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Effectiveness of varicella vaccine in children infected with human immunodeficiency virus (HIV)

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Abstract

Background—Varicella vaccine is now frequently administered to HIV-infected children who remain relatively healthy because it has been shown to be safe and immunogenic, but its effectiveness for this population remains unknown.

Methods—The effectiveness of varicella vaccine in preventing varicella and/or herpes zoster in HIVinfected children was assessed by chart review at two pediatric academic medical centers. These children had proven HIV infection, were receiving antiretroviral therapy, and were closely monitored between 1989 and 2007. Records were examined for immunologic data, antiretroviral therapy, varicella immunization, and the development of varicella or zoster. The vaccine's effectiveness for varicella and for zoster was calculated by subtracting from one, rate-ratios for the incidence rates of varicella or zoster in vaccinated vs. unvaccinated children.

Results—The effectiveness of varicella vaccine for preventing varicella was 82% (95% CI: 24%–99%; p = 0.01) and for preventing zoster was 100% (95% CI 67%–100%; p<0.001). When only those receiving highly active antiretroviral therapy (HAART) were included in this analysis (to assess effectiveness of vaccine independent of the effect of HAART), the vaccine's effectiveness against zoster was 100% (95% CI: 63%–100%; p=0.001).

Conclusion—Varicella vaccine is highly effective in preventing both varicella and zoster in HIV-infected children.

Introduction

HIV-infected children may develop severe varicella, and are >15 times more likely than the general population to develop herpes zoster (HZ), which is often severe [1]. Live attenuated varicella vaccine is safe, immunogenic, and protective against varicella-zoster (VZV) infection in both healthy and certain immunocompromised children [2]. Based on clinical trials, 2 doses of varicella vaccine 2 months apart were recommended in 1999 for relatively healthy HIV-infected children with CD4 cell counts ≥ 25% [3]. Later children with CD4 counts of ≥ 15%

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were safely vaccinated [4]. Although the vaccine is widely used, there is no published information on its effectiveness in these children [5,6]. Therefore we assessed the effectiveness of varicella vaccine in preventing varicella and HZ in this population.

Methods

We conducted a longitudinal cohort study with clinical data collected from 2 units of the Pediatric AIDS Clinical Trials Group (PACTG): Columbia University-New York Presbyterian Hospital and St. Jude Children's Research Hospital. This study was approved by both IRBs.

The medical records of 164 perinatally HIV-infected children between 1989 and 2007, determining whether and when they had received varicella vaccine, developed varicella, and/or developed HZ. All perinatally HIV-infected children were included except for those who developed varicella before one year of age, because varicella vaccine is not given before then. Vaccine was offered to children based on the recommendations of the Centers for Disease Control at the time.

Varicella was defined as an illness with a generalized pruritic vesicular rash with fever, diagnosed by a clinician. HZ was an illness with a unilateral vesicular rash in a dermatomal distribution without another identifiable cause. Laboratory confirmation of VZV usually was not obtained. Immunized children had at least 1 dose of live attenuated varicella vaccine. Highly active antiretroviral therapy (HAART) was defined as receipt of ≥ 3 antiretroviral agents, two non-nucleoside reverse transcriptase inhibitors, and either a protease inhibitor or a nucleoside reverse transcriptase inhibitor. HZ that occurred within 6–8 weeks after initiation of HAART was considered to be a possible instance of the immune reconstitution inflammatory syndrome (IRIS).

The statistical significance of differences of baseline characteristics of groups being compared was assessed with chi-squared tests for categorical variables and with t-tests for continuous variables. All follow-up times were calculated in person-years (P-Y). Rate ratios, their associated 95% confidence intervals and their statistical significance (two-tailed $p \leq 0.05$) were calculated using PEPI [7]. The effectiveness of the vaccine was calculated as 1 minus the rate-ratio.

Incidence rates of varicella were calculated for two periods: the pre-vaccine era for HIV-infected children, 1989–1998 (when none of the children received varicella vaccine) and the vaccine era 1999–2007. For unvaccinated subjects, time 0 was defined as one year of age, and the endpoint for time at risk (when they were censored from the denominator) was either the occurrence of varicella, receipt of varicella vaccine, or the last clinic visit. For vaccinated patients time 0 was the date they received varicella vaccine. Vaccinated subjects were censored at either onset of "breakthrough" varicella or the date of the last clinic visit.

Since HZ is a reactivation of a latent infection, only individuals previously infected with VZV through either natural disease or varicella vaccine were analyzed to assess the vaccine's effectiveness against HZ [8]. Time 0 was either the date of immunization or the date of onset of varicella; subjects were censored at onset of HZ or the last clinic visit.

In the patients who developed natural varicella, HZ incidence rates were calculated for two periods: the pre-vaccine era (1989–1998) and the vaccine era (1999–2007). Rate-ratios for development of HZ among children who had been immunized versus those who had varicella were calculated.

The incidence rates and incidence-rate-ratio for HZ were also calculated for patients at risk of developing HZ among only those who were receiving HAART (to control for the possibility

that HAART alone might decrease the risk of HZ). Time 0 was the date when the patients both had had varicella (or had received varicella vaccine) and were also receiving HAART. Censoring occurred at the date either of onset of HZ or of the last clinic visit.

Results

Half of the subjects were female and 63% were non-Hispanic African Americans. Of 72 vaccinated children, 39 (54%) had received two doses of vaccine. Baseline characteristics of patients who developed varicella, received varicella vaccine and/or developed HZ, such as CD4 counts, were similar and not statistically significantly different (Table 1). In the pre-vaccine era, only 6% of unvaccinated patients were receiving HAART at the onset of varicella; in contrast, after 1998, 63% were receiving HAART when they contracted varicella. Of the 32 patients who developed HZ after varicella, 15 (47%) were receiving HAART (60% in the HAART era). Of the vaccinated patients, 85% were receiving HAART when immunized. None developed HZ.

Vaccine's Effectiveness against Varicella

Unvaccinated children—There were 83 cases of varicella. In the pre-vaccine era (before 1999), the incidence was 64/619 P-Y (103.3/1000 P-Y; 95% CI: 79.6–131.9/1000) (Table 1). In the vaccine era, the incidence was 19/516 P-Y (36.8/1000 P-Y; 95% CI: 22.2–57.5/1000). The attack rate of varicella decreased by 63% since 1999 ($p < 0.001$) (Table 2).

Vaccinated children—Two of 72 (3%) developed breakthrough varicella, 3.9 and 4.7 years after last immunization, respectively; one child received 1 dose of vaccine and the other received 2 doses.,. The incidence of varicella was 2/296 P-Y (6.8/1000 P-Y; 95% CI: 0.82–24/1000) (Table 2). The vaccine's effectiveness against varicella (6.8/1000 P-Y in the vaccinees vs. 36.8/1000 P-Y in the unvaccinated children) was 82% (95% CI: 24%–99%; $p = 0.01$).

Vaccine's Effectiveness against HZ

Unvaccinated children—HZ developed in 32 (39%) of the 83 unvaccinated patients who had had varicella. In the pre-HAART era, the incidence of HZ in the unvaccinated children was 7/116 P-Y (59.4/1000 P-Y; 95% CI: 23.9–122.3/1000). In the post- HAART era, the incidence of HZ in the unvaccinated children was 25/619 PY (40.4/1000 P-Y; 95% CI: 26.2–59.7/1000) (Table 2). This was not significantly different from the incidence of HZ in the pre-HAART era ($p = 0.49$). Median time between varicella and HZ was 4.1 years in the pre-HAART era and was 4.8 years in the HAART era.

Vaccinated children—The 72 HIV-infected children who were immunized were followed for a total of 298 P-Y, and there were no cases of zoster (0/1000 P-Y; 95% CI: 012.2/1000 P-Y); neither of the two children who had breakthrough varicella developed zoster. Median follow-up after immunization was 4.4 years. The vaccine's effectiveness against zoster was 100% (95% CI 67%–100%; $p < 0.001$). (Table 2)

Vaccine's effectiveness against HZ among subjects receiving HAART

Sixty unvaccinated patients who were receiving HAART and who had varicella were followed for 344 P-Y. Fifteen patients developed HZ (median of 6.5 years after initiation of HAART), an incidence of 43.6/1000 P-Y (95% CI 24.4 – 71.9/1000 P-Y).. When the 3 children with possible IRIS HZ were excluded, the incidence of HZ was 12/344 p-y (34.9/1000 P-Y; 95% CI 18.0–60.9 P-Y). Of the 65 vaccinated children who were receiving HAART, none developed HZ, 0/1000 P-Y (95% CIs 0–15.3) (median follow-up of 4 years after initiation of HAART). The vaccine's effectiveness against HZ in these children overall was 100% (95% CI: 63%–

100% ($p<0.01$); 95% CI was 54%–100% when cases with possible IRIS were excluded ($p<0.01$).(Table 2)

Discussion

Before 1999, VZV infections, particularly HZ, were frequent causes of morbidity among HIV-infected children. Varicella vaccine was recommended for HIV-infected children based on safety and immunogenicity but its efficacy in these children was not evaluated. [3,5,6]. Our study indicates that varicella vaccine protects against both varicella and HZ. There was a 63% decrease in the incidence of varicella among unvaccinated children after 1999, likely due to herd immunity from widespread use of vaccine. Despite the lower attack rate of varicella in the vaccine era, however, we were still able to show that immunization was highly protective in the HIV-infected children.

Immunization also protected HIV-infected children against HZ. The Oka vaccine strain can establish latent infection and can reactivate; protection from HZ is probably not entirely related to the Oka strain itself. Possibly protection against HZ is due to the relatively normal immune function in vaccinees when they were immunized[1,9] which may have resulted in only rare skin rashes after vaccination that in turn correlates with a lower risk of subsequently developing zoster. [10]

The incidence of HZ may increase transiently after the institution of HAART, [11,12] often attributed to IRIS. To account for the possibility that some of the cases of HZ could be attributed to “immune reconstitution,” we excluded these cases in one of our analyses. Even when we excluded 3 cases of HZ that developed within 6–8 weeks after starting HAART, the vaccine was still statistically significantly effective in preventing HZ.

HAART was used more frequently after 1997, improving immune function and the quality of life and survival rates in HIV-infected children. In one report, introduction of HAART decreased HZ incidence by 50% in HIV-infected children [13]. In that study, however, vaccinees and those with natural varicella were analyzed together. Another study indicated that even in the HAART era, zoster remained a significant cause of morbidity for unvaccinated HIV-infected children [14]. In a different study in HIV-infected children, it was not possible to determine whether a decrease in HZ was attributable to immunization or to HAART [15]. In our study, by assessing the incidence rates of HZ only in children receiving HAART (vaccinated children and unvaccinated children who had had varicella), we found varicella vaccine to be highly effective in preventing HZ, even if children with possible IRIS were excluded from the analysis. Varicella vaccine, rather than HAART, therefore, appears to be the major factor in the reduction of HZ in immunized patients.

It also did not appear that the explanation for the vaccine’s effectiveness could be that vaccinees had better overall immunity than the unvaccinated children. The median CD4 cell percentage for the unvaccinated and unvaccinated groups were similar, suggesting minimal immunosuppression in both groups.

There are several possible limitations to this study. Our study was observational and not a randomized clinical trial; the data were obtained in a review of medical records. The diagnoses of VZV infection were not laboratory verified. The HIV-infected children included in our study, however, were intensively and prospectively followed under study conditions of the PACTG, and the data are therefore of high quality.

Regarding protection against HZ, the median age of the immunized group was lower than that of the unvaccinated group. Younger children were less likely to have already had varicella and more likely to have been immunized, in comparison with older children. However, there is

evidence that the age at the time of the primary infection with VZV, except in children less than one year of age, is unrelated to the risk of zoster unlike that in adults [20].

In summary, our data show that varicella vaccine was highly effective in preventing varicella and HZ in a cohort of perinatally-HIV-infected children followed between 1989 to 2007. Additional follow-up over a longer period, with larger numbers of subjects may be useful to confirm our findings.

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Table 1

Baseline demographic and clinical characteristics of study HIV-infected children

Varicella/Vaccinated Patients	**Natural Varicella**		**Vaccinated**
	Pre-Vaccine Era (1989–1999)	**Vaccine Era (1999–2007)**	
No. of patients	64	19	72
CDC clinical class, *n* (%)	9 (14)	1 (5)	20 (28)
A	10 (16)	4 (21)	19 (26)
B	28 (44)	9 (48)	19 (26)
C	16 (25)	4 (21)	14 (20)
Unknown	1 (1)	1 (5)	0 (0)
Median age, *y*	3.87	5.97	3.66
Median CD4+ cells/μL at varicella/vaccine	760[a]	820[b]	1161
Median CD4+ cell % per μL at varicella/vaccine	25[a]	31[b]	32
CD4+ cells, *n* (%)≥25%	20[a] (57)	11[b] (69)	62 (86)
15%–24%	8[a] (23)	3[b] (19)	10 (14)
<15%	7[a] (20)	2[b] (12)	0 (0)
Median HIV-1 plasma viral RNA/mL at varicella/vaccine	3,123,422[a]	3967[b]	399
HAART @ varicella/vaccine, *n* (%)	4 (6)	12 (63)	65 (90)
VZIG treatment, *n* (%)	10 (16)	2 (11)	6 (8)
Zoster Patients	**Pre-HAART Era (1989–1996)**	**HAART Era (1997–2007)**	
No. of patients	7	25[d]	
CDC clinical class, *n* (%)	1 (14)	2 (8)	
A	0 (0)	3 (12)	
B	5 (72)	9 (36)	
C	1 (14)	10 (40)	
Unknown	0 (0)	1 (4)	
Median CD4+ cells/μL at HZ	400	407	
Median CD4+ cell/μL %/ at HZ	18	24	
CD4+ cells, *n* (%)≥25%	2 (29)	11 (44)	
15%–24%	3 (42)	10 (40)	
<15%	2 (29)	4 (16)	
Median HIV-1 plasma viral RNA/mL at HZ	10,118[c]	12,580	
HAART at time of HZ, *n* (%)	0 (0)	15 (60)	

[a] Information available on 35/64 patients

[b] Information available on 16/19 patients

[c] information available on 1/7 patients

[d] 3/25 HZ cases were possibly due IRIS

Table 2

Incidence rates of varicella and HZ in HIV-infected children who were either vaccinated against varicella or had natural infection

	Varicella[x]	
Group	**n**	**Incidence**
Unvaccinated Pre vaccine era	64	103.3/1000 P-Y
Unvaccinated, Vaccine era	19	36.8/1000 P-Y*
Vaccinated[xx]	2	6.8/1000 P-Y
		Zoster
Unvaccinated, pre-HAART era	7	59.4/1000P-Y
Unvaccinated, HAART era	25	40.4/1000 P-Y
Unvaccinated on HAART	15	43.6/1000 P-Y
Unvaccinated on HAART, excluding IRIS	12	34.9/1000 P-Y
Vaccinated	0	0/1000 P-Y

*Decrease in incidence in vaccine era of 63%, compared to the pre-vaccine era

[x]83 unvaccinated children developed varicella
32 subsequent cases of HZ in this group

[xx]72 Vaccinated children; 2 developed breakthrough varicella, 0 developed HZ

The differences in incidence of varicella and zoster after vaccination are significantly lower in vaccinees than following natural infection ($p<0.01$). (Details in text) The effectiveness of varicella vaccine in preventing varicella was 82%, and in preventing zoster was 100%.