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Safety and immunogenicity of an investigational quadrivalent meningococcal CRM_{197} conjugate vaccine, MenACWY-CRM, compared with licensed vaccines in adults in Latin America

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SUMMARY

Background: This study compared the investigational quadrivalent meningococcal CRM_{197} conjugate vaccine, MenACWY-CRM, with licensed quadrivalent polysaccharide (MPSV4) and conjugate (MenACWY-D) meningococcal vaccines.
Methods: In this phase III multicenter study, 2505 adults (aged 19–55 years) were randomized to receive either MenACWY-CRM or MenACWY-D, and 326 adults (aged 56–65 years) were randomized to receive either MenACWY-CRM or MPSV4. Sera obtained pre-vaccination and at 1-month post-vaccination were tested for serogroup-specific serum bactericidal activity using human complement (hSBA) for immunogenicity non-inferiority and superiority analyses.
Results: The vaccines in all groups were well tolerated. In the 19–55 years age group, post-vaccination geometric mean titers (GMTs) were consistently higher for MenACWY-CRM than for MenACWY-D for all four serogroups. MenACWY-CRM was non-inferior to MenACWY-D for all serogroups, and superior for serogroup Y. In the 56–65 years age group, post-vaccination GMTs were 1.2- to 5.4-fold higher for MenACWY-CRM than for MPSV4 for the four serogroups.
Conclusions: MenACWY-CRM is well tolerated and immunogenic in adults aged 19–65 years, with at least non-inferior immunogenicity compared with the currently licensed meningococcal vaccines.

1. Introduction

Meningococcal disease caused by *Neisseria meningitidis* is a major cause of morbidity and mortality worldwide.[1] The highest incidence of meningococcal disease is in infants aged < 12 months, and a second peak in incidence often occurs in adolescents.[2] Although the incidence of meningococcal disease is highest in infants, 50% of meningococcal disease in Europe[3] and 62% of meningococcal disease in the USA occurs among persons aged ≥10 years and ≥11 years, respectively.[2] In other regions, such as Latin America, the adolescent peak is not so obvious, with approximately 25% of meningococcal disease cases occurring among persons ≥15 years of age.[4] Furthermore, case-fatality rates are higher in young adults aged 15–24 years (22.5%) and in adults aged >25 years (16.5%), than in children aged <15 years (4.6%).[5]

The global epidemiology of meningococcal serogroups is dynamic and unpredictable, and can differ by region. In 2007, USA Active Bacterial Core Surveillance data showed that meningococcal serogroups B, C, and Y accounted for 25%, 30%, and 37% of isolates in that year, respectively,[6] with a markedly increased contribution from serogroup Y, which was <5% in the early 1990 s.[7] Similarly, in Colombia between 1994 and 2002, and between 2003 and 2006, serogroup Y increased from accounting for 2.2% of all invasive meningococcal disease to over 29.5%.[8] Epidemics in Africa and elsewhere in the world have most frequently been caused by serogroup A, and more recently serogroup W-135.[9] The recent emergence of serogroup W-135 was underscored by an outbreak in 2000 that was associated with the Hajj – this was the first recognition of the potential for outbreak in this serogroup.[10] In Brazil, the prevalence of serogroup W-135 increased significantly in the period 2003–2005.[11] An unprecedented incidence of serogroup X was reported in Niger, Africa in 2006.[12] Serogroups B and C are predominant in most regions, including Europe and Latin America.[13]

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The variability in the expression of serogroup B immunodominant surface proteins, coupled with the poor immunogenicity of the capsular polysaccharides, has prevented the successful introduction of a broadly protective serogroup B meningococcal vaccine.[14] This will take some years and until this is possible, the best option for protection is offered by quadrivalent (meningococcal serogroups A, C, W-135, and Y) vaccination. Of the two types of licensed quadrivalent meningococcal vaccine, only the plain polysaccharide vaccine is licensed outside North America, and it remains the only vaccine anywhere in the world that is licensed for adults aged >55 years. Such unconjugated meningococcal polysaccharide vaccines have been shown to be well tolerated and immunogenic in children >2 years of age and adults,[13] but are poorly immunogenic in children aged <2 years.[15] Polysaccharide vaccines do not promote T cell-dependent responses, and therefore do not induce immunologic memory.[16,17] They also provide a limited duration of protection[18] and do not confer sustainable reduction of nasopharyngeal carriage of *N. meningitidis*.[19,20]

In comparison, conjugated meningococcal vaccines have been shown to contribute to the control of meningococcal infection by indirect protection or herd immunity, by reducing the attack rate in the unvaccinated population,[21] and can generate T cell-dependent responses, therefore inducing immunologic memory.[22]

An investigational quadrivalent meningococcal conjugate vaccine (MenACWY-CRM, Novartis Vaccines, Bellaria-Rosia, Italy), which includes *Corynebacterium diphtheriae* cross-reactive material (CRM_{197}), a naturally occurring non-toxic mutant of diphtheria toxin, has been shown to be well tolerated and immunogenic in infants,[23,24] children,[25] and adolescents.[26] In two studies carried out in adolescents in the USA, MenACWY-CRM elicited a non-inferior immune response compared with an unconjugated meningococcal polysaccharide vaccine, Menomune (MPSV4; Sanofi Pasteur Inc., Swiftwater, PA, USA),[26] and generated higher antibody titers to all four serogroups than with a polysaccharide–protein conjugate vaccine, Menactra (MenACWY-D; Sanofi Pasteur Inc., Swiftwater, PA, USA), conjugated to denatured diphtheria toxoid carrier proteins.[27]

In the present study in Latin America, the safety and immunogenicity of MenACWY-CRM were compared with the licensed vaccines to establish non-inferiority: MenACWY-D in subjects aged 19–55 years and MPSV4 in subjects aged 56–65 years (as MenACWY-D is not licensed for use in subjects >55 years of age).

2. Methods

A phase III, observer-blind, multicenter, randomized, controlled study was conducted in Argentina and Colombia to evaluate the safety and immunogenicity of MenACWY-CRM in healthy subjects aged 19–65 years. Ethics committee approval of the protocol was obtained before enrollment, and written informed consent was obtained from each subject. The study was performed in accordance with the current Good Clinical Practice and International Conference on Harmonisation guidelines.

2.1. Subjects

Subjects were approached via posters displayed in medical clinics. Healthy subjects aged 19–65 years were eligible for inclusion in the study. Subjects were excluded from the study if they had previously received meningococcal vaccine; had been vaccinated with any licensed vaccines ≤1 month before enrollment; had a previous or suspected disease caused by *N. meningitidis*; had received any investigational agents or vaccines ≤90 days before enrollment; had any serious acute, chronic, or progressive disease; or had a known or suspected impairment/alteration of immune function.

2.2. Vaccines and vaccinations

A total of 2831 subjects were enrolled and randomized in the study. Of these, 2505 subjects aged 19–55 years were randomly assigned to receive either MenACWY-CRM or MenACWY-D. Immunogenicity testing was performed for the first 200 subjects in both the 19–34 years and the 35–55 years age groups; these subjects were randomized in a 1:1 ratio. The subsequent subjects were randomized in a 2:1 ratio to receive MenACWY-CRM or MenACWY-D. The 326 subjects aged 56–65 years were randomized in a 2:1 ratio to receive either MenACWY-CRM or MPSV4, and the first 225 subjects were tested for immunogenicity.

All subjects received a single dose (0.5 ml) of one of the three vaccines, administered intramuscularly in the left upper deltoid area (MenACWY-CRM or MenACWY-D), or subcutaneously in the left upper arm (MPSV4). Each dose of MenACWY-CRM consisted of two components: 10 μg of lyophilized meningococcal serogroup A capsular polysaccharide, conjugated to CRM_{197} (MenA), and 5 μg of capsular polysaccharide of serogroups C, W-135, and Y, conjugated to CRM_{197} in 0.5 ml of phosphate-buffered saline, which was used to reconstitute the lyophilized MenA component, pre-vaccination. Blinding was maintained by using designated nurses or physicians to administer the study vaccines to the subjects, while the investigators and other investigative site personnel remained blinded.

2.3. Safety monitoring

Each subject was observed for 30 min post-vaccination for any local or systemic reactions, or anaphylaxis. Oral or axillary temperature was recorded, and subjects were given diary cards to record solicited local (pain, erythema, and induration) or systemic (chills, nausea, malaise, myalgia, arthralgia, headache, and rash) reactions that occurred between day 1 and day 7. Any adverse events (AEs) requiring medical attention were recorded for 1 month post-vaccination, and any medically significant and serious AEs (SAEs) were recorded for 6 months post-vaccination.

2.4. Serology

Blood samples (20 ml) were obtained pre-vaccination and at 1-month post-vaccination. The immunogenicity of the study vaccines was evaluated by serum bactericidal activity using human complement (hSBA) for meningococcal serogroups A, C, W-135, and Y according to methods described previously.[24]

For comparisons of the immunogenicity of the vaccines, three immunologic endpoints were defined. For each serogroup, these endpoints included the post-vaccination hSBA geometric mean titer (GMT), the proportion of subjects with a post-vaccination hSBA titer ≥1:8, and the proportion of seroresponders. Seroresponse was a composite endpoint that incorporated two categories of pre-vaccination immune status: for initially seronegative subjects, i.e., with a baseline hSBA titer <1:4, seroresponse was defined as a post-vaccination hSBA titer of ≥1:8; for those initially seropositive, with a baseline hSBA titer ≥1:4, seroresponse was defined as at least a 4-fold increase in the pre-vaccination titer.

2.5. Statistical methods and analyses

The immunogenicity of MenACWY-CRM was considered non-inferior to the immunogenicity of MenACWY-D for any of the four serogroups, if the lower limit (LL) of the two-sided 95% confidence interval (CI) around the difference (MenACWY-CRM minus