Successful trials for a cervical cancer vaccine

UK trials of a vaccine aimed at protecting women against cervical cancer have demonstrated its effectiveness at preventing transmission of the sexually transmitted disease human papilloma-virus (HPV), which is a known trigger for the cancer. Research has demonstrated that the vaccine is 100% effective at protecting against two of the most high-risk strains of HPV. Cervical cancer is diagnosed in approximately 3200 women in the UK each year and half of these cases result in death.

There are more than 100 different strains of HPV, which can result in warts on the feet, hands or around the genital area - the vulva, vagina, cervix, rectum, anus, penis or scrotum. Approximately 50% of women have been exposed to the virus but the majority are asymptomatic and recover within 6 months with no long-term health problems. However, certain high-risk strains of HPV are not easily disposed of by the immune system and can cause long-term infection; these strains are associated with 99.9% of precancerous abnormal cell changes or cervical cancers.

The four center trials, involving 400 women, are taking place at the Margaret Pyke Centre (London, UK), St George's Hospital (London, UK), St Mary's Hospital (Manchester) and the University of Aberdeen (Scotland). Anne Szarewski, a Clinical Consultant at Cancer Research UK and the lead researcher of the London trials said, “This vaccine is the most exciting development in cervical cancer research because it is mainly caused by a virus so the obvious thing to do is get a vaccine.” Although screening tests are available for early detection of the disease, this does not address the cause of the problem. Szarewski highlighted an additional benefit of the vaccine, “At the moment women are anxious about having smears and a lot find it uncomfortable, unpleasant and off-putting, so if there was a vaccine it may eventually eliminate the need for them.” Smear tests are currently recommended every 3-5 years for all women 20 to 64 years of age. Szarewski hopes that in the future the vaccine may be able to protect against more strains of HPV and eventually remove the need for screening entirely. However, she highlights that this would require the vaccine to protect against 80% of HPV and everyone would have to be vaccinated. “It would be amazing if we found a cancer that we could eradicate through a vaccine,” Szarewski concluded.

To date, the Cervarix vaccine trials have involved 1100 women, 15-25 years of age, in trials taking place in 14 countries including the USA, Canada and Brazil. If further trials are successful, the Cervarix vaccine, developed by GlaxoSmithKline, may be available within the next 3 years. The vaccine would be administered to girls in three doses, spread over 6 months, before they become sexually active, to provide immunity against the virus. GlaxoSmithKline plan to submit an application for Cervarix to the Medicines and Healthcare Products Regulatory Agency in 2006.

promising phase II trials for lung cancer vaccine

Early promising results for a vaccine against advanced stage lung cancer have been presented at the 29th European Society for Medical Oncology Congress (Vienna, Austria). The vaccine has demonstrated the ability to stimulate the immune system to specifically target and kill lung cancer cells. Due to the success of the results generated by the Phase II study, a larger Phase III trial is expected to begin next year.

The Phase II trial, led by Charles Butts from the Cross Cancer Institute in Edmonton (Canada), involved 171 patients, 83 of which had stable or responding Stage IIIB or IV non-small cell lung cancer following chemotherapy and were provided with high-quality supportive care. The remaining 88 were given supportive care and treated with the vaccine, L-BLP25. The vaccine was administered to patients once weekly over a period of 8 weeks and was followed by boosters every 6 weeks.

The results demonstrated that the median survival time for patients who received the vaccine was significantly greater than for those patients who received supportive care only; 17.4 months compared with 13 months respectively. Patient follow-up has demonstrated that 60% of the patients who received the vaccine were still alive after 24 months compared with 36.7% of the unvaccinated group, and one patient is still receiving the vaccine after 43 months.

Butts commented on the data, “The really interesting results are in a specific subset of patients with locally advanced, locoregional disease, which is disease too advanced for surgery but not spread to distant organs. It is this group that appears to benefit substantially from the vaccine in this trial.”

The vaccine, developed by Biomira, Inc. (Edmonton, Canada), in collaboration with Merck KGaA (Darmstadt, Germany), targets a specific sugar-protein molecule, MUC1, situated on the surface of tumor cells. The vaccine aims to stimulate the patient's immune system to recognize the abnormal MUC1 molecules and specifically attack the cells that carry it. The US Food and Drug Administration granted L-BLP25 fast-track status in September 2004. Trials for the vaccine took place in Canada and at four centers in the UK - Guy’s Hospital and St George’s Hospital in London, Western General Hospital in Edinburgh and Clatterbridge Center for Oncology in the Wirral.
The originality of the present study is that the vaccine consisted of a defined antigen, MUC1, which can be produced on a large scale by a pharmaceutical company and used for all patients with a particular disease. Furthermore, another disease responding to a vaccine can now be added – lung cancer. Finally, the trial demonstrated that vaccine treatment can be active in advanced disease after chemotherapy where the majority of patients had remaining macroscopic disease. There is now no doubt that the non-toxic vaccine treatment concept will be incorporated into the therapeutic arsenal of cancer drugs.”

The Phase III trials are expected to include 1000 patients from all over the world and are likely to last 2 years. Butts concluded, “These favorable results seen in the locoregional patients have encouraged us to proceed with plans for a more definitive Phase III trial in this specific population of patients. The details of the study are being worked out now with plans to go forward some time in 2005.”

Positive results for intradermal flu vaccine

Two recent studies published in the New England Journal of Medicine investigate the potential for an intradermally administered influenza vaccine. The benefit would be a reduced dose with no reduction in effectiveness and an expanded supply of available vaccine doses.

Intradermal administration should potentially increase antigen exposure to antigen-presenting cells, such as dendritic cells and macrophages, as these are present in higher quantities in skin than muscle. Therefore, a smaller dose of the vaccine would be required to induce the same effect as a larger intramuscular dose.

The first study carried out by Robert Belshe from St Louis University (MO, USA) and colleagues, involved 238 volunteers, half of which were randomized to receive an intradermal injection of trivalent inactivated influenza vaccine, containing 6 µg of hemagglutinin for each antigen (40% of the usual dose) and half to receive an intramuscular injection of the standard dose of 15 µg of hemagglutinin for each antigen.

The results demonstrated an age-related effect in the volunteers. Individuals 18 to 60 years of age demonstrated a similar, strong serum antibody response in both the intradermal and intramuscular groups. In subjects 60 years of age and above, there was a strong antibody response, however, there was a significantly greater response in those who had received the intramuscular injection. This finding was significant only for antigen to the H3N2 strain. However, 100% of those over 60 years of age vaccinated intramuscularly and 93% vaccinated intradermally had a hemagglutination-inhibition (HAI) antibody titer to the H3N2 strain of more than 1:40. All subjects in each group had a titer of this level for both the H1N1 and B strains.

Different adverse events were associated with each route of vaccine administration. Intramuscular injection was associated with more pain, while intradermal injection was associated with greater inflammation.

The researchers commented on the significance of the results, “As compared with an intramuscular injection of full-dose influenza vaccine, an intradermal injection of a reduced dose resulted in similarly vigorous antibody responses among persons 18 to 60 years of age but not among those over the age of 60 years. In times of vaccine shortage such as the present, intradermal vaccination of healthy young persons with reduced dose inactivated influenza vaccine could be considered in order to stretch vaccine supplies.”

The intradermal route of administration is acknowledged to be more challenging and would require specific training. However, the researchers expect that tuberculin syringes and needles could be used to administer the influenza vaccine intradermally at a dose of 6 µg of hemagglutinin per strain, with a high success rate.

The second study, undertaken by Richard Kenney from Iomai (MD, USA) and colleagues, was a randomized trial involving 100 healthy adults 18 to 40 years of age. The subjects were assigned to one of two groups. The first group received an intramuscular injection of 0.5 ml of trivalent influenza vaccine, containing at least 15 µg of hemagglutinin per strain, using a prefilled syringe. The second group received an intradermal injection of 0.1 ml, containing at least 3 µg of hemagglutinin per strain, using a fine-gauge needle. The researchers analysed the antibody titer of the two groups.

The results of the study demonstrated an increase in the HAI titer in both groups by day 21, however, the increase was significantly greater for the intradermally administered vaccine. The seroconversion and seroprotection rates were similar in the two groups, ranging from 66 to 82% and 84 to 100%, respectively. However, the researchers found that local adverse reactions were more common among those who received the intradermal injection.

The researchers concluded, “In this study of young adults, intradermal administration of one fifth of the standard intramuscular dose of an influenza vaccine elicited immunogenicity that was similar to or better than that elicited by intramuscular injection. Intra-dermal administration could be used to expand the supplies of influenza vaccine but further studies are needed before this strategy can be recommended for routine use.”

La Montagne and Fauci from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (MD, USA) suggest that although these results appear promising, further research is needed regarding the mechanism by which intradermal vaccination optimized the immune response. In addition, they highlight that this route of administration will require the development of regulatory policy and specific training for personnel.

La Montagne and Fauci said, “Technological innovation, such as the use of new vaccines delivered by the intradermal...”
route, offers great promise to change and improve on current immunization strategies. It is our responsibility to pursue these and other approaches in order to advance our ability to meet the inevitable challenges of emerging and re-emerging infectious diseases, particularly influenza.”

Routine malaria vaccine may be on the horizon

The first positive results for a malaria vaccine have been demonstrated in a clinical study of 2,000 children in Mozambique. The researchers hope that these results will encourage a campaign of routine immunization in those countries where the mosquito-borne disease is common.

The study published in the *Lancet* involved 2,000 children 1-4 years of age, who were injected with either the vaccine or a placebo. Children administered with the three-stage vaccine demonstrated a 30% lower risk of being infected with malaria, compared with the control group. The incidence of severe symptoms of disease and hospitalization was 60% less in the group of children who had received the vaccine. Pedro Alonso, lead author of the study, commented on the results, “We’ve never seen a result like this before. These are clearly the best results we’ve ever seen with a candidate malaria vaccine.”

In an additional arm of the study, concerning those who are already infected with the disease, the vaccine has proven effective in delaying the time to reinfection by 45% compared with controls, following antimalarial treatment.

Malaria kills an estimated 1 million individuals every year and is the leading cause of death in children on the continent, costing sub-Saharan countries at least US$15 billion each year. The quest to develop an effective vaccine against the disease has been ongoing for decades but has so far failed. Malaria is caused by the parasite *Plasmodium falciparum*, which invades the red blood cells and liver of infected individuals. Until now there has been no vaccine capable of targeting the many different forms the parasite can adopt.

The new candidate vaccine, RTS,S/AS02A, contains an artificial form of a protein which is present in the protective coat of an infective parasite after it has entered the bloodstream. It is this artificial protein that triggers the immune response necessary to attack the parasite and remove the infection. The trial with this vaccine is the first to demonstrate a protective effect in children for a sustained period of time.

Although the success rate for RTS,S/AS02A is less than those used in existing immunization campaigns such as that for polio, Alonso is optimistic that it would have a significant impact in reducing the pain, sickness and number of deaths of children attributed to malaria.

Joe Cohen of GlaxoSmithKline Biologicals, which developed the vaccine, commented, “This is the first ever convincing evidence that a vaccine against malaria will one day be here, that a vaccine against malaria is feasible.” The Bill and Melinda Gates Foundation funded the trial for the vaccine. Melinda Moree, Director of the Malaria Vaccine Initiative explained, “A malaria vaccine is a neglected product; there are hundreds of millions of people who are in a position to need the product but not in a position to pay for it. It’s a high-need but low-market-potential vaccine, so as a result of that, very few companies are involved in trying to make a malaria vaccine.”

Despite these early promising results, it is likely to be at least 6 years before the malaria vaccine is widely available. Further research is needed to establish any adverse effects and interactions associated with the vaccine. It also needs to be tested in children elsewhere in order to establish whether it is effective worldwide.

The President of GlaxoSmithKline Biologicals, Jean Stéphenne, says the company are determined to make the vaccine available in the developing world, providing there is a reasonable return. The vaccine is expected to cost approximately US$13-26 per vaccination and the company are in talks with Unicef, the World Health Organization and the Global Fund to Fight AIDS, Tuberculosis and Malaria regarding the source of funding which will be used to provide the vaccine to children in Africa.