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Safety and immunogenicity of a single dose of a quadrivalent meningococcal conjugate vaccine (MenACYW–D): a multicenter, blind-observer, randomized, phase III clinical trial in the Republic of Korea

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SUMMARY

Objectives: To assess the safety and immunogenicity of a meningococcal polysaccharide diphtheria toxoid conjugate vaccine (MenACYW–D) in a Korean population.
Methods: This was a phase III, blind-observer, controlled study in which participants aged 11–55 years were randomized (2:1 ratio) to a single dose of MenACYW–D or tetanus/diphtheria/acellular pertussis (Tdap) vaccine. Outcomes included rates of seroconversion against all serogroups (≥4-fold increase in antibody titer from pre-vaccination), geometric mean titers (GMTs) at days 0 and 28 based on a serum bactericidal assay using baby rabbit complement, rates of seroprotection (titer ≥1:128) at day 28, and safety.
Results: A total of 300 participants were enrolled in the study (200 MenACYW–D and 100 Tdap). Seroconversion rates for serogroups A, C, Y, and W-135 were 77.8%, 88.3%, 74.6%, and 92.4%, respectively, for the MenACYW–D group and 9.3%, 8.1%, 12.2%, and 8.2%, respectively, for the Tdap group. The proportions of participants with pre-vaccination titers ≥1:128 were 57.3%, 12.6%, 51.5%, and 22.2% for serogroups A, C, Y, and W-135, respectively; post-vaccination rates were 98.5%, 89.4%, 96.0%, and 95.0% for the MenACYW–D group. A lower proportion of participants reported solicited reactions with MenACYW–D (46.2%) compared with Tdap (76.8%).
Conclusion: A single dose of MenACYW–D was well tolerated and elicited a robust immune response in Korean adolescents and adults.

1. Introduction

Meningococcal disease is caused by the Gram-negative aerobic diplococcus *Neisseria meningitidis*. Meningococci are classified by serogroup based on the immunochemistry of the polysaccharide capsule.[1] Invasive meningococcal disease (IMD), such as meningitis and meningococcemia, is most frequently caused by serogroups

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A, B, C, Y, and W-135, and more recently in Africa by serogroup X.[2] IMD is rapidly progressive and associated with high mortality rates of 7% to 19%.[3] Approximately 10% to 20% of patients suffer from permanent disabilities such as limb loss, deafness, seizures, or psychomotor retardation.[2] Meningococci colonize the nasopharynx of approximately 4.5% to 25% of the normal population.[4] The reported incidence of meningococcal disease varies widely, but recent outbreaks provide evidence for the continued potential of the meningococcus to cause global morbidity and mortality.[4]

Meningococcal meningitis is a notifiable disease in the Republic of Korea (ROK). The annual number of reported cases varied between 1 and 38 in the years 2001–2014, or approximately 0.01 to 0.08 cases per 100 000 population per year.[5] However, the number of reported cases increased dramatically in 2002 (n = 27) and 2003 (n = 38). In particular, an outbreak caused by serogroup W-135 in military recruits in 2011 raised the issue as to whether military personnel should be vaccinated with a quadrivalent meningococcal conjugate vaccine (serogroups ACYW).[6] No meningococcal vaccine was licensed at that time in the ROK. In November 2012, the Korean Ministry of Defense introduced a new vaccine policy, including mandatory meningococcal vaccination (serogroups ACYW) for all new recruits.

Polysaccharide meningococcal vaccines have been used widely in high-risk individuals and for the control of outbreaks. These vaccines elicit a largely T-cell-independent response and are poorly immunogenic in children, and therefore do not confer long-lasting immunity. Repeated administration of these vaccines may result in hyporesponsiveness.[7,8] They are unlikely to reduce nasopharyngeal carriage in the long term, and therefore are unlikely to induce herd immunity. On the other hand, meningococcal conjugate vaccines induce a largely T-cell-dependent response, can provide broad, long-lasting primary protection, and induce immunologic memory, as well as possible herd protection by reducing carriage. The development and introduction of meningococcal conjugate vaccines hold great potential for the control of meningococcal disease.[4]

The meningococcal (groups A, C, Y, and W-135) polysaccharide diphtheria toxoid conjugate vaccine (MenACYW–D, Menactra; Sanofi Pasteur, Swiftwater, Pennsylvania, USA) has been shown to be safe, immunogenic, and to induce immune memory and provide durable protection in multiple clinical trials as required by the World Health Organization.[8–12] The purpose of this study was to assess the safety and immunogenicity of a single dose of MenACYW–D in a healthy Korean population aged 11 to 55 years. The primary objective of the study was to demonstrate that the seroconversion rates were >60% for serogroups A, C, Y, and W-135 after a single dose of MenACYW–D.

2. Materials and methods

2.1. Study design

A phase III, blind-observer, randomized, controlled, single-dose, multicenter study was conducted in the ROK. Healthy participants 11 to 55 years of age were randomized in a 2:1 ratio to MenACYW–D and Tdap. All participants received a single dose of vaccine on day 0 and provided blood samples for immunogenicity assessment on day 0 (pre-vaccination) and on day 28 (post-vaccination). Vaccines were administered intramuscularly in the deltoid. Safety data, including serious adverse events (SAEs), were collected from day 0 through day 28 (+7 days).

Participants were enrolled by age group (children/adolescents and adults) and assigned a number for randomization. Scratch-off randomization lists were generated by an independent statistician who was not involved in conducting the study; this was done through randomization by block using programming under SAS version 9.2 and Proc Plan. Investigators, participants, and the study sponsor were blinded to the treatment arm. Enrollment ensured that ≥30% of participants were children and adolescents (11 to 17 years of age) and ≥40% were adults (18 to 55 years of age).

The primary endpoint was the seroconversion status (defined as a ≥4-fold increase in antibody titer compared to the pre-vaccination level) against meningococcal serogroups A, C, Y, and W-135 at 28 days after vaccination. Secondary endpoints included the rates of seroconversion and seroprotection (titer ≥1:128) at 28 days after vaccination. Seroconversion was defined as a ≥4-fold increase in antibody titers from the pre-vaccination level against meningococcal serogroups A, C, Y, and W-135 at 28 days after vaccine administration.

Safety outcomes included (1) the occurrence and relationship to vaccination of any SAEs occurring at any time during the study, (2) the occurrence of systemic unsolicited adverse events (AEs) reported within 30 min after vaccination, (3) the occurrence, time to onset, number of days of occurrence, and intensity of pre-defined (solicited) injection site reactions and systemic reactions occurring from day 0 through day 7 after vaccination, and (4) the occurrence, nature, maximum intensity (for non-SAEs only), and relationship to vaccination (for systemic AEs only) of unsolicited (spontaneously reported) AEs within 28 days after vaccination.

Solicited injection site reactions were categorized as grade 1 (no interference with activity), grade 2 (some interference with activity), or grade 3 (significant; prevents daily activity). Erythema and swelling were categorized as grade 1 (≥25 to ≤50 mm), grade 2 (≥51 to ≤100 mm), or grade 3 (>100 mm). Solicited systemic reactions were graded for fever, headache, malaise, and myalgia. Fever was categorized as grade 1 (≥38.0 °C to ≤38.4 °C), grade 2 (≥38.5 °C to ≤38.9 °C), or grade 3 (≥39.0 °C). Headache, malaise, and myalgia were categorized as grade 1 (no interference with activity), grade 2 (some interference with activity), or grade 3 (significant; prevents daily activity).

The protocol was approved by the Korea Food and Drug Administration (KFDA) and by the institutional review board at each site. The study complied with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice, and with local and national regulations and directives. At least one parent/legal representative for participants aged 11 to 19 years and all participants aged 20 to 55 years provided written informed consent. This trial was registered under ClinicalTrials.gov identifier NCT01642589.

2.2. Participants

Eligible participants were 11 to 55 years of age and had health insurance coverage. Exclusion criteria included the following: previous vaccination against meningococcal disease; vaccination against diphtheria or tetanus in the past 5 years or any previous vaccination with any other tetanus/diphtheria/acellular pertussis (Tdap) vaccine; receipt or planned receipt of any vaccine in the previous 4 weeks or following trial vaccination (except for influenza vaccines); receipt of immune globulins, blood, or blood-derived products in the past 3 months; receipt of oral or injectable antibiotic therapy within the 72 h prior to the first blood sample collection; congenital or acquired immunodeficiency, immunosuppressive therapy within the previous 6 months, or long-term corticosteroid use for more than two consecutive weeks in the previous 3 months; thrombocytopenia, bleeding disorder, or receipt of anticoagulants in the previous 3 weeks; known hypersensitivity to any vaccine components; high risk for IMD or history of confirmed IMD; history of Guillain–Barré syndrome; chronic illness that could interfere with participation in the trial; pregnancy or lactation; or participation in another clinical trial within 4 weeks of initiating this trial.