organisms in subgingival plaque.[2]

Since the etiology of periodontitis has polymicrobial and multilayered characteristics,

monovalent vaccines targeting single bacterial species will have limited efficacy in clinical application.

An effective vaccine should prevent the shifting of the sub-gingival microbiome toward pathologic dysbiosis by specifically suppressing the key etiologic microorganisms in the dental plaque biofilm. Therefore, the polyvalent vaccine strategy targeting keystone periodontitis pathogens would be an ideal method for the prevention and treatment of periodontal diseases.[3]

Basis of Vaccination

Vaccination is a process that induces specific immune resistance to a bacterial or viral infection and are preparation of live or killed microorganisms or their products. The foremost step in vaccine development is the identification of an antigenic component from various organisms that can provide immune protection.

- **Active Immunization**
  Here, an individual immune system is stimulated by administrating killed or live attenuated products derived from micro-organisms.
- **Passive Immunization**
  Here, the antibodies formed in one individual are transferred to another.[4]
- **DNA Vaccination**
  Here, DNA plasmids encoding genes required for antigen production are transferred to an individual.[5]

Indication for Periodontal Immunotherapy

- Severe periodontal disease with loss of bone around teeth.
- Inflammation and association with oral bacterial infection below gum line.
- Exacerbated diabetes and Cardio Vascular Diseases.
- Where mouth rinses don't work.[6]

Development of Immunity

The immunologic response is an outcome of the mechanism in which an antigen, directly or through antigen-presenting cells, recognizes lymphocytes and differentiates into effector cells and memory cells specific to that particular antigen. This response takes two forms, humoral and cell-mediated.

Humoral immunity depends on the appearance of antibodies produced by plasma cells in the blood, whereas cell-mediated immunity depends mainly on the development of T cells that are specifically responsive to the inducing agent and are generally active against intracellular organisms. The antibody produced by effector B lymphocytes following contact with an antigen for the first time is usually of shorter duration and is characterized by a slow rise and rapid fall of immunoglobulin in the serum. This response is known as the primary response.[7]

Need for Development of periodontal Vaccine

1. For bacteria which are capable of evading host immune responses and invading the tissues.
2. To decrease the incidence of periodontal disease related systemic diseases.
3. Financial.[7]

Developing Periodontal Vaccine

Main limitation in the vaccine preparation is the fact that periodontal disease is multifactorial and polymicrobial in origin. Thus, a vaccine targeting only the most probable pathogenic organism may have to be used. Apart from this, efficacy in each individual may not be same due to the variations in the serotypes or genotypes of the organisms among different individuals.

Animals differ qualitatively from humans, with respect to the oral microbial ecosystem, the histological components of the periodontal lesions, the nature of immune responses and control over immunoglobin class and subclass responses. So, results of animal studies may not be directly generalized to humans.

Porphyromonas gingivalis (P. g) whole cell as a target antigen

This was one of the first approaches tried in various animal models. In preliminary studies, Persson et al reported that active immunization of nonhuman primate, Macaca fascicularis, with killed P.g whole cell conjugated with syntex adjuvant formulation inhibits the progression of periodontal tissue destruction. Later, Houston LS et al and Page et al reported raised specific serum IgG and IgA titers with significant opsonic capacity.

But the major drawback was only humoral immune response was elicited, which lasted for a short period. No cell-mediated immune response was triggered that could provide immune memory and thus provide long-term protection.[12]

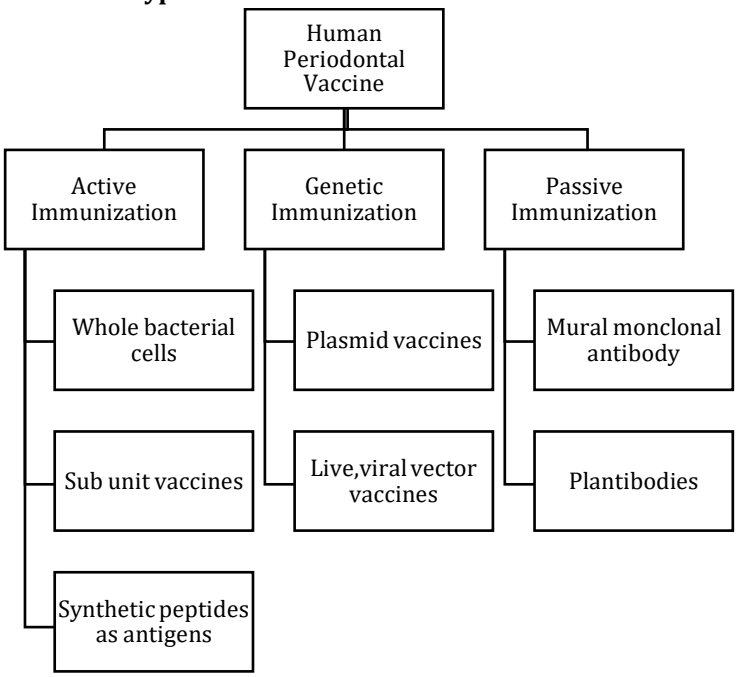
Targeting Aggregatibacter Actinomycetemcomitans *(A.a)*

Development of a vaccine against this pathogen has been tried using its different antigens. A synthetic oligopeptide was prepared based on the amino acid sequence of A.a fimbriae which was found to be effective in a rabbit model, ensuring inhibition of adhesion and its subsequent colonization. Apart from this, Subcutaneous and intranasal immunization of mice with capsular serotype b-specific polysaccharide antigen has given positive results. Mice immunized with antisurface associated material from A. a exhibited a rise in protective antibody levels acting as an opsonin.[8]

Plantibodies

A very recent approach for vaccination strategies is a molecular biological technique to express bacterial or viral antigens in plants, which could be used as orally administered vaccines. This suggests the potential use of plants in synthesizing adjuvant fimbrial protein for the development of adjuvant mucosal vaccines against P.g.[5]

Types of Periodontal Immunization



Active Immunization

- **Whole cells**
  Here the host is inoculated in the entire cell with its components to bring about active immunization. For this various key organisms like *P. g* and *A. a* for vaccine preparation have been tried owing to their active role in the etiopathogenesis of periodontal disease.[9]
- **Sub Unit Vaccines**
  Here the *P. g* virulence factors are used as subunits for the immunization:
  1. **Outer component**
     P.g outer component or the fimbriae are highly immunogenic and play a key role in adhesion to oral tissues and is used for active immunization.[10]
  2. **Gingipains**
     Gingipains is the specific term used to describe cysteine proteases that impart major pathogenic capability to *P.g*. Gingipain vaccines are mainly DNA vaccines, which induce both humoral and cellular immunity.[9]
  3. **Fimbriae as target antigens**
     Fimbriae mediates adherence and colonization of the oral cavity by *P.g* and may, therefore, have potential for use as antigen in an anti-*P.g* vaccine. These induce opsonic antibodies that enhance phagocytosis by human leucocytes. Another option would be to combine fimbrial components from various strains to create a multivalent vaccine, but this approach is applicable only if evidence can be obtained showing that fimbrial proteins of *P.g* are, in fact, accessible to opsonic antibodies.[11]
  4. **Heat Shock Protein (HSP)**
     These proteins participate in the cell function such as folding, assembly, and translocation of polypeptides across membranes and after cell damage play a role in protein repair. There is a phenomenon termed heat shock response, wherein a cell by enhanced transcription experiences increased temperature or any other stress factor, starts producing elevated amounts of HSP.[10]
- **Synthetic peptides**
  Such peptides are weakly immunogenic by itself, based on the microbial antigens known sequence, these require synthesis of linear and branched polymers of 3-10 amino acid and to induce antibody response need to be conjugate to larger proteins.
  Two ways of developing synthetic peptide vaccines are:
  - From RNA sequence data, by deduction of the protein sequence of microbial antigens.
  - By testing overlapping peptides and by mutational analysis.[12]

Genetic Immunization

In early 1990's, a new approach to the production of vaccines through recombinant DNA technology had begun as that varies in structure from conservative ones.[10]

Gene therapy is insertion of genes into individual cells and tissues to treat a disease and involves genetic engineering or recombinant DNA technology.

- **Plasmid vaccines**
  DNA does not have ability to grow whereas plasmids have the ability to grow. With this ability of the plasmids, they are fused with DNA of a particular pathogen of interest and inoculated in an animal for production of antibodies. These are then transferred to the host for immunization.
- **Live, viral vector vaccines**
  Variety of infectious but non-disease causing DNA or RNA viruses or bacteria

has been engineered to express the proteins of a disease producing organism. The vector enters the body cells where the proteins are generated and then induce humoral or cellular immune responses.[9]

Passive Immunization

This approach employs preformed antibodies administered to "at risk" individuals or to individuals during "at risk" intervals to interfere with microbial pathogenic processes. Here, the antigens are injected into a vector that produces antibodies. These antibodies, when inoculated into a host, bring about passive immunization.

Passive immunization is short lived because host does not respond to immunization and protection lasts only as long as injected antibody persists.[9]
Passive immunization of humans using *P.g* monoclonal antibodies temporarily prevents colonization of *P.g*.[11]

- **Murine Monoclonal Antibodies**
  In this, the antibodies are obtained by inoculating the antigens into mice. These antigens are then injected into the host that brings about passive immunization.
  Booth, in 1996 developed a murine monoclonal antibody to *P.g* that prevented its recolonization in deep pockets in periodontitis patients.[9]
  Literature has shown passive immunization with a monoclonal antibody (61BG1.3) to prevent selective colonization by *P.g* in humans.[7]
- **Plantibodies**
  A very recent approach for vaccination strategies is molecular biological techniques to express bacterial or viral antigens in plants, which could be used as orally administered vaccines.[9]

  Recently, the possibility of edible plants synthesizing biologically active P.g fimbrial antigen, for application as an oral vaccine, was tested. A cDNA fragment of P.g major fimbrial protein (fimA) was cloned into a plant expression vector. When this chimeric plasmid was transferred into potato (Solanum tuberosum) cells, the ctb-fimA cDNA fragment was detectable in its genome. This suggests the potential use of plants in synthesizing adjuvant fimbrial protein for the development of adjuvant mucosal vaccines against P.g. Further studies are needed to test the efficacy of plantibodies in eliminating periodontopathic bacteria.[8]

Plant Derived Vaccines

Plant based vaccines involve application of molecular biologic techniques to create transgenic plants which will be used to produce antigens or antibodies. In transgenic plants the DNA is modified by artificial insertion of desired genes using genetic engineering techniques. The inserted gene sequence is known as TRANS GENE, which can be expressed in the plants either by a stable transformation system or by transient transformation system, depending on the location where the transgene has been inserted into the cells.[13]

Probiotics

According to the World Health Organization, probiotics are defined as live cultures of microorganisms which, when administered in adequate amounts, confer a health benefit on the host.[14]

Probiotics help in repopulating the beneficial bacteria, which can kill pathogenic bacteria and fight against infection.[15]

It has been seen that despite mechanical sub-gingival debridement in combination with improved oral hygiene, there is a temporary shift toward less pathogenic composition of bacteria within 1–2 weeks of baseline. There is a re-establishment of a more aggressive microbiota within weeks to months.

It was thought that restoring the decreased number of beneficial bacteria via probiotics might be of considerable interest in the treatment of plaque-related periodontal diseases.

In 1954, the first attempt was made in Russia on the use of probiotics in the treatment of periodontitis. The use of Russian probiotics preparation called ACILACT, a complex of five lyophilized lactic acid bacteria with or without "Bifidumbacterium", is claimed to improve both clinical and microbiological parameters in patients with gingivitis and periodontitis.

Recently, it has been seen that inoculation of Streptococcus sanguis inhibits the growth of periopathogens, like *P.g, A.a* and *T. forsythia*.[7]

Toll-like Receptor Adjuvants, Periodontal Vaccines and Immunomodulation

Subgingival bacteria initiate and sustain a nonresolving inflammation that is ineffective at controlling the infection. In as much as toll-like receptor agonists can function as adjuvants, linking innate to adaptive immunity and modulating both, it is conceivable that an appropriately adjuvanted periodontal vaccine could both reduce the bacterial challenge and favorably modulate the host response to infection. At least in principle, vaccination against periodontitis could be used preventively or therapeutically as an adjunct to scaling and root planing.

Periodontal vaccines may confer specific protection via antibody-mediated blockade of bacterial colonization, neutralization of virulence factors, or through opsonophagocytosis and killing of periodontal pathogens. Moreover, a vaccine that induces specific cell-mediated immunity may potentially protect against periodontal intracellular pathogens which find refuge in permissive cells.[16]

Adjuvanted vaccination against periodontal bacteria

The discovery of toll-like receptors has not only resulted in an increased interest in innate immunity, but also in additional suggestions of novel approaches to adjuvant development, some of which may be suitable for consideration in periodontal vaccine formulations.

Toll-like receptors can function as adjuvant receptors by recognizing and responding to certain microbial molecules, thus effectively stimulating antigen-presenting cells and alerting the immune system.

Currently, besides the enterotoxin-based approaches, toll-like receptor agonists and synthetic analogues are key targets of the pharmaceutical industry for developing vaccine adjuvants to prevent infectious diseases or destroy tumors.

Although mostly old-generation adjuvants have been used so far, significant advancements have been made in periodontal vaccine development, and it is likely that the future use of novel toll like receptor adjuvants will lead to further progress.

Subunit vaccine approaches have so far concentrated mainly on P.g virulence proteins, particularly its cysteine proteinases, as well as the fimbriae of both P.g and A.a. Vaccination with defined-subunit immunogens requires the use of appropriate adjuvants even more so than in the case of immunization with whole bacterial cells, which intrinsically contain adjuvant substances.[16]

Developing the Advanced Tools for Enhancing Vaccine Efficacy

Recently, a variety of strategies to enhance the immunogenicity of antigenic components of B or T-lymphocytes have been adopted in vaccine trials against various periodontal diseases. These include, immunization of dendritic cells pulsed with antigens, the use of improved adjuvant formulas (e.g. the use of alum as an alternative to HSP-based adjuvant), the use of recombinant plant

monoclonal antibodies, and the use of transgenic microorganisms as antigen vectors.

These attempts leave challenging areas to be pursued further in the quest for a more sophisticated design that may guarantee the efficacy and safety of prolonged immune memory.[17]

The Future of Periodontal Vaccines

As yet, there are no periodontal vaccine trials that have been successful in satisfying all the criteria ie:

- To prevent the colonization of multiple pathogen biofilm in the subgingival area.
- To elicit a high level of effector molecules such as immunoglobulin sufficient to opsonize and phagocytose the invading organisms.
- To suppress alveolar bone loss, and to stimulate helper T-cell polarization that exerts cytokine functions optimal for protection against bacteria and tissue destruction.

As an innovative strategy, vaccines using cross-reactive immunodominant epitopes as antigenic molecules in an attempt to stimulate antigen-specific regulatory T-cells (Tregs, CD4+,CD25+, FoxP3+), secreting IL-10 and TGF-β, may provide new clues for periodontal disease prevention, through the induction of either immune tolerance or an effector function.

Periodontal disease as a multifactorial and polymicrobial disease requires a sophisticated vaccine design regimen targeting multiple pathogenic species. Vaccine regimens including the commonly shared antigens by selected periodonto pathogenic species would be considered an innovative strategy.

Traditional periodontal vaccine trials aim to stimulate the immune system to produce increased levels of immunoglobulin of desired specificity. To accomplish this end, a conjugate vaccine (i.e. protein-CPS conjugate), dendritic-cell based immunotherapy, and subunit DNA vaccine encoding the desired immunogenic epitope have been devised.

Animal models for vaccine trials may pose discrepancies with human models in major histocompatibility complex-restriction of antigens presented by antigen presenting, thus obscuring the immunodominant epitope(s).

A humanized mouse system has been proposed that has been reconstituted with human peripheral blood lymphocytes. This system needs to meet the requirement of least leakiness of a mouse immune system. More recently, a genetically engineered mouse system, such as the NOD.CB17-prkdcscid/J mouse, has been introduced for the study of infectious and autoimmune diseases in humans. This model may also prove useful for the study of periodontal disease and putative periodontal vaccines.[17]

Recent Advances

Of late, distinct literature is coming forth that highlights the ongoing efforts to develop an effective, biocompatible and practical mode of periodontal vaccination. Based on the rationale that periodontal diseases are complex oral inflammatory diseases initiated by keystone bacteria.

Huang, et al. investigated cell free protein synthesis as a platform to produce vaccinable targets suitable for efficacy testing in a P.g induced murine oral bone loss model. They reported recombinantly generated P.g minor fimbriae protein, RgpA gingipain hemagglutinin domain 1, and RgpA gingipain hemagglutinin domain 2, possessed high fidelity to predicted size and elicited protein-specific IgG following immunization. Importantly, immunization with the vaccine cocktail protected from P.g elicited oral bone loss.

Other contemporary research groups have also consistently reported the prevention of the

development of periodontitis by aiming vaccination strategies specifically against the perio pathogen P.g and its components.

O Brien Simpson, et al. reported parenteral or intraoral administration of KAS2-A1-specific polyclonal antibodies protected against the development of P.g-induced bone resorption. In another study, the efficacy of vaccination by recombinant and native RgpA in modulating the early local anti-inflammatory and immune responses and periodontal bone loss were examined. Recombinant RgpA shifted the humoral response toward high IgG1 and low IgG2a titers, representing an in vivo anti-inflammatory response.[18]

In a study done by Chang et al , it was found that Nasal immunization of mice with GroEL using CpG oligodeoxynucleotides (CpG ODN as a mucosal adjuvant increased high levels of GroEL- specific serum immunoglobulins IgG and IgA, and secretory immunoglobulin A (S – IgA) anti- GroEL antibody (Ab) titers. Importantly, when P.g was orally administered to mice, micro computed tomographydata showed that vaccination with GroEL and GpG ODN significantly reduced alveolar bone loss. In addition, TNF -α, IL - 6, and HSP60 mRNA levels increased by P.g challenge were significantly suppressed by nasal immunization using GroEL plus GpG ODN. It was concluded that the GroEL nasal vaccine using CpG ODN is an efficient and lean mucosal vaccine that can suppress chronic periodontitis caused by P.g infection.[19]

Limitations

Human periodontal disease is multifactorial caused by several pathogens. The intricacy of the periodontopathic bacteria might be a problem as a substantial number of bacteria appear to be involved in periodontal disease. The multiplicity of pathogenic organisms indicates that vaccine design against periodontitis is very complex.

Secondly, bacterial whole cells or crude extract preparation for vaccination is not desirable because the antigenic determinants of bacteria potentially possess a high risk of cross reactivity with human counterparts.

Some more serious complications may stem from the vaccine or from the patient itself. Vaccines may be contaminated with unwanted proteins or toxins, or even live viruses. Supposedly killed vaccines may not have been properly killed; attenuated vaccines may revert to the wild types. The patient may be hypersensitive to minute amounts of contaminating proteins, or immune-compromised, in which case any live vaccine is usually contraindicated.

Furthermore, importantly, animal models for vaccine trials may pose inconsistencies with human models in major histocompatibility complex-restriction of antigens presented by antigen-presenting, thus obscuring the immunodominant epitope(s).

Recently, a variety of strategies to enhance the immunogenicity of antigenic components of B or T lymphocytes have been adopted in vaccine trials against periodontal disease. These include, but not limited to, immunization of dendritic cells pulsed with antigens, the use of improved adjuvant formulas (e.g., the use of alum as an alternative to HSP based adjuvant), the use of recombinant plant monoclonal antibodies, and the use of transgenic microorganisms as antigen vectors. These efforts leave challenging areas to be chased further in the search for a more refined design that may guarantee the efficiency and safety of extended immune memory.[20]

Conclusion

The current treatment of periodontitis is nonspecific and is focused on the removal of subgingival plaque by mechanical debridement.

The elucidation of the specific bacterial etiology of periodontitis suggests that the development of

specific treatment modality to target site colonization or virulence of P.g, T. denticola, T. forsythia and A.a is now a more rational approach to treat the disease.

The significant reduction in periodontal disease progression in the nonhuman primates and rodents by immunization with either killed whole P.g cells or P.g antigens suggests that vaccination may be an important adjunctive therapy to mechanical debridement in humans to prevent colonization of periodontal pathogens.

The development of multispecies vaccine that is able to target all four prime bacterial species, which have been implicated in the development of periodontitis, may be more successful than a vaccine against a single species.

Vaccination may also have a therapeutic benefit even in the situations where the bacteria are more resistant to adaptive immune response. When present in sub-gingival plaque as an undisturbed biofilm, specific antibodies may still restrict the progression of disease by blocking the penetration of major virulence factors into the gingival tissues and neutralizing the key virulence factors associated with acquisition of essential nutrients, thereby restricting proliferation.

The development of vaccine is dependent on the identification of bacterial antigens that are expressed in vivo and induction of a protective response.

Thus, it is important to use a combined proteomic, genomic and immunologic strategy to identify bacterial antigens of periodontopathogens and evaluate their potential as vaccine candidates for the development of a multispecies vaccine for periodontitis as an adjunct to current periodontal therapies.

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