The Dengue Human Challenge Model: Has the Time Come to Accept This Challenge?

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(See the major article by Sun et al on pages 700–8.)

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In an important article in this issue of the Journal, Sun et al describe the first human challenge of recipients of a live attenuated tetravalent dengue vaccine (TDV) with dengue virus (DENV) known to induce symptomatic disease [1]. The challenge viruses were originally evaluated as candidate vaccines for inclusion in a TDV vaccine but were underattenuated and induced mild dengue illness in vaccinees [2, 3]. In the current study, investigators evaluated the relationship between neutralizing antibody at the time of challenge and the ability to protect against viremia and symptomatic illness. Although the number of subjects was small, the authors found that subjects with higher titers of neutralizing antibody were protected. Importantly, enhanced viremia and enhanced disease were not observed.

A human challenge model for dengue could be useful in addressing the complexities of vaccine and drug development for dengue. These include the lack of an animal model that reproduces the disease observed in humans, the necessity of the vaccine to be effective against all 4 DENV serotypes, and the lack of an identified correlate of protection. Previously, experimental infection of humans was essential in identifying the individual DENV serotypes, the mode of transmission of dengue, the incubation period of DENV, the kinetics of viremia, and the role of antibody in protection [4, 5].

Human challenge models have been used effectively in early phase clinical trials to provide a preliminary estimate of vaccine efficacy prior to engaging in large field efficacy studies and have also been used for drug development [6–11]. Vaccines that may have otherwise been evaluated in thousands of volunteers in phase III efficacy trials were eliminated from further evaluation. Although a human challenge model could be very useful for dengue vaccine and drug development, experimental DENV infection presents some unique challenges, primarily related to safety. There is the well-characterized risk of more severe dengue with subsequent, heterotypic infection. As a result, infecting volunteers with wild-type DENV after vaccination could induce severe illness should the vaccine not be protective.

Despite these hurdles, a dengue human challenge model (DHCM) workshop, sponsored by the Walter Reed Army Institute of Research and the National Institutes of Health, was convened in Philadelphia in 2011. Experts in dengue vaccine research, dengue immunopathology, challenge models for other diseases, and regulatory officials discussed the potential of a DHCM. The consensus from the workshop was that a DHCM could be developed safely, should appropriate challenge strains of DENV be identified and produced under current good manufacturing practices. Topics of discussion included potential areas of use for the DHCM, the clinical end points of the model, the strains of DENV that should be used, and the regulatory hurdles that must be addressed.

Although the DHCM has the potential to accelerate the development of dengue vaccines and therapeutics, the greatest concern remains its safety. Unlike human challenge models involving malaria, influenza, and enteric bacterial infection, a licensed antidengue therapeutic agent does not exist that could treat a volunteer who becomes ill following challenge. Although the majority of natural DENV infections are mildly symptomatic, dengue illness can be severe and, in some cases, even life threatening. For this reason, the clinical end points of any DHCM must be carefully designed and must be reproducible. The consensus from the DHCM workshop was that the end points of a useful challenge model could be peak virus titer and duration of viremia, with or
without mild clinical illness; illness resulting in a vascular leak syndrome or other clinical signs and symptoms of severe dengue would not be acceptable. Viruses chosen for use in the DHCM would have to induce reproducible levels of viremia and reproducible clinical signs and symptoms. As a higher titer of virus has correlated with more severe symptoms, the titer of virus administered may be adjusted to control the clinical outcome [12, 13]. For this reason, dose-ranging studies may need to be performed with each challenge virus to achieve the goal of measurable viremia with only mild illness. These viruses would then need to be produced under current good manufacturing practices, meet the regulatory requirements of an investigational agent, and be filed under an investigational new drug application.

Areas of research where the DHCM could have great impact include vaccine and drug development. Although dengue vaccine development has made great progress over the past decade, there are still many unanswered questions. A correlate of protection remains unidentified, and although neutralizing antibody is thought to be the protective mechanism, the titer and specificity of antibody required to confer protection are unknown. The study by Sun et al. did provide some evidence of a positive correlation between antibody titer and protection from illness [1]. Nevertheless, an additional factor in the protection from illness may be the quality of the antibody induced. The TDV that was administered 12–42 months prior to challenge did not induce a balanced antibody response, as DENV-1 was immunodominant for the majority of the subjects recruited for the challenge study. It is unclear whether the DENV-3 antibody detected following vaccination was induced by the DENV-3 component of the vaccine or whether it was cross-reactive antibody induced by the immunodominant DENV-1 component. Although this specific question was not addressed in the study, its answer could be found by a careful investigation of the postvaccination and prechallenge specimens that were collected. Additionally, because severe disease has only rarely been observed with a third or fourth infection, many experts in the field believe that a successful dengue vaccine may not need to protect against all 4 serotypes [14]. With an increased number of subjects in a study modeled after that by Sun et al, it might be possible to determine the real need for a tetravalent antibody response following vaccination and the need for subsequent booster immunizations.

The recently published results of a phase IIb trial of the Sanofi Pasteur TDV candidate CYD raised similar questions regarding antibody titer and protection [15]. Despite the ability of the vaccine to induce measurable neutralizing antibody titers against DENV-2, the vaccine surprisingly did not provide protective efficacy against DENV-2 infection. Although the full immunology results from this trial have not yet been published, the authors of the study suggested that the unexpected lack of efficacy could be due to either an antigenic mismatch between the DENV-2 component of the vaccine and the DENV-2 causing disease in the cohort or to an overestimation by the plaque reduction neutralization test of the true immunogenicity of the DENV-2 component. Additionally, the authors commented that the role of DENV nonstructural proteins in the immune response needs clarification, as the CYD vaccine contains only the nonstructural proteins of the yellow fever 17D vaccine. A DHCM could be helpful in testing these hypotheses.

A DHCM could provide greater insight into the immune response to dengue infection. Importantly, a preliminary evaluation of the efficacy of a candidate dengue vaccine could be ascertained in a study enrolling tens of volunteers as opposed to thousands. Candidates that did not provide a predetermined level of protection against infection would not continue the path to development. Additionally, drug development for dengue could be accelerated using the human challenge model. Because of the limited value of the known animal models, it is currently difficult to establish a proof of concept for novel therapeutics. Without some indication of effectiveness, these are unlikely to enter field studies. The DHCM could provide the needed signal for further evaluation of these novel agents.

Despite the many hurdles to establishing a DHCM, Sun et al have shown it to be a feasible endeavor and one that could become extremely useful in the successful development of dengue vaccines and therapeutics. Investing in such a model will eventually provide valuable insight into DENV infection and the human immune response and can be achieved with a high level of safety.

Note

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