

The immunogenicity and safety of a nicotine vaccine in smokers and nonsmokers: Results of a randomized, placebo-controlled phase 1/2 trial

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This randomized, placebo-controlled phase 1/2 trial evaluated the safety and immunogenicity of four doses of a nicotine vaccine in smokers and nonsmokers. Subjects were 21 smokers and 9 nonsmokers in good physical and mental health. They were aged 24–60 years, were recruited from the general public using newspaper advertisements, and were evaluated at University Hospital Maastricht. Each volunteer received four spaced intramuscular injections of 100 µg of purified 3'-aminomethylnicotine conjugated to detoxified *Pseudomonas aeruginosa* r-exoprotein A or placebo both adsorbed to 800 µg aluminum into the deltoid muscle of alternating arms. Clinical safety was determined by vital signs, reactogenicity, and adverse events, and immunogenicity was measured by enzyme-linked immunosorbent assay. Intensive follow-up for 266 days revealed the vaccine to be well tolerated. We found no significant differences in adverse events between the vaccine and placebo groups. Significant increases in the geometric mean titer (GMT) levels of nicotine-specific antibodies were observed from 7 days after the second vaccination (day 21), reaching nicotine-specific antibody levels of at least 8 µg/ml in half of the subjects (50%) at day 49. A fourth dose administered at day 182 significantly boosted waning antibody levels to a GMT of 10.8 µg/ml at day 217 (95% CI 6.0–19.3). Results showed that the immunogenicity of the vaccine was not impeded by the presence of nicotine. These observations provide evidence in humans that the vaccine we used may represent a feasible strategy for evoking type-specific antibodies against nicotine.

Introduction

Cigarette smoking is the leading cause of preventable death worldwide and produces substantial health-related economic costs to society. Between 1995 and 1999, smoking caused an annual average of 264,087 deaths among men and 178,311 deaths among women in the United States (Centers for Disease Control and Prevention [CDC], 2002). Among adults, most smoking-related deaths were attributed to lung cancer (124,813), ischemic heart disease (81,976), and chronic airway obstruction (64,735; CDC, 2002). As a result, smoking cessation is an

effective way of reducing individual health risk and disease burden.

Currently available pharmacological interventions for smoking cessation either partly replace the nicotine delivered by cigarettes (nicotine replacement therapy) or act on sites in the central nervous system to reduce withdrawal symptoms during smoking cessation (e.g., bupropion; Balfour, 2001). However, pharmacological approaches that transiently relieve symptoms of nicotine addiction but fail to attenuate or block the reinforcing effects of nicotine will most likely have limited long-term efficacy (Hughes, Stead, & Lancaster, 2004; Silagy, Lancaster Stead, Mant, & Fowler, 2002; Wagena, Knipschild, & Zeegers, 2005).

A novel treatment, a nicotine vaccine, makes the nicotine molecule a target for an immunotherapeutic approach to smoking cessation. The amount of nicotine reaching the brain, and the rate at which it does so, are important determinants of the initiation and maintenance of smoking (Benowitz, 1996). The vaccine aims to prevent nicotine from acting on its

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