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Meningococcal Conjugate Vaccine

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On January 14th, the Food and Drug Administration (FDA) approved the first quadrivalent meningococcal polysaccharide conjugate vaccine (MCV4) for use in people between 11 and 55 years of age.[1] Following the licensing of this new product, the Advisory Committee on Immunization Practices (ACIP) issued a recommendation for the routine immunization of children 11 to 12 years of age, using this new vaccine.[2] Prior to this announcement, meningococcal vaccine was only recommended for young adults at high risk for invasive meningococcal disease. This issue of *Pediatric Pharmacotherapy* will describe the new meningococcal conjugate vaccine and review the available studies documenting its efficacy and safety in children.

Meningococcal Disease and Available Vaccines

Meningococcal disease has an annual incidence in the United States of approximately 1,400 to 2,800 cases. There is a 10 to 14% incidence of mortality and an 11 to 19% incidence of permanent disabilities (such as neurological damage, seizures, deafness, or limb amputation) associated with this disease. The rate of disease is similar in most industrialized countries. Because of the epidemic nature of meningococcal disease, there has been considerable variation in the incidence over time, but the rate of infection in the United States has been relatively stable for the past several decades.[2-4]

There are 12 known serogroups of *Neisseria meningitides*. Approximately 60% of all cases of meningococcal disease in the United States, and 80-90% of all cases in adolescents, are caused by serogroups C, Y, and W-135. Both the polysaccharide vaccine (PSV4, marketed as Meromune®-A/C/Y/W-135 by Aventis Pasteur) and MCV4 (marketed as Menactra® by Aventis Pasteur) provide protection against these three strains, as well as serogroup A. Unfortunately, neither vaccine provides protection against serogroup B. This serogroup causes nearly one third of all cases of meningococcal disease in the United States and is the most frequent cause of meningococcal disease in infants.[1]

Efficacy in Children

The MCV4 vaccine contains capsular polysaccharide antigens of *Neisseria meningitides* serogroups A, C, Y, and W-135 strains individually conjugated to diphtheria toxoid protein. The quadrivalent conjugate vaccine was developed in an effort to produce a greater antibody response to PSV4 in young children and provide a more long-lasting immunity. Nasopharnygeal carriage rates may also be decreased by use of the conjugate vaccine, reducing bacterial transmission.[3] The previous success of a conjugate vaccine to meningococcal serogroup C in reducing the incidence of disease in young children in the United Kingdom supports the efficacy of this technology.[5,6]

The efficacy and safety of the MCV4 vaccine was compared to PSV4 in two randomized, multi-center, controlled trials, one involving adolescents and another in adults. In the adolescent trial, 881 patients between 11 and 18 year of age were enrolled. The median age of the patients was 14 years. Immune response was evaluated by identifying the percentage of patients with a four-fold or greater increase in serum bactericidal antibody to each serogroup, as well as the rate of seroconversion.[1]

The results of the study showed comparable levels of immune response in the PSV4 and MCV4 groups. For serogroup A, 92.7% of patients in the MCV4 group had at least a four-fold rise in antibody, compared to 92.4% in the PSV4 group. This level of immune response was present for serogroup C in 91.7% of the MCV4 patients and 88.7% of the PSV4 group. For serogroup Y, the values were 81.8% and 80.1%, respectively, and for the W-135 serogroup, the values were 96.7% and 95.3%. Seroconversion rates in the MCV4 group were 100% for serogroup A, 99% for serogroup C, 98% for serogroup Y, and 99% for serogroup W-

135. Seroconversion rates for the patients given PSV4 were 100% for serogroup A, 99% for serogroup C, 100% for serogroup Y, and 99% for serogroup W-135.[1]

There is currently only one clinical trial of MCV4 published in the medical literature. Pichichero and colleagues conducted a randomized, modified double-blind, controlled trial comparing MCV4 and PSV4 in 1,398 children between 2 and 10 years of age.[7] Serum bactericidal activity (SBA), a measure of functional antibody production, and adverse reactions were assessed at 28 days and 6 months after immunization.

In the MCV4 patients, the SBA geometric mean titers against serogroups A, C, Y, and W-135 were 1700, 354, 637, and 750, respectively, at 28 days. Titers in the PSV4 group were significantly lower at 893, 231, 408, and 426 ($p < 0.001$ for all comparisons). This difference remained at the 6-month follow-up. Both vaccines were well tolerated, with no serious adverse events reported. The incidence of injection site reactions and systemic effects were similar in both groups. The authors concluded that MCV4 has a safety and tolerability profile equal to that of the PSV4 vaccine in current use, but appears to provide significantly higher and longer-lasting antibody response.[7] Based on the results of this study and two others, the manufacturer has filed a supplemental license application with the FDA to amend the vaccine's license to include children between 2 and 10 years of age.

Contraindications and Precautions

The MCV4 vaccine is contraindicated in patients with a known hypersensitivity to any component of the vaccine, including diphtheria toxoid, and in patients with a history of a severe reaction to any other vaccine containing similar components. The stopper of the vaccine vial contains latex, and may produce an allergic reaction in latex-sensitive patients. Because of the potential for hypersensitivity reactions to the vaccine or latex, the manufacturer recommends that epinephrine and equipment for the management of anaphylaxis be available at the time of use.[1]

Patients at risk for hemorrhage should not receive MCV4, including those with hemophilia, thrombocytopenia, or receiving anticoagulants, unless the benefit clearly outweighs the risk for bleeding after vaccination. Although MCV4 has not been associated with teratogenic effects in animal models, women who are pregnant should only receive the vaccine if clearly needed. The manufacturer has created a registry for pregnant women who receive MCV4 to track response. Information on the program is available by contacting Aventis Pasteur at 1-800-822-2463. It is not known whether MCV4 is excreted into breastmilk.[1]

Patients receiving immunosuppressive drug therapies or undergoing radiation therapy may have a reduced immunologic response to MCV4.[1]

Adverse Effects

Information on the safety of MCV4 has been determined from the cumulative results of six clinical trials in patients between 11 and 55 years of age. The most commonly reported adverse events in these trials were pain at the site of injection, headache, and fatigue. The majority were reported as mild to moderate in severity. When separated by age group, patients between 11 and 18 years of age reported the following adverse events: pain at the site of injection (59.2% of patients), induration (15.7%), redness and/or swelling (10.9 and 10.8%), headache (35.6%), fatigue (30%), malaise (21.9%), arthralgia (17.4%), diarrhea (12%), anorexia (10.7%), chills (7%), fever (5.1%), vomiting (1.9%), and rash (1.6%).[1]

In their study of children 2 to 10 years of age, Pichichero and colleagues found a 58.8% incidence of injection site reactions in the children given MCV4.[7] Fussiness was reported in 35.2% of the patients, with drowsiness in 26%, transient anorexia in 22.7%, diarrhea in 15.9%, fever $\geq$ 38º C in 11.4%, vomiting in 5.9%, and hives in 1.2%. These results were similar to the percentages reported in the children given PSV4.

Availability and Dosing

Menactra® is available in single 0.5 ml vials. It must be refrigerated at 2° to 8° C until use. The dose should be administered intramuscularly, preferably in the deltoid region. It may be administered at the same time as typhoid or tetanus-diphtheria vaccine (Td). Concomitant administration of other vaccines with MCV4, or the mixing of other vaccines in the same syringe as MCV4, has not been studied and is not recommended.[1]

The ACIP recommends administration of MCV4 at the preadolescent (11 to 12 year) visit. In adolescents beyond this age, the vaccine is recommended before high school, at approximately 15 years of age. Other adolescents, particularly those attending college, should also be immunized.[2]

Cost

Menactra® is available in one and five vial boxes. The average wholesale price of the vaccine is $82.00 per single-dose 0.5 ml vial.[8] A cost-effectiveness analysis of the MCV4 vaccine was published in the May issue of *Pediatrics*.[9] A hypothetical model incorporating MCV4 into the routine childhood immunization schedule was developed, using a cohort of children 11 years of age based on 2003 US census data. With this model, the authors predicted that MCV4 use would prevent 270 cases of meningococcal disease and 36 deaths in the 2003 cohort over a 22 year follow-up, resulting in a 46% decrease in the expected burden of disease. Using the current pricing information, routine vaccination at 11 years of age would cost approximately $121,000 per life-year saved. While this analysis shows the vaccine to be relatively high in cost to society, the values are in line with other recently adopted vaccines.

Summary

The new MCV4 vaccine offers a high level of immunity against meningococcal disease caused by serogroups A, C, Y, and W-135 in adolescents and adults. New research has shown that MCV4 is effective in younger children as well, and licensure in a wider age-range is anticipated later this year. As with any new vaccine, post-marketing surveillance will be important to confirm the efficacy and safety of MCV4 that was documented in clinical trials.

References

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Pharmacology Literature Review

Abacavir pharmacokinetics in children

The pharmacokinetic profile of abacavir was studied in 105 children with human immunodeficiency virus ranging in age from 1 month to 16 years. Using population analysis (NONMEM) and a one-compartment open model, the authors found an absorption rate constant of 1.79 hr^{-1} (58% percent interindividual variability), an apparent volume of distribution of 42.9 L (53%), and an apparent plasma clearance of 24.3 L/hr (30%). Clearance was positively related to body weight. Using currently recommended weight-based dosing, the calculated area under the curve value was 8.5±2.5 mg·hr/L, slightly greater than that reported in adults. The authors concluded that current dosing recommendations for abacavir in children are appropriate. Jullien V, Urien S, Chappuy H, et al. Abacavir pharmacokinetics in human immunodeficiency virus-infected children ranging in age from 1 month to 16 years: a population analysis. **J Clin Pharmacol 2005;45:257-64.**

Control of gastric acid suppression in children

This study compared the efficacy of two proton pump inhibitors, pantoprazole and omeprazole, and a $histamine_2$-blocker (ranitidine), administered enterally, in children with gastroesophageal reflux disease (GERD). All 17 patients had gastric tubes and were already receiving one of the study drugs. Mean doses were 1.3 mg/kg/day of pantoprazole, 1.4 mg/kg/day of omeprazole, and 6.8 mg/kg/day of ranitidine. Gastric pH was assessed weekly for 4 weeks. Mean gastric pH was 4 with pantoprazole, 4.3 with omeprazole, and 3 with ranitidine. A total of 29% of the pH readings for ranitidine were greater than 4, compared to 66% of the omeprazole and 60% of the pantoprazole readings. While the proton pump inhibitors were more successful in achieving a pH greater than 4, the duration of benefit waned by 12 hours. The authors concluded that proton pump inhibitors appeared more effective than ranitidine, but were not likely to provide adequate control with once daily dosing. Cuttica C, Chicella MF, Butler DE, et al. Comparison of pantoprazole, omeprazole, and ranitidine in children requiring acid suppression: a prospective pilot study**. J Pediatr Pharmacol Ther 2004;9:198-201.**

Etanercept pharmacokinetic analysis

The population pharmacokinetic parameters of etanercept were evaluated in 69 juvenile rheumatoid arthritis patients (JRA) between 4 and 17 years of age. The authors compared two subcutaneous dosing regimens: 0.8 mg/kg given

once weekly and 0.4 mg/kg given twice weekly. The mean (SD) simulated trough concentrations were 1.56±1.07 mg/L for the once weekly regimen and 1.93±1.09 mg/L for the twice weekly regimen. Peak concentrations for the weekly and twice weekly regimens were 2.92±1.41 mg/L and 2.62±1.23 mg/L, respectively. Based on these results, the 0.8 mg/kg once weekly dose has been approved by the Food and Drug Administration as an alternative regimen for children with JRA. Yim D, Zhou H, Buckwalter M, et al. Population pharmacokinetic analysis and simulation of the time-concentration profile of etanercept in pediatric patients with juvenile rheumatoid arthritis. **J Clin Pharmacol 2005;45:246-56.**

Pneumococcal vaccine review

This extensive review covers both the polysaccharide and conjugate pneumococcal vaccines. The focus of the article is a review of the clinical trials demonstrating vaccine efficacy in terms of prevention of invasive disease, pneumonia, and acute otitis media. The authors also address safety data with the products currently available, as well as concerns about changes in antimicrobial resistance patterns resulting from wide-spread vaccination. Bernatoniene J, Finn A. Advances in pneumococcal vaccines: advantages for infants and children. **Drugs 2005;65:229-55.**

Topical anesthetics for neonatal eye exams

The authors of this paper conducted a randomized, double-blind, placebo-controlled cross-over study to examine the efficacy of proparacaine HCl ophthalmic solution 0.5% in reducing the pain associated with eye exams in premature neonates. The Premature Infant Pain Profile (PIPP) was used to evaluate response. Twenty-two patients were enrolled. The patients had significantly lower PIPP scores with proparacaine than with the saline placebo (paired difference –2.5±3.4, p = 0.001). Marsh VA, Young WO, Dunaway KK, et al. Efficacy of topical anesthetics to reduce pain in premature infants during eye examinations for retinopathy of prematurity. **Ann Pharmacother 2005;39:829-33.**

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 4/22/05:

1. Basiliximab (Simulect®), an interleukin-2 receptor antagonist, was added to the Inpatient Formulary for prophylaxis of acute rejection in renal, liver, and pancreatic transplant patients.

2. The restriction on insulin glargine (Lantus®) to use by only Endocrinology was removed from both the Inpatient and Outpatient Formularies.

3. The restriction on recombinant factor VIIa (NovoSeven®) was amended to include prescribing with approval of the following physicians:

- hemophilia and warfarin reversal in patients with serious bleeding (Dr. Macik, Hematology or Drs. Dunsmore, Kupfer, and Waldron, Pediatric Hematology)
- liver disease patients (Drs. Caldwell, Berg, Al-Osaimi, and Northrup, Hepatology)
- intracerebral hemorrhage (Drs. Bleck, Durbin, Fletcher, Nathan, Schwenzer, NNICU)
- any other unlabeled use (Dr. Macik, Hematology or Drs. Dunsmore, Kupfer, and Waldron, Pediatric Hematology)

4. Temozolomide (Temodar®) was added to the Outpatient Formulary with restriction to the treatment of primary central nervous system tumors.

5. Auranofin and gold sodium thiomalate were removed from the Inpatient Formulary.

6. Requests for the addition of an enteric-coated formulation of mycophenolate and a dietary supplement containing folic acid, vitamins B_6 and B_{12}, and omega-3 acids were rejected.

7. The medication error reports for the 3rd and 4th quarters of 2004 were presented. For more information, contact Sharon Boyer in the Department of Pharmacy Services.

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