News Editor: Matthew Thorne
m.thorne@elsevier.com

news

Cervical cancer vaccines available in 2007

Mariam Andrawiss, mariam_andrawiss@hotmail.com

Cervical cancer is the most important manifestation of genital Human Papilloma Virus (HPV) infection and is one of the leading causes of cancer mortality in women worldwide. Gardasil, a HPV vaccine developed by Merck, has shown very promising results in a Phase II study published last May in the *Lancet Oncology* [1]. In this trial, the quadrivalent vaccine reduced by 90% the combined incidence of new cervical pre-cancers and genital warts related to HPV types 6, 11, 16 and 18.

This study follows GSK's Cervarix Phase II trial results published in November 2004 in the *Lancet* [2]. By contrast to Gardasil, Cervarix is a bivalent vaccine against HPV 16 and 18. Cervarix efficacy results were also promising because in this study, it protects 91.6% and 100% of women against incident infection and persistent infection, respectively.

Up to 70% of sexually active women will become infected with HPV during their life. Over 35 types of HPV infect the genital tract. Types 16 and 18 cause about 70% of cervical cancer and high-grade cervical intraepithelial neoplasia, whereas HPV 6 and 11 cause 90% of anogenital warts, for which recurrence is common and treatment painful and expensive. The global cervical cancer burden is estimated at 470,000 of new cases and 230,000 deaths every year, of whom 35,000 are in the USA and Europe. Most cases arise in the developing world where Pap test screening programmes have not been routinely carried out. It is the leading cancer killer of women in developing countries. Screening reduces the risk of cervical cancer but do not prevent for HPV infections.

Bivalent vs quadrivalent vaccines

The GSK and Merck trials were Phase II randomized, multicentre, double-blind placebo-controlled studies, including young women (15–25 years of age). Both vaccines were very effective in protecting women against incident and persistent HPV infections. GSK's bivalent vaccine Cervarix contains recombinant virus-like particles (VLPs) of HPV 16 and HPV 18 produced on insect cells. Merck's quadrivalent vaccine Gardasil is a mixture of four recombinant VLPs of HPV 6, 11, 16 and 18 synthesized in yeast. The adjuvants differ.

> 'Up to 70% of sexually active women will become infected with HPV during their life'

One of the differences between the two vaccines is that Gardasil also protects against genital warts. 'Prevention of genital warts is a major contribution', says Luisa Villa from the Ludwig Institute of Cancer Research in Sao Paulo, Brazil, and first author of the Merck's study. 'Although it is a benign condition, it has an important social and psychological implication for the sexual life of young people and couples. So we do think this is a great advantage.'

'The fight against genital warts is not really a key in what we are trying to achieve', says Chris Hunter-Ward, spokesperson at GSK. 'The big ones are HPV 16 and 18, and the protection against HPV 16 and 18 is slightly higher with Cervarix. We do believe that is because of our adjuvant', he added. 'In terms of HPV-16 and 18 protection, I would say that both vaccines, from the studies published, are comparable, except that we do believe that certain aspects of the immune responses observed cannot be compared', says Villa. 'I would like to stress that the assays used by different companies are not directly comparable. You may have high titers [of antibodies], but they might not be as meaningful since you are measuring broad responses and not those that are specifically required to control infection, those directed against neutralizing epitopes of the various VLPs of the vaccine'.

New data from GSK

Even though Cervarix does not protect against genital warts, GSK has announced new data on its vaccine, presented at the International Papillomavirus Conference in Vancouver, Canada last May. GSK's candidate, as well as protecting against HPV 16 and 18, which together are responsible of 70% of cervical cancers, might also provide some protection against infection by types 31, 45 and 52. Together, these three HPV types are responsible for causing a further 12% of cervical cancers worldwide. So far, cross-protection between different HPV type was considered unlikely. 'Nobody was expecting to get that level of cross-protection', says Hunter-Ward. 'It is great but these are still early data and more work needs to be done'. 'We are really looking forward to see how

1359-6446/05/$ – see front matter PII: S1359-6446(05)03526-9

news

Gardasil performs in protecting against other HPV types. We should be able to show these possibilities in a few months', says Villa.

Because women are at risk of HPV infection for as long as they are sexually active, protection induced by a HPV vaccine must be durable. 'Regarding the durability of the vaccine, we have in our Phase II study a longer follow-up time, but a smaller group of women', says Villa. Merck's vaccine data were indeed followed up until month 36, whereas GSK's stopped at 27 months. 'The current data gives us up to three years now', says Hunter-Ward. 'My understanding is at the time of filing, we expect a good four to five years of protection. We are hoping for a lifetime protection but obviously it has not been tested for this duration', he added.

'Several Phase III clinical trials are ongoing, where up to 25,000 women are vaccinated' says Villa. 'The protocols include not only young women but also mid-age women, because we want to see whether the vaccine could be helpful in already exposed women'.

Studies examining the potential health and economic effects of an HPV vaccine in a setting of screening every two or three years studies are under process. Several reports [3,4] predict that a type-specific HPV vaccine will reduce but not eliminate the risk of cervical cancer. The best balance between costs and benefits appeared to be vaccination at the age of 12, followed by triennial screening starting at age 25 years. It remains to be seen whether these vaccines will be affordable in developing countries.

References

1 Villa, L.L. *et al.* (2005) Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol.* 6, 271–278

2 Harper, D.M. *et al.* (2004) Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 364, 1757–1765

3 Kulasingam, S.L. and Myers, E.R. (2003) Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *J. Am. Med. Assoc.* 290, 781–789

4 Goldie, S.J. *et al.* (2004) Projected clinical benefits and cost-effectiveness of a human Papillomavirus 16/18 vaccine. *Natl Cancer Inst.* 96, 604–615

Cancer prevention a step nearer

Scott Ewan, scott_ewan@hotmail.com

Cancer remains the most feared of diseases. New research from the University of Dundee, UK, provides an insight into how we might be able to protect ourselves against cancer. Environmental factors play a big role in cancer, particularly oxidants. Much has been said about how diet can protect against oxidants by stimulating the body's natural defences. Foods like broccoli, cauliflower, garlic and onions are all known to cause increases in levels of antioxidant proteins. 'Our cells run lots of processes, held in balance,' said John Hayes, Professor of Molecular Carcinogenesis at Dundee University's Biomedical Research Centre, and leader of the team at Dundee. 'The oxidant:antioxidant balance is regulated – it's a bit like a see-saw', Hayes continued. 'Too many oxidants are harmful, and it is possible to have too much antioxidant in our cells. For example, we know high levels of the antioxidant vitamin E can be harmful.'

Balancing the see-saw

The use of chemicals to protect against cancers has been mooted since the 1970s. Certain chemicals are known to stimulate cells into switching on their complex antioxidant machinery, to remove oxidants. It has been clear for some time that the oxidant:antioxidant balance is held in place by some very complex mechanisms. There are currently >200 proteins recognized to play a part in the process. Surprisingly, recent research has shown that the battery of 200 or so proteins balancing the see-saw is controlled by just a single protein, Nrf2. Shortly after its discovery, it became clear that Nrf2 is very unstable, and is undergoing constant turnover. This instability is a negative feedback system, designed to prevent an excess of antioxidant accumulating in the cell.

'The feedback system is sensitive to Nrf2 accumulation through the protein Keap1,' continued Hayes. 'Oxidants entering the cell inactivate Keap1, allowing Nrf2 to switch on the antioxidant system.' Activating the antioxidant system reduces the oxidant levels in the cell, ultimately allowing Keap1 to regenerate and resume turnover of Nrf2. Looking for a way to increase levels of antioxidant, to protect against cancers, the team looked for a way to stabilise Nrf2.

'The oxidant:/antioxidant balance is regulated – it's a bit like a see-saw'

Of mice and men

Significantly, Hayes' team set out to remove Keap1 from their system, following the logic that, to activate the battery of antioxidant proteins, all that's needed is to remove Keap1. To achieve this they employed a small interfering RNA (siRNA). 'siRNAs trick the cell into thinking they are 'a viral problem,' said Hayes. 'The cell then seeks out all mRNA with similar base-pair sequences and destroys them. Using siRNA designed with a sequence unique to Keap1 effectively removes Keap1 from the cell.'

One other factor of this research is that it shows a mechanism in humans. Virtually all previous work in this field has been through studies in mice and rats. Parallels across species are not always as straightforward as researchers might hope. 'Using siRNA against Keap1 has been critical to identifying which human genes are important in this pathway,' agreed Professor Kensler of John Hopkins University.

1359-6446/05/$ – see front matter PII: S1359-6446(05)03527-0