FRESH FROM THE PIPELINE

Meningococcal group A, C, Y and W-135 conjugate vaccine

Lee H. Harrison, Nitin Mohan and Peter Kirkpatrick

In February 2010, a quadrivalent conjugate vaccine (Menveo; Novartis Vaccines and Diagnostics) was approved by the US FDA to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, Y and W-135 in people aged 11–55 years.

Meningitis — acute infection of the membranes that surround the brain and spinal cord — can be fatal within hours, and can result in serious sequelae such as deafness in up to a third of survivors[1,2]. The application of effective polysaccharide–protein conjugate vaccines has dramatically reduced the incidence of bacterial meningitis caused by *Haemophilus influenzae* type b and *Streptococcus pneumoniae*, both through direct and herd immunity effects, illustrating the value of disease prevention with conjugate vaccines[1,2]. The Gram-negative bacterium *Neisseria meningitidis* is another important cause of bacterial meningitis and other invasive bacterial infections, and so has been a focus of substantial efforts for further vaccine development[2].

Basis of discovery

Pathogenic strains of *N. meningitidis* possess a polysaccharide capsule that serves as a major virulence factor[2]. Five pathogenic strains — serogroups A, B, C, Y and W-135, determined by the composition of the polysaccharide — are common causes of invasive bacterial infections, and the polysaccharides of these strains have been targeted for vaccine development[2]. Serogroup B polysaccharide is not suitable for vaccine development, however, owing to its poor immunogenicity and immunological cross-reactivity with human neural antigens[2].

The first meningococcal vaccine licensed in the United States — MPSV4 (Menomune; Sanofi Pasteur), which was approved in 1981 — is based on polysaccharides from serogroups A, C, Y and W-135 (REF. 2). However, as with polysaccharide vaccines in general, it has important limitations, including lack of induction of immunological memory, relatively short duration of protection and lack of immunogenicity in infants.

To improve the immunological response, conjugate vaccines in which meningococcal polysaccharides are covalently linked to a carrier protein have been developed. In 2005, the quadrivalent meningococcal vaccine MCV4 (Menactra; Sanofi Pasteur) — which contains *N. meningitidis* serogroup A, C, Y and W-135 polysaccharides conjugated individually to diphtheria toxoid — became the first such product to be approved in the United States. It has now been joined by a second such product, MenACWY–CRM (Menveo; Novartis Vaccines and Diagnostics), in which meningococcal oligosaccharides are covalently linked to diphtheria cross-reactive material (CRM_{197}).

Vaccine properties

Menveo contains *N. meningitidis* serogroup A, C, Y and W-135 oligosaccharides conjugated individually to *Corynebacterium diphtheriae* CRM_{197} protein[3,4]. Polysaccharides are purified from bacterial fermentations of the respective *N. meningitidis* strains, and CRM_{197} is purified from fermentations of *C. diphtheriae*[4]. Oligosaccharides are prepared for conjugation from purified polysaccharides by hydrolysis, sizing and reductive amination, and then covalently linked to the CRM_{197} protein[3,4]. The resulting glycoconjugates are purified to yield the four vaccine components[4]. Each dose of vaccine contains 10 μg serogroup A oligosaccharide, 5 μg each of serogroups C, Y and W-135 oligosaccharides, and 32.7–64.1 μg of CRM_{197} (REF. 4).

Clinical data

The immunogenicity of Menveo (administered by intramuscular injection) in subjects aged 11–55 years was investigated in a randomized controlled trial in which the serum bactericidal antibody responses were compared to those of Menactra[4]. The trial was conducted in 3,539 adolescents (11–18 years of age) and adults (19–55 years of age) in the United States, who were randomized to receive a dose of Menveo ($n = 2,663$) or Menactra ($n = 876$)[4].

Sera were obtained from participants before vaccination and 28 days after vaccination, and serogroup-specific anticapsular antibodies with bactericidal activity were measured using pooled human serum that lacked bactericidal activity as the source of exogenous complement (hSBA)[4]. The primary immunogenicity end points were hSBA serological response rates to each serogroup 28 days after vaccination[4]. Serological response was defined as a post-vaccination titre of ≥1:8 for subjects with a pre-vaccination hSBA titre of <1:4, and a post-vaccination titre at least fourfold higher than baseline for subjects with a pre-vaccination hSBA titre of ≥1:4 (REF. 4).

Non-inferiority of Menveo to Menactra in adolescents (aged 11–18 years) was demonstrated for all four serogroups based on the primary end point of hSBA serological response[4]. Non-inferiority of Menveo to Menactra in adults (aged 19–55 years) was also demonstrated for all four serogroups[4].

Concomitant administration of Menveo and other vaccines recommended for adolescents was assessed in another trial involving 1,620 subjects aged 11–18 years[4,5]. Participants were randomized to three groups (1:1:1) to receive Menveo concomitantly or sequentially with combined tetanus, reduced diphtheria and acellular pertussis (Tdap) vaccine (Boostrix; GlaxoSmithKline) and quadrivalent human papilloma virus (HPV) vaccine (Gardasil; Merck)[5]. The hSBA serological response, and antibodies to Tdap antigens and HPV virus-like particles were determined before vaccination and 1 month after vaccination[5].

The proportions of subjects with hSBA titres ≥1:8 for the four meningococcal serogroups A, C, Y and W-135 were non-inferior for both concomitant and sequential administration[5]. The immune responses to Tdap and HPV antigens were comparable when these vaccines were given alone or concomitantly with Menveo, and concomitant or sequential administration did not increase reactogenicity[5].

Indications

Menveo is approved by the FDA for active immunization to prevent invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, Y and W-135 in people 11–55 years of age[4]. ▸

ANALYSIS | MENINGOCOCCAL VACCINES

Analysing issues for meningococcal vaccines is Lee H. Harrison, M.D., Professor of Medicine and Epidemiology at the University of Pittsburgh School of Medicine and Graduate School of Public Health, Pittsburgh, Pennsylvania, USA.

N. meningitidis is a major cause of bacterial meningitis and other serious infections worldwide[6]. To prevent infection, quadrivalent meningococcal conjugate vaccine is recommended for all adolescents aged 11–18 years old and other high-risk people[7]. Menveo has recently become the second such vaccine to be licensed in the United States — currently for people aged 11–55 years — providing an alternative option to Menactra, which is currently licensed for people aged 2–55 years[7], and might eventually be licensed for children as young as 9 months old.

Menveo is novel because it both covers four (A,C,W-135,Y) of the five major meningococcal serogroups and is immunogenic and safe when given as a four-dose schedule starting at 2 months of age[8]. This supports the ultimate plan to also obtain licensing approval for infants. Efficacy in infants is important because this group has the highest risk of developing meningococcal disease. Indeed, serogroup C meningococcal conjugate vaccines have been used with great success for more than a decade in infants in the United Kingdom and elsewhere.

There has also been other recent progress in meningococcal vaccine development. A conjugate vaccine that combines protection of infants against *H. influenzae* type b and meningococcal serogroups C and Y is in late-stage development[9]. Ideally, meningococcal vaccines should cover as many clinically important serogroups as possible. However, serogroup A disease rarely occurs in the United States and serogroup W-135 currently accounts for a small proportion of infections in infants. A serogroup A conjugate vaccine for the prevention of meningococcal disease in the African meningitis belt (covering an area from Senegal to Ethiopia) will probably be available soon[10], which is exciting because this region suffers from periodic, devastating meningococcal epidemics. Finally, there has been considerable progress in the development of broadly protective serogroup B meningococcal vaccines[11,12], which are urgently needed because a substantial proportion of meningococcal disease in many parts of the world is caused by serogroup B strains[6].

One of the striking features of meningococcal epidemiology in general is that it is highly dynamic, which makes formulation of an immunization policy for this disease akin to trying to hit a moving target. In the United States, rates of meningococcal disease have declined by more than 60%, to historically low levels[13]. Whether the decline in meningococcal disease incidence is part of the usual cyclical nature of meningococcal disease or represents a sustained change in the epidemiology remains to be seen. Based in part on the low incidence and that the majority of infant disease is caused by serogroup B strains, the US Advisory Committee on Immunization Practices is currently considering not recommending routine meningococcal immunization of infants.

Overall, with the recent licensure of Menveo, and other vaccines in the pipeline, the prospects for comprehensive vaccine prevention of meningococcal disease have never looked better. How Menveo and other meningococcal vaccines are ultimately utilized will depend on serogroup-specific measurements of disease burden, considerations of cost-effectiveness and programme implementation issues.

Box 1 | The market for meningococcal vaccines

Analysing the market for meningococcal vaccines is Nitin Mohan, IMS Health Americas, Canada.

The global market for meningococcal vaccines was valued at more than US$700 million in 2009 (REF. 14). The current leading product is the quadrivalent conjugate vaccine Menactra (Sanofi Pasteur), which had sales of 446 million euros ($593 million) in 2009 (REF. 14). Menactra is approved and sold solely in the United States and Canada. It has now been joined by Menveo (Novartis Vaccines and Diagnostics), which was approved by the US FDA in February 2010, and has also became the first quadrivalent conjugate vaccine available in Europe following its marketing approval in March 2010. However, the European market for quadrivalent vaccines is substantially smaller than in the United States given the different distribution of meningococcal serogroups and the availability of a vaccine for serogroup C. Serogroup B is the largest prevailing serogroup in Europe, but no broadly protective vaccines for this serogroup are currently available. Both Novartis and Pfizer have serogroup B vaccines in development.

Globally, infants are at the highest risk of infection with meningococcal disease, and so vaccines that can be administered to infants are desirable, and represent the largest potential market. Menveo was originally anticipated to be approved for use in infants by 2010, but the FDA has requested an additional 1,500-patient safety study prior to filing for this indication, which is anticipated to occur in 2011. The ability to give Menveo as part of the routine infant vaccination schedule starting at 2 months of age could be a significant advantage over Menactra. According to analysts, annual sales of Menveo are anticipated to be more than $550 million by 2013, following successful approval in the infant indication, and could increase to more than $1.5 billion by 2015 (REFS 15,16).

Lee H. Harrison is at the Infectious Diseases Epidemiology Research Unit, University of Pittsburgh Graduate School of Public Health and School of Medicine, Pittsburgh, Pennsylvania 15101, USA.
Nitin Mohan is at IMS Health Americas, Toronto, Canada.
Peter Kirkpatrick is at Nature Reviews Drug Discovery.
e-mails: lharriso@edc.pitt.edu; NMohan@ca.imshealth.com; p.kirkpatrick@nature.com

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Competing financial interests
L.H.H. declares competing financial interests: see web version for details.