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Five year follow-up after primary vaccination against tick-borne encephalitis in children☆

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ABSTRACT

Background: A first tick-borne encephalitis (TBE) vaccine booster in children is currently suggested 3 years after completing either a conventional (doses on Days 0, 28 and 300) or accelerated conventional (doses on Days 0, 14 and 300) TBE immunization schedule. This recommendation, however, may not be appropriate in cases where different TBE vaccines have been used interchangeably during the primary immunization series.

Methods: To provide robust data to better inform such recommendations, TBE antibody persistence was evaluated after 3–5 years in four groups of children (aged 5–15 years): two groups previously primed with three doses of Encepur® Children (conventional/accelerated conventional schedule); and two groups previously primed with two doses of FSME-IMMUN® followed by a third dose of Encepur® Children (conventional/accelerated conventional schedule). Immunogenicity was evaluated using neutralization (NT) assays based on both vaccine antigens as well as on the Enzyme Linked Immunosorbent Assay (ELISA).

Results: In the two Encepur® Children groups (full series), protective NT titers of ≥10 were detected in 98–100% of children up to 5 years after their last primary vaccination, irrespective of schedule. In contrast, only 65–70% subjects in the FSME-IMMUN® Junior groups (mixed series) displayed NT titers ≥10 after 3 years. Thus, due to lower probability of achieving/maintaining long-term protective antibody levels (recently defined by the World Health Organization as an NT titer ≥10) after this time point, both FSME-IMMUN Junior groups were discontinued.

Conclusion: A strong antibody response persists for at least 5 years after full primary vaccination with Encepur® Children. The study thus provides support for extending the time interval for a first booster dose after primary vaccination (conventional/accelerated conventional schedule) with Encepur® Children from 3 to 5 years.

1. Introduction

Tick-borne encephalitis (TBE) is a viral infection of the central nervous system (CNS) transmitted by infected ticks. The disease is endemic across many areas of Europe, including regions of Scandinavia and extending to parts of Asia [1], but increasing reports have shown that the disease is spreading to previously unaffected regions [2]. Because there is no cure for TBE, and because long term neurological consequences can ensue following infection or in rare instances even death, prevention is crucial. Prophylactic TBE vaccinations are highly effective and thus currently recommended for travelers to such regions and especially for those living or working in TBE endemic areas, including children ≥1 year of age [1,3].

Abbreviations: TBE, tick-borne encephalitis; NT, neutralization test; ELISA, Enzyme Linked Immunosorbent Assay; ICH-GCP, International Conference on Harmonization-Good Clinical Practice; GMT, geometric mean titer; GMCs, geometric mean concentrations; PPS, per protocol data set; FAS, full analysis set; CI, confidence interval; ANOVA, analysis of variance; GMR, geometric mean ratio.

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In general, while TBE tends to be milder in children than in adults [4,5], it can still have severe consequences [6]. Moreover, a higher likelihood of mild long term neurological and neuropsychological deficits has been reported, even in children who recover fully [5]. Routine TBE vaccination is therefore recommended for children in many European countries. Two pediatric TBE vaccines, Encepur® Children (Novartis Vaccines, Germany) and FSME-IMMUN® Junior (Baxter AG, Austria) are licensed and available in various countries in Europe for children aged between 1–11 years and 1–15 years, respectively [3]. Both Encepur® Children and FSME-IMMUN® Junior are based on European strains of the virus (K23 and Neudörfl, respectively), which are genetically and antigenically highly related [7,8]. Three doses of TBE vaccination are required for immunogenicity (priming) and can be administered according to a 'conventional' schedule (Encepur® Children: injections on Day 0, at 1–3 months and 9–12 months; FSME-IMMUN® Junior: injections on Day 0, at 1–3 months, and 5–12 months) [1], or an 'accelerated conventional' schedule (Encepur® Children: doses on Days 0, 14 and at 9–12 months; FSME-IMMUN® Junior: injection on Days 0, 14, and at 5–12 months). Clinical studies to date have already established the immunogenicity and safety of both pediatric vaccines [3,9,10], and some have even demonstrated that Encepur® Children and FSME-IMMUN® Junior can be successfully interchanged during the primary vaccination series [10,11]. For example, in the parent study to this investigation [9], it was demonstrated that a primary vaccination course initiated with FSME-IMMUN® Junior (two doses) could be effectively completed with Encepur® Children (one dose). Likewise, it has been shown that a primary vaccination course initiated with Encepur® Children (two doses) can be effectively completed with FSME-IMMUN® Junior (one dose) [10]. Regardless of vaccine used, however, a booster dose is recommended 3 years after a primary immunization series following a conventional schedule.

To date, while the persistence of protective antibodies has been investigated following a first booster dose with Encepur® Children and found to last up to 5 years [11], persistence of protective antibodies following primary immunization, particularly when vaccines have been interchanged, has not been investigated. Consequently, in the present study, we extended the parent investigation [9] to examine the duration of antibody responses following two different primary immunization schedules (conventional versus accelerated conventional) and two different vaccine combinations (Encepur® Children alone versus FSME-IMMUN® Junior + Encepur® Children). Ultimately, the aim of this investigation was to determine whether 3 years represents an optimal interval for a first TBE vaccine booster dose following a conventional/accelerated conventional schedule or whether this interval could be extended.

2. Materials and methods

This Phase IV, open-label extension study was conducted across ten centers in Germany between May 2009 and May 2011 (NCT01106482). Healthy children and adolescents (aged 5–15 years), previously enrolled in a trial comparing different primary vaccination schedules with either Encepur® Children or FSME-IMMUN® Junior given alone or in combination, were invited to participate in this extension study. The study protocol was designed in accordance with the Declaration of Helsinki and conformed to the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines as well as local regulatory requirements. The study was also approved by local Ethics Review Committees and written informed consent was obtained from the parents or guardians of all participants prior to enrollment.

2.1. Subjects and study design

The primary objective of this study was to evaluate the long term antibody responses in children and adolescents at 3, 4 and 5 years post-primary immunization. In the original parent study [9], subjects were divided into the following four groups, each of which received a different primary vaccination schedule:

- Group Encepur-28: received Encepur® Children according to the conventional schedule (Days 0, 28 and 300).
- Group Encepur-14: received Encepur® Children according to the accelerated conventional schedule (Days 0, 14 and 300).
- Group FSME-28: received FSME-IMMUN® Junior according to the conventional schedule and a final dose with Encepur® Children (FSME-IMMUN® Junior on Days 0 and 28, Encepur® Children on Day 300).
- Group FSME-14: received FSME-IMMUN® Junior according to the accelerated conventional schedule on Days 0 and 14 and a final dose with Encepur® Children on Day 300.

Of the 334 subjects enrolled in the parent study, 267 returned for this follow-up investigation. The study began approximately 3 years after subjects received the last vaccination of their primary immunization series. Blood samples were collected on the first day of the study (Year 3) and then annually at Years 4 and 5. See Fig. 1 for study design. Because no vaccine was administered during this study, safety data were not collected and only serological testing was conducted.

Subjects were excluded if they did not receive a complete primary TBE vaccination schedule in the parent study, they were enrolled in other investigational studies (either concurrently or up to 3 months prior to this study), and/or they had any condition which, in the opinion of the investigator, might interfere with the evaluation of the results.

2.2. Immunogenicity assessments

Blood samples (5 mL) for immunogenicity analyses were collected approximately 3, 4 and 5 years after the last injection of the primary immunization series. Antibody responses against the TBE virus were assessed by (a) neutralization test (NT) using both the K23 TBE strain (Encepur® Children) as well as the Neudörfl strain (FSME-IMMUN® Junior), and (b) Enzyme Linked Immunosorbent Assay (ELISA; Enzygnost®, Dade Behring). The NT-K23 serological evaluations were performed at Novartis Vaccines, Clinical Laboratory Sciences Department, Marburg, Germany (as described previously [12,13]), as were the evaluations using ELISA. NT-Neudörfl serological evaluations (described previously [14]) were performed at an external laboratory at the Medical University in Vienna, Austria. The lowest limits of antibody detection with the NT-K23 test are titers $\geq$2 (seroconversion), while NT titers $\geq$10 are considered protective (seroprotection). The lowest limits of antibody detection with the NT-Neudörfl test are titers $\geq$10.

Assessments of immunogenicity are expressed as: geometric mean titers (GMTs) against K23; percentage of subjects with NT-K23 titers $\geq$2; percentage of subjects with NT-K23 titers $\geq$10; GMTs against Neudörfl and percentage subjects with NT-Neudörfl titers $\geq$10; and geometric mean concentrations (GMCs) and percentage of seropositive subjects (ELISA).

2.3. Statistical analysis

Immunogenicity analyses were primarily performed on the per protocol data set (PPS). The PPS included all subjects who had belonged to the PPS of the parent study [11] and who had no major protocol violations during the study i.e. a deviation that would have

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