IMPACT OF YELLOW FEVER VACCINATION ON SUBSEQUENT TBE VACCINATION

Background

All flaviviruses are genetically related and can broadly induce flavivirus specific cross-reactive antibodies. However, cross-protection is not found among distantly related flaviviruses. The immunological memory to cross-reactive antigenic sites and the formation of immune complexes can modulate the antibody response in sequential infections or vaccinations with anti-genetically related viruses or antigens. This phenomenon is called original antigenic sin and may play a role as a result of sequential exposure to different flaviviruses and/or antigens (vaccines). Various flavivirus vaccines are available, and the induction of neutralizing antibodies conferring long-lasting protection is related to the envelope glycoprotein E (E), especially to the fusion loop at the tip of the DII domain. The authors analyzed the effect of pre-existing antibodies for yellow fever (YF) on the immune response of TBE vaccination.

Results

Antibody response to TBE vaccination was analyzed from samples derived from groups of flavivirus-naïve and YF-pre-vaccinated individuals who had received a primary TBE vaccination (three injections 0, 4, and 24 weeks).

In the pools of the flavivirus-naïve group, TBE ELISA and NT both showed substantial increase of antibody titers after the second dose, followed by a decline and a further strong increase (boost) after the third injection. The YF-pre-vaccinated group showed a similar pattern in ELISA, but the NT values were significantly lower for blood samples taken after the first, second and third immunization. In the flavivirus pre-vaccinated group, boosting of YF ELISA-reactive antibodies was detected, but no NT antibodies were observed. Nearly no such effect was seen in the YF-naïve group.

Development of broadly flavivirus cross-reactive antibodies to Dengue 1 virus (Den 1) and the Rio Bravo virus (RB) were analyzed. A strong ELISA-reactive antibody response was measured in the YF-pre-vaccinated group, but a much weaker response in the flavivirus- naïve group after the first and second TBE immunization. Depletion of the RB E reactive antibodies resulted in a complete loss of RB, Den 1 and YF E reactivity in the flavivirus- naïve group (consistent with the cross-reactive antigenic site in all three viruses). The YF-pre-vaccinated group revealed a similar pattern, however, YF-reactive antibodies were not completely deleted, consistent with the presence of not only cross-reactive, but also type-specific antibodies.

Discussion

This data shows that the immune response to TBE vaccination can significantly be altered by pre-existing YF vaccine-induced antibodies. The TBE-NT antibody response was impaired compared to a flavivirus- naïve group, whereas non-neutralizing antibodies to cross-reactive epitopes were boosted. However, all individuals had TBE NT titers of at least 40 after the primary TBE vaccination course showing that these vaccinees are protected also in the YF pre-vaccinated group (at least if the interval between YF and TBE vaccination is relatively long). The quantitative differences between the two groups needs more investigation regarding long-term protection and may have an impact on the recommendation of booster intervals for YF pre-vaccinated individuals. The effect of immunological memory on the antibody response may vary with different combinations of pre-existing immunity and heterologous flavivirus vaccinations. The regression line was less steep in the ratio of TBE NT titers to ELISA values observed in the YF pre-vaccinated group, consistent with a higher

proportion of cross-reactive antibodies reactive in ELISA relative to NT antibodies. This can induce a bias in using ELISA data for measuring vaccine responses and may cause an overestimation of protection. The boosting of cross-reactive, non-neutralizing antibodies through sequential flavivirus vaccinations also deserves attention regarding the phenomenon of infection and disease enhancement. Of note, however, is the fact that higher values of broadly cross-reactive antibodies in the YF-pre-vaccinated group was observed only in the initial phase of TBE vaccination, but not after the booster at 24 weeks.

Literature

Bradt et al.

Pre-existing yellow fever immunity impairs and modulates the antibody response to tick-borne encephalitis vaccination

npj Vaccines 2019, 4:38, doi.org/10.1038/s41541-019-0133-5

Author: Dr. Michael Bröker

Compiled: October 2019