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Takeda's live chimeric tetravalent dengue vaccine: moving forward with a two-dose schedule into Phase 3 trials

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Seven decades of dengue vaccine research have shown how challenging it is to develop a highly efficacious vaccine that protects against all four serotypes (DENV1-4) for all ages. In light of the rapidly rising incidence of dengue currently estimated to clinically affect about 100 million individuals annually[1], the recent licensure of the first dengue vaccine developed by Sanofi Pasteur (CYD-TDV) was a welcome step forward.[2] However, the first vaccine does not present a simple solution. Vaccine efficacy estimates vary by prior seropositivity against dengue, infecting serotype, clinical severity, and age, with prior dengue exposure being the main determinant of vaccine efficacy.[3] Furthermore, this vaccine requires three doses given six months apart - which makes programmatic role-out and high population vaccine coverage rates difficult to achieve. Due to the higher efficacy among participants vaccinated at 9 years and older, as well an elevated risk of hospitalized dengue in the 2-5 year age group seen transiently in the third year after vaccination, licensure was obtained in several countries only for those aged 9 and above.[4]

The performance of second-generation dengue vaccines such as those developed by Takeda[5] is therefore avidly anticipated. In this issue of the Lancet, Takeda published their interim Phase 2 trial results.[6] Similarly to CYD-TDV, Takeda's dengue vaccine (TDV) is a live attenuated chimeric tetravalent dengue vaccine. So where is the difference? Whilst Sanofi Pasteur's CYD-TDV contains four chimeric viruses (containing pre membrane and E genes of DENV-1 to 4) with yellow fever virus as the 'backbone', Takeda's TDV comprises an attenuated DENV-2 strain plus three chimeric viruses (containing prM and E genes of DENV-1, -3 and -4) cloned into an attenuated DENV-2 'backbone'. The theoretical advantage of TDV is hence that its conserved nonstructural proteins within the DENV-2 backbone may generate T-cell mediated responses to dengue infection in addition to the humoral responses to the premembrane and envelope proteins.[7] CD8+ T cells play a key role in controlling dengue infections[8]; and TDV was shown to elicit such CD8+ T cells that were predominantly

multifunctional, producing IFN- γ and TNF-α. These multifunctional, mainly DENV-2 reactive T cells also showed some cross-protection against DENV 1, 3 and 4.[9] However, NS1 proteins from different serotypes differ significantly in their amino acid sequences and serotype immune dominance of DENV-2 may suppress the immune response of the other serotypes, analogue to the DENV-4 serodominance seen in the Pasteur Sanofi trials. [10] Hence, the question whether the above in-vitro findings will indeed translate into sustained clinical protection balanced against all four serotypes can only be answered by efficacy trials.

The study published in this issue[6] was conducted to inform whether Takeda should progress with a one or two dose schedule into their Phase 3 efficacy trials. The primary endpoint was geometric mean titres (GMT) of neutralizing antibodies to DENV-1-4 at months 1, 3, and 6, and the main comparison was between a schedule of a single dose versus two doses 3 months apart. Consistent with previous Phase 1 and 2 studies[11-14], TDV induced by far the highest GMTs to DENV-2, followed by DENV-1, with DENV-3 and 4 associated with relatively low GMTs. The high GMT for DENV-2 is best explained by the fact that DENV-2 is the only full-genome serotype in this vaccine composition. Comparing the one and two dose schedule, GMTs were similar for seropositive and seronegative subjects combined. The secondary immunogenicity endpoint was the seropositivity rate. More than 80% of TDV-vaccinated participants in each study group had tetravalent seropositivity, and 96% or more had at least trivalent seropositivity. Even a trivalent vaccine (eg, a vaccine effective only against serotypes 1, 2 and 3, and not 4) could have a substantial benefit in terms of reducing severe disease, as in natural infections third and fourth infections tend to be mild.[15,16]

Given that Sanofi Pasteur's CYD-TDV efficacy results were strongly driven by baseline seropositivity status, it is important to have a closer look at the subset of seronegatives in Takeda's Phase 2 trial. Indeed, similar to Sanofi Pasteur's findings, GMTs were generally lower for all serotypes for the baseline-seronegative compared with baseline-seropositive subjects, and also appeared to somewhat decline over time whilst GMTs for seropositives remained elevated over the 6 months observation. There was no difference in GMTs observed for one versus two doses for baseline-seronegatives, except in months 6 for DENV-3 and 4. This observation was also reflected by the seropositivity rates: in those who were baseline-seronegative, the two-dose schedule led to higher seropositivity rates to DENV 3 and 4 by month 6.

Previous studies showed that the T-cell response to TDV was evident after primary vaccination, did not increase by a booster vaccination, and was detectable 6 months after the last immunization.[9] Such findings together with the fact that the GMTs and seropositivity

rates in the baseline-seropositive participants were as high after a single dose as after two doses (indicating sterilizing immunity) provide hope that a single dose schedule may be sufficient in baseline seropositive individuals. However, for population based vaccination programmes that include seropositive and seronegative individuals, there may be an advantageous edge to a two dose schedule, as a second TDV dose was needed to enhance immunogenicity against DENV-3 and -4 in baseline-seronegative children. In conclusion, the good safety profile combined with the immunogenicity findings from this trial supports moving forward to a large-scale phase 3 evaluation of efficacy and safety of TDV, using a two-dose schedule 3 months apart.

Sanofi Pasteur's well-conducted efficacy trials have taught us that good neutralizing antibody levels may not necessarily predict or induce complete vaccine efficacy.[3,17] Although analyses of immunogenicity studies demonstrated that Sanofi Pasteur's CYD-TDV induced balanced neutralizing antibody responses to all four DENV after three doses[18], these responses were insufficient to generate balanced protection against symptomatic virologically confirmed dengue.[3] As Takeda's TDV was designed to induce both humoral and cellular immune responses, we are now all eagerly awaiting how the immunogenicity data derived from the investigations published in this issue of Lancet ID will translate into durable clinical protection (efficacy) dependent on dengue serotypes, age, and prior exposure to dengue.

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