ACTIVE AND PASSIVE TBE VACCINATION: NEW APPROACHES

Background

Prophylactic (active) vaccination is the most effective form of protection against TBE. Currently, TBE vaccines based on European and Far Eastern virus strains are produced which provide cross-protection against different strains of European, Siberian, and Far Eastern subtypes. For virus propagation, primary cell culture is used (chicken embryo fibroblasts or hamster kidney cells). According to recommendations by the World Health Organization, it is warranted to replace primary cell culture by continuous cell lines to produce antiviral vaccines. This approach, conducted by a Russian team, has been disclosed in a publication discussed below.

In the past, immunoglobulin preparations have been used to treat TBE in individuals (passive immunization), which have not been actively vaccinated. This practice has been discontinued due to concerns that non-neutralizing antibodies in these preparations and/or too low specific neutralizing antibody concentrations may enhance the severity of disease, a phenomenon termed antibody-dependent enhancement (ADE), which has been documented for dengue and is discussed for other flavivirus induced infections. In the second publication discussed below, a monoclonal antibody (mab) is presented which may be developed to treat TBE.

Results

New TBE vaccine in development

All TBE vaccines are so far adjuvanted with aluminum hydroxide (alumn) and are produced on primary cells. A Russian team has developed a new TBE vaccine, based on the Far Eastern TBE virus strain Sofjin, which has already been used for production of the TBE-Moscow vaccine (MV). This new vaccine is produced on the continuous Vero cell line. The virus is inactivated by 0.02% formaldehyde. The inactivated virus preparation is clarified, concentrated by ultracentrifugation, and purified by gel chromatography. Then, the vaccine preparation is lyophilized, and the new vaccine - called Evervac - contains in its final formulation 250 µg human albumin, 37.5 mg sucrose and 5 mg of gelatose per dose, after reconstitution with 0.5 ml solvent 0.75 ± 0.15 µg inactivated TBE virus antigen.

In a phase I study, Evervac was compared to MV in 20 participants (10 in each group) for tolerability and safety. Incidence of local and systemic reactions were mild and did not differ in both groups.

Then, safety and immunogenicity of the vaccine was evaluated in 100 participants (50 participants in each group), in healthy adults (18-60 years of age), giving 2 doses with an interval of 30 days. Local reactions were mild and Evervac and MV vaccines did not differ in the rate of local reactions. Systemic reactions were mild, were observed 1-3 days after vaccination and mainly resolved within 1-3 days. No severe AEs and no allergic reactions were observed. Immunogenicity in initially seronegative individuals, measured by the „VectoTBE IgG“ ELISA kit, showed a significant increase in antibody titers after the first dose (3fold) and more than 14fold after the second injection. The seroprotection level after the first and second dose were 69% and 100%, respectively, and similar data were obtained for MV. In initially seropositive participants, antibody titers remained almost unchanged after the second dose.

In total, Evervac demonstrated an acceptable safety and tolerance and immunogenicity profile in individuals 18 – 60 years of age and was equivalent to the commercially available TBE-Moscow vaccine.

TBE specific monoclonal antibody for passive immunization

A neutralizing mouse mb (termed 14D5) has been raised against the envelope glycoprotein E of the Far Eastern subtype strain Sofjin, which has been shown to neutralize not only the strain Sofjin but also strain Absettarov which belongs to the European subtype at a concentration (IC50) of 0.5 µg/ml.

When BALB/c mice, i.p. challenged with TBE virus strain Absettarov, were treated by post exposure administration of mab 14D5 at a dose of 100 µg/ mouse, a survival rate of 70% was observed, while no protection was seen at a dose of 10 µg/mouse. Administration of low dose of mab 14D5, as well as anti-TBE-Ig preparations, did not enhance infection by TBE virus in the mouse model. When mice were treated with mab 14D5 at 100 and 10 µg/mouse one, two or three days after infection, a survival rate of 50% was observed at day +1 treatment, but only a weak improvement was seen when mice received the mab at day +2 and no protection was seen at day +3. However, there was no enhancement of disease observed in these experiments with low dose treatment and high dose treatment at day +2 and +3. Pre-exposure protection at day -1, -2 and -3 was determined with a dose of 100 µg/mouse, while the low dose did not influence the survival rate. Again, no enhancement of infection was observed when mab 14D5 was administered prophylactically. It was found out that mab 14D5 binds to the domain III of gE in a region between aa 301 and 339.

The authors concluded that a cocktail of well-characterized protective mabs would be preferable for post-exposure treatment and prophylaxis, while anti-TBE-Ig preparations might include antibodies that could augment rather than inhibit TBE virus infection. Such mabs, humanized and chimeric, should be produced based on the hypervariable regions or variable domains of mabs that cannot induce enhancement of infection with TBE virus in vivo.

Discussion

Although various TBE vaccines with an acceptable immunogenicity and safety profile have been available for decades, the development of new formulations goes on. Here, the development of a novel TBE vaccine is discussed which would be the first one produced on a continuous cell line and which would not contain alum. The upcoming phase III studies will show if the promising results of the phase II studies can be seen in greater study populations. In contrast, the development of a mab-cocktail for prophylactic and/or therapeutic treatment of TBE is yet in an early non-clinical stage and, if continued, will require more time until licensure.

Literature

Vorovitch et al.

Evervac: phase I/II study of immunogenicity and safety of a new adjuvant-free TBE vaccine cultivated in Vero cells

Hum. Vaccine Immunother. 2020, doi: 10.1080/21645515.2020.175990

Matveev et al.

Characterization of neutralizing monoclonal antibody against tick-borne encephalitis virus in vivo

Vaccine. 2020;38:4309-4315

Editor: Dr. Michael Bröker

Compiled: August 2020