TBE VACCINES MAY CONTAIN NON-STRUCTURAL PROTEIN 1

Background

All current licensed TBE vaccines are based on formalin-inactivated, culture-derived whole virus. These vaccines induce neutralizing antibodies directed to glycoprotein E (gE) and this immune response confers protein against disease. Two vaccines are based on TBE virus EU subtype strains (Encepur, GSK, since January 2020: Bavarian Nordic and FSME-IMMUM Pfizer), while three Russian and one Chinese vaccines are based on TBE virus subtype FE.

It is believed that TBE vaccines do not contain any of the non-structural proteins NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. Therefore, based on antibodies directed to NS1, one can distinguish between an immune response induced by vaccination (no NS1 antibodies detectable) and by virus infection (NS1 antibodies present in sera) (see Snapshot week 9/2020). A Czech group has analyzed if NS1 really is absent from the two TBE vaccines Encepur and FSME-IMMUN.

Results

One lot of either Encepur or FSME-IMMUN was analyzed by filter-aided sample preparation and liquid chromatography-mass spectrometry (LC-MS/MS). In Encepur, 40 and 25 peptides were identified for either gE or NS1, representing 68.3% or 65.6% respectively of gE or NS1 of strain K23.

Based on signal intensities, gE was approximately 10-fold more abundant than NS1. In FSME-IMMUN samples, only gE specific for strain Neudörfl could be identified (24 peptides, coverage 47%), while no NS1 could be detected due to the high surplus of albumin (stabilizer) in this vaccine - or to much lower abundance compared to Encepur.

Both vaccines were used to immunize mice (six doses, 2-week intervals). After the third and the sixth immunization, serum samples were collected and analyzed by ELISA. Mice immunized with FSME.-IMMUN revealed a robust NS1 antibody response, but no positive NS1 immune response could be detected with Encepur.

Next, serum samples from 26 healthy blood donors, 34 patients with acute TBE, and 22 TBE vaccinees were analyzed via Western blot technique. Sera from healthy blood donors were negative for NS1 IgG in most cases (88%) and only three samples were slightly positive. In contrast, sera from TBE patients were NS1 positive in 82 % and three samples were negative and three were low positive. From 16 samples of vaccines, who had received more than three injections, 12.5% were NS1 IgG positive and 56% were low positive.

BALB/c mice which were immunized with recombinant NS1 antigen (three times, 2-week intervals) developed a robust NS1 specific immune response determined by ELISA. After challenge with a lethal dose of virus these mice had a longer survival time (10.2 days) compared to control animals (8.2 days). However, in both groups, mortality was 100%.

Discussion

Since NS1 is not a structural component of the virus, it was believed that this antigen is not present in the available TBE vaccines which are based on inactivated virions. However, here it was shown that NS1 is present in the two vaccines based on TBE-EU virus subtype and that a high percentage of vaccinees develop antibodies to NS1, which contrasts to the observation by a Swedish group (see Snapshot week 9/2020). The amount of NS1 in the vaccines is low and several injections may be needed to induce a significant immune response. NS1 in

Encepur seems to be very poorly immunogenic. However, only one lot has been used in this study.

In addition, it could be shown that NS1 antibodies can contribute to protection against challenge with virus in a mouse model, which agrees with other studies. Thus, NS1 specific antibodies may increase the protective effect of TBE vaccines (so far believed to be based only on gE). Further studies are needed to analyze the consistency of NS1 in TBE vaccines in order to study the mechanism of protection by NS1 antibodies and to clarify the discrepancy between this study and that of the Swedish group (see Snapshot week 9/2020). This could show that NS1 can be used for distinction between serological responses following TBE virus infection and vaccination, while the results shown in this publication may indicate that such a distinction may be complicated. In addition, it remains to be analyzed if the TBE vaccines based on subtype FE may also contain NS1.

Literature

Salat et al.

Tick-borne encephalitis virus vaccines contain non-structural protein 1 antigen and may elicit NS1-specific antibody responses in vaccinated individuals

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