Immunogenicity and safety of tick borne encephalitis vaccination in healthy elderly individuals

K. Wanke[a], A. von Braun[a], L. Häberli[a], A. Mekker[a], R. Steffen[b], K. Stiasny[c], F.X. Heinz[c], B. Unger[d] and U. Karrer[ae]

[a] Division of Infetious Diseases and Hospital Epidemiology, University Hospital of Zürich, Switzerland [b] Institue for Social and Preventive Medicine, University of Zürich, Switzerland [c] Institute of Viirology, Medical University of Vienna, Austria [d] Global Clinical&Medical Affairs, Baxter BioScience, Vienna, Austria [e] current address: Cantonal Hospital of Winterthur, Brauerstrasse 15, CH-8401 Winterthur, Switzerland

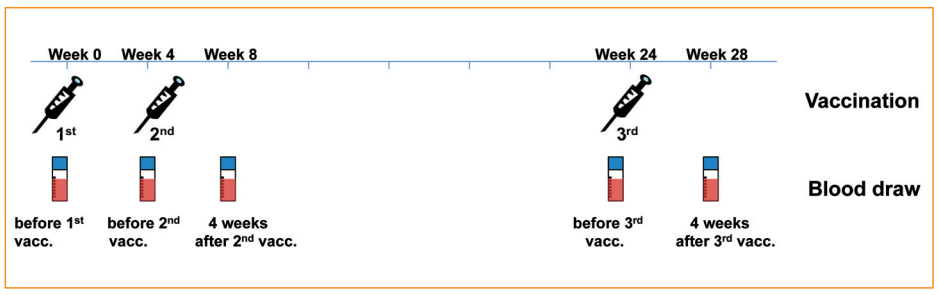
INTRODUCTION

Tick born encephalitis (TBE) is a major cause for viral central nervous system (CNS) disease in Europe. It is caused by tick-borne encephalitis virus (TBEV), which is endemic from Western Europe to Japan. After TBEV-infection, elderly subjects have an increased risk for severe CNS-disease including long-term debilitating neurological sequelae. Antiviral treatment is not available but prevention by active immunization is highly efficacious and widely recommended in Europe. In small cohorts of elderly volunteers decreased primary immune responses after TBE vaccination were reported but overall, evidence for TBE vaccine immunogenicity and protective efficacy in the elderly population is scarce. Since the risk for serious TBE is increased and immunogenicity of vaccines is generally reduced in the elderly, additional data on immunogenicity of TBE vaccine in a naive elderly population is highly warranted. Here, we report the results of a phase IV study on the immunogenicity and safety of a licensed TBEV-vaccine (FSME-IMMUN® CC[I]) after primary immunisation of 137 subjects above 70 years of age.

METHODS

Study design:

- Prospective, single centre, phase IV evaluation of the efficacy and safety of TBEV-vaccination using one of the currently licensed TBEV-vaccines for adults (FSME-Immun® CC).
- Subjects were vaccinated with FSME-Immun® CC according to the standard vaccination regime at screening and after 4 and 24 weeks.
- Blood was collected at screening and at week 4, 8, 24 and 28 to measure immune responses. Adverse events were assessed at these visits.



- The study was performed according to ICH-GCP and the Declaration of Helsinki with approval by the responsible ethics committees. Written informed consent was obtained before study entry. The study is registered with ClinicalTrials.gov, number (NCT00461695).

Patients:

Main inclusion/exclusion criteria:

- ≥ 70 years, not institutionalized;
- healthy:
  - no history, signs or treatment for chronic disease:
    - vascular disease (brain, heart), COPD, cancer
    - depression, cognitive impairment (dementia)
    - diabetes, malnutrition, severe renal impairment
  - ≤ 1 regular medication
  - BMI 18-30, RR < 140/90
  - Hb >12g/dl; glucose < 7mmol/l; calculated Creatinin-Clearance > 50ml/min
- TBEV naive (history, vaccination and serology)

Study Vaccine:

- FSME-IMMUN® CC[I] 0.5 ml contains 2.4 µg of antigen of a formaldehyde-inactivated, sucrose gradient purified TBE virus (strain Neudoerfl) stabilized by human serum albumin. The vaccine antigens is preservative-free and adsorbed to $Al(OH)_3$.

Serological tests of vaccine immunogenicity:

- ELISA TBE IgG, according to Holzmann et al[1], 1996
- Neutralization Test (NT) according to Adner et al[2], 2001

Statistical analysis

- To assess immunogenicity, point estimates and 95% CIs were calculated for all immunogenicity variables at all depicted time points. Seropositivity was defined as a NT titer ≥ 10 and an ELISA titer > 126 VIEU/ml.

RESULTS

STUDY POPULATION

183 subjects aged ≥70 years were screened and 137 were enrolled and vaccinated according to the study protocol. Main reasons for exclusion were positive TBEV-serology at baseline (n=23), >1 medication (n=9) and co-morbidities (n=6). The baseline characteristics of the enrolled subjects are depicted in table 1.

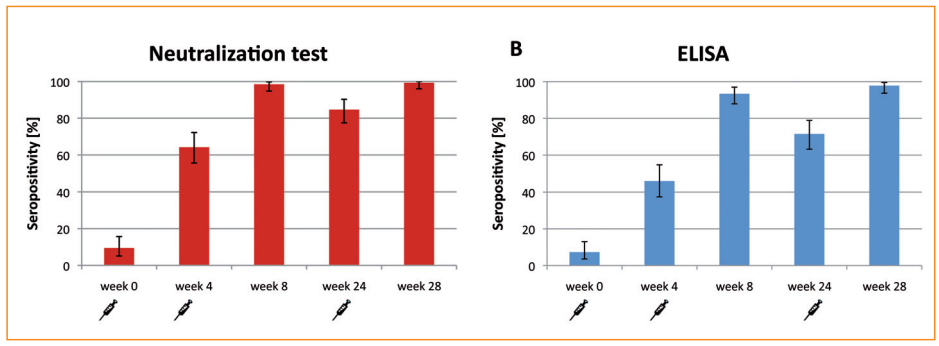
Table 1: Baseline characteristic of study subjects

Median Age (range)	74 (70-87)
Gender (w:m)	67:70
Comorbidities	
0	78
1	59
Medication	
0	79
1	58
Yellow Fever Vaccine	38

IMMUNOGENICITY

Blood samples were analyzed by neutralization test (NT) and ELISA at baseline and at week 4, 8, 24 and 28. The seropositivity rates according to a NT titer ≥1:10 are illustrated in figure 1A. Eight weeks after the 1st and 4 weeks after the 2nd vaccination seropositivity rates were 98.5% (95% CI: 94.8-99.8%), decreased to 84.7% (77.5-90.3%) after 24 weeks and finally reached 99.3% (96.0-100%) 4 weeks after the third vaccination. The seropositivity rates measured by ELISA (>126 VIEU/ml) were 93.4% (87.9-97.0%), 71.5% (63.2-78.9%) and 97.8% (93.7-99.5%) at the above specified time points, respectively (Fig. 1B).

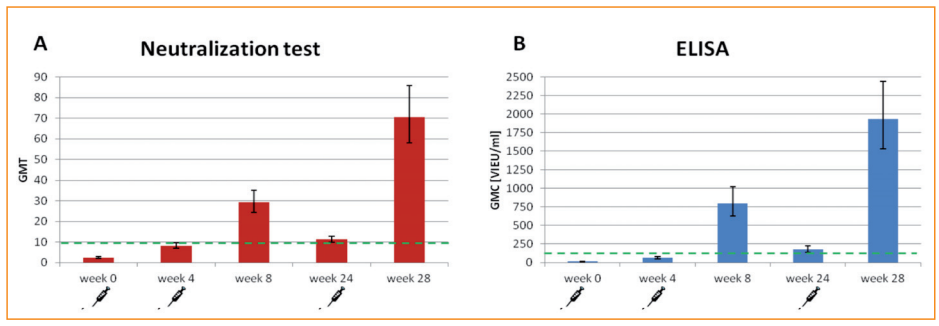
Figure 1: Seropositivity rates measured by NT (A) and ELISA (B) after vaccination with FSME-IMMUN



Geometric mean titers (GMT) for NT and GM concentrations (GMC) for ELISA are illustrated in figures 2A and 2B. Two vaccinations were required for a significant increase of GMT and GMC well above the protective limit (week 8: NT 29.2 [CI 95% 24.3-35.0]; ELISA 799 VIEU/ml [625-1022]). After the third vaccination, GMT and GMC were boosted significantly (week 28: NT 70.6 [57.9-86.0]; ELISA 1933.8 VIEU/ml [1532-2442]).

Figure 2: Immune response measured by NT (A) and ELISA (B) after vaccination with FSME-IMMUN

The dotted green line represents the threshold for seropositivity



Comparison of neutralising antibody responses in the elderly with younger cohorts

In table 2 the NT results from the current study were compared with results from earlier studies in different age groups with the same vaccine (reduced dose in children), immunization schedule and test system (NT according to Adner et al., 2001). Antibody responses one month after the third dose of primary immunisation are compared. While seropositivity rates were comparable across the different age groups, the GMT was significantly lower in the elderly cohort.

Table 2: Immune response of different age groups measured by NT after completion of primary vaccination

	Children[3]	Children/Adolescents[3]	Adults[4]	Elderly
	1-5 years; n=194 (95% CI)	6-15 years; n=290 (95% CI)	16-66 years; n= 416 (95% CI)	70-87 years; n=137 (95% CI)
Seropositivity	99.5% (97.2-100.0)	99.7% (98.1-100.0)	99.3% (97.9-99.9)	99.3% (96.0-100.0)
GMT	547 (510-586)	352 (320-387)	259 (235-285)	71 (58-86)

SAFETY:

During the study period with an observation time of 73.8 patient years, we recorded 84 adverse events (AEs) in total. None of the serious AEs were judged to be vaccine or study related (surgery for cancer (n=4), bone fractures (n=2), vascular complications (n=2), bleeding injury (n=1) and pyelonephritis (n=1)). Forty seven AEs (56%) were judged to be vaccination related. The severity grading of the AEs (total and vaccine-related) at the various time points are depicted in table 3.

Table 3: Summary of total and vaccine-related adverse events during the study period

	All AEs			Vaccine-related AEs		
Visit	Minor	Moderate	Serious	Minor	Moderate	Serious
week 4	26	5	1	25	1	0
week 8	9	10	1	9	3	0
week 24	0	6	6	9	3	0
week 28	6	12	2	4	5	0
Total	41	33	10	38	9	0

SUMMARY:

- This study represents the biggest data pool of TBEV-vaccine immunogenicity after primary immunisation of healthy elderly.
- FSME-IMMUN was highly immunogenic in healthy elderly showing high seropositivity rates already after two vaccine doses. Nevertheless, the third dose seems to be required to induce more robust antibody titers.
- Seropositivity rates were high in elderly and comparable to younger age groups (> 99%). However, neutralizing GMT were substantially lower in the elderly compared to children and younger adults.
- Vaccine related AEs were mostly mild and preferentially occurred after the 1st vaccine dose. Rates and severity of AEs in the elderly were comparable to historical data in younger adults[4].

CONCLUSIONS:

A conventional course of primary TBE immunisation with FSME-IMMUN leads to very satisfactory antibody responses in an unprimed healthy elderly population. Seropositivity rates were excellent and antibody titers were well above levels considered protective. However, due to lower antibody titers, the duration of protective immunity may be shortend in the elderly.

REFERENCES:

1) Holzmann et al., Journal of Medical Virology 48: 102-107, 1996
2) Adner et al., Scand J Infect Dis 33: 843-7, 2001
3) Loew-Baselli et al., 14th ISW-TBE meeting, February 2-3, 2012
4) Loew-Baselli et al., Vaccine 24: 5256-5263, 2006

FOOTNOTE:

I) FSME-IMMUN is distributed under the trade name of TicoVac in the UK

FUNDING and CONFLICTS of INTEREST:

This study was supported by the Swiss national Science foundation (grant PP0033-110737 to UK), the Aetas Foundation (Geneva, Switzerland), the Heuberg Foundation (Zürich, Switzerland) and by an unrestricted educational grant from Baxter Bioscience (Vienna, Austria) which also provided the vaccine free of charge. BU is an employee of Baxter and KW, AvB, PS, KS, FH and UK have received travel grants and/or speaker fees from Baxter.