Revisión bibliográfica.

Ensayos clínicos reportados en la Base de datos Medline – Tema Vacunas Dengue

Acambis, Inc., Cambridge, Massachusetts.


Abstract: A randomized double-blind Phase I Trial was conducted to evaluate safety, tolerability, and immunogenicity of a yellow fever (YF)-dengue 2 (DEN2) chimera (ChimeriVax-DEN2) in comparison to that of YF vaccine (YF-VAX). Forty-two healthy YF naive adults randomly received a single dose of either ChimeriVax-DEN2 (high dose, 5 log plaque forming units [PFU] or low dose, 3 log PFU) or YF-VAX by the subcutaneous route (SC). To determine the effect of YF preimmunity on the ChimeriVax-DEN2 vaccine, 14 subjects previously vaccinated against YF received a high dose of ChimeriVax-DEN2 as an open-label vaccine. Most adverse events were similar to YF-VAX and of mild to moderate intensity, with no serious side-effects. One hundred percent and 92.3% of YF naive subjects inoculated with 5.0 and 3.0 log10 PFU of ChimeriVax-DEN2, respectively, seroconverted to wt DEN2 (strain 16681); 92% of subjects inoculated with YF-VAX seroconverted to YF 17D virus but none of YF naive subjects inoculated with ChimeriVax-DEN2 seroconverted to YF 17D virus. Low seroconversion rates to heterologous DEN serotypes 1, 3 and 4 were observed in YF naive subjects inoculated with either ChimeriVax-DEN2 or YF-VAX. In contrast, 100% of YF immune subjects inoculated with ChimeriVax-DEN2 seroconverted to all 4 DEN serotypes. Surprisingly, levels of neutralizing antibodies to DEN 1, 2 and 3 viruses in YF immune subjects persisted after 1 year. These data demonstrated that (1) the safety and immunogenicity profile of the ChimeriVax-DEN2 vaccine is consistent with that of YF-VAX, and (2) preimmunity to YF virus does not interfere with ChimeriVax-DEN2 immunization, but induces a long lasting and cross neutralizing antibody response to all 4 DEN serotypes. The latter observation can have practical implications toward development of a dengue vaccine.

Centre for Military and Veterans Health, Mayne Medical School, Herston, Queensland 4006, Australia.


Abstract: We conducted a Phase 1b study to evaluate the immunogenicity and safety of two live attenuated tetravalent dengue vaccines in healthy adult volunteers. After one injection, all subjects reported systemic reactions consistent with a mild dengue-like syndrome. Seven volunteers developed dengue 3 viraemia after vaccination. All subjects developed a neutralizing antibody response against serotype 3 with partial response against other serotypes. The trial was stopped early (after 10 subjects enrolled) due to formulation issues, which were related to the dengue 3 vaccine component. Managing viral interference and balancing attenuation to produce acceptable tetravalent immunogenicity with minimal reactogenicity may be a recurring problem for future multivalent live vaccines.

Department of Virus Diseases, Walter Reed Army Institute of Research, USA.


Abstract: As part of a larger vaccine study, peripheral blood mononuclear cells (PBMC) were collected from volunteers for analysis of vaccine-induced T cell responses. The PBMC were re-stimulated in vitro with live dengue virus and assayed for T(H)1 or T(H)2 memory cell responses. Re-stimulated PBMC from the volunteers predominantly secreted interferon-gamma. Little interleukin-4 (IL-4) or IL-10 secretion was detected, indicating a T(H)1 type of T cell response. The interferon-gamma response was primarily serotype-specific with some serotype cross-reactivity. T cell depletion studies showed that the interferon-gamma was being secreted by CD4+ T lymphocytes and/or by cells other than CD8+ T lymphocytes that were being stimulated by the CD4+ T lymphocytes. CD3+ or CD8+ T cell depletion showed that granzyme B
mRNA expression correlated with the presence of CD4+ T lymphocytes. However, depletion of CD4+ T cells after four days of stimulation indicated that the granzyme B mRNA was produced by cells in culture other than lymphocytes. In summary, an antigen-specific T(H)1 type T cell response was seen as a response to vaccination using live attenuated dengue virus.

Institute of Science and Technology for Research and Development, Mahidol University, Salaya, Thailand.

Abstract: The development of a live attenuated tetravalent dengue vaccine is currently the best strategy to obtain a vaccine against dengue viruses. The Mahidol University group developed candidate live attenuated vaccines by attenuation through serial passages in certified primary cell cultures. Dengue serotype 1, 2 and 4 viruses were developed in primary dog kidney cells, whereas dengue serotype 3 was serially passaged in primary African green monkey kidney cells. Tissue culture passed strain viruses were subjected to biological marker studies. Candidate vaccines have been tested as monovalent (single virus), bivalent (two viruses), trivalent (three viruses) and tetravalent (all four serotype viruses) vaccines in Thai volunteers. They were found to be safe and immunogenic in both adults and children. The Mahidol live attenuated dengue 2 virus was also tested in American volunteers and resulted in good immune response indistinguishable from those induced in Thai volunteers. The master seeds from the four live attenuated virus strains developed were provided to Pasteur Merieux Connaught of France for production on an industrial scale following good manufacturing practice guidelines.

Abstract: A live attenuated dengue virus type 2 candidate vaccine (16681-PDK53) was evaluated in a phase I trial in 10 nonimmune adult volunteers. The dengue virus-specific memory T cell responses were analyzed as part of this study. Dengue virus-specific T cell proliferative responses were observed in all subjects after stimulating their peripheral blood mononuclear cells with live viruses or noninfectious viral antigens. The highest proliferative response was against dengue virus type 2, although cross-reactivity with other flaviviruses was detected to a lesser degree in some subjects. Dengue virus type 2-specific CD4+ and CD8+ cytotoxic T lymphocytes were generated in all vaccinees. This study investigated whether the candidate vaccine was efficacious in inducing dengue virus-specific CD4+ and CD8+ T cell memory after a single immunization in nonimmune recipients.

R&D Department, Aventis Pasteur, Lyon, France.

Abstract: Sera from Thai children immunized with a live-attenuated tetravalent dengue virus vaccine or from naturally infected age-matched site-control subjects were examined for immune enhancement capacity by a highly reproducible flow cytometric assay in Fc receptor-bearing K562 human cells. None of the sera under study corresponded to cases of severe dengue disease. In parallel assays employing each dengue virus serotype, we found no or only minimal antibody-dependent enhancement (ADE) when sera from vaccinated or control subjects were used at a low serum dilution [1/12] that approximated the in vivo condition. Among sera that exhibited homotypic neutralizing antibody activity against DV1-3, the level correlated with absence of ADE or infection with the respective serotype. Similarly, a broad heterotypic neutralizing antibody response that included all four serotypes was linked to complete absence of K562 cell infection. In contrast, at higher serum dilutions a correlation between breadth of antibody response and heightened immune enhancement emerged, a pattern identical to that observed among control subjects. These findings support the use of live dengue vaccines and protocols that induce broad serotype-specific neutralizing antibody responses, but they also suggest that clinically relevant immune enhancement may not be likely if this is not uniformly achieved after the first immunization.

Abstract: A live dengue 2 vaccine was tested in 38 volunteers in an evaluation of the safety, infectivity, and immunogenicity of doses of 10(1.8)-10(5.5) plaque-forming units. Twenty yellow fever-immune and 18 yellow fever-nonimmune individuals received 0.5 ml of vaccine sc. Immunization was dose related in yellow fever-immune volunteers, with a 50% immunizing dose of 10(3.3) plaque-forming units. In the group not immune to yellow fever, some but not all recipients of each vaccine dilution were immunized, and no 50% immunizing dose could be estimated. Volunteers immune to yellow fever developed adequate titers of neutralizing antibody to dengue 2 virus and maintained them for at least three years; those not immune to yellow fever developed lower antibody titers that disappeared within six months in half of the cases. More than 40 isolates of dengue 2 virus from 12 volunteers retained the in vitro growth characteristics of the vaccine virus; this result affirmed the genetic stability of the virus. Common clinical signs in immunized individuals were leukopenia (55%), macular rash (15%), and fever (10%).

Sanofi Pasteur, Research and Development Department, Marcy l'Etoile, France.


Abstract: VDV3, a clonal derivative of the Mahidol live-attenuated dengue 3 vaccine was prepared in Vero cells. Despite satisfactory preclinical evaluation, VDV3 was reactogenic in humans. We explored whether immunological mechanisms contributed to this outcome by monitoring innate and adaptive cellular immune responses for 28 days after vaccination. While no variations were seen in serum IL12 or TNFalpha levels, a high IFNgamma secretion was detected from Day 8, concomitant to IFNalpha, followed by IL10. Specific Th1 and CD8 responses were detected on Day 28, with high IFNgamma/TNFalpha ratios. Vaccinees exhibited very homogeneous class I HLA profiles, and a new HLA B60-restricted CD8 epitope was identified in NS3. We propose that, among other factors, adaptive immunity may have contributed to reactogenicity, even after this primary vaccination. In addition, the unexpected discordance observed between preclinical results and clinical outcome in humans led us to reconsider some of our preclinical acceptance criteria. Lessons learned from these results will help us to pursue the development of safe and immunogenic vaccines.

U.S. Army Medical Component AND Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand.


Abstract: Encephalitis caused by Japanese encephalitis virus occurs in annual epidemics throughout Asia, making it the principal cause of epidemic viral encephalitis in the world. No currently available vaccine has demonstrated efficacy in preventing this disease in a controlled trial. We performed a placebo-controlled, blinded, randomized trial in a northern Thai province, with two doses of monovalent (Nakayama strain) or bivalent (Nakayama plus Beijing strains) inactivated, purified Japanese encephalitis vaccine made from whole virus derived from mouse brain. We examined the effect of these vaccines on the incidence and severity of Japanese encephalitis and dengue hemorrhagic fever, a disease caused by a closely related flavivirus. Between November 1984 and March 1985, 65,224 children received two doses of monovalent Japanese encephalitis vaccine (n = 21,628), bivalent Japanese encephalitis vaccine (n = 22,080), or tetanus toxoid placebo (n = 21,516), with only minor side effects. The cumulative attack rate for encephalitis due to Japanese encephalitis virus was 51 per 100,000 in the placebo group and 5 per 100,000 in each vaccine group. The efficacy in both vaccine groups combined was 91 percent (95 percent confidence interval, 70 to 97 percent). Attack rates for dengue hemorrhagic fever declined, but not significantly. The severity of cases of dengue was also reduced. We conclude that two doses of inactivated Japanese encephalitis vaccine, either monovalent or bivalent, protect against encephalitis due to Japanese encephalitis virus and may have a limited beneficial effect on the severity of dengue hemorrhagic fever.

University of Maryland School of Medicine, Baltimore.

Abstract: A dengue-1 candidate vaccine (45AZ5), previously found to be underattenuated in 2 volunteers, was further attenuated by passage in primary dog kidney (PDK) cell cultures. New candidate vaccines prepared from three levels of PDK-passaged virus, PDK-10, PDK-20, and PDK-27, were each injected into 9 or 10 volunteers. There was a significant, progressive decline in viremia, clinical illness, and hematologic changes from low to high PDK cell passage level. PDK-20 infected all 10 vaccinees and induced viremia in 5, transient fever in 3, symptoms that resulted in curtailed activities for < or = 1 day in 4, and neutralizing antibody in all 10, which persisted for > or = 1 year in 5 of 8 vaccinees tested. Progressive passage in PDK cell culture progressively attenuates vaccine candidate strain 45AZ5 for humans. Because passage level PDK-20 may be suitable for healthy adults at high risk of dengue fever, additional clinical trials of this strain are warranted.


Abstract: Laboratory-attenuated strains of each of the four dengue serotypes previously tested as monovalent vaccines in volunteers were combined and tested for immunogenicity, safety, and reactogenicity in 16 dosage combinations. Tetravalent vaccines made using combinations of high (10(5-6) plaque-forming units [PFU]/dose) or low (10(3.5-4.5) PFU/dose) dosage formulations of each of the four viruses were inoculated in 64 flavivirus non-immune adult volunteers to determine which, if any, formulation raised neutralizing antibodies in at least 75% of volunteers to at least three of four dengue serotypes following one or two inoculations. Such formulations, if safe and sufficiently non-reactogenic, would be considered for an expanded Phase II trial in the future. Formulations 1-15 were each inoculated into three or four volunteers (total = 54) on days 0 and 28. Formulation 16 was tested in 10 volunteers, five volunteers inoculated on days 0 and 30, one volunteer on days 0 and 120, and four volunteers on days 0, 30, and 120. Blood was drawn for serologic assays immediately before and one month after each vaccination, and for viremia assay on day 10 after each vaccination. The 16 formulations were safe, but variably reactogenic after the first vaccination, and nearly non-reactogenic after the second and third vaccinations. Reactogenicity was positively correlated with immunogenicity. Similar proportions of volunteers seroconverted to dengue-1 (69%), dengue-2 (78%), and dengue-3 (69%), but significantly fewer volunteers seroconverted to dengue-4 (38%). The geometric mean 50% plaque reduction neutralization test titers in persons who seroconverted were significantly higher to dengue-1 (1:94) than to dengue-2 (1:15), dengue-3 (1:10), and dengue-4 (1:2). Seven formulations met the serologic criteria required for an expanded trial, and three of these were sufficiently attenuated clinically to justify further testing.

Vaccine Trial Center, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand.


Abstract: OBJECTIVE: The safety and immunogenicity of tetravalent live-attenuated dengue vaccines after a three dose vaccination series were evaluated in Thai children. METHOD: One hundred three healthy flavivirus-seronegative schoolchildren ages 5 to 12 years were randomized to receive either dengue vaccine containing 3, 2, 1 and 2 log10 of the 50% cell culture infective dose, respectively, of the live-attenuated dengue vaccine serotypes 1, 2, 3 and 4 per dose (F3212; n = 40) or 3, 3, 1 and 3 log10 of the 50% cell culture infective dose (F3313; n = 42) or purified Vero cell rabies vaccine (control group; n = 21) given in a two dose schedule (3 to 5 months apart). A third dose was administered 8 to 12 months after the second dose to 90 subjects. Safety and immunogenicity were evaluated within 28 days after each injection. RESULTS: No serious adverse event related to the vaccines occurred. Most children experienced mild to moderate fever, rash, headache and myalgia occurring within 12 days after Dose 1 and generally lasting 3 days or less. One subject in Group F3212 had a 1-week dengue-like fever. Reactogenicity was minimal after Doses 2 and 3. Transient mild variations in liver enzymes and hematologic indices were noted mainly after Dose 1. After the third dose 89% of the subjects in Group F3212 seroconverted (neutralizing antibody response, > or =10) to all four serotypes, and all children in Group F3313 seroconverted. CONCLUSION: This study demonstrates a moderate although improvable reactogenicity and high seroconversion rates against the four serotypes of dengue after a three dose schedule of tetravalent live-attenuated dengue vaccine in children.


Abstract: Dengue fever, caused by four serotypes of a mosquito-borne virus, is a growing problem in tropical countries. Currently, there is no treatment or vaccine. We evaluated safety and immunogenicity of two doses, given six months apart, of seven formulations of dengue tetravalent live-attenuated vaccine (containing different concentrations of the component viruses) versus placebo in 59 flavivirus-seronegative Thai adults. The first dose was the more reactogenic. Most volunteers experienced clinically moderate fever, headache, myalgia, eye pain or rash 7-11 days after injection, generally lasting three days or less. Modest decreases in platelets and neutrophils were observed. After one dose, 58% of dengue recipients seroconverted (neutralizing antibody level ≥ or = 1:10) against ≥ or = 3 serotypes; 35% seroconverted against all four. After the second dose, seroconversion was 76% and 71%, respectively. All subjects seroconverted to serotype 3 after one dose. Serotype 4 elicited the lowest primary response but the highest increase in seroconversion after the second dose.

Walter Reed Army Institute of Research, USA.


Abstract: We describe the results of initial safety testing of 10 live-attenuated dengue virus (DENV) vaccine candidates modified by serial passage in primary dog kidney (PDK) cells at the Walter Reed Army Institute of Research. The Phase 1 studies, conducted in 65 volunteers, were designed to select an attenuated vaccine candidate for each DENV serotype. No recipient of the DENV candidate vaccines sustained serious injury or required treatment. Three vaccine candidates were associated with transient idiosyncratic reactions in one volunteer each, resulting in their withdrawal from further clinical development. Increasing PDK cell passage of DENV-1, DENV-2, and DENV-3 candidate vaccines increased attenuation for volunteers, yet also decreased infectivity and immunogenicity. This effect was less clear for DENV-4 candidate vaccines following 15 and 20 PDK cell passages. Only one passage level each of the tested DENV-2, -3, and -4 vaccine candidates was judged acceptably reactogenic and suitable for expanded clinical study. Subsequent studies with more recipients will further establish safety and immunogenicity of the four selected vaccine candidates: DENV-1 45AZ5 PDK 20, DENV-2 S16803 PDK 50, DENV-3 CH53489 PDK 20, and DENV-4 341750 PDK 20.


Abstract: A randomized, controlled, double-blinded study was conducted to determine safety and immunogenicity of five live attenuated dengue vaccines produced by Aventis Pasteur (AvP). The study was completed with 40 flavivirus non-immune volunteers: five recipients of each monovalent (dengue-1, dengue-2, dengue-3, or dengue-4) vaccine, ten recipients of tetravalent (dengue-1, dengue-2, dengue-3, and dengue-4) vaccine, and ten recipients of vaccine vehicle alone. All vaccines were administered in a single subcutaneous dose (range, 3.6-4.4 log(10) plaque forming units). No serious adverse reactions occurred in volunteers followed for 6 months after vaccination. Five vaccine recipients developed fever (T ≥ or = 38.0 degrees C), including four tetravalent vaccinees between days 8 and 10 after vaccination. Dengue-1, dengue-2, dengue-3, or dengue-4 vaccine recipients reported similar frequency of mild symptoms of headache, malaise, and eye pain. Tetravalent vaccinees noted more moderate symptoms with onset from study days 8-11 and developed maculopapular rashes distributed over trunk and extremities. Transient neutropenia (white blood cells < 4000/mm3) was noted after vaccination but not thrombocytopenia (platelets < 100,000/mm3). All dengue-3, dengue-4, and tetravalent vaccine recipients were viremic between days 7 and 12 but viremia was rarely detected in dengue-1 or dengue-2 vaccinees. All dengue-2, dengue-3, and dengue-4, and 60% of dengue-1 vaccine recipients developed neutralizing and/or immunoglobulin M antibodies. All tetravalent vaccine recipients were viremic with dengue-3 virus and developed neutralizing antibodies to dengue-3 virus. Seven volunteers also had multivalent antibody responses, yet the highest antibody titers were against dengue-3 virus. The AvP live attenuated dengue virus vaccines are safe and tolerable in humans. The live attenuated tetravalent dengue vaccine was most reactogenic, and preferential replication of dengue-3 virus may have affected its infectivity and immunogenicity.

Abstract: Four serotypes of monovalent live attenuated dengue virus vaccine candidates were tested for reactogenicity and immunogenicity in 49 flavivirus non-immune adult human volunteers. The four monovalent candidates were then combined into a tetravalent formulation and given to another 10 volunteers. Neutralizing antibody seroconversion rates after a single-dose monovalent vaccination ranged from 53% to 100%. Solicited reactogenicity was scored by each volunteer. A composite index, the Reactogenicity Index, was derived by these self-reported scores. Reactogenicity differed among the four serotype candidates with serotype-1 associated with the most vaccine related side effects. A second dose of monovalent vaccines at either 30 days or 90 days was much less reactogenic but did not significantly increase seroconversion rates. Seroconversion rates in the 10 volunteers who received a single dose of tetravalent vaccine ranged from 30% to 70% among the four serotypes. Similar to the monovalent vaccines, a second dose of the tetravalent vaccine at one month was less reactogenic and did not increase seroconversion. A third dose of the tetravalent vaccine at four months resulted in three of four volunteers with trivalent or tetravalent high-titer neutralizing antibody responses.