Canadian Agency for Drugs and Technologies in Health

Issues in Emerging Health Technologies

Nicotine Vaccines for Smoking Cessation

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Summary

- ✓ **Cigarette smoking is the leading cause of preventable disease and death in the world.**
- ✓ **Nicotine vaccines produce antibodies that bind nicotine, the chief addictive agent in cigarettes, and prevent it from entering the brain.**
- ✓ **Early trials suggest nicotine vaccines are safe and well tolerated, but the duration of effect is unclear, and immunological response varies across recipients.**
- ✓ **Nicotine vaccines have not yet been studied in phase 3 trials and the relative performance of different vaccines, alone or in combination with existing therapeutic options, is unknown.**

Background

Cigarette smoking is the leading cause of preventable disease and death in the world. Smoking was responsible for an estimated 100 million deaths in the 20th century, and is expected to cause 10 times that number in the current century.[1] A recent study estimated that smoking accounted for 16.6% of all deaths in Canada in 2002 – a total of 37,209 deaths.[2] The direct and indirect costs of smoking in Canada have been estimated at $8 to $11 billion per year.[3] Nicotine, the principal addictive agent in cigarettes, is a common addiction throughout the world.[4] Existing smoking cessation therapies are only modestly effective.

The Technology

The nicotine molecule is too small to generate an immune response. In order to be immunogenic, it must be linked to a larger carrier protein or to virus-like particles. The nicotine vaccines work by producing nicotine-specific antibodies that bind a substantial proportion of the nicotine molecules when they enter the bloodstream. The antibody-bound nicotine molecules are too large to cross the blood-brain barrier, thus preventing most of the nicotine from entering the brain and exerting its addictive effects. In immunized individuals, nicotine is also less available for metabolizing, which markedly slows its elimination half-life. This may enable smokers to reduce their rate of smoking, as the effect of any nicotine that succeeds in entering the brain is prolonged.[5]

Nine nicotine vaccines have been tested in animals and at least five companies are reported to be actively developing vaccines.[5,6] Three vaccines are in clinical trials: TA-NIC (Celtic Pharma, Hamilton, Bermuda), NicQb (Cytos Biotechnology, Zurich, Switzerland), and NicVAX® (Nabi Pharmaceuticals, Boca Raton, Florida).[5] Each of the nicotine vaccines uses a unique antigenic molecular approach. TA-NIC links nicotine to recombinant cholera toxin B, whereas NicQb uses virus-like particles from the bacteriophage Qb, and NicVAX® uses recombinant exoprotein A.[6]

Regulatory Status

Nicotine vaccines are still at the investigational stage and none have been licensed for use in Canada or elsewhere. NicVAX® received a fast-track designation from the US Food and Drug Administration (FDA) in February 2006. Trial results from the NicVAX phase 2 proof-of-concept and optimal-dosing study are expected in the latter half of 2007.[7] Celtic Pharma anticipates seeking FDA approval for TA-NIC in 2009.[8]

Patient Group

The primary indication for nicotine vaccines is relapse prevention in former smokers.[9] Relapse can be triggered by

physical withdrawal symptoms, sensory and environmental stimuli, and exposure to nicotine.[4,10] Regardless of the relapse trigger, nicotine vaccines appear to mitigate the reinforcing effects of nicotine ingestion. An estimated 27% (7.2 million) of Canadians ≥15 years of age are former smokers, but the number that might benefit from nicotine vaccines is unknown.[11]

Nicotine vaccines may also be useful for individuals who want to quit smoking, despite early concerns that nicotine vaccines might actually precipitate withdrawal symptoms in quitting smokers.[5] An estimated 18% (4.5 million) of Canadians ≥15 years of age are current smokers.[12] Evidence from other countries suggests up to 70% of current smokers want to quit or have tried to quit at least once, and up to 35% try to quit each year.[4,13]

The possibility of vaccinating adolescents to prevent smoking initiation has also been identified, although this potential use has been criticized on ethical grounds.[9,14,15] However, the characteristics of the vaccines, such as their relatively short duration of effect, may limit their utility for primary prevention.[10]

Current Practice

Current pharmacological aids for smoking cessation typically function by replacing the nicotine previously delivered by cigarettes, or by acting on central nervous system sites to reduce withdrawal symptoms. Nicotine replacement therapy (NRT) delivers nicotine via chewing gum, transdermal patches, nasal sprays, inhalers, or lozenges and improves the odds ratio of quitting by 1.5 to 2-fold over placebo.[14] Bupropion (Zyban®), an antidepressant, doubles the odds of quitting, although the precise mechanism of action is not well understood.[1,14,16] NRT and bupropion can also be used in combination, further enhancing the quit rate; bupropion offers the added benefit of lessening weight gain associated with smoking cessation.[14] Behavioural interventions, such as individual or group counselling, or cognitive therapy, are also used for smoking cessation, either alone or in combination with drug therapies. There is some evidence that behavioural interventions improve success rates, although conclusive evidence on which of these interventions are most effective is still lacking.[17]

NRT and bupropion are commonly identified as first-line therapies in clinical practice guidelines, but both have important limitations.[18,19] NRT presents some health risks if users continue to smoke.[1] Bupropion is contraindicated in up to 33% of smokers, including those with a history of seizures, head trauma, anorexia, schizophrenia, and heavy alcohol use.[14,20] Recent guidelines also identify varenicline (Champix™ or Chantix™) – a nicotine receptor partial agonist – as a first-line therapy for smoking cessation.[21] Varenicline's agonist effect on nicotinic receptors mimics the dopamine effects of nicotine sufficiently to offset cravings, while its antagonist effect on the very same receptors suppresses nicotine's reinforcing effects.[1] Varenicline increases the odds ratio of quitting threefold over placebo, and no contraindications or serious side effects have thus far been reported.[20,22]

Overall, pharmacological approaches to smoking cessation have achieved limited success. Long-term (one year) smoking cessation rates range from 5% to 20%.[4,13]

The Evidence

TA-NIC, NicQb, and NicVAX® have all completed at least initial phase 2 studies.[7,8,23] No sources presenting phase 2 results for TA-NIC were identified. Review articles or web-posted phase 2 study results were identified for NicQb and NicVAX.[4,7,8,23]

The safety, tolerability, and efficacy of NicQb 100 µg were evaluated in a 12-month multi-centre, randomized, double-blind, placebo-controlled trial (n=341).[4,23,24] Moderate to heavy smokers were recruited and were immunized five times with 100 µg NicQb formulated in alum, or placebo with alum, at monthly intervals. All participants also received individual counselling. Efficacy was assessed by continuous abstinence, as determined by self-reporting and independently validated by biochemical testing, during weeks 8 to 24 and weeks 8 to 52. The vaccine was well-tolerated and all smokers in the active arm of the study demonstrated an immunological response while none in the placebo group did. An intent-to-treat analysis at 6 and 12 months showed no significant difference between the vaccine and placebo groups with respect to continuous abstinence from smoking. A sub-group analysis (n=159) stratified vaccine-treated smokers into three groups based on the level of antibody response. The data showed that 42% (22/53) of smokers who achieved high antibody levels had abstained from smoking for 12 months compared to 21% in the placebo group (p=0.012). Cigarette consumption amongst high-responders who did not achieve abstinence was lower than that found in the placebo group (p=0.16).[4,23,24]

A subsequent dose-optimization study (n=10) was undertaken to identify the vaccine dose necessary to induce high antibody levels in the majority of patients. A 300 µg NicQb dose was well tolerated and produced a 4.2-fold increase in the mean antibody level. It was estimated that 87% of the vaccinated smokers in the initial phase 2 study would have been in the high responder group at this dosing level.[23,24]

NicVAX is currently under investigation in a phase 2 trial to determine optimal dose ranges for an anticipated phase 3 trial. The phase 2, placebo-controlled study includes 301 participants, all of whom were heavy smokers (defined as smoking an average of 24 cigarettes per day). The study is comparing two different doses (200 µg and 400 µg) and administration regimes. Preliminary results posted on the company's web site suggest that NicVAX efficacy is also linked to antibody response, with high responders having a higher smoking cessation rate.[7]

The available evidence is very preliminary, especially in the absence of more detail regarding clinical trial designs and outcomes. The results to date appear to provide proof-of-concept in terms of the ability to generate a nicotine-specific immunogenic response in vaccinated individuals, but efficacy in terms of smoking cessation requires further study. The evidence shows an association between high antibody levels and smoking cessation. However, there is marked variation in the magnitude of the immunogenic response in vaccinated individuals. Efficacy may ultimately depend on development of vaccine formulations or dosing schedules that permit all vaccinated individuals to achieve high antibody levels.

Adverse Effects

Nicotine vaccines are generally described as being well tolerated with no serious side effects reported to date. Injection site reactions are common and systemic reactions such as headache, fever and malaise occur occasionally. Most adverse events were rated as mild in severity (93%) with the balance rated as moderate.[25,26]

Administration and Cost

Nicotine vaccines are administered by intramuscular injection. Details regarding dosing, number of injections required, duration of effect, and timing of boosters will not be known until the completion of clinical trials. No cost information is available.

Concurrent Developments

Greater understanding of the neural circuits and pathways associated with smoking and nicotine addiction may give rise to new, and perhaps better, smoking cessation therapies. Agents currently under development, or drugs approved for other indications and also under investigation or in use for smoking cessation, include: nortriptyline, clonidine, rimonabant, mecamylamine, monoamine oxidase inhibitors (such as selegiline), and dopamine D3 antagonists. Inhibitors of nicotine metabolism are also being considered as possible agents for smoking reduction and cessation.[6,14]

Rate of Technology Diffusion

If a nicotine vaccine is licensed for smoking cessation, there will likely be significant demand from the public and health care providers. Given the considerable interest amongst smokers in quitting and the limited effectiveness of currently available options, many smokers may be anxious to try a new therapy, even if the likelihood of quitting remains somewhat modest. Vaccines also offer the convenience of avoiding daily dosing and, thus far, they appear to have few or no contraindications.

Implementation Issues

Ideally, nicotine vaccines will be effective for smoking cessation in general. Should the vaccines prove effective for even one indication, such as relapse prevention or smoking reduction, they will be of interest not only to smokers, but to clinicians and, possibly, policy makers, as well. Early evidence suggests that a high immunogenic response will be critical to vaccine effectiveness, but at present it is not possible to assess the relative performance of the vaccines in this regard. The place of vaccines in combination with other therapies is also unknown, although NRT would be contraindicated in the presence of vaccination. Other emerging pharmaceuticals may prove to be as effective as vaccines, which could undermine the attractiveness of nicotine vaccines or point the way to new therapeutic combinations.

References

1. Johnson BA. *Arch Intern Med* 2006;166(15):1547-50.
2. Baliunas D, et al. *Chronic Dis Can* 2007;27(4).
3. Federal, Provincial and Territorial Advisory Committee on Population Health. *Statistical report on the health of Canadians*. Revised 2000. Ottawa: Statistics Canada; 1999. Available: http://www.statcan.ca/english/freepub/82-570-XIE/82-570-XIE1997001.pdf
4. Maurer P, et al. *Curr Opin Mol Ther* 2006;8(1):11-6.
5. LeSage MG, et al. *AAPS J* 2006;8(1):E65-75. Available: http://www.aapsj.org/articles/aapsj0801/aapsj080108/aapsj080108.pdf
6. Siu EC, et al. *Annu Rev Pharmacol Toxicol* 2007;47:541-64.
7. NicVAX® (Nicotine Conjugate Vaccine). In: *NABI Biopharmaceuticals* [web site]. Boca Raton (FL): NABI Biopharmaceuticals; 2007. Available: http://www.nabi.com/pipeline/pipeline.php?id=3

8. TA-NIC. In: *Celtic Pharma* [web site]. Hamilton (Bermuda): Celtic Pharma; 2007. Available: http://www.celticpharma.com/theportfolio/ta-nic.html

9. Le Houezec J. *Clinical Pharmacology Therapeutics* 2005;78(5):453-5.

10. Fagerström K, et al. *Expert Opin Invest Drugs* 2006;15(2):107-16.

11. Table 1: Smoking status and average number of cigarettes smoked per day, by age group and sex, age 15+ years, Canada 2006. In: *Canadian Tobacco Use Monitoring Survey (CTUMS) 2006. Supplementary tables*. Ottawa: Health Canada; 2007. Available: http://www.hc-sc.gc.ca/hl-vs/tobac-tabac/research-recherche/stat/ctums-esutc/2006/ann-table1_e.html

12. Tobacco Control Programme. Summary of results for the first half of 2006 (February - June). In: *Canadian tobacco use monitoring survey (CTUMS) 2006*. Ottawa: Health Canada; 2006. Available: http://www.hc-sc.gc.ca/hl-vs/tobac-tabac/research-recherche/stat/ctums-esutc/2006/wave-phase-1_summary-sommaire_e.html

13. Graul AI, et al. *Drugs Today (Barc)* 2005;41(6):419-25.

14. Frishman WH, et al. *Cardiology in Review* 2006;14(2):57-73.

15. Hasman A, et al. *J Med Ethics* 2004;30(4):344-5.

16. Hughes JR, et al. *Cochrane Database Syst Rev* 2007;(1). CD000031.

17. Aveyard P, et al. *BMJ* 2007;335:37-41.

18. The Smoking Cessation Guidelines Expert Panel, et al. *Smoking cessation guidelines--how to treat your patient's tobacco addiction*. Sherbrooke: Pegasus Health Care International; 2000. Available: http://www.smoke-free.ca/pdf_1/smoking_guide_en.pdf

19. Fiore MC, et al. *Treating tobacco use and dependence: clinical practice guideline*. Rockville (MD): U.S. Department of Health and Human Services. Public Health Service; 2000. Available: http://www.surgeongeneral.gov/tobacco/treating_tobacco_use.pdf

20. Tonstad S. *Br J Cardiol* 2006;13(6):405-10.

21. University of Michigan Health System. *Smoking cessation. Guidelines for clinical care.* Ann Arbor (MI): University of Michigan Health System; 2006. Available: http://cme.med.umich.edu/pdf/guideline/smoking06.pdf

22. Cahill K, et al. *Cochrane Database Syst Rev* 2007;(1). CD006103.

23. *CYT002 Nic Qb: a novel vaccine for nicotine addiction*. Zurich: Cytos Biotechnology; 2006 Jun. Available: http://www.cytos.com/doc/NicQb_June06_E_fv.pdf

24. Heading CE. *Curr Opin Investig Drugs* 2007;8(1):71-7.

25. Maurer P, et al. *European Journal Immunology* 2005;35(7):2031-40.

26. Hatsukami DK, et al. *Clinical Pharmacology Therapeutics* 2005;78(5):456-67.

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