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Immunity to hepatitis A and B persists for at least 15 years after immunisation of adolescents with a combined hepatitis A and B vaccine☆

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ABSTRACT

Background: The exact duration of antibody persistence to hepatitis A and B and the need for booster dosing following primary immunisation remains undefined. A long-term study was designed to follow antibody persistence and immune memory on an annual basis for up to 15 years following vaccination during adolescence.

Methods: Subjects received a combined hepatitis A and B vaccine (*Twinrix*™, GSK Vaccines, Belgium) at 12–15 years of age, either as 2-dose of the adult formulation or 3-dose of the paediatric formulation. Blood samples were taken every year thereafter to assess antibody persistence and immune memory to hepatitis A and B. Antibodies to hepatitis A virus (anti-HAV) and hepatitis B surface antigen (anti-HBs) were measured at Years 11–15. At Year 15 immune memory was further assessed by measuring the anamnestic response to a challenge dose of the monovalent vaccine, which was administered to subjects whose antibody concentrations fell below the pre-defined cut-offs (anti-HAV: <15 mIU/mL; anti-HBs: <10 mIU/mL).

Results: 209 subjects returned for follow-up at Year 15 of whom 162 were included in the long-term according-to-protocol immunogenicity cohort. All subjects remained seropositive for anti-HAV antibodies, while 81.1% and 81.8% still had anti-HBs antibodies ≥10 mIU/mL in the 2- and 3-dose groups, respectively. Following hepatitis B vaccine challenge dose administration to 19 subjects, all except one in the 3-dose group, mounted a robust anamnestic response. The safety and reactogenicity profile of the hepatitis B challenge was consistent with previous experience.

Conclusion: Immunity to hepatitis A and B persists 15 years after adolescent vaccination with a combined hepatitis A and B vaccine. Highly effective anamnestic response indicates that a booster dose should not be required for 15 years after primary vaccination.

Trial registration: http://www.clinicaltrials.gov NCT00875485.

1. Introduction

Both hepatitis A virus (HAV) and hepatitis B virus (HBV) infections have a worldwide distribution and impose a considerable healthcare burden; with significant morbidity and mortality [1–3]. Vaccination is the most effective and safe method of conferring long-term protection against both of these viruses [4] and has resulted in a steady reduction in infections worldwide [5]. Although monovalent vaccines against both HAV and HBV are known to be immunogenic and safe [6]; a dual vaccination against both viruses is highly desirable due to the considerable overlap of risk factors and areas of high-endemicity for both diseases [7].

A combined hepatitis A and B vaccine (*Twinrix*™ Junior, GSK Vaccines, Belgium) which contains 360 ELISA Units (EL.U) of

Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HBs, hepatitis B surface antigen; anti-HBs, antibodies to hepatitis B surface antigen; anti-HAV, antibodies to hepatitis A virus; ATP, according-to-protocol; CI, confidence interval; CLIA, chemiluminescence immunosorbent assay; ELISA, enzyme-linked immunosorbent assay; GMC, geometric mean concentration; IU, International units; LT-ATP, long-term-according to protocol; EL.U, ELISA Units.

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inactivated HAV antigen and 10 μg of hepatitis B surface antigen (HBs) is licensed as a 3-dose regimen, for administration at 0, 1 and 6 months to children aged 1–15 years. The adult formulation (*Twinrix*™ Adult; containing 720 EL.U of inactivated HAV antigen and 20 μg of HBs antigen) is licensed for vaccinating children aged 1–11 years, as a 2-dose regimen administered at 0 and 6 months. This 2-dose schedule is also licensed as *Ambirix*™ (GSK Vaccines, Belgium) in some countries [8].

The safety, immunogenicity and long-term antibody persistence of the combined hepatitis A and B vaccine are comparable to those of the respective monovalent vaccines [9,10]. Further, long-term antibody persistence lasting for up to 17 years following the conventional 3-dose regimen in adults has been established [11]. However, the exact duration of protection and whether booster doses of vaccine are needed to maintain long-term immunity remains debatable, particularly for HBV vaccination [6,12].

In 1998, a randomised clinical trial comparing the safety and immunogenicity of primary vaccination of 12–15 years old adolescents with either 2 doses of the adult formulation or 3 doses of the paediatric formulation was initiated. After 24 months, the non-inferiority of the two regimens with respect to immunogenicity was demonstrated [10]. After 10 years of follow-up, the two regimens conferred similar long-term protection against hepatitis A and B [8]. The present study re-assessed persistence up to 15 years after primary vaccination. In addition, immune memory was assessed at Year 15 by measuring the anamnestic response to a challenge dose of either monovalent vaccine administered in subjects whose corresponding antibody levels had dropped below pre-defined cut-offs (anti-HAV: <15 mIU/mL; anti-HBs: <10 mIU/mL) during the long-term follow-up.

2. Methods

2.1. Study design and population

Full details on the study design have been previously published [8,10]. This long-term follow-up study concluded in June 2014 (NCT00875485) and the subjects remained in the group they were randomised to 15 years earlier. Subjects who completed 10 years follow-up were invited to attend further annual follow-up visits from Year 11 to 15. If, during this long-term follow-up period the subjects had anti-HAV concentrations ≤15 mIU/mL and/or anti-HBs concentration below ≤10 mIU/mL, they were invited to receive a challenge dose of monovalent hepatitis A (*Havrix*™, GSK Vaccines, Belgium) and/or hepatitis B (*Engerix-B*™, GSK Vaccines, Belgium) vaccines, respectively. Only subjects who took part in the primary study and had consented to participate in the long-term extension were included in the follow-up. The exclusion criteria from the primary study remained the same for the challenge dose, with the addition of pregnant or lactating females. Written informed consent was obtained from all the subjects before initiating any study related procedure. The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki, with necessary approvals from the relevant Ethics Committees.

2.2. Assessment of immunogenicity

Blood samples were collected annually until Year 15 after primary vaccination. Anti-HAV antibody concentrations were measured at all time-points using a commercial enzyme immunoassay (*Enzygnost*™ Anti-HAV, Siemens Healthcare, Marburg, Germany, cut-off: 15 mIU/mL). The anti-HBs concentrations were measured using a commercial chemiluminescence assay (*ADIVA Centaur*™ Anti-HBs, Siemens Healthcare, Marburg, Germany, cut-off: 6.2 mIU/mL).

2.3. Assessment of safety

The safety assessment included retrospective reporting of serious adverse events (SAEs) by subjects during the entire follow-up period.

All and grade 3 solicited local (pain, redness, swelling) and general (fatigue, gastrointestinal symptoms, headache, fever) symptoms were recorded for 4 days after the challenge dose and SAEs were recorded for 30 days post-challenge.

2.4. Statistical analysis

The primary analysis of immunogenicity was performed on the long-term according-to-protocol (LT-ATP) cohort, which included all subjects who returned for blood sampling at defined time-points and met all eligibility criteria. The analyses for the challenge dose were performed on the LT-ATP cohort, which included all evaluable subjects who had received the challenge dose and had available data for the immunogenicity endpoint at the post-challenge dose time-point.

The percentage of subjects who were seropositive for anti-HAV and had anti-HBs antibodies ≥10 mIU/mL; with their corresponding geometric mean concentrations (GMCs) from one month after their last vaccination dose to Year 15 were tabulated with 95% confidence intervals (CI). GMCs were calculated as the antilog of the mean of log-transformed anti-HAV and anti-HBs concentrations.

The anti-HBs anamnestic response was defined as anti-HBs antibody concentrations ≥10 mIU/mL one month post-challenge in subjects who were seronegative pre-challenge or ≥4-fold increase in anti-HBs antibody concentrations one month post-challenge dose in subjects who were seropositive at the pre-challenge time-point. The percentage of subjects with an anamnestic response to the hepatitis B challenge dose, percentage of subjects with anti-HBs concentrations ≥10 mIU/mL, ≥100 mIU/mL and corresponding GMCs were tabulated with 95% CIs pre- and post-challenge dose.

The statistical analyses were performed using the SAS (Statistical Analysis Software, SAS Institute Inc., Cary, NC, United States).

3. Results

3.1. Study population

The number of subjects included in the primary study, those who returned at each of the long-term follow-up time-points, and those included in the LT-ATP cohort are presented in Fig. 1. Of the 300 subjects who participated in the primary study, 209 subjects returned for the Year 15 follow-up, of whom 162 subjects (2-dose group, $N = 74$; 3-dose group, $N = 88$) were included in the LT-ATP cohort. The demographic characteristics in both study groups (3-dose and 2-dose groups) were similar at the 15-year follow-up time-point; the mean age of subjects was 28.4 ± 1.09 years and 55.6% were male.

3.2. Immunogenicity

The non-inferiority of a 2-dose regimen of the adult formulation to a 3-dose regimen of the paediatric formulation of the combined hepatitis A and B vaccine has been previously established [8]. Fifteen years after primary vaccination, all subjects in both groups remained seropositive for anti-HAV antibodies. 81.1% subjects in the 2-dose and 81.8% in the 3-dose groups had anti-HBs antibody concentrations ≥10 mIU/mL (Fig. 2). At year 15, the anti-HAV antibody GMCs (2-dose: 387.5 mIU/mL; 3-dose: 299.4 mIU/mL) and anti-HBs antibody GMCs (2-dose: 87.2 mIU/mL; 3-dose: 69.6 mIU/mL) were similar in both groups (Fig. 3).