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A PHASE I–II STUDY OF LIVE ATTENUATED VARICELLA-ZOSTER VIRUS VACCINE TO BOOST IMMUNITY IN HUMAN IMMUNODEFICIENCY VIRUS-INFECTED CHILDREN WITH PREVIOUS VARICELLA

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Abstract

Herpes zoster, may be severe and recurrent in HIV-infected children. We determined the safety and immunogenicity of live attenuated varicella-zoster virus (VZV) vaccine in 46 HIV-infected children who had experienced varicella. There were no serious adverse events. Two years after vaccination 82% of subjects remained VZV-antibody positive and 60% had VZV-specific cell-mediated immunity. No child developed herpes zoster.

Keywords

Herpes zoster; varicella vaccination; HIV

Primary infection with varicella-zoster virus (VZV) and reactivation of VZV as herpes zoster (HZ) are often serious in HIV-infected children.^{1–5} HZ remains a common infection in HIV-infected children despite the widespread use of highly active antiretroviral therapy. 2–6 HZ in HIV-infected children might be prevented or attenuated by boosting VZV CMI with a live VZV vaccine as has been achieved in healthy elderly persons.^{7–10} Such an approach is likely to be safe, since varicella immunization of relatively healthy seronegative HIV-infected children with CD4⁺ T cells 15% was accomplished safely.^{2,3,11–13}

PATIENTS AND METHODS

Vaccine recipients (n = 46) were 7 to 12-year-old children with perinatally acquired HIV infection who had few or no signs or symptoms of HIV infection, and whose CD4% ranged from 15% to >25% (Table 1). All had a history of varicella and were seropositive for VZV antibodies at study entry. Informed consent was obtained from parents, and assent from children 7 years old. All subjects were receiving HAART and had low or undetectable viral loads.

Vaccine

Oka/Merck live attenuated varicella vaccine (1350 plaque-forming units of virus/0.5 mL at expiry) was injected subcutaneously. The vaccine was stored and handled according to the instructions in the package insert.

Immunologic Testing

Antibodies to VZV were measured by FAMA.¹⁴ VZV-specific CMI was measured by a modified ELISPOT assay¹⁶ and a responder cell frequency assay.^{17,18} Results were reported as spot forming cells/1,000,000 peripheral blood mononuclear cells (PBMC) and responders/100,000 PBMC, respectively.

Plasma HIV RNA Load

The HIV RNA load was quantified using the Amplicor HIV Monitor Test (Roche Diagnostic Systems, Basel, Switzerland) in laboratories certified by the Pediatric AIDS Clinical Trials Group (PACTG). The lower quantification limit was 400 HIV RNA copies/mL of plasma.

Trial Design (Protocol ACTG 391 of the PACTG)

This protocol was similar to protocol PACTG 265,^{11,12} which studied varicella vaccination of VZV-seronegative HIV-infected children. The current study differed in requiring that subjects had a prior history of varicella and were seropositive to VZV by FAMA at study entry. They could not have had HZ; received other vaccines in the recent past; be receiving corticosteroid or other immune suppressing or enhancing therapy; or have a recent exposure to VZV. Subjects received 2 doses of live attenuated monovalent varicella vaccine 8 weeks apart. Adverse reactions were sought by telephone calls to parents weekly for the first 3 weeks after each dose. Parents maintained a diary card for 42 days after vaccination to record possible adverse signs and symptoms, particularly including fever and rash. Subjects with rashes were examined in clinic. Vaccinees had regular laboratory testing that included white blood cell counts and hepatic enzymes. Specific immunologic testing was undertaken before to vaccination; at 1 and 2 months, after the first dose of vaccine; at 1 and 4 months after the second dose of vaccine; and at 1, 1.5, and 2 years after the start of the trial.

RESULTS

The study cohort of 46 children had a mean age of 9.3 years; mean CD4 count of 803 cells/mL³; and mean CD4% of 33%. Their median viral load was 2.7 Log₁₀ copies/mL. Forty subjects reported adverse events (considering the worst grade reported) that were considered unrelated to vaccination. One subject had a grade 1 creatine phosphokinase elevation that was considered possibly treatment related and one subject had a transient grade 2 neutropenia that was considered possibly treatment related. There were 2 grade 1 injection site reactions. No grade 3 or 4 treatment-related adverse events were reported. One child had a vesicle on the right forearm 27 days after the first vaccine dose, from which VZV was not detected. Adverse events were not more common after the second dose compared with the first dose.

VZV-specific immune assessments are presented in Table 1. All vaccinees had positive FAMA titers (1:2) before to vaccination, with a geometric mean titer (GMT) of 9.6 (95% CI = 8.1, 11.3). The proportion of seropositive subjects varied from 82% to 95% thereafter. The FAMA GMT increased significantly 4 weeks after the first dose of vaccine to 11.4 ($P < 0.01$). Thereafter, GMTs ranged between 7.3 and 10.0. The second dose did not further increase the GMT. The median fold-increase in titer was only 2-fold after the first dose of vaccine, which is not a biologically significant increase. Eighteen percent of subjects were

seronegative by this assay 2 years after vaccination. At 1 and 2 years after vaccination the GMT was not significantly different from prevaccination levels.

The ELISPOT assay, which measures anti-VZV effector CD4⁺ T cell responses, was positive in 31% of the participants at baseline, 50% to 54% after the first dose of vaccine, and in 65% after the second dose of vaccine (Table 1). The incidence of positive tests was 48%, except for a 38% incidence at 16 weeks after the second dose of vaccine. There was a statistically significant increase in ELISPOT values after each dose of the vaccine compared with baseline values ($P = 0.04$ for both weeks 4 and 12). The mean increase was 11 spot forming cells/10⁶ PBMC at 1 month after the first immunization. There was no additional increase in ELISPOT values after the second dose of vaccine. The responder cell frequency assay which measures anti-VZV memory CD4⁺ T cell responses, was positive in 59% of study participants at baseline and 62% to 73% after 2 doses of vaccine with the exception of week 12, when data were available on 22 subjects only (compared with 26 to 39 subjects at each of the other time points).

DISCUSSION

This phase I–II study was undertaken to examine the safety and immunogenicity of the licensed live attenuated varicella vaccine in HIV-infected children with prior varicella who were VZV-seropositive. All were receiving HAART and had good preservation of CD4⁺ T lymphocytes and low viral loads. The vaccine appeared to be safe, which was anticipated because it is also well tolerated in HIV-infected children with no pre-existing immunity to VZV.^{11,12}

Administration of VZV vaccine to HIV-infected children had little sustained effect on VZV-specific antibody, even after a second dose. In the study subjects, who were initially chosen because of a positive FAMA test, the subsequent seropositive rate of 82% to 95% in 2 years was consistent with previous reports of subjects with prior varicella who were immunosuppressed by HIV.¹¹

The vaccine appeared to generate an anamnestic VZV-specific ELISPOT response. The magnitude of the response to the vaccine was small, however, across all outcome measures, which makes its biologic significance unclear. Because there was no control group it is possible that these vaccinated children could have had stronger immune responses to VZV than they would have had they not been immunized. The absence of a strong immune response to VZV vaccine in children is very similar to the outcome of a trial in HIV-infected adults in which 2 doses of the licensed varicella vaccine were administered to subjects with >200 CD4 cells. In that trial safety was established, but boosting of VZV-specific CMI responses was limited.^{19,20}

None of the vaccinated children developed clinical HZ during the 2 years of the trial (92 person-years). Although there was no comparator control group, this absence of HZ is of interest given the reported high frequency of HZ in HIV-infected children. ^{1,2,6} In a recent study of similar children on HAART with well-preserved CD4 cells, but somewhat higher viral loads,² a rate of HZ of 4% to 5% of annually (roughly 4 cases per 100 patient-years) was observed in a cohort of unvaccinated HIV-infected children who had a history of varicella.²

In 2 studies of HIV-infected children on HAART who were vaccinated against varicella, the rate of subsequent HZ was low.^{2,3} Thus in assessing the incidence of HZ in HIV-infected children, those vaccinated against varicella and those with past varicella should be considered separately.

Given the limited immune response to the dose administered, this Phase I–II study should be repeated with the more potent licensed HZ vaccine. The HZ vaccine successfully boosted VZV-specific immune responses in healthy elderly subjects who had low levels of VZV-specific CMI8·9; vaccination was associated with a 51% efficacy against HZ.8 Although there is 14 times more virus in the HZ vaccine than in varicella vaccine, the safety profiles from our study and from the use of the varicella vaccine in VZV-seronegative HIV-infected children, suggest that the administration of HZ vaccine to an appropriately chosen cohort of HIV-infected children who have experienced varicella could be safely undertaken.

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Antibody and Cell-Mediated Immune Responses After Live Attenuated Varicella Vaccine in HIV-Infected Children Who Had Natural Varicella Before Immunization

TABLE 1

	Week							
	0	4	8	12	24	52	78	104
FAMA								
Positive (%)	46/46 (100)	45/45 (100)	38/43 (88)	39/41 (95)	32/35 (91)	36/40 (90)	25/29 (86)	32/39 (82)
GMT (95% CI) *	9.6 (8.1–11.3)	11.4 (10–13)	7.3 (5.5–9.6)	10 (8–12.4)	8.7 (6.5–11.5)	8.4 (6.5–10.9)	8.8 (6–12.9)	7.1 (5–9.9)
ELISPOT [†]								
Positive total (%)	9/29 (31)	14/26 (54)	8/16 (50)	17/26 (65)	11/29 (38)	13/27 (48)	12/21 (57)	12/20 (60)
Mean (95% CI)	9 (5–17)	20 (10–42)	25 (10–62)	20 (9–41)	12 (7–23)	15 (9–4)	14 (7–30)	20 (9–42)
RCF [‡]								
Positive total (%)	23/39 (59)	19/33 (58)	15/29 (52)	8/22 (36)	18/29 (62)	18/30 (60)	19/26 (73)	19/29 (66)
GMC (95% CI)	1.1 (0.7–1.7)	1.5 (0.8–2.7)	1.3 (0.7–2.4)	0.4 (0.2–1.0)	1.5 (0.9–2.3)	1.2 (0.6–2.2)	2.3 (1.3–3.8)	1.5 (0.8–2.7)

* CI indicates 95% confidence interval.

[†] ELISPOT assay for VZV-specific CMI was expressed in number of spot-forming cells/ 10^6 PBMC.

[‡] Responder cell frequency assay for VZV-specific CMI were expressed in number of responder cells/ 10^5 PBMC.