Review Article

Review on Anti-nicotine Vaccine - The Smoker's Angel

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Abstract

Tobacco is the leading preventable cause of death in the world, estimated to cause nearly six million deaths a year. Addiction statistics indicates a shocking 1.2 billion smokers worldwide. Tobacco contributes to five million deaths every year. There are various nicotine replacements and non-nicotine replacement therapies (Medications). However overcoming nicotine-dependence is difficult and takes commitment, support and time. The development of a nicotine conjugate vaccine suggests that immunization may hold promise as a future therapeutic and preventive strategy for tobacco smoking. Using gene therapy, researchers were able to create a genetically-modified harmless virus which produces nicotine antibodies. After infecting the liver of mice with this virus, the nicotine antibodies were produced and were released into the blood-stream. The nicotine-antibody combo, which is constantly pumped out by the liver cells, get removed from the blood, then metabolized by the body and excreted. The design of the vaccine as a treatment for drug abuse and dependence is aimed at breaking the cycle of nicotine addiction and relapse. Allowing parents to immunize their children against smoking could be an infringement of children's right to an open future and is not ethically problematic.

Keywords: Anti-nicotine vaccine, Nicotine addiction, Nicotine-replacement therapy, Smoking cessation

INTRODUCTION

The World Health Organization estimates that there are 1.2 billion smokers worldwide[1] and five million tobacco related deaths annually by cardiovascular, respiratory and malignant diseases, accounting for ten percent of global mortality.[2] Much is known about the contents, mechanism of addiction, side effects of smoking nicotine. Tobacco dependence, being a chronic disease, necessitates effective long term treatment for both economy and public health. Besides conventional counseling and other medicinal therapy have low efficacy and high relapse rate.[3,4] Nicotine conjugated vaccines are a novel,immunologic approach in smoking cessation currently in pipeline,[5] (Figure 1, Tables 1 and 2).

MATERIALS AND METHODS

The electronic database chosen for developing this review was PubMed database. Following keywords were used for searching relevant papers: Anti-nicotine vaccine, nicotine replacements. Papers were selected if the combination of words appeared anywhere in the paper, were published over the time period of 25 years (1987-2012) and were written in English. The reference list of each paper was reviewed and any paper appearing in the reference list was added to the list of papers to be manually reviewed. A total of 57 papers were retrieved from the PubMed database, out of which only 24 papers were chosen which presented substantial information about anti-nicotine vaccine. The remaining papers listed in the reference list of this paper are regarding the various other nicotine replacements.

The main aim of this paper is to review the literature for various studies done on anti-nicotine vaccine as a replacement of nicotine addiction.

VACCINE DEVELOPMENT: RATIONALE & PRACTICAL ASPECTS

Working Mechanism of a Nicotine Vaccine

Nicotine itself is a small molecule that easily crosses the blood–brain barrier in less than one minute upon inhalation but does not induce an immune response from the body. Thus, nicotine must be chemically linked or conjugated to a carrier protein to elicit an immune response that forms anti-nicotine antibodies. Upon inhalation, nicotine from cigarette smoke is reversibly bound to these circulating antibodies, ensuing an immune complex that is too large to cross the blood–brain barrier. This reversible binding with nicotinic receptors causes a decreased release of dopamine and prevents activation of the reward pathway.[6] The term 'vaccination' (synonym: active immunization) refers to the administration of an immunogenic substrate that causes T and B cell activation, which leads to the formation of specific antibodies within the studied individual. By virtue of imprinting this response to the immunological memory, this approach yields longer lasting protection. However, therapeutic antibody levels are only established several weeks after the first vaccine injection. Passive immunization, in which preformed monoclonal or polyclonal high-affinity antibodies are injected in the body, offers immediate protection.

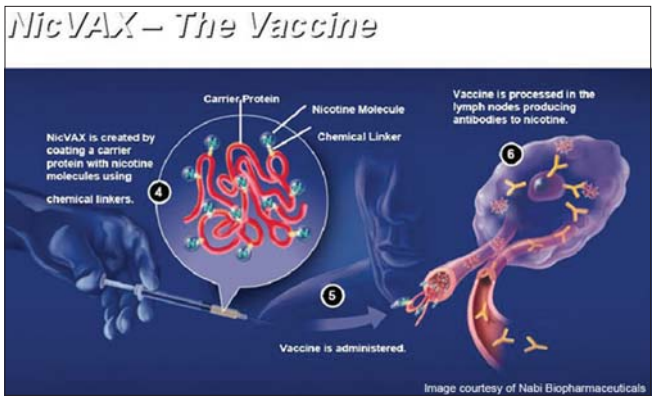

Figure 1: Working mechanism of anti-nicotine vaccine

IMMUNOLOGICAL METHODS

Active Versus Passive Immunization

Immunization against nicotine can be achieved by two methods. Active immunization (hereafter referred to as vaccination) involves repeated administration of an immunogen to the subjects being studied in order to stimulate the immune system to produce nicotine-specific antibodies. Passive immunization involves the production of antibodies in some other species (e.g., rabbits) or in vitro, which are then purified and administered to the subjects being studied.[7]

Table 1: Types of immunity

Active immunity	Passive immunity
1. Antigens are administered	1. Preformed antibodies are administered
2. Irreversible (with booster dose)	2. Reversible
3. Relatively inexpensive	3. Relatively expensive
4. Delay achieving antibody level in serum	4. Antibodies immediately enters serum
5. Booster dose needed after long interval	5. Frequent injections

VACCINES UNDER TRIAL

Table 2: Vaccines currently under trial[8-11]

Vaccine	Conjugate protein	Stage of trial
NicVAX	Pseudomonas aeruginosa Exoprotein-A	Phase III
CYT002-NicQb	Virus like particle Qb (host escherichia coli)	Phase II
TA-NIC	Inactivated cholera toxin	Phase II

STUDIES IN HUMANS

Immunogenicity

The results of phase I and II clinical trials have been reported for three nicotine vaccines: NicVAX, NicQb, and TA-NIC. The vaccination schedule in these clinical trials consisted of two to six doses of vaccine at an interval of two to four weeks, and a later booster dose was administered in two trials. As in animal studies, serum antibody levels were low after the first dose and increased significantly after each subsequent dose. Marked variability in antibody levels between subjects was observed. Antibody levels decreased by 50% over six to eight weeks after the last vaccine injection of the initial immunization period but increased again when a booster dose was administered. Thus, periodic booster doses would be needed to maintain antibody levels above some minimally acceptable value.[12]

CLINICAL ISSUES

Advantages of Immunologic Approaches

As discussed above, immunologic approaches to treating tobacco dependence have three key advantages. First, immunization appears to be safe because of its low cross-reactivity with compounds other than nicotine. Second, immunization only requires a brief series of monthly injections to produce effects that can endure for months.

The lack of major side effects and relatively minimal dosing requirements could be associated with improved patient compliance.[6] Third, its unique mechanism of action makes it well suited for combination with other pharmacotherapies. Despite best efforts to improve on immunologic methods in their own right, combining immunization with other medications may be necessary to maximize efficacy.[12]

Potential Concerns

The lack of control over antibody levels and large variability between subjects is the primary limitation of vaccination and achieving the highest antibody levels possible will be essential to maximizing the efficacy of vaccination. In addition, the slow development of antibody levels and onset of effect could discourage tobacco users who are eager to quit from trying vaccination, as treatment would need to be initiated months before the quit attempt. Passive immunization with a high affinity antibody could be combined with vaccination to provide any desired antibody level and an immediate onset of effect. However, passive immunization is much more expensive and requires more frequent dosing, and potential side effects could occur (e.g., allergic reactions). To the extent that nicotine plays a role in the adverse effects of maternal smoking on fetal outcomes, immunization against nicotine could play a role in protecting the fetus from some of these adverse effects.[12] Studies are needed to assess the safety of immunizing pregnant smokers and the efficacy of immunization in reducing fetal exposure to nicotine. Animal studies have shown that immunization reduces nicotine distribution to maternal brain in pregnant female rats to a similar extent as in male rats.[13,14] In addition, immunization reduces nicotine distribution to fetal brain by up to 63% after a single nicotine dose. Although nicotine distribution to whole fetus is not reduced, immunization reduces the concentration of unbound nicotine in fetal serum. There is concern that compensatory increase in smoking could occur to surmount the effects of immunization, possibly leading to increase in exposure to other harmful constituents in tobacco. However, there has been no evidence of compensation in either animals self-administering nicotine or smoking in humans. It is also possible that immunization could precipitate withdrawal. Although this has not been examined in animal models of nicotine withdrawal, one clinical trial found no evidence of vaccination precipitating withdrawal.[15]

CONCLUSION

Immunization against nicotine can extensively attenuate several behavioral effects of nicotine in animals which is considered relevant to tobacco dependence in humans. These findings suggest that immunologic interventions can be used in the treatment of tobacco dependence. Initial clinical trials have demonstrated that nicotine vaccines are safe and produce substantial serum levels of nicotine-specific antibody in humans. Although preliminary data from these small trials suggest that vaccination may facilitate abstinence from tobacco use,[1] more advance trials are needed to validate this finding. Taken together, the research to date suggests that immunological interventions could play an important role in future treatments for tobacco dependence.[16] The primary role of such interventions will likely be in preventing relapse in smokers who are motivated to quit. By preventing a lapse from producing positive subjective and reinforcing effects, vaccination might prevent progression to full relapse. Another potential role for immunologic interventions is in facilitating reduction of tobacco use in people who are unwilling or unable to quit. It is generally accepted that the most effective approach to treating tobacco dependence is concurrent use of medications and behavioral therapy. Despite the significant therapeutic potential of immunological interventions, they do not target the non-pharmacological factors that maintain tobacco dependence and will likely be maximally effective when combined with behavioral interventions that motivate abstinence from tobacco use.[12]

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