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One or two doses of live varicella virus-containing vaccines: Efficacy, persistence of immune responses, and safety six years after administration in healthy children during their second year of life ☆

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ABSTRACT

Background: This phase III B follow-up of an initial multicenter study (NCT00226499) will evaluate the ten-year efficacy of two doses of the combined measles-mumps-rubella-varicella vaccine (MMRV) and one dose of the live attenuated varicella vaccine (V) versus a measles-mumps-rubella control group (MMR) for the prevention of clinical varicella disease. Here we present efficacy results for six years post-vaccination.

Methods: In phase A of the study, healthy children aged 12–22 months from ten European countries were randomized (3:3:1) and received either two doses of MMRV, or one dose of combined MMR and one dose of monovalent varicella vaccine (MMR+V), or two doses of the MMR vaccine (control), 42 days apart. Vaccine efficacy against all and against moderate or severe varicella (confirmed by detection of viral DNA or epidemiological link) was assessed from six weeks up to six years post-dose 2 for the MMRV and MMR+V groups, and was calculated with 95% confidence intervals (CI). The severity of varicella was calculated using the modified Vázquez scale (mild $\leq$ 7; moderately severe = 8–15; severe $\geq$ 16). Herpes zoster cases were also recorded.

Results: 5289 children (MMRV = 2279, mean age = 14.2, standard deviation [SD] = 2.5; MMR+V = 2266, mean age = 14.2, SD = 2.4; MMR = 744, mean age = 14.2, SD = 2.5 months) were included in the efficacy cohort. 815 varicella cases were confirmed. Efficacy of two doses of MMRV against all and against moderate or severe varicella was 95.0% (95% CI: 93.6–96.2) and 99.0% (95% CI: 97.7–99.6), respectively. Efficacy of one dose of varicella vaccine against all and against moderate or severe varicella was 67.0% (95% CI: 61.8–71.4) and 90.3% (95% CI: 86.9–92.8), respectively. There were four confirmed herpes zoster cases (MMR+V = 2, MMR = 2), all were mild and three tested positive for the wild-type virus.

Abbreviations: VZV, varicella-zoster virus; MMR, measles-mumps-rubella; MMRV, measles-mumps-rubella-varicella; CI, confidence interval; SAE, serious adverse event; HZ, herpes zoster; VE, vaccine efficacy; ATP, according-to-protocol; CDC, Centers for Disease Control and Prevention; PCR, polymerase chain reaction; IDMC, Independent Data Monitoring Committee; ELISA, enzyme-linked immunosorbent assay; GMC, geometric mean concentration; TVC, total vaccinated cohort; HR, hazard ratio; LL, lower limit; UL, upper limit.

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Conclusions: Two doses of the MMRV vaccine and one dose of the varicella vaccine remain efficacious through six years post-vaccination.

1. Introduction

Varicella (chickenpox), caused by the varicella-zoster virus (VZV), is a highly contagious vaccine-preventable disease, responsible for 4.2 million hospitalizations and 4200 deaths annually, worldwide [1]. In countries where universal vaccination was introduced, the incidence of varicella cases, including hospitalizations and deaths, has substantially declined [2–5].

An important aspect in the design of universal immunization programs against varicella is the number of doses. While one-dose schedules were shown to be effective against the disease, breakthrough cases were still reported [2–6]. Out of the 33 countries that recommended varicella containing vaccines, 14 recommended a two-dose schedule. Another important aspect is the choice of vaccine, i.e. monovalent or combined varicella vaccine. Improved uptake rates might be achieved by the co-administration of varicella-containing vaccines with routine childhood vaccines or with the use of combined varicella-containing vaccines [7].

GSK's trivalent measles-mumps-rubella vaccine (MMR; *Priorix*) and the monovalent live attenuated varicella vaccine (V; *Varilrix*) are licensed in many countries worldwide. Both vaccines are indicated for active immunization of children at least 9 months of age, and can be given concomitantly, but at separate injection sites [8,9].

GSK has developed a combined tetravalent measles-mumps-rubella-varicella vaccine (MMRV; *Priorix-Tetra*) that offers convenience for parents and medical practitioners by combining the benefits of measles-mumps-rubella and varicella vaccination in a single injection, and would therefore improve the vaccine coverage both against chickenpox and against measles, mumps and rubella. Moreover, meningococcal vaccines could be co-administered with MMRV at the same clinical visit [10]. The immunogenicity and safety of the combined MMRV have been demonstrated in clinical trials; MMRV was licensed based on comparative immunogenicity trials versus monovalent varicella vaccines [11–13].

Phase A of this phase III, observer-blinded, randomized, controlled, multicenter study (NCT00226499) assessed protection against varicella in naive children who received two doses of MMRV or one dose of monovalent varicella vaccine at 12–22 months of age. After a mean follow-up of approximately three years, efficacy of two doses of MMRV against all varicella was 94.9% (97.5% confidence interval [CI]: 92.4–96.6), and against moderate to severe varicella was 99.5% (97.5% CI: 97.5–99.9). Efficacy of one-dose varicella vaccine was 65.4% (97.5% CI: 57.2–72.1) against all varicella and 90.7% (97.5% CI: 85.9–93.9) against moderate to severe varicella [14].

We report the efficacy, antibody persistence and safety data up to six years after the second vaccine dose. Long term follow-up is ongoing and will extend up to ten years post-vaccination.

2. Methods

2.1. Study design and participants

The study design was previously described [14]. Briefly, this study is a follow-up of the phase A, observer-blind, controlled, study conducted in Czech Republic, Greece, Italy, Lithuania, Norway, Poland, Romania, Russian Federation, Slovakia and Sweden between 2009 and 2015, in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines [15,16]. The study protocol was reviewed and approved by independent ethics committees. Protocol deviations were presented elsewhere [14].

In phase A of the study, healthy children aged 12–22 months from the ten countries mentioned above were randomized (3:3:1) to one of the three treatment groups, and received either two doses of MMRV (*Priorix-Tetra*, GSK) at Day 0 and Day 42 (MMRV group), or one dose of MMR (*Priorix*, GSK) at Day 0 and one dose of monovalent varicella vaccine (*Varilrix*, GSK) at Day 42 (MMR+V group), or two doses of the MMR (*Priorix*, GSK) vaccine (control) at Day 0 and Day 42 (MMR group).

Study population (with inclusion and exclusion criteria), randomization and blinding, as well as vaccine composition and administration route, were previously described [14].

For phase B, the study remained observer-blind for all groups with the exception of the MMR+V group in countries where the national vaccination schedules included a second dose of MMR vaccination at 4–8 years of age (Italy, Lithuania, Romania, Russian Federation, Sweden). Independent Data Monitoring Committee (IDMC) members also remained blinded to the study treatment group when assessing varicella cases.

The objectives of this phase B study were secondary and descriptive, i.e. to assess: the long-term efficacy of one dose of monovalent varicella vaccine or two doses of MMRV in preventing probable and confirmed varicella cases after vaccination, the efficacy of the study vaccines according to the severity of varicella cases and the occurrence of complicated varicella cases reported as serious adverse events (SAEs) (efficacy objectives). The varicella immune response in terms of varicella seropositivity rates and geometric mean antibody concentrations (GMCs) in all children four and six years post-vaccination (immunogenicity objectives) were also assessed. The safety of the study vaccines was evaluated in terms of occurrence of SAEs and by description of occurred herpes zoster (HZ) cases, in all children following vaccination (safety objectives).

The current analysis was designed to monitor the severity of varicella in vaccinated and unvaccinated children, and to determine whether or not susceptible individuals remained in the control group and to assess the benefit of two doses or one dose of varicella vaccination versus control.

2.2. Efficacy assessment

The main analysis of vaccine efficacy (VE) was based on the according-to-protocol (ATP) cohort for efficacy in phase A + B and children were followed up for a median duration of 6.4 years. VE was also evaluated for phase B alone. All children's parents/guardians were provided with diary cards to record maximum information related to varicella/zoster case(s) to aid grading of severity.

Case ascertainment and confirmation have been described previously [14]. Briefly, the study followed a varicella case definition used by the Centers for Disease Control and Prevention (CDC) with slight modifications. A varicella case was confirmed when it met the clinical case definition and the polymerase chain reaction