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NicVAX™

Aid to Smoking Cessation
Nicotine Vaccine

AMNic-rEPA
3-AMNic-Suc-rEPA

Nicotine conjugate vaccine consisting of the hapten 3'-aminomethylnicotine conjugated through a succinic acid linker to recombinant *Pseudomonas aeruginosa* exoprotein A (rEPA)

EN: 275155

Abstract

According to the World Health Organization (WHO), the number of smokers worldwide is about 1.3 billion, and tobacco use is considered to be involved in nearly 5 million deaths each year around the globe. A large proportion of smokers try to quit each year, but fewer than 5% are able to maintain abstinence. The addictive effects of smoking are due, in part, to the nicotine contained in tobacco smoke. When nicotine enters the brain, it stimulates the release of dopamine and other neurotransmitters associated with pleasurable effects. The NicVAX™ nicotine conjugate vaccine elicits high titers of nicotine-specific antibodies in experimental animals and humans, which blocks nicotine distribution to the brain. Potential strategies to aid in smoking cessation based on NicVAX™ include direct vaccination and passive immunization with nicotine-specific antibodies. NicVAX™ has been shown to be safe and well tolerated at doses of up to 400 μg.

Background

Nearly 50 million people smoke in the U.S. and tobacco use is responsible for over 440,000 deaths in that country each year, according to data from the U.S. Centers for Disease Control and Prevention (CDC). The World Health Organization (WHO) estimates the number of smokers worldwide to be about 1.3 billion, and tobacco use is considered to be involved in nearly 5 million deaths each year worldwide. The 2004 Surgeon General's Report estimates that about 75% of smokers desire to quit, but fewer than 5% of those who try are able to abstain from smoking for 3-12 months. The primary culprit in the addictive effects of smoking is nicotine, which passes through the blood-brain barrier and stimulates the release of neurotransmitters such as dopamine. These neurotransmitters cause pleasurable sensations, relaxation and appetite suppression (1, 2).

The NicVAX™ nicotine conjugate vaccine (3-AMNic-Suc-rEPA) consists of a nicotine derivative bound to a carrier protein. Preclinical studies have shown that high titers of nicotine-specific antibodies are generated in experimental animals in response to vaccination. These antibodies bind to and sequester nicotine in serum and extracellular fluid, preventing this substance from entering the brain and generating neurotransmitter release. Due to its elimination of the positive stimulus in the brain normally caused by nicotine, NicVAX™ may help smokers to quit. Since the antibodies produced by the vaccine are expected to be long lasting, NicVAX™ may also be effective in preventing smoking relapse. An alternative therapeutic strategy under investigation using the NicVAX™ vaccine involves passive immunization via the infusion of nicotine-specific antibodies. NicVAX™ has completed a phase II dose-ranging study and enrollment in a proof-of-concept phase II study is expected to commence this year. The vaccine has also been granted fast track designation by the FDA (3, 4).

Preclinical Pharmacology

A study was conducted to determine the effects of NicVAX™ on the acquisition and maintenance of nicotine self-administration in rats. In the acquisition protocol, rats vaccinated with NicVAX™ prior to nicotine self-administration showed a significant 38% reduction in the number of self-administered nicotine infusions as compared to rats given a control immunogen. In the vaccinated group, 36% of rats met acquisition criteria compared to 70% in the control group; however, this difference was not statistically significant. The vaccine did not influence the acquisition of cocaine self-administration, thus demonstrating its specificity for nicotine. In the maintenance protocol, rats vaccinated after nicotine self-administration training showed a significant mean 57% reduction in self-administered nicotine infusions as compared to controls after

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the final vaccine injection. Vaccinated rats did not appear to compensate for the changes in nicotine distribution by increasing their nicotine intake (5).

To assess the effects of NicVAX™ during continued nicotine administration, two experiments were conducted for 11 weeks in rats. Experimental animals received saline, 20 i.v. bolus injections (0.015 mg/kg) of nicotine per day for a total daily dose of 0.3 mg/kg to simulate 1-pack-a-day cigarette smoking, or continuous s.c. infusions of nicotine for a total daily dose of 1 mg/kg to produce the maximal serum nicotine concentration of a moderate to heavy smoker. The quantities of nicotine-specific antibodies elicited by the vaccine after the third booster dose were similar in all three groups. At the end of each experiment, a single additional i.v. dose of [^{3}H]-nicotine was administered to all rats. Distribution of the final bolus dose of nicotine to the brain was reduced by 40% and 61%, respectively, in vaccinated animals following the continuous infusion and intermittent dosing protocols compared to those receiving saline. Neither concurrent nicotine administration protocol affected nicotine-specific antibody titers or the vaccine-induced reduction in [^{3}H]-nicotine distribution to the brain. In the bolus dosing protocol, the brain concentrations of unlabeled nicotine (reflecting the cumulative nicotine from repeated dosing) were reduced by 60% in rats receiving chronic nicotine and by 75% in those receiving chronic saline. Similarly, in the chronic dosing protocol, the brain concentrations of unlabeled nicotine were reduced by 29% and 42% in rats receiving chronic nicotine and chronic saline, respectively (6).

In another study, rats were vaccinated with three doses of either NicVAX™ or a control vaccine over a 6-week period, and then pretreated with an s.c. infusion of either nicotine (1 mg/kg/day) or saline for 1 week. All rats receiving NicVAX™ had nicotine-specific antibody titers above 1:50,000, and log antibody titers did not differ in the groups subsequently treated with nicotine or saline. Following a final i.p. nicotine injection, brain nicotine concentrations were reduced by 38% and 20%, respectively, in vaccinated animals receiving chronic nicotine and chronic saline infusion. Vaccination decreased the incidence of seizures induced by the administration of a single 2-mg/kg i.p. dose of nicotine. Furthermore, rats receiving a combination of NicVAX™ and chronic nicotine infusion showed a lower incidence of seizures than rats receiving either treatment alone. The occurrence of seizures was significantly higher in rats with higher brain nicotine concentrations (7).

The effects of vaccination with NicVAX™ on the distribution of nicotine from mother to fetal brain were examined in pregnant rats using several nicotine dosing protocols. As compared to controls, maternal vaccination with NicVAX™ reduced maternal brain and fetal brain nicotine concentrations by 44% and 17%, respectively, 5 min after a single nicotine dose administered on gestational day 20. When measured 25 min after a single nicotine dose on gestational day 20, the nicotine concentrations in maternal and fetal brain were reduced by 47% and 39%, respectively, in the vaccination group as compared to controls. In contrast, after continuous nicotine infusion, maternal vaccination reduced the maternal brain and fetal brain concentrations of nicotine by 16% and 19%, respectively, as compared to controls. In rats receiving repeated nicotine doses, vaccination reduced [^{3}H]-nicotine concentrations (representing the final nicotine dose) by 41% in maternal brain and by 35% in fetal brain as compared to controls. However, the unlabeled nicotine concentrations (representing cumulative nicotine from repeated dosing) in maternal and fetal brain were not altered by vaccination. Whole-fetus nicotine concentrations were similar in most groups, except for the group receiving repeated nicotine doses, which showed a 28% reduction in [^{3}H]-nicotine levels in the vaccinated group as compared to controls. The maternal/fetal serum nicotine-specific antibody concentration ratios were approximately 1:10 in all protocols, and the transfer of antibodies to fetal brain was negligible. Nevertheless, in spite of the limited transfer of nicotine-specific antibodies from mother to fetus, this quantity appeared to be sufficient to enhance nicotine binding in fetal serum and to reduce the distribution of nicotine to the fetal brain (8).

In contrast to an active immunization strategy where rats are vaccinated with NicVAX™ in order to elicit nicotine-specfic antibodies, passive immunization with nicotine-specific antibodies or monoclonal antibodies generated from vaccinated animals, another treatment strategy, offers the advantages of permitting the selection of antibodies with optimized affinity for nicotine, controlling variability in antibody titer and avoiding the 1-2-month lapse before sufficient quantities of nicotine-specific antibodies are generated. Preclinical studies conducted thus far have generally demonstrated that the effects of passive immunization with nicotine-specific antibodies are similar to those found in studies using the active vaccination strategy. Specifically, both strategies appear to slow rather than prevent nicotine distribution to the brain (9-13).

Safety

In preclinical studies, NicVAX™ has been administered to animals as single or multiple doses and assessed for a complete range of toxicological parameters. No toxicological effects were noted at vaccine dosing levels up to 350 times the intended human dose, even when nicotine was administered following vaccination (14). Vaccination with NicVAX™ has also been well tolerated in clinical testing (see below).

Clinical Studies

Preliminary results from a randomized, double-blind, placebo-controlled, phase I trial in 20 healthy nonsmokers showed that a single 200-μg dose of NicVAX™ resulted in a rapid immune response and generated substantial amounts of nicotine-specific antibodies. Antibody levels were detected within 7 days of vaccination and were

maintained or continued to increase for 60 days following vaccination (15).

In a double-blind, placebo-controlled phase I/II trial, researchers tested the ability of NicVAX™ to generate specific antibodies against nicotine following multiple injections of the vaccine. A series of 4 NicVAX™ or placebo injections were administered to 30 healthy volunteers (21 smokers and 9 nonsmokers) over a 6-month period. Vaccination was well tolerated and elicited high nicotine-specific antibody titers. Three doses of NicVAX™ administered on days 0, 14 and 28 produced significant levels of antibodies that declined slowly over the next several months. A fourth dose given on day 182 resulted in even higher levels of nicotine-specific antibodies, which then declined more slowly over time (16).

The safety and immunogenicity of NicVAX™ in smokers were assessed in a multicenter, randomized, double-blind, placebo-controlled study. A total of 68 current smokers received NicVAX™ (50, 100 or 200 μg) or placebo injections on days 0, 28, 56 and 182, and were followed for 38 weeks. Vaccine immunogenicity was dose-related, although large individual variations in immunogenicity were observed. The 200-μg dose of NicVAX™ elicited serum antibody concentrations within the anticipated target range for efficacy. No evidence was observed suggesting that vaccination caused compensatory smoking behavior or precipitated nicotine withdrawal. Abstinence from smoking for at least 30 days was achieved by 6, 1, 0 and 2 subjects receiving 200-, 100- and 50-μg doses of NicVAX™ and placebo, respectively. The shortest time required to achieve 30-day abstinence occurred in the group receiving the 200-μg dose of the vaccine. All doses of NicVAX™ used in this trial were safe and well tolerated (17).

Further phase II testing with NicVAX™ was conducted to assess the tolerability and antibody response at higher doses. In this dose-ranging trial, 50 healthy smokers were randomized to NicVAX™ (100, 200, 300 or 400 μg) administered as 5 injections given on days 0, 21, 42, 56 and 182. A total of 20 patients received the 200-μg dose, with 10 patients receiving each of the other doses. The vaccine used in this study was manufactured with a lower level of adjuvant in an effort to further optimize the formulation. NicVAX™ was well tolerated at all doses tested in this study (3).

Source

Nabi Biopharmaceuticals Corp. (US).

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