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An Update on Quadrivalent Meningococcal Conjugate Vaccines

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Meningococcal conjugate vaccines for serogroups A, C, W-135, and Y have been available in the United States since 2005.[1-4] Two quadrivalent meningococcal conjugate vaccines are currently on the market: MenACWY-D (Menactra®), the original product, and MenACWY-CRM (Menveo®), introduced in 2010. These conjugate vaccines replaced the polysaccharide vaccine (Menomune®) licensed in 1981, providing seroprotection at least that of the original, as well as improved immunogenicity in infants and young children.[1]

Several changes in use of the quadrivalent meningococcal conjugate vaccines have occurred within the last year, including approval in a wider patient age range and the addition of a booster dose for older adolescents.[1-4] This issue of *Pediatric Pharmacotherapy* will review the quadrivalent meningococcal conjugate vaccines and describe recent changes in labeling from the Food and Drug Administration (FDA) and in immunization practice from the Advisory Committee on Immunization Practices (ACIP).

Vaccine Formulation

The incidence of meningococcal disease varies widely throughout the world. There are approximately 1,000 to 3,000 cases diagnosed each year in the United States.[5,6] Of the 13 meningococcal serogroups, only five (A, B, C, W, and Y) produce invasive disease. Over the past decade, serogroups B, C, and Y have predominated in this county. None of the currently available meningococcal vaccines protect against infection by serogroup B.[6-8]

Seroresponse

In studies comparing MenACWY-D to the polysaccharide meningococcal vaccine in adolescents and adults, the conjugate vaccine produced similar rates of seroresponse (defined as antibody titers at least four-fold higher than baseline). In studies enrolling subjects from 11 to 55 years of age, seroresponse rates ranged from 73.5% to 96.7% in the subjects receiving MenACWY-D and 79.4 to 95.3% in those given the polysaccharide vaccine.[1,9]

Seroresponse rates differ significantly, however, when the polysaccharide and conjugate vaccines are given to younger children. In a comparison study by Pichichero and colleagues of 1,398 children between 2 and 10 years of age, the group given MenACWY-D had average seroresponse rates of 98.6% for serogroup A, 87.9% for serogroup C, 96% for serogroup W-135, and 86.2% for serogroup Y.[10] In comparison, children given the polysaccharide vaccine had rates of 94.7%, 80.1%, 89.6%, and 75% for the four serogroups, respectively.

Likewise, the MenACWY-CRM vaccine has been shown to provide a greater immune response in 2-10 year olds than the polysaccharide vaccine. Black and colleagues conducted a phase II randomized single-blinded study in 619 children. Seroresponse rates of 82% for serogroup A, 83% for serogroup C, 95% for serogroup W-135, and 91% for serogroup Y were reported for the children receiving MenACWY-CRM.[11] Rates in the polysaccharide vaccine group were 45%, 66%, 71%, and 61% one month after vaccination.

The MenACWY-CRM vaccine has also been compared to the MenACWY-D vaccine in several non-inferiority studies conducted by the manufacturer.[12,13] Overall, MenACWY-CRM produces rates of seroresponse similar to MenACWY-D in both adults and children. Halperin and colleagues conducted a phase III multicenter randomized study to compare the immunogenicity and safety of MenACWY-CRM to MenACWY-D in 2,907 children between 2 and 10 years of age. The authors found average rates of seroresponse were 72%, 60%, 72%, and 66% (for serogroups A, C, W-135, and Y, respectively) in the children given MenACWY-CRM and 77%, 56%, 58%, 45% for those given MenACWY-D.[13]

Contraindications and Precautions

Hypersensitivity reactions, including anaphylaxis, have been reported after meningococcal immunization but appear to be rare. MenACWY-D vials have a rubber stopper;

use of this product in patients with a latex allergy is not recommended. Neither conjugate vaccine has been studied in pregnant women. Immunization of women who are pregnant is not currently recommended. Although a causal relationship between the quadrivalent meningococcal conjugate vaccine and Guillain-Barré syndrome (GBS) has not been proven, it is recommended that patients previously diagnosed with GBS not receive this vaccine.

Adverse Reactions

Studies comparing the meningococcal conjugate vaccines to the polysaccharide vaccine have shown similar rates of adverse effects. In their safety and immunogenicity study of 2,907 children, Halperin's group reported local or mild systemic adverse effects in 60% of the children given MenACWY-CRM and 51% of those given the polysaccharide vaccine.[13] Pain, erythema, and induration were the most commonly reported local reactions, reported in 18-33% of patients. Irritability and sedation were the most common systemic effects, reported in 16 to 22% of patients of either group. Fever was uncommon, occurring in only 2% of patients. Headache, malaise, arthralgia or myalgia, nausea, and anorexia have also been reported in more than 10% of patients after vaccination.

Administration

Quadrivalent meningococcal conjugate vaccine is administered as a 0.5 mL intramuscular injection.[10,12] MenACWY-D is supplied in a single dose vial.[10] It should be refrigerated until use. MenACWY-CRM is supplied in two vials, one with the meningococcal A component as a lyophilized powder and the other a liquid with the meningococcal C, W-135, and Y components.[12] The liquid is used to reconstitute the powder immediately before use. The vials must be refrigerated and protected from light. Once reconstituted, MenACWY-CRM should be used within 8 hours.

In adolescents or adults, the quadrivalent meningococcal conjugate vaccines may be administered concomitantly with the human papillomavirus (HPV) vaccine and the combined tetanus, reduced diphtheria, and acellular pertussis vaccine (Tdap). In a study of 1,072 adolescents and young adults randomized to receive MenACWY-CRM with Tdap or a saline placebo, Gasparini and colleagues found no increase in adverse effects and similar rates of meningococcal seroresponse when the two vaccines were given together.[14] There was a slightly lower response to the pertussis vaccine, but the difference was not considered clinically significant.

Recent Changes

Administration to Younger Patients

Meningococcal vaccines have traditionally been administered during adolescence to provide protection during the high-risk period from ages 14 to 24 years. While the incidence of meningococcal disease is higher in this age group than it is in adults, it is not as high as that in infants.[5] Surveillance data from 1998 to 2007 revealed an infection rate of 5.38 per 100,000 infants, with a rate of 0.74 per 100,000 adolescents from 14 to 17 years of age and 0.76 per 100,000 young adults from 18 to 24 years of age.[6] While the polysaccharide vaccine was of limited utility in young children, the meningococcal conjugate vaccines, with their ability to induce immunologic memory, makes protection of this population feasible.

Last year, the FDA approved the use of MenACWY-D vaccine in children 2-10 years of age, extending the age range for immunization from 2 to 55 years of age. On January 28, 2011, the FDA approved a similar expansion of the age range for MenACWY-CRM.[7] The principle evidence supporting this approval came from the Halperin study described earlier.[13] Patients in the 2-5 year old group were randomized to a single dose or a two dose series. Patients between 6 and 10 years of age received a single dose. Immunogenicity was determined by the percentage of children with at least a four-fold rise in antibody at 28 days post-immunization.

MenACWY-CRM immunogenicity was shown to be equivalent or better than that produced by MenACWY-D after a single dose. As in previous studies conducted by the manufacturer, antibody titers increased with increasing patient age. In the younger children, the 2-dose series produced significantly higher antibody titers and a greater rate of seroresponse (89-98% for the four strains with 2 doses compared to 60-72% after a single dose, $p < 0.001$).

On April 22nd, the FDA approved an extension of the age range for MenACWY-D to include patients from 9 months to 55 years of age.[10] Both of these licensing changes reflect on-going clinical trials demonstrating adequate seroconversion, as well as safety, in younger patients. It is expected that meningococcal immunization will eventually be shifted to infancy rather than adolescence.

Updated ACIP Recommendations

Prior to this year, the ACIP childhood immunization schedule called for a single dose of a quadrivalent meningococcal conjugate vaccine at 11-12 years of age.[3] It was thought that a single dose at that age would provide effective antibody titers throughout adolescence and early adulthood, when patients are at higher risk for disease and have the greatest risk for fatality (approximately 20%).[5] Recent evidence, however, suggests a shorter duration of vaccine efficacy.[1,3,9] Results from a case-control study initiated in January 2006 were presented to the ACIP at their October 2010 meeting, showing a decrease in vaccine effectiveness from 91% in patients less than 1 year post-immunization to 58% in those immunized 2 to 5 years previously.[10]

An additional post-licensure surveillance study has revealed similar results, with vaccine effectiveness declining within 3 to 4 years after immunization.[15] Based on these findings, the ACIP published updated recommendations for meningococcal vaccination in the January 28, 2011 issue of *Morbidity and Mortality Weekly Report*, adding a booster at 16 years of age to provide better protection through age 21.[3]

On August 5th, the ACIP published a subsequent update to clarify immunization recommendations for children and adults who are at increased risk for meningococcal disease.[4] A two-dose series, with the second dose given 2 months after the first, is recommended for patients 2 years of age and older with persistent complement deficiencies (involving C5-C9, properidin, factor D, or factor H), anatomic or functional asplenia, or HIV infection. Patients 7 years of age and older who are in these high-risk categories should receive an additional booster dose every five years. Patients receiving their primary immunization at less than 7 years of age should receive a booster dose every 3 years until they reach 7 years of age. The two vaccines are considered interchangeable by the ACIP and either one may be used for primary and booster doses.

The ACIP update also recommends a single dose of meningococcal conjugate vaccine for children between 2 and 10 years of age who are traveling to or reside in countries where meningococcal disease occurs in greater frequency, such as sub-Saharan Africa or Saudi Arabia.[4]

Meningococcal Vaccine Research

Meningococcal A Conjugate Vaccine

In the June 16, 2011 issue of the *New England Journal of Medicine*, Sow and colleagues published the results of two studies using a new meningococcal A conjugate vaccine (MenAfriVac™). This single-serogroup vaccine was designed for use in the "meningitis belt" in sub-Sarahan Africa, extending from Senegal to Ethiopia. The rate of meningococcal disease within this region is estimated to be more than 100 times that reported in the United States. Epidemics have occurred there approximately every 10 years, despite routine use of the quadrivalent polysaccharide meningococcal vaccine.

The first study compared seroresponse in 601 children 1-2 years of age who were randomized to receive either a single dose of the new group A conjugate vaccine, a quadrivalent polysaccharide vaccine, or the control (*Haemophilus influenzae* type b vaccine). Ten months later, patients were randomized to a booster dose of one of the three vaccines. The second study involved 900 patients between 2 and 29 years of age randomized to receive a single dose of either group A or quadrivalent polysaccharide vaccine.

In the first study, the infants and toddlers in the meningococcal A conjugate vaccine group had a 96% seroresponse, compared to 63.7% in the quadrivalent polysaccharide group. In the second study, rates of seroresponse were 78.2% in the meningococcal A group and 46.2% in the quadrivalent polysaccharide group. As anticipated, the meningococcal A group demonstrated higher antibody titers at 40 weeks and a stronger response to a booster dose, reflecting immunologic memory. Adverse effects were similar between the groups. The results of these studies support the use of a single strain conjugate vaccine to combat the periodic epidemics of meningitis A in sub-Saharan Africa.

Meningococcal B Vaccine

The lack of an effective vaccine for meningococcal group B remains a gap in the ability to prevent invasive disease in the United States and many European countries. Group B capsular polysaccharide is not highly immunogenic and is similar to human cell proteins. Administration poses a risk for the development of an autoimmune response.[8,17] A different type of vaccine will likely be needed to combat group B disease. In a recent study of 60 infants conducted in the United Kingdom, more

than 90% of the subjects had appropriate antibody titers after their third injection of either of two MenB vaccines containing factor H-binding protein, Neisserial adhesion A, and Neisserial heparin-binding antigen.[18]

Summary

Changes in the immunization schedule for the quadrivalent meningococcal conjugate vaccine have the potential to further reduce the risk for invasive disease in the pediatric population. Extension of the age range for immunization to children ages 2 and older is the first step in protecting younger children, and may lead to additional studies to support immunization of infants. New recommendations for a booster dose in late adolescence are expected to provide greater coverage during early adulthood. While it will take several years for the effects of these changes to become evident, it is hoped that conjugate vaccine technology will have the same impact on meningococcal disease that it has had on *Haemophilus influenza* type b and streptococcal disease.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their September meeting:

1. Meningococcal conjugate vaccine (Menveo®) was added to the formulary. It will replace the current product, Menactra®.
2. Ticagrelor (Brilinta™) was added to the formulary as an alternative to clopidogrel.
3. The following agents were added to the formulary as Category A antimicrobials: rilpivirine (Endurant™), a non-nucleoside reverse transcriptase inhibitor of HIV-1, the combination emtricitabine/rilpivirine/tenofovir disoproxil fumarate (Complera™), maraviroc (Selzentry™), a selective chemokine receptor CCR5 antagonist with anti-HIV-1 activity, and fidaxomicin (Dificid™), used in the treatment of *C. difficile* diarrhea in adults.
6. Porfimer sodium (Photofrin®) was returned to the formulary with restriction to selected patients with Barrett's esophagus or endobrachial non-small cell lung cancer.

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