UNIT NO. 6

VACCINES 2006 : NEW HORIZONS

Dr Wong Sin Yew

ABSTRACT

Despite all our medical advances, medical practitioners continue to face challenges with new emerging infectious disease threats and immunizations have always been looked upon as an important public health strategy to control and eradicate these pathogens. At the recently concluded 12th International Congress of Infectious Diseases in June 2006, at least 1/3 of the congress scientific programme had focused on vaccines. The new vaccines that will soon become available have challenged traditional vaccine dogma and utilize virus reassortment and virus like particles. This article will review some of the potential adult vaccines that may become available in the next 12-24 months and also provide an update on some of the trials and tribulations with other "highly sought after" vaccines that had been pursued for the past 2 decades.

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PREVENTION IS BETTER THAN CURE

Vaccinations have been one of the most successful interventions in medical history and have allowed mankind to control numerous diseases and eradicate several devastating infections. Despite all our medical advances, medical practitioners continue to face challenges with new emerging infectious disease threats and immunizations have always been looked upon as an important public health strategy to control and eradicate these pathogens. It is noteworthy that at the recently concluded 12th International Congress of Infectious Diseases in June 2006, at least 1/3 of the congress scientific programme had focused on vaccines.

The history of immunization began as an empirical science with Edward Jenner and the success of smallpox vaccine. Following on, most "viral" vaccines had contained either live attenuated or killed viruses. In contrast, most of the vaccines that focused on bacteria (with the notable exception of BCG) were "protein based". The new vaccines that will soon become available have challenged traditional vaccine dogma and utilize virus reassortment and virus like particles. Whilst, earlier vaccines measured immunogenicity utilizing seroconversion of antibodies, the more recent approaches to vaccine design have also concentrated on the development of cell mediated T cell responses. The quality of such cell mediated responses includes achieving adequate cytokine secretion, proliferative capacity and lytic capacity for CD8 cells. The epitope target breadth of the response and the clonotypic breadth of effector recognition as well as the affinity also need to be sufficient.

This short article will review some of the potential adult vaccines that may become available in the next 12-24 months and also provide an update on some of the trials and tribulations with other "highly sought after" vaccines that had been pursued for the past 2 decades.

HPV Vaccine

Globally, cervical cancer kills 250,000 women every year and is the second most common type of cancer in women. This cancer is largely preventable through screening programmes (utilizing regular PAP smears) designed to diagnose and treat cervical lesions that may progress to invasive cancer. This strategy has shown good success rates in developed countries. In the past decade, the wealth of epidemiological and molecular evidence has led to the understanding that virtually all cases of cervical cancer and its precursor intra-epithelial lesions are the result of prior infection with genital human papillomavirus (HPV). It follows that the prevention of infection by prophylactic vaccination would be an effective anti-cancer strategy. Numerous serotypes have been identified to be associated with cervical cancers and 2 of them, serotypes 16/18 have been reported to cause 65-70% of cervical cancers. Phase III trials using DNA free recombinant HPV major capsid protein L1 has been reported. To date, 2 large randomized controlled trials targeting HPV serotypes 16/18 have been published, one on the GSK vaccine and the other on the MSD vaccine. The vaccinees were in the 15-25 year age group. In both studies, vaccine efficacy was 100% in preventing acquisition of persistent HPV infection of the target types (HPV 16/18). Both studies also showed encouraging data on prevention of CIN (carcinoma in situ). The MSD vaccine is a quadrivalent formulation which also target 2 HPV serotypes (6/11) that are important for genital warts. This quadrivalent vaccine was also highly efficacious in preventing genital warts. Sustained efficacy of up to 4.5 years with good safety profile has been demonstrated in the GSK vaccine.

The MSD vaccine has been approved by the Food and Drug Administration, USA on June 8th, 2006 for registration and it is likely that other vaccines will also be approved shortly. Cost effectiveness studies to evaluate the impact of such vaccines in public health strategies against cervical cancer have been reported in the medical literature and will likely form the basis for policy decisions.

Herpes Zoster Vaccine

Herpes zoster (HZ) results from reactivation of latent varicella-zoster virus (VZV) within the sensory ganglia. It is characterized by unilateral radicular pain and a vesicular rash usually involving a single dermatome. All of us are familiar with this clinical syndrome. It has been estimated that the lifetime risk of this

WONG SIN YEW, Consultant Physician, Infectious Disease Physician, Gleneagles Medical Centre

disease is 10-20%. Older persons bear the greatest burden of illness related to zoster. It has been estimated that fifty percent of persons surviving to 85 years will have an episode of zoster. Annual zoster incidence varies from 1.6/1000 person-years in persons <20 years to almost 11/1000 person-years in persons > 50 years. The most likely reason for this is age related waning immunity.

The complications of HZ in otherwise "immunocompetent persons include debilitating postherpetic neuralgia (PHN), neurologic problems (segmental paralysis), ophthalmological problems and bacterial superinfection.

Antiviral therapy is effective in reducing these complications but there is a limited time window for its use. Acyclovir and valalcyclovir have to be administered within 48 hours to have an impact on the disease. In addition to antiviral therapy, there are improved agents to control the neuropathic pain associated with PHN. However, it is also important to consider the problems of polypharmacy and drug interactions that may occur in the elderly.

Oxfam et al reported a placebo controlled trial of 38,546 adults > 60 years of age of an investigational live attenuated Oka strain of VZV vaccine (Zostavax). Main exclusion criteria were those without a history of varicella infection and immunocompromised persons. In vaccine recipients, the incidence of HZ was reduced by 51.3%, PHN was reduced by 66.5% and the burden of illnesses caused by HZ was reduced by 62.6%. The main adverse effect was injection site reaction (48% in vaccine recipients compared to 16% in placebo recipients). The vaccine was less efficacious in those >70 years of age and the duration of protection is still not clear. It is important to highlight that the zoster vaccine in this trial contained 18,700 to 60,000 plaque forming units of virus. This is much more than the usual varicella vaccine registered for use which typically contains 1350 plaque forming units of virus.

Although reactivation of VZV resulting in HZ is rarely life threatening, the effect of PHN and its impact on the quality of life is serious for many older persons and the utility of this vaccine should be viewed in this context.

Avian Influenza H5N1 Virus

Many people have significant pre-existing and disease moderating levels of immunity to seasonal influenza. By definition, most people will have little or no such immunity to a novel pandemic influenza virus. The timing and strain of the next pandemic cannot be predicted but the major focus has been on the avian influenza H5N1 epidemic which has been ongoing and spreading to different geographic locales since 2003. In general, it will take 6-8 months after the onset of a pandemic before a "pandemic vaccine" can be produced for use in the general population.

The current focus is on developing a "pre-pandemic H5N1" vaccine that would hopefully produce cross reactive antibodies that will provide partial immunity if/when a H5N1 pandemic occurs. There have been 2 major reports on the safety and immunogenicity of inactivated H5N1 vaccines. Bresson et al reported the use of a split virion with and without aluminium hydroxide adjuvant and Treanor et al reported the use of a subvirion vaccine. In humans, it would require at least 2 doses of these prototype H5N1 vaccines administered intramuscularly to produce "protective" levels of hemagglutiin inhibition antibodies (67% seroconversion with 30mcg of split virion vaccine + adjuvant and 58% with 90mcg of the subunit vaccine). Much higher amount of hemagglutinin antigens of H5N1 are required to produce antibodies compared to the current seasonal influenza strains. Obviously, we have some way to go before an effective H5N1 vaccine will become available.

Dengue Virus

There are 4 major dengue serotypes which circulate in the tropical and subtropical regions that populate 2.5 billion people. Dengue is known to be endemic in approximately 100 countries. Annually, it is estimated that 50 to 100 million dengue infections occur. The number of cases reported in Singapore has reached an all time high in 2005. Thus a dengue vaccine should be a global health priority and appears to be a reasonable target. After all, for many years, we have an attenuated vaccine against yellow fever virus, another mosquito borne virus. However, development of a live attenuated dengue virus vaccine has met several problems. Firstly, it has been difficult to develop monovalent vaccines against each of the serotypes that exhibit a satisfactory balance between attenuation and immunogenicity. In addition, the vaccine must be a tetravalent formulation because multiple serotypes typically co-circulate. Thus far, it had been difficult to formulate a tetravalent vaccine with low reactogenicity that induces broad neutralizing antibody response against all 4 serotypes. The "appropriate" vaccine must confer protection against a wide range of genetically diverse subtypes which are dispersed around the world. Of course, the vaccine has to be economical as the majority of persons at risk for dengue infection and re-infection live in developing countries.

Blaney et al developed a recombinant tetravalent dengue virus vaccine with 30 nucleotide deletion in the 3' untranslated region. In the Rhesus monkey model of dengue virus infection, seroconversion occurred but at varying levels of neutralizing antibodies. However, a booster at 4 months induced adequate protection against wild type virus challenge for all major dengue strains. This formulation appears promising and has been considered for evaluation in clinical trials. The group from Walter Reed Army Institute of Research also reported the protective efficacy of a different live attenuated tetravalent dengue virus vaccine in Rhesus monkeys. This particular vaccine also warrants further study.

TB Vaccine

It has been estimated that 1/3 of the world's population or 2 billion persons have been infected with tuberculosis. Annually, there are an estimated 9 million new cases and 2 million deaths from tuberculosis. There are 400,000 new cases of multi-drug resistant tuberculosis. BCG, a live

attenuated M. bovis vaccine had some effect in preventing disease, particularly in children. However, BCG is far from ideal and developing a new and better vaccine against tuberculosis has been the "holy grail" of many researchers. There have been many disappointments but recent advances in understanding of the immunology, TB genome information and improved vaccine adjuvants or delivery systems capable of inducing T cell responses have renewed interest in TB vaccines.

HIV Vaccine

WHO has estimated that there are 40 million infected with HIV infection. Annually, there are 8 million new cases of HIV infection and 3 million die of AIDS. It has been a 2 decade quest for a HIV vaccine and at this time, there have been more misses than hits. The biology of HIV infection requires a "paradigm shift" in our approach to vaccine design. Needless to say, the approach has been increasingly sophisticated but also complicated. It has been well appreciated very early on that humoral immunity to HIV infection plays only a small (if any) part in the immunity against this infection. The ongoing research has focused on cellular immunity and the development of "T cell vaccines". Recent positive advances include improved understanding of HIV envelope structure, improved immune assays and candidate vaccines which utilize replication- incompetent vectors that induce strong cellular immune responses. In addition to the "traditional" concept of a vaccine that provides "protection" against infection, many researchers are also working on "therapeutic" vaccines administered to HIV infected persons to "improve / enhance" their immune reconstitution.

Reche et al reported on the "success" of a T-cell vaccine approach. Using bioinformatics tools, the group identified conserved T cell epitopes of HIV that were necessary for viral fitness and matched these by computer binding to 55 HLA I alleles that were common in the 5 major ethnicities in the US. In HIV negative individuals, they demonstrated that HIV peptide specific cytotoxic T cell mediated lysis (CTL) lines could be generated which were reactive to the specific peptides. These long term CTL lines produced significant amounts of IFN-g and were capable of lysis of peptide pulsed target cells as well as HIV infected cells. This approach shows promise and identifying such conserved epitope that can generate effective CTL is another important step in the quest for a HIV vaccine

CONCLUSIONS

In conclusion, there are exciting times ahead for vaccinology. Not only are there new vaccines for prevention of infection, researchers are also working on therapeutic vaccines for cancer, and allergy.

RECOMMENDED READING

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LEARNING POINTS

- **Prevention of infection with genital human papillomavirus (HPV) by prophylactic vaccination would be an effective anti-cancer strategy.**
- **The current focus in fighting pandemic influenza is on developing a "pre-pandemic H5N1" vaccine. It is expected to produce cross reactive antibodies that will provide partial immunity when a H5N1 pandemic occurs.**
- **There are 4 major dengue serotypes which circulate in the tropical and subtropical regions that populate 2.5 billion people. Multiple serotypes typically co-circulate.**
- **Apart from developing vaccine that provides protection against infection, many researchers are also working on therapeutic vaccines administered to improve immune reconstitution.**