Editorial

Immunologic surrogate of protection for inactivated enterovirus 71 vaccines

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In the context of vaccines, the immunological surrogate of vaccine-induced protection implies an immunological marker to prevent or reduce frequency or severity of infection or disease (1). The availability and reliability of such surrogates of protection often play an important role in the development, evaluation, licensure, or utilization of vaccines. World Health Organization (WHO) recommend using the term "surrogate" to mean a vaccine-induced immune response (either humoral or cellular immune) that predicts protection against clinical endpoints, and can be expected to predict vaccine efficacy in vaccine clinical trials (2).

Enterovirus 71 (EV71), first isolated in California in 1969, is a neurotropic human pathogen of genus enterovirus in the picornaviridae family, and associated with severe outbreaks of hand, foot, and mouth disease (HFMD) occurred in the Asian-Pacific region in the past two decades (3,4). According to the data from national notifiable diseases surveillance system in China, more than 13 million HFMD cases have been reported, resulting in around 3,310 fatalities since May 2008 (5). EV71 and coxsackievirus A16 (CA16) are the main prevalent pathogens in mainland China and EV71 caused around 80% of the severe cases and over 90% of the fatal cases (6). Most of the cases striking children aged under 5 years.

In order to fight against the EV71 prevalence, three inactivated EV71 vaccine candidates were developed in mainland China, and had been evaluated through clinical trials (7). Results from the trials showed that the inactivated EV71 vaccines were highly efficient and safe in children. Currently, all the three have been licensed for market in mainland, which may start a new era for EV71 epidemic controlling in China (8-10). However, the marketing of these inactivated EV71 vaccines also means that new candidates of EV71 vaccine in development have to use the licensed EV71 vaccine as positive control in the future. Clinical trials using placebo as control will no longer be feasible due to the potential ethical issues. Generally, a non-inferiority efficacy trial with an experimental vaccine comparing with a positive vaccine needs a larger sample size and a longer surveillance period to capture diseases as clinical endpoints than the conventional efficacy trial compared with a placebo. Besides, trials measuring immunological endpoints could reduce both the human and financial costs of a clinical trial significantly. In that case, an immunologic surrogate for EV71 vaccine protection will be crucial role in evaluation of the new EV71 vaccines or multivalent enterovirus vaccines for HFMD.

The immunological surrogates for the vaccine-induced protection were firstly raised in the EV71 vaccine efficacy trials, by applying the receiver operating characteristic method (8,9), which had also been used in exploring a surrogate of protection for a vero-cell culture-derived trivalent influenza vaccine (11). In the trials, each confirmed EV71 case was matched with four case-free participants to make a case-control subcohort. Assuming a possible NTAb (neutralizing antibodies) titre as a cutoff, the sensitivity (proportion of participants with EV71-associated disease who have a titre less than the cutoff at day 56), specificity (proportion of matched controls who have a titre equal or greater than the cutoff at day 56), and corresponding Youden index were calculated. The cutoff with the maximum Youden index could be thought of as a surrogate

of protection for it could provide the clearest distinction between cases and controls. Results from the EV71 vaccine trials showed a significant correlation between EV71 neutralizing antibody level and the vaccine protection and a titer of 1:16 or 1:32 was suggested as a possible surrogate of EV71 vaccine protection. But, this result was based on the analysis of data from the case-control subcohort with limited number of population, and the selection bias of the controls can hardly be ignored.

Address to the issue above, further analysis were conducted by applying scaled logit model for the immunogenic surrogate of EV71 vaccines on the basis of the whole cohort of the Beijing Vigoo's efficacy trial (12). A protection curve was fitted with the post-vaccination EV71 antibody titre, which showed that the antibody levels of 14.7, 27.8, 55.7, 129.0 and 459.4 (U/mL) were associated with 50%, 60%, 70%, 80% and 90% clinical protection rate, respectively. Since the standardized EV71 NTAb titer of 15.1 (U/mL) is equal to a dilution titer of 1:16, the result supported that a post-vaccination titer of 1:16 could provide at least a 50% protection against EV71-associated disease. Although the scaled logit model could separates the protection effects of NTAb titers from exposure factors and generate the estimates from the whole study cohort, there were still some limitations. First, some of the participants had a seropositive baseline with EV71 titer at the enrollment, indicating a pre-exposure to the EV71 before the vaccination. The natural exposure to EV71 can induce solid protective immune responses, not only humoral immunity, but also cell-mediated immunity. The immunity acquired from natural exposure to EV71 would provide a lifelong protection (13). Since the mechanisms of immune response induced by natural exposure to wild EV71 strain and vaccine elicited responses were different, involving all the cohort in a scaled logit model regardless the pre-existing EV71 immunity may result in some underestimate of the antibody level needed for protection. Besides, other potential confounding factors such as the populations of different ages or ethnicities, or residents of different geographical locations and sanitary conditions also may affect the estimation. Therefore, the NTAb titer 1:16 in the previous clinical trials may be worked well as the correlate of protection just for healthy children aged 6–35 months for a certain period of time, but its generalizability still needs to be verified as specific immune marker in enough different and multiple settings and populations in the future studies.

Qin (14) and Gilbert *et al*. (15) grouped surrogates of protection into two categories: specific surrogates of protection (surrogate of protection for the same setting) and general surrogates of protection (surrogate of protection for different setting). An ideal surrogate of protection theoretically could be equally useful for predicting vaccine efficacy across vaccine lots, viral populations, human populations, and even species, which often needs various studies and a long period of time to determine. The meta-analysis of multiple efficacy and/or proof of-concept trials, possibly including post-licensure epidemiologic surveillance, is suitable for evaluating a surrogate of protection that is predictive of vaccine efficacy in different settings. However, the predictions based on meta-analysis approach are data intensive and may not always be feasible. In addition, using meta-analysis to validate the surrogate of protection requires the incorporation of biological information, standardization of the value of an immunological measurement, the duration of protection, and the definition of endpoints. Different endpoints such as infection, illness, death, infectiousness and protection against clinical endpoints may require not just different quantities of a specific immune marker but involve different markers (2).

Up to now, immunogenic surrogates of protection for several vaccines have been generally accepted, such as yellow fever vaccine, influenza vaccine, and pneumonia vaccine. All these immunogenic surrogates were identified by researchers in developed western countries, but the surrogate of inactivated EV71 vaccine protection was first conducted by Chinese study teams. Nevertheless, the marketing of these inactivated EV71 vaccines is an invaluable and timely gift for children in China, and the investigations on the immunologic surrogate of protection for EV71 vaccine represent a key milestone of controlling the EV71 prevalence.

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