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Immunogenicity and safety of a quadrivalent meningococcal conjugate vaccine administered concomitantly with measles, mumps, rubella, varicella vaccine in healthy toddlers

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ABSTRACT

Background: Invasive meningococcal disease can have devastating outcomes, especially in high-risk groups such as infants. As infants are recommended to receive multiple vaccines during a single office visit, this phase 3 study assessed the safety and immune response to MenACWY-CRM at alternative visits in older infants and concomitant use with measles, mumps, rubella, varicella vaccine (MMRV) at 12 months of age.

Methods: Two age groups were concurrently enrolled: 7- to 9-month-old infants who received 2 doses of MenACWY-CRM at 7–9 and 12 months and were randomized 1:1 to receive MenACWY-CRM with or without MMRV at 12 months, and 12-month-old infants who received MMRV only at12 months. Using predefined non-inferiority criteria, immune responses to the antigens in MMRV were compared between those who did and did not receive MenACWY-CRM; immune responses to MenACWY-CRM as measured by the percentage of subjects with human serum bactericidal activity (hSBA) titers ≥ 8, were compared between those who did and did not receive concomitant MMRV. Adequacy of the immune response to 2 doses of MenACWY-CRM administered at 7–9 and 12 months was also assessed. Local and systemic reactions, adverse events resulting in withdrawal or requiring medical attention and serious adverse events were monitored.

Results: Concomitant administration of MMRV with MenACWY-CRM did not affect the immune response to either vaccine. The 2-dose series of MenACWY-CRM induced adequate immune response to all 4 serogroups. No increased reactogenicity was observed with MenACWY-CRM + MMRV compared with MMRV alone, and there were no study-related serious adverse events.

Conclusions: Concomitant administration of MenACWY-CRM with MMRV vaccinations at 12 months was well-tolerated, without safety concerns. Robust immune responses to all components of both vaccines were produced and all criteria for non-inferiority were met, supporting the use of a 2-dose regimen of MenACWY-CRM in this age group.

1. Introduction

Infants are particularly vulnerable to meningococcal disease [1,2], and rates of disease are highest in the first year of life [2]. Two quadrivalent meningococcal conjugate vaccines, Menveo® (MenACWY-CRM; Novartis Vaccines) and Menactra® (MenACWY-D; Sanofi Pasteur) have been licensed in the US and Canada for ages 2–55 years. MenACWY-D was also licensed beginning from 9 months of age in the US in 2011, although the immunogenicity of MenACWY-D administered earlier in infancy was not optimal [3]. More recently, a phase 3 study of MenACWY-CRM administered as a 4 dose series to infants at 2, 4, 6 and 12 months of age demonstrated sufficient immunogenicity to all 4 serogroups without substantial concern for clinically relevant immunological interference with routine infant vaccines [4]. Although providing protection against as many meningococcal serogroups as possible early in infancy is important to prevent the greatest number of cases, vaccination with MenACWY-CRM later in infancy may also be

Abbreviations: MMRV, measles, mumps, rubella, varicella, vaccine; MMR, measles, mumps and rubella virus vaccine; hSBA, serum bactericidal activity assay with human complement; ELISA, enzyme-linked immunosorbent assay; LL, lower limit; CI, confidence interval; GMT, geometric mean titer; AE, adverse event; SAE, serious adverse event.

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of interest given differential global epidemiologic or programmatic considerations.

The main objectives of this phase 3 study were to assess the safety and immune responses to measles, mumps, rubella, and varicella vaccine [MMRV, (ProQuad®, Merck & Co., Inc.] and MenACWY-CRM concomitantly administered at 12 months of age and to evaluate the adequacy of the immune response to a two-dose vaccination regimen of MenACWY-CRM administered at 7–9 and 12 months of age.

2. Methods

2.1. Study design

Novartis study V59P21 enrolled 3 groups into a phase 3, open-label, randomized, multicenter study of healthy children 7–9 and 12 months of age, conducted at 90 centers in the United States (ClinicaTrials.gov identifier, NCT00626327). The first 2 groups were comprised of 7- to 9-month-old infants who were randomized in a 1:1 ratio to receive MenACWY-CRM at 7–9 months and MenACWY-CRM alone (Group 2) or with MMRV at 12 months of age (Group 1). A third open-label group (Group 3) was contemporaneously enrolled at 12 months and received only MMRV at that visit (Fig. 1). Laboratory staff who performed the immunogenicity analyses were blinded as to vaccines received. We obtained blood samples from subjects in all 3 groups 6 weeks after the 12-month vaccination. For subjects in Groups 1 and 3, we also obtained blood prior to the 12 month vaccination, while for subjects in Group 2, we obtained blood 1 month after the first dose of MenACWY-CRM administered at 7–9 months (Fig. 1). The rationale for the timing of the blood sampling was (1) to evaluate the immune response to MMRV with and without MenACWY-CRM by comparing antigen specific seroconversion/seroprotection rates between Groups 1 and 3; (2) to compare the immune responses to the second dose of MenACWY-CRM with and without MMRV between Groups 1 and 2; (3) to assess the immune response 1 month after a single dose of MenACWY-CRM at 7–9 months of age in Group 2. Because Groups 1 and 2 did not differ in treatment received at 7–9 months of age, both having received a first dose of MenACWY-CRM, we considered the post-first dose blood draw in Group 2 sufficient as the only blood draw at that time point, making it possible to limit blood draws to two per group.

2.2. Study subjects

We enrolled healthy subjects whose parents or legal guardians provided written informed consent. We excluded infants who had previous or suspected disease caused by *Neisseria meningitidis* or previous or suspected infection with measles, mumps, rubella, varicella, or herpes zoster. We also excluded infants if they had been exposed to any vaccine antigens under study within 60 days before enrollment, if they received any investigational agents or vaccines within 90 days, or if they received any licensed vaccines within 30 days before enrollment. We permitted receipt of inactivated influenza vaccine up to 15 days before and any time beyond 15 days after study vaccination. All subjects were eligible to receive recommended age-appropriate vaccines at 13.5 months of age.

2.3. Vaccines

MenACWY-CRM (Menveo®, Novartis Vaccines and Diagnostics) was obtained by extemporaneous mixing of the lyophilized MenA component with the liquid MenCWY component. One 0.5-mL dose of MenACWY-CRM was administered by intramuscular injection in the anterolateral area of the right thigh. Each 0.5-mL dose contains 10 μg MenA polysaccharide and 5 μg each of MenC, MenW-135, and MenY conjugated to CRM (total, 47 μg). Excipients included sodium chloride (4.5 mg), sucrose (12.5 mg), sodium phosphate buffer (10 mM), and potassium dihydrogen phosphate (5 mM).

ProQuad or its equivalent (MMR [M-M-R® II; measles, mumps and rubella virus vaccine live] plus varicella [Varivax®; Merck & Co., Inc.]) was administered subcutaneously in the anterolateral area of the left thigh. Owing to a shortage of ProQuad in 2009, a subset of subjects received separate M–M–R plus varicella rather than ProQuad. M–M–R was administered subcutaneously in the left thigh and the varicella vaccine was administered subcutaneously in the left thigh (at least 2 inches separated from the M–M–R injection site) or in either arm. The combination vaccine was found to be the immunogenic equivalent to the component vaccines [5]. The term MMRV in this report refers to either ProQuad or M–M–R plus varicella.

2.4. Immunogenicity

We defined immunogenicity endpoints as the percentage of subjects with serum bactericidal activity using human complement (hSBA) titers ≥ 8 against each *N. meningitidis* serogroup measured 6 weeks after the 12-month vaccination, as described previously [6]. Seroresponses to measles, mumps, and rubella were evaluated by enzyme-linked immunosorbent assay (ELISA) and varicella by glycoprotein-based ELISA 6 weeks post-vaccination (PPD Vaccines and Biologics Lab, Wayne, PA) [7]. Definitions for seroresponse and seroconversion criteria used are given in the legend to Fig. 2.

2.5. Statistical analysis

The prespecified success criterion for the trial was a composite analysis that required all of the primary immunogenicity comparisons associated with the three co-primary objectives to be met; therefore, because there was a single composite analysis, no statistical adjustment for multiplicity was required. The first co-primary objective was comparison of the seroresponses of measles, mumps, rubella, and varicella 6 weeks after 1 dose of MMRV administered with and without MenACWY-CRM at 12 months of age. All available samples were tested for the MMRV antigens. We considered an MMRV seroresponse as non-inferior if the lower limit (LL) of the 2-sided 95% confidence interval (CI) of the difference in the percentages of subjects with seroconversion for measles, mumps, and rubella, and seroprotection for varicella ($P_{\text{MMRV + MenACWY-CRM}} - P_{\text{MMRV}}$) was greater than −5% for measles, mumps, and rubella and −10% for varicella. Seroconversion was defined as a change from a prevaccination to postvaccination specific antibody levels against the vaccine antigens (Measles, <255 mIU/mL to ≥255 mIU/mL; Mumps, <10 ELISA Ab units to ≥10 ELISA Ab units; Rubella, <10 IU/mL to ≥10 IU/mL; Varicella seroconversion, <1.25 gp ELISA units/mL to ≥ 1.25 gp ELISA units/mL; Varicella seroprotection, <1.25 gp ELISA units/mL to ≥5 gp ELISA units/mL). As a secondary endpoint, immune responses of MMRV, administered with or without MenACWY-CRM, were also assessed in terms of geometric mean titers (GMTs). Additional exploratory analyses were performed to test whether bias was introduced by the switch from ProQuad to M–M–R II plus Varivax (as separate injections) in order to determine whether these subjects could be treated as a single group in the analysis.

The second co-primary objective was a comparison of the immune responses to MenACWY-CRM administered with and without MMRV as assessed by the percentage of subjects with hSBA titers ≥ 8 directed against each serogroup. To obtain sufficient power, and based on previous studies finding lower immune responses to serogroup A in the hSBA [8], all available samples were tested for serogroup A, but a randomly selected group of 208 subjects in the MenACWY-CRM + MMRV and MenACWY-CRM