Immunogenicity and reactogenicity of co-administered tetanus–diphtheria–acellular pertussis (Tdap) and tetravalent meningococcal conjugate (MCV4) vaccines compared to their separate administration

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ABSTRACT

In the United States, co-administration of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine and tetravalent meningococcal conjugate vaccine (MCV4) is recommended in adolescents. In this clinical study, 1341 adolescents received Tdap (Boostrix® GlaxoSmithKline) and MCV4 (Menactra®, Sanofi-Pasteur) simultaneously or sequentially one month apart. Co-administration of Tdap + MCV4 was well tolerated and immunogenic, resulting in high levels of antibodies against diphtheria, tetanus, pertussis and meningococcal serogroup A,C,W-135 and Y antigens. The data provide support for current recommendations for co-administration of Tdap and MCV4 vaccines at the same office visit. © 2010 Published by Elsevier Ltd.

1. Introduction

Booster vaccination of adolescents against pertussis was introduced into the United States’ routine immunization program in 2005 [1]. A single dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine is recommended for all adolescents 11–12 years of age, and for catch-up vaccination of 13–18 year olds if they have not received a Td vaccine within the last 5 years. In the same year, the Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination of adolescents 11–12 years of age against meningococcal disease [2]. This recommendation was extended in 2007 to include catchup vaccination of 13–18 years olds [3]. In adolescents, immunization against meningococcal disease is provided through administration of a single dose of meningococcal vaccine, either tetravalent meningococcal serogroups A, C, Y and W-135 diphtheria toxoid conjugate vaccine (MCV4; Menactra®, Sanofi-Pasteur) or the recently approved meningococcal (groups A, C, Y, and W-135) oligosaccharide diphtheria CRM197 conjugate vaccine (MenACWY-CRM; Menveo®, Novartis). Based on studies examining simultaneous and sequential administration of Td and MCV4 vaccines, the American Academy of Pediatrics recommends that both the Tdap and MCV4 vaccines should be administered at the same office visit. If co-administration is not feasible, the vaccines are recommended to be given sequentially, with at least one month separating each vaccination [4].

The Tdap vaccine Boostrix® (GlaxoSmithKline Biologicals [GSK], Rixensart, Belgium) is licensed in the US as a single-dose booster vaccination for adolescents and adults between 10 and 64 years of age. Boostrix® contains the same antigens as GSK’s pediatric DTaP vaccine (Infanrix®), but in reduced quantities. Efficacy of Infanrix® in preventing pertussis (as defined by the World Health Organization) was demonstrated in a household contact study in Germany [5], and in a National Institutes of Health-sponsored efficacy study conducted in Italy [6].

Both Tdap vaccine and the MCV4 vaccine used in this study contain diphtheria toxoid, and concerns about the potential for increased reactogenicity following their sequential administration have been raised [1]. The present study was undertaken to evaluate immunogenicity and safety of co-administered Tdap and MCV4, relative to their sequential administration, in adolescents.

2. Methods

2.1. Study design and subjects

This Phase IV study (GSK study identifier 105753; NCT00282295, www.clinicaltrials.gov) was conducted in 24

Subjects were healthy adolescents 11–18 years of age who had completed routine childhood vaccination against tetanus, diphtheria and pertussis. Subjects were excluded from participation if they had received their DTP booster (fifth dose) or a Td vaccine within the previous 5 years, or if they had previously been vaccinated against meningococcal disease. Subjects were also excluded if they had received any other investigational or non-registered drug or vaccine within 30 days of study entry; if they had a history of allergic reactions to any vaccine component; if after a previous dose of pertussis vaccine they had experienced clinically significant reactions including encephalopathy, hypotonic–hyporesponsive episodes or abnormal crying, seizures or temperature ≥40.5 °C (105 °F); if they had any progressive neurologic disorder, uncontrolled epilepsy or progressive encephalopathy; acute disease at the time of vaccination; or if they had received immunoglobulins and/or any blood products within the three months before, or their planned administration during, the study. Pregnant or lactating women, and women planning to conceive during the study were also ineligible.

In order to compare both possible sequential vaccination schemes for Tdap and MCV4 to co-administration, subjects were randomized (1:1:1) into one of three groups, all of whom received vaccination with Tdap and MCV4 vaccines. The vaccines were either administered simultaneously in separate limbs (group Tdap → MCV4); or one month apart: Tdap followed one month later by MCV4 (group Tdap → MCV4), or, MCV4 followed one month later by Tdap (group MCV4 → Tdap).

The study was open label with respect to simultaneous or sequential vaccination. Subjects receiving simultaneous vaccination with Tdap and MCV4 were not told which vaccine was injected into which arm. Vaccination in the sequential groups was observer blind. Neither the subjects in the sequential groups nor study site personnel involved in the clinical evaluation of study subjects knew which vaccine was given at any time. Vaccines were prepared and administered by study site staff, who were not otherwise involved in the clinical evaluation of subjects.

The study was conducted according to Good Clinical Practice and in accordance with the Declaration of Helsinki. The protocol and associated documents were reviewed and approved by ethics committees at each study center. Written informed consent was obtained from the parents/guardians of subjects less than 18 years of age before study entry. Subjects 18 years of age provided their own written informed consent. Written assent was also required from subjects younger than 18.

2.2. Study vaccines and administration

A single 0.5 mL dose of Tdap (Boostrix®; GlaxoSmithKline) contained: 2.5Lf diphtheria toxoid (D); 5Lf tetanus toxoid (T); 8 μg pertussis toxoid (PT); 8 μg filamentous hemagglutinin (FHA); 2.5 μg pertactin (PRN); with ≤0.39 mg aluminum hydroxide. One 0.5 mL dose of MCV4 (Menactra®; Sanofi Pasteur) contained 4 μg each of meningococcal serogroup polysaccharides A, C, W-135 and Y, conjugated to 48 μg diphtheria toxoid. Neither vaccine contained preservative. Injections were given intramuscularly into the deltoid using a 22–25 gauge needle, 1–1.5 in. long. In the group receiving simultaneous vaccinations, Tdap was given in the left arm and MCV4 in the right arm. In the sequential administration groups, all vaccinations were given in the left arm.

2.3. Assessment of immunogenicity

Blood samples were collected from all subjects prior to and approximately one month after each vaccination. Sera were stored at −20 °C until analysis at GSK’s laboratories, using assays with standardized and validated procedures, and with adequate controls.

Standardized enzyme-linked immunosorbent assays (ELISA) were used to determine serum concentrations of antibodies against diphtheria, tetanus, PT, FHA, and PRN. Antibody concentrations ≥0.1 IU/mL against diphtheria and tetanus toxoids were considered indicative of seroprotection [7,8]. Antibody concentrations ≥5 ELISA units (EL U/mL) against PT, FHA, and PRN, which represented the cut-off for these assays, were pre-specified to indicate seropositivity [9,10].

Antibody levels against meningococcal antigens A, C, W-135 and Y were determined by a serum bactericidal assay based on the CDC protocol [11] using baby rabbit complement. Titers were expressed as the reciprocal of the dilution resulting in 50% inhibition of bactericidal activity. A titer of 8 represented the cut-off of each assay [12,13].

2.4. Assessment of reactogenicity

Subjects were given a diary card at the first visit on which they were asked to record local symptoms (pain, redness and swelling at the injection site) and general symptoms (fatigue, fever [oral temperature ≥37.5 °C or 99.5 °F], gastrointestinal symptoms and headache) that occurred during a 4-day follow-up period (Days 0–3) after each vaccination.

Intensity of solicited symptoms was graded on a scale of 0 (absent) to 3. Grade 3 symptoms were defined for redness and swelling as diameter ≥50 mm; for fever, as temperature ≥39.0 °C (≥102.2 °F); and for pain and all other adverse events, as preventing normal daily activities.

Subjects who experienced a large injection site reaction, defined as swelling with diameter >100 mm at the injection site, diffuse swelling of the injected arm that interfered with or prevented normal activities, or diffuse swelling of the injected arm that involved the shoulder, elbow or chest, were instructed to contact the study site immediately for evaluation. Specific pages for recording of large swelling event data were included in the case report form for completion by the investigator.

All other (unsolicited) adverse events were recorded for 31 days after each vaccine dose. Serious adverse events occurring within 31 days of the final vaccination were recorded. Adverse event symptom intensity was graded by the investigator on a scale of 0–3, where ‘Grade 0’ was absent and ‘Grade 3’ referred to symptoms that prevented normal activity.

2.5. Statistical analysis

The primary study objective was to demonstrate non-inferiority, with respect to immune responses, of co-administered Tdap and MCV4 vaccines to those of separately administered vaccines. Immune responses were evaluated in terms of geometric mean antibody concentrations/titers (GMTs/GMTs) and percentages of subjects with booster responses to pertussis antigens and vaccine responses to meningococcal antigens. Booster responses for pertussis antigens were defined as post-vaccination antibody levels ≥20 EL U/mL in subjects who were seronegative (<5 EL U/mL) prior to vaccination, a 4-fold rise in antibody level for subjects with pre-vaccination antibody levels between 5 EL U/mL and 20 EL U/mL, and a 2-fold rise in antibody level for subjects with pre-vaccination antibody levels ≥20 EL U/mL. Vaccine responses for meningococcal antigens were defined as a post-vaccination antibody titer of at least 32 for subjects with pre-vaccination antibody titers below the assay cut-off of 8, and a 4-fold rise in antibody titer for subjects with pre-vaccination titers of at least 8.

Groups were compared by calculating the 2-sided standardized asymptotic 95% CI for group differences in the percentage of
Antibody GMC/GMTs were compared by calculating the 2-sided 95% CIs of the GMC/GMT ratio between treatment groups using an analysis of covariance (ANCOVA) model on the logarithm10 transformation of the concentrations with prevaccination concentration as a covariate.

For between group comparisons of booster responses, vaccine responses, or percentages of subjects achieving defined serum antibody levels, non-inferiority was defined as the lower limit of the 95% CI for the difference between the co-administered vaccines group and the sequentially administered vaccines group being ≥−10%. For between group comparisons of antibody GMCs, non-inferiority was defined as the lower limit of the 95% CI for the GMC ratio between the co-administered vaccines group and the sequentially administered vaccines group being ≥0.67.

The safety analysis was performed on the total vaccinated cohort that included all vaccinated subjects for whom post-vaccination safety data was available.

Calculations for estimating statistical power showed that with 1200 evaluable subjects (400 evaluable subjects per group), the global power of the study to meet all co-primary objectives would be 89.3%. Assuming that approximately 10% of subjects would be non-evaluable, the study was planned to enroll approximately 1320 subjects. Statistical analyses were performed using Proc StatXact 5.0.

3. Results

3.1. Study cohort

A total of 1341 adolescent subjects, 11–18 years of age (mean age 13.4 ± 2.22 years) were enrolled in the study and 1313 subjects completed the study. A total of 1277 subjects were included in the according-to-protocol immunogenicity analyses (Fig. 1). One subject withdrew due to a serious adverse event and one due to a non-serious adverse event. Approximately half of the study subjects (50.3%) were male, and 86.6% were white/Caucasian. The 3 vaccine groups appeared to be similar with respect to mean age, gender, ethnic and racial characteristics.

3.2. Immunogenicity

3.2.1. Response to Tdap antigens

One month after vaccination with Tdap, all subjects had seroprotective levels of anti-D and anti-T antibodies (≥0.1 IU/mL), and at least 97.6% achieved serum concentrations of 1.0 IU/mL or greater for one or both antibodies. Booster responses to one or more pertussis antigens were observed in 77.0–96.7% of subjects, and post-vaccination increases in antibodies to acellular pertussis antigens were observed in all vaccine groups (data not shown).

Non-inferiority of the Tdap + MCV4 co-administration group compared to the sequential Tdap → MCV4 group was demonstrated with respect to diphtheria, tetanus, PT and FHA according to predefined criteria (Table 1). Non-inferiority of immune response to PRN was met with respect to diphtheria, tetanus, PT and FHA according to predefined criteria (Table 1). Non-inferiority of the Tdap + MCV4 co-administration group compared to the sequential Tdap → MCV4 group was demonstrated with respect to diphtheria, tetanus, PT and FHA according to predefined criteria (Table 1).

3.2.2. Response to MCV4 antigens

One month after vaccination with MCV4, all subjects had seroprotective levels of anti-D and anti-T antibodies (≥0.1 IU/mL), and at least 97.6% achieved serum concentrations of 1.0 IU/mL or greater for one or both antibodies. Booster responses to one or more pertussis antigens were observed in 77.0–96.7% of subjects, and post-vaccination increases in antibodies to acellular pertussis antigens were observed in all vaccine groups (data not shown).

Non-inferiority of the Tdap + MCV4 co-administration group compared to the sequential Tdap → MCV4 group was demonstrated with respect to diphtheria, tetanus, PT and FHA according to predefined criteria (Table 1). Non-inferiority of immune response to PRN was met with respect to booster response rates, but was not met with respect to post-vaccination GMC, as the lower limit of the 95% CI for the between-group GMC ratio (0.63) marginally exceeded the pre-defined limit of 0.67 (Table 1).
immune response to the MCV4 vaccine when co-administered with Tdap, compared to sequential MCV4 → Tdap administration, was demonstrated according to pre-defined criteria (Table 1).

3.3. Reactogenicity

The reporting of solicited local symptoms within 4 days of vaccination in each vaccine group, both overall and for each injection site, is shown in Fig. 2. The percentages of subjects reporting solicited local symptoms at the Tdap injection site, of any or grade 3 intensity appeared to be similar between subjects receiving co-administered Tdap and MCV4 and subjects receiving Tdap alone on day 0 (Fig. 2). When Tdap was given one month after MCV4 vaccination, the percentages of subjects reporting solicited local symptoms at the Tdap injection site appeared to be less than when Tdap was co-administered with MCV4. The percentages of subjects reporting solicited local events at the MCV4 injection site appeared to be similar between subjects receiving co-administered Tdap and MCV4 and subjects receiving sequential vaccination with Tdap and MCV4.

Three subjects reported a large local swelling event during the study. Two of these events, occurring in the Tdap → MCV4 group, were associated with the Tdap vaccination site. The other event, occurring in the MCV4 → Tdap group, was associated with the MCV4 injection site. No swellings involving the adjacent joint or chest were observed. All resolved without sequelae.

The incidence of solicited general symptoms also appeared to be similar between the vaccine groups (Fig. 3). Solicited symptoms of grade 3 intensity were infrequently reported in all groups. In the sequential vaccination groups, there was a tendency for fatigue, headache, and gastrointestinal symptoms to be reported more frequently following the first vaccine in the series, while the reporting of fever appeared to be similar following either vaccination in the series (Fig. 3).

Unsolicited adverse event reporting was slightly higher in the Tdap → MCV4 and MCV4 → Tdap vaccine groups (33.4% and 34.5% of subjects in these groups, respectively, reporting at least 1 unsolicited AE) than in the Tdap + MCV4 group (27.8%). This may have been due to the longer observation period in the sequential vaccination groups (observation period defined as 31 days after each vaccination, for a total of 62 days in the sequential groups). Aside from this observation, there were no apparent differences between treatment groups in the incidence or nature of unsolicited adverse events reported during the study (data not shown).

Two serious adverse events were reported during the study. One subject in the MCV4 → Tdap group was diagnosed with leukemia 26 days after receiving Tdap, resulting in withdrawal of the subject from the study. The other SAE was an orbital fracture with epidural hematoma reported 34 days after vaccination in the Tdap + MCV4 group. Neither serious adverse event was considered by the investigator to be related to vaccination. One subject, in the Tdap → MCV4 group, was withdrawn from the study due to a non-serious adverse event. This subject’s parents withdrew their consent for participation after the subject experienced flu-like symptoms after the first study vaccination. The subject received only the Tdap vaccine and no additional information could be obtained.

4. Discussion

The Tdap vaccine, *Boostrix®*, has been licensed for use in the United States since 2005 and may be administered as a booster dose to adolescents and adults between 10 and 64 years of age. Clinical studies have shown that *Boostrix®* is immunogenic and well tolerated in adolescents and adults [14–16].

In the present study, the Tdap vaccine was immunogenic and well tolerated regardless of whether it was administered on the same day as MCV4, or given one month before, or one month after MCV4 vaccine. Non-inferiority of the Tdap + MCV4 co-administration group compared to the sequential Tdap → MCV4 group was demonstrated according to pre-specified criteria in terms of the immune response to diphtheria, tetanus, PT, FHA and was met for one out of two pre-specified analyses in terms of the immune response to PRN. Tdap + MCV4 was non-inferior to Tdap → MCV4 with respect to percentages of subjects achieving booster responses for PRN, but not with respect to post-vaccination anti-PRN GMC. Non-inferiority of the Tdap + MCV4 co-administration group compared to the sequential MCV4 → Tdap group was demonstrated according to pre-specified criteria in terms of the immune response to all 4 meningococcal antigens contained in MCV4 vaccine.
Currently, Tdap and MCV4 vaccines are recommended to be given concurrently rather than sequentially, partly because of concerns that sequential administration could lead to increased reactogenicity, due to the diphtheria toxoid content of both vaccines [1]. Data from this study indicate that this is not the case. Reactogenicity of sequentially administered Tdap and MCV4 did not appear to be increased over that of co-administered vaccines; rather, solicited adverse events were reported with similar or lower frequency following the second sequential vaccine dose than for the first sequential dose or for coadministered vaccines.

The results of this study are in general agreement with those of a separate study conducted with MCV4 and another US-licensed Tdap vaccine (Adacel®, Sanofi-Pasteur) [17]. A study assessing the co-administration of Tdap with MenACWY-CRM and HPV vaccine (Gardasil®, Merck) showed immune responses to be comparable between the coadministered and sequentially administered vaccines, with no increase in reactogenicity with concomitant administration [18].

Adolescent vaccination programs face specific challenges and are often characterized by poor compliance and low coverage.
Factors that contribute to poor compliance with vaccine recommendations in adolescents include low provider and public awareness of adolescent health issues and vaccine recommendations, along with the absence in many countries of population vaccination registries for adolescents [19,20]. Use of combination vaccines, as well as minimizing the number of vaccination visits required to complete a vaccination course, have been identified as means by which immunization compliance amongst adolescents could be improved [19]. Co-administration of Tdap and MCV4 vaccines would reduce the required number of vaccination visits by one in US adolescents, thus promoting better compliance in this age group.

In this study, co-administration of Tdap vaccine with MCV4 was shown to be well tolerated and immunogenic compared to sequential administration of these vaccines. Sequential administration of Tdap and MCV4 vaccines does not appear to lead to increased reactogenicity compared to when these vaccines are coadministered.

The data from this study support the AAP’s current preference that Tdap and MCV4 vaccines be given to adolescents at the same office visit [4]. However, if co-administration is not possible or feasible, the data also show that the vaccines may be given sequentially, in either order, without increased risk of reactogenicity or interference with immunogenicity.

Trademarks

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References


