Meeting of the WHO Task Force on Clinical Trials of Dengue Vaccines.
Siam City Hotel, Bangkok, Thailand.
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Minutes of the Meeting
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Final version

The fourth meeting of the WHO Task Force on clinical trials of dengue vaccines was held on 17 October 2004 in Bangkok, Thailand. The meeting was organized back-to-back with a regional scientific meeting by the Paediatric Dengue Vaccine Initiative, PDVI. The general objectives of the task force are to:

- To review current status of vaccine development, analyse data and provide scientific advice;
- To identify common obstacles and recommend activities to advance the field;
- To provide a forum for exchange of scientific ideas.

The current meeting addressed the objectives under three broad headings:
- progress with existing vaccines
- preparation for clinical trials
- immunological parameters to be assessed in vaccine studies

The meeting was attended by researchers from academia, government and non-government organizations and the private sector being involved in dengue vaccine development, and having reached clinical stage.. The plenary meeting was followed by a closed session, attended by WHO temporary advisers who identified a list of recommendations to WHO which are attached to this document.

Progress with existing vaccines

Dr S. Thomas reported on progress on the live attenuated tetravalent GSK/WRAIR dengue vaccine that was evaluated in a small-scale phase I study in flavivirus seronegative Thai children 6-9 years of age. The vaccine contained 5-6 logs of each dengue virus serotype in 1 ml and two doses were administered sub-cutaneously six months apart. Primary endpoint of the study was safety. Formulation 17 was used at the same dose as previously administered in adult studies. A complex screening process was necessary that required enrolment of 89 children in order to have 7 seronegatives to participate in the trial. Most adverse events were mild and local injection site swelling was the most frequently reported local symptom (up to 50%). The reaction at the vaccination site was most common after the first injection. For general symptoms, headache was most frequent after dose 1 (5/7 or 71%), while

headache, fatigue and elevated temperature were reported with equal frequency after dose 2 (3/7 or 43%). Fifty to 80% of participants developed lymphadenopathy and 2/7 developed elevated platelet levels. One study subject developed a generalized rash after the second dose, similar to a rash following natural infection. Three subjects developed measurable viraemia of DEN-4 strain. There were no alert laboratory values or serious adverse events. Overall, this small study suggests that reactogenicity is somewhat lower than in adults. In terms of immunogenicity, in the According to Protocol (ATP) analysis there were no tetravalent seroconversions and only one trivalent seroconversion following one dose of vaccine. Following two doses, 6/6 children in the ATP analysis seroconverted to all four dengue viruses. The one child not included in the ATP analysis demonstrated a trivalent seroconversion following 2 doses. The GMT of neutralizing antibody responses appeared to be a bit higher than in adults.

Dr B Tomlinson described efforts of Sanofi-Aventis to develop a vaccine strain of dengue 3 virus that would be immunogenic, but would not out-compete other dengue viruses and would not produce elevated adverse reactions, as observed in a previous formulation of the company's live attenuated tetravalent vaccine. The vaccine virus DENV3 16562 was used for cloning. Historically, this virus was isolated from a DHF patient in Bangkok and was grown in primary green monkey cells because it did grow poorly in primary dog kidney cells. It was subsequently grown in foetal rhesus lung cells prior to formulation as vaccine. In preliminary trials in Thailand, it appeared to be attenuated in both adults and children, but in tetravalent formulation, it appeared under-attenuated. The vaccine strain was shown subsequently to contain two plaque variants. A small plaque variant was recovered from a pre-vaccine seed lot on Vero cells and formulated for the trial described. 100 $TCID_{50}$ of the small plaque variant vaccine was injected s.c. into 15 participants with a median age of 23 years. Adverse reactions were observed in all participants. Three had reactions at the injection site, 13 had severe systemic reactions (prevention of normal daily activities). Six had platelet levels below 100,000 per cu. mm., 12 developed a neutropenia (<1,600 per cu.mm) and AST and ALT levels were elevated in most vaccinees. All subjects recovered. Virus was detected in 12 vaccinees by RT-PCR and in all 15 by tissue culture. Virus titres reached log 4-5 between days 6-10. Antibody GMT as measured by PRNT50 reached 1,000 twenty-eight days after vaccination. Virus re-isolated from vaccines showed large plaque size without apparent mutation. It was suggested that history of DEN 3 vaccine strain derivation should be analysed in further detail, but it appears obvious that properties of quasispecies vaccine strains can differ significantly from biological features of cloned species.

Preclinical and clinical data were presented by F Guirakhoo on the Acambis candidate vaccine ChimeriVax-DEN. Detailed safety data was presented for the evaluation of the ChimeriVax DENV-1-YF chimera in monkeys. The vaccine produced fewer pathological changes when given i.c. to monkeys than did the YF vaccine. Monkeys injected i.c. with 5 logs tetravalent YF-DEN chimeric vaccine also showed fewer neurological changes than monkeys injected i.c. with YF vaccine. The chimeric DEN-YF viruses grew to lower titre in hepatic cell lines than did YFV. Furthermore, *Aedes aegypti* mosquitoes did not become infected when fed the tetravalent vaccine although the viruses did replicate when injected intra-thoracically. The immunogenicity of two tetravalent formulations was evaluated in monkeys. One contained 5 logs of each DEN virus strain and the second contained 3 logs of each DENV serotype. All

monkeys developed approximately 2.5 logs of viraemia. Those given 5 logs of tetravalent vaccine developed PRNT titres in the range 113-1140 and those given 3 logs of the tetravalent vaccine developed PRNT titres of 56-1120. 83-100% of the monkeys failed to develop any detectable viraemia when challenged s.c. with 5 logs of any DEN virus 180 days after vaccination. A tetravalent vaccine formulation containing 4 logs of each DEN1-4 chimera has been administered to adults, allocated to three treatment groups (ChimeriVax-DEN, YF vaccine, placebo, with N=33 per group). Booster administration is done after 5-9 months. The study is ongoing, but no significant adverse reactions were observed after the first injection.

Efforts to develop a dengue vaccine at the US National Institutes of Health were discussed by S. Whitehead. This team is taking two approaches to the development of dengue vaccines. One is to prepare chimeric viruses with prM-E from an attenuated DENV-4 (rDEN4Δ30) replaced with the corresponding genes from an heterologous DEN virus and the second is to introduce mutations found to attenuate DENV-4 into other DEN virus strains. The attenuating mutations are in NS3, NS4B, NS5 and a 30 nucleotide deletion in the 3' untranslated region. The effect of each potentially attenuating change has been evaluated with each DEN virus serotype in SCID mice engrafted with HuH7 cells. Preliminary data suggested that the magnitude of the attenuation associated with the change at each site varies between DEN viruses. Various tetravalent combinations of recombinant DENV are being evaluated in monkeys. Boosting after 4 months resulted in anamnestic immune responses. Antibody from the monkeys immunized with tetravalent vaccine neutralized multiple strains of each DEN virus *in vitro*. Human volunteers have been immunized with 1, 2, 3 or 5 logs of attenuated rDEN4Δ30. About half developed a low titre viraemia, and 95-100% seroconverted. While there were no serious adverse events, most participants developed an asymptomatic rash (50-75%, dependent on dose). Equally, monovalent rDEN1Δ30 is being evaluated in a phase I acute safety study. In parallel, mosquito transmission studies are being actively pursued. A premaster seed has been established in Vero cells, showing some substrate-adapted mutations that are genetically stable.

Hawaii Biotech, represented by BA Coller, is developing a subunit dengue vaccine which is formulated in proprietary adjuvant. The DENV envelope (E) and NS1 proteins are produced in Drosophila cells and purified by immunoaffinity chromatography. Rationale for the vaccine was demonstrated in the suckling mouse challenge model. A range of mixtures of E and NS1 proteins, with or without adjuvant, have been evaluated in the mouse model. These studies have included measures of cell-mediated immunity (antigen-induced lymphoproliferation and IFN gamma production). New data were presented on the evaluation of four different tetravalent formulations in primates. Four doses of between 1 and 5 ug 80%Eand 0.1-05 ug NS1 were administered to rhesus monkeys and NT antibody for all 4 serotypes reached a plateau after the third immunization (PRNT 2-3 logs). Cell-mediated immunity is variable, but appears stable over time. Challenge studies were done six months after last dose using selected DEN viruses. Protection (absence of viraemia) was observed in high-titred monkeys, corroborated by the lack of a pronounced anamnestic response. More extensive safety, immunogenicity and protection studies against all four serotypes are in preparation. Hawaii Biotech anticipates clinical evaluation as of 2006.

W Sun provided an update on efforts of the Walter Reed Army Institute of Research (WRAIR) to evaluate dengue vaccine candidates in a human volunteer challenge model. WRAIR is continuing with efforts to develop strains of DENV which will produce mild disease when administered to volunteers. Challenge of vaccines with such viruses would provide valuable preliminary information about the possible efficacy of the vaccine. To date, DENV-1 and DENV-3 challenge preparations have been developed and preliminary results for a DENV-4 challenge virus were reported to be promising. Clinical data were presented from five volunteers previously vaccinated with GSK/WRAIR live, attenuated tetravalent vaccine. For DEN1 challenge, all volunteers were protected with virtually no evidence of fever or viraemia. No anamnestic antibody response was observed, despite one of these volunteers having a pre-challenge PRNT antibody titre of <10. A second volunteer with a pre-challenge PRNT titre of 531 was viraemic on day 7 after challenge but did not develop any symptoms. A different picture emerged after DEN3 challenge, where three of the five volunteers developed clinical symptoms. Their pre-challenge PRNT antibody titres were <10-16. The remaining two volunteers with PRNT titres of 57 and 116 did not develop any clinical symptoms. Strong anamnestic antibody responses were observed in all cases, but kinetics were not much different from what is observed after primary infection. None of the participants developed more severe disease than non-immune individuals infected with the challenge viruses. In contrast to DEN 1 challenge, the specificity of the NT antibodies broadened after challenge. A constraint of the model is that we do not know the minimum infective dose of challenge viruses.

Preparation for Clinical Trials

Sanofi-Aventis, in collaboration with Institut Pasteur at Ho Chi Minh City, has a long-standing investment into a site at An Giang in South Vietnam, near the Cambodian border, which studies dengue epidemiology in retrospective and protective studies. This site could ultimately be used for evaluation of dengue candidate vaccines. C Luxemburger presented data on a recently launched prospective cohort study. The site employs approximately 100 staff and aims to enrol some 2,500 children between 3 and 11 years of age from 3 Kindergartens and from two Primary Schools. During School Terms, potential dengue cases are identified by absence from School. During holidays, homes are visited to identify sick children. In a preliminary cross-sectional seroprevalence study, 3% (66/2186) of children had anti-DENV IgM antibody detectable by ELISA and 21% (459/2186) had anti-DENV IgG antibody, also detected by ELISA. In 2002-2003, 7 DENV-1, 95 DENV-2, 1 DENV-3 and 10 DENV-4 were recovered from patients. During follow up from January to August 2004 of the cohort, there were 183 clinically diagnosed dengue cases. Sixty four of these were confirmed by laboratory testing. DENV was recovered from 23 of these patients, mostly DENV-2 and some DENV-4. No DENV-1 or 3 were recovered. The data from An Giang are remarkable in the sense that the median age of dengue disease is quite late with 9 years of age. While there are some vector control efforts in the region, there is no JE vaccination occurring in that region.

Immune Readouts in Vaccine Studies

The section on immune parameters and measurements was introduced by a presentation from F Ennis on the immunology of dengue infection. He reviewed

antibody and T cell responses to dengue, highlighting the antigenic properties of the viral components and their cross-reactive potential. There is ample evidence for immunopathogenic mechanisms in severe dengue and DHF, and a model for the immune-mediated pathogenesis of the plasma-leakage syndrome was presented. Viral load is a key determinant of disease severity, and a combination of antibody and cell mediated immunity appears most suited to contain viraemia. He reminded participants that "correlates of protection" do not necessarily coincide with protective mechanisms, and that clinical trials should not be delayed by search for correlates. The working hypothesis is that neutralizing antibodies and some degree of cellular immunity, including cytotoxic effector function, correlate with some protection against natural challenge. Sterilizing immunity might not need to be achieved to confer protection from disease. Clinical as well as epidemiological studies should be accompanied by sample collection for more comprehensive immunological analysis.

J Cardosa discussed parameters that should be measured in the context clinical trials of dengue vaccines, addressing the determination of prior exposure, the immune response to the vaccine, as well as the memory status. In Japanese encephalitis (JE) endemic areas, there is necessity to run both DEN and JE serology. However, previous exposure cannot be assessed with (GAC) ELISA, and current PRNT assays are not suitable for large sample sizes. The measurement of prM antibodies was mentioned as a means to determine past flavivirus exposure, even though a differentiation between DEN viruses would not be possible. Alternatively, exposure can be assessed retrospectively. A possibility to assess cross neutralisation to allow distinction between homotypic and heterotypic infection would represent a further advantage. Hence, there remains an open agenda for diagnostic tools with both the discriminatory power and scalability to collect the desirable data in context of phase II- III clinical trials.

S Thomas gave a perspective on dengue vaccine trial readouts and the relationship to vaccine licensure. He described previous efforts of WHO to conduct a collaborative study to assess dengue sera, both monovalent and polyvalent, to serve as reference to compare results between laboratories. The results between laboratories were quite variable, and it appeared that only some had used the standard operating procedure (SOP) that was provided. In a subsequent workshop organized by the Paediatric Dengue Vaccine Initiative in collaboration with WHO at the laboratories of Dr Sutee at Mahidol University in Bangkok, the 11 participants were able to obtain far more reproducible results with the same sera, viruses and SOPs (report by S Halstead). The potential of new functional assays with higher throughput characteristics was discussed, in particular efforts to develop a dengue microneutralisation test. Such a test is under development by WRAIR which is conducted in 96 well plates and can be analysed in an optical reader system. Currently, correlation with PRNT50 is good for primary infection but less convincing for secondary infections. Another strategy constitutes to develop a dendritic cell SIGN neutralization assay that could be read using flow cytometry. Further assay optimization is required. Assay validation will be critical and should be guided by regulatory considerations.

There were extensive discussions of immunological changes in dengue patients and the utility of measuring them. Concern was expressed that the lack of a validated assay to measure anti-DENV neutralizing antibody would inhibit the ability to analyse end-points and would inhibit licensing of vaccines. Given reports during this meeting,

and in the literature that hosts with PRNT antibody titres of $\geq$ 10 became viraemic or developed disease following infection, there was discussion on the relative merits of "constant antibody concentration, virus titre varied" neutralization tests compared to "constant virus titre, antibody titre varied".

Recommendations:

- The standard dengue antisera, both monovalent and polyvalent, which were assessed in the inter-laboratory evaluation, should be made available to vaccine developers for assessment using their in-house neutralization tests. Results should be available at the forthcoming meeting of the Steering Committee (April 2005). Thereafter, the Steering Committee would make its recommendation on assignment of standard unitage.
- Priority should be attached to the development of high throughput neutralization or alternative functional assays to enable rapid analysis of sera from large scale phase II and III vaccine trials. The use of ELISA should receive consideration as well. Coordination should be assured with activities led by TDR and PDVI.
- WHO should be encouraged to host a workshop on correlates of protection in dengue, with a particular view on defining minimum protective antibody titres and differentiation between the four dengue viruses.
- Consideration should be made to careful storage of sera and peripheral blood mononuclear cells in the context of larger dengue clinical trials for subsequent immunological analysis. This issue should be addressed in context of the above workshop.
- Even though the current vaccine pipeline looks promising, WHO should be encouraged, if funds available, to support exploratory research into new dengue vaccine candidates.

The next meeting of the WHO task force on clinical trials of dengue vaccines is tentatively scheduled for 11 December 2005 at Washington DC, in conjunction with the annual meeting of the American Society for Tropical Medicine and Hygiene.

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