Live Attenuated Varicella Vaccination in Immunocompromised Children

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SUMMARY Live attenuated varicella vaccine (OKA strain) was administered to 42 children ranging in age from three to 13 years, they consisted of nine normal controls, 21 children on chemotherapy for acute leukaemia and lymphoma, and 12 children receiving steroid treatment. The immunisation was performed without suspending the administration of immunosuppressive agents in an attempt to stop the spread of varicella infection that was occurring at the time in the paediatric ward. After vaccination, seven immunocompromised children developed clinical varicella within 16-41 days. The symptoms were mild to moderate in all except one who had severe disseminated clinical symptoms. The attempt to isolate and identify vaccine virus markers in these patients was not successful, but there was no further spread of varicella in the paediatric ward. The overall seroconversion rate as determined by immune adherence haemagglutination test was found in 85 per cent of the vaccinees at three months after vaccination and significant antibody level persisted for 15 months in 60 per cent of them. Children with acute leukaemia and lymphoma had a good antibody response (93.3%) which was similar to that of normal children (75%) even without suspending cytotoxic drugs at the time of vaccination. Poorer antibody response (50%) was found in children who received steroid treatment. Positive skin test to varicella antigen was found in 50 per cent of the vaccinees at one month after vaccination; it declined to 31.5 per cent at six months. Only 6.2 per cent of the vaccinees had a positive skin reaction at 9-12 months. It was concluded that live attenuated varicella vaccine (OKA strain) is sufficiently safe and immunogenic in immunocompromised children even without suspending immunosuppressive agents at the time of vaccination. In addition, this vaccine was found to be effective for preventing the spread of varicella in the paediatric ward.

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Varicella infection is often severe, or even fatal, in children with acute leukaemia and in other immunocompromised hosts.[1,2] During the period February 1981 through March 1982, epidemics of varicella-zoster virus (VZV) occurred twice in paediatric wards at Siriraj Hospital, especially among patients with nephrotic syndrome receiving steroid therapy and children on chemotherapy and/or irradiation for their malignancies. Five of 38 (13.2%) children with malignancies, mostly acute leukaemia and lymphoma, who contracted varicella died in spite of intensive treatment with passive immunisation and antiviral therapy.[3] As has been observed in other infectious diseases, active immunisation appears to be the best alternative to stop the epidemics and to prevent additional deaths. Recently a live varicella vaccine has been developed and safely used for children with chronic diseases who had been receiving steroid therapy as well as for those with acute leukaemia and other malignant diseases receiving chemotherapy.[4-10] Immediate vaccination has been reported to be effective for preventing the spread of varicella in the hospital without serious complications.[4,11-14] In the present study, we attempted to vaccinate such children both in the hospital and in the out-patient clinic with live attenuated varicella vaccine (OKA strain) without suspending immunosuppressive agents in order to stop the spread of varicella infection, and to evaluate

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whether these immunocompromised children, who were at high risk of developing severe varicella, would be able to respond adequately and safely to this vaccination.

MATERIALS AND METHODS

Live attenuated varicella vaccine (OKA strin)[15] was given to 42 vaccinees in March and April 1982 at the Department of Paediatrics, Siriraj Hospital. The vaccinees, ranging in age from 3 to 13 years, were divided into three groups (Table 1). Group 1 consisted of six children (mostly the patients' siblings), one case of beta-thalassaemia haemoglobin E disease and two cases of acute lymphoblastic leukaemia in remission who had not received chemotherapy for 1 to 3 years and who were in good health. These patients served as a control group and received no chemotherapy or steroid treatment. Group 2 consisted of 18 cases of acute lymphoblastic leukaemia (ALL) in remission who were still receiving chemotherapy and three cases of Hodgkin's disease also on treatment with irradiation and/or chemotherapy. Group 3 consisted of three cases of aplastic anaemia, seven cases of nephrotic syndrome, and one case each of systemic lupus erythematosus (SLE) and myeloproliferative disorder. All patients in the latter group received corticosteroid treatment ranging in duration from one month to two years. Informed consent was obtained from all vaccinees and/or their parents. Before vaccination, haematologic examination and delayed hypersensitivity skin tests to purified protein derivative (PPD), *Candida,* mumps and trichophyton antigens were done to examine the immunological potential of the patients.[16] Previous history of varicella and pre-existing antibody to VZV were also determined to evaluate immunity to VZV prior to vaccination. Vaccine was administered subcutaneously, usually in the left deltoid area; the dose was 0.5 ml (containing 500 plaque-forming units/dose). It was administered without suspending immunosuppressive agents. After vaccination, the children in the hospital were observed daily; those at the outpatient clinic were observed at weekly intervals by physicians. Parents of the outpatients were asked to record and report in the form provided, data on body temperature and other clinical manifestations that developed. When skin lesions were reported, physicians examined the patients carefully and obtained lesion scrapings for viral culture. Antibody titres to VZV were measured by microcomplement fixation (CF) method[17] and the immune adherence haemagglutination assay (IAHA)[18,19] before and at 1, 3, 6, 9, 12 and 15 months after vaccination. In our laboratory, a VZ-CF titre of $\geqslant$ 1:8 and a VZ-IAHA titre of $\geqslant$ 1:2 were considered to indicate that the vaccinees were immune to VZV. Skin tests with varicella antigen were also performed at 1, 6 and 9 months after vaccination.[20,21] One tenth millilitre of viral antigen was injected intracutaneously at the forearm and the skin reaction was

Table 1 Patients' grouping, underlying diseases, age and immune status of vaccinees before vaccination.

Group*	Underlying disease	No. of cases	Age in years			DHST positive (%)	Immunity to varicella	
			3 – 5	6 – 10	11 – 13		CF positive (%)	IAHA positive (%)
1	Normal	6	4	1	1			
	β-thalassaemia HbE	1		1		88.9	0	0
	ALL in remission (off treatment)	2		2				
2	ALL in remission (on treatment)	18	6	12		66.7	4.7	9.5
	Hodgkin's disease (on treatment)	3		2	1			
3	Aplastic anaemia	3		2	1			
	Nephrotic syndrome	7	1	5	1			
	SLE	1		1		81.8	0	0
	Myeloproliferative disorder	1		1				
Total		42	11	27	4	75.6	2.4	4.8

ALL = Acute lymphoblastic leukaemia
SLE = Systemic lupus erythematosus
DHST = Delayed hypersensitivity skin test
CF = Complement fixation test
IAHA = Immune adherence haemagglutination test

*1 = no treatment; 2 = on chemotherapy; 3 = on steroid treatment

evaluated 48 hours later. The erythematous change and an induration larger than 5 mm in diameter was considered to be positive, indicating cell-mediated immunity to varicella. The Student's t-test was used for the statistical analysis.

RESULTS

In the haematological and immunological check-up prior to vaccination, the number of white blood cells was more than 2,000 per cu mm in all cases including three patients with aplastic anaemia. Positive delayed hypersensitivity skin test was detected with at least one of the four antigens tested (mostly with *Candida* antigen) in 88.9 and 81.8 per cent of the patients in group 1 and group 3 respectively but in only 66.7 per cent of those in group 2 (Table 1). Except for three patients in group 2, pre-existing antibody to varicella was not detected in any of them. The clinical symptoms, including peak body temperature elevations during the first 21 days after immunisation and the appearance of skin lesions following vaccination, are shown in Table 2. Of the 42 children who received live attenuated varicella vaccine (OKA strain), nine of them had temperature elevation of between 37.5 and 39°C during the first 21 days after immunisation, a phenomenon that could not be explained by concurrent illness and was thought to be vaccine-related. The body temperature elevation in these nine cases lasted only 1-2 days and none of them had a skin rash. Seven of 42 patients (16.7%), six in group 2 (ALL in remission) and one in group 3 (myeloproliferative disorder) developed skin lesions consisting of papular and small vesicular eruptions 16-41 days after vaccination. The appearance of skin rashes was associated with a low-grade fever of 37.3 to 38.5°C for a few days in all the patients affected.

Two patients had moderate, generalised skin lesions (more than 20) but no other systemic symptom was observed. One patient (ALL in remission) who had fewer than 20 vesiculopapular skin lesions developed severe systemic symptoms including abdominal pain, jaundice, elevation of SGOT and serum amylase levels. All three of the latter patients were treated with convalescent varicella plasma transfusion and adenine arabinoside and they recovered without any serious complications. Virus isolations and identification of vaccine virus markers were attempted unsuccessfully from these patients' aspirated vesicles.

The CF and IAHA serological assays were used to measure antibody responses following immunisation; the results are shown in Table 3. Seroconversion by IAHA assay was found in 75 per cent and 93.3 per cent of the patients in group 1 and group 2 respectively 1-3 months after vaccination but in only 50 per cent of those in group 3. Seroconversion measured by the immune adherence haemagglutination test in all three groups

Table 2 Number of patients with vaccine-related temperature elevation and skin lesions after vaccination

Complications	Days after vaccination					
	0 – 7	8 – 14	15 – 21	22 – 28	29 – 35	36 – 42
Body temperature (°C)						
< 37.5						
37.5–38.5	1	3	1			
> 38.5	2		2			
Skin lesions (number)						
< 5			1		1	
5–20				1	1	1
> 20			2			

Table 3 Serological responses in VZ vaccinees following immunisation with live attenuated varicella vaccine (OKA strain)

Group*	No. of cases	Seroconversion after vaccination (%)									
		1 month		3 months		6 months		9 months		12 – 15 months	
		CF	IAHA	CF	IAHA	CF	IAHA	CF	IAHA	CF	IAHA
1	9	12.5	75	0	66.6	0	60	0	75	0	66.6
2	21	57.1	80.9	73.3	93.3	61.5	84.6	33.3	83.3	35.7	64.3
3	12	18.2	50	0	50	20	40	0	16.7	0	33.3
Total	42	37.5	71.8	64.7	85	39.1	69.6	12.5	56.3	25	60

*1 = no treatment; 2 = on chemotherapy; 3 = on steroid treatment
CF = Complement fixation test; IAHA = Immune adherence haemagglutination test.

was found in 85 per cent of the vaccinees at three months after vaccination. The geometric mean titres as measured by the IAHA test in each group are shown in Figure 1. It may be seen that the antibody response began to rise in the first month, reached a peak at approximately three months after vaccination and lasted for 15 months. The antibody titre, however, declined gradually and only 60 per cent of the patients in all three groups had significant antibody titre (mean $\log_{10}$ titre of 0.9-1.5) 15 months after immunisation. Skin test reaction with varicella antigen was examined in 27 patients after vaccination (Table 4). One month after immunisation, positive skin test was found in 60 per cent and 50 per cent of the patients in group 1 and group 2 respectively but not in group 3. The percentage of those with a positive skin test declined to 33.3 per cent in both group 1 and group 2 at six months; no patient showed a positive skin reaction when tested 9-12 months after vaccination. One patient in group 3, who previously had a negative skin test to varicella antigen, had a positive skin test at nine months.

The details of the immunological status prior to vaccination and the immune response after immunisation of seven patients who developed clinical varicella are presented in Table 5. Five of seven patients had a positive delayed hypersensitivity skin test (DHST) to recalled antigens prior to immunisation but none of them showed positive skin test to varicella antigen at the time that clinical varicella appeared. All of these patients were able to produce varicella antibody, mostly in high titre; significant antibody titre could be detected in five cases prior to or shortly after the appearance of skin rashes. However, patient No. 6, who developed severe systemic symptoms of varicella, had a negative skin test to varicella antigen and no detectable varicella antibody when clinical varicella appeared, but the varicella skin test became positive along with a rising of antibody titre at six months after vaccination. Besides the appearance of varicella in these seven patients, no further case of varicella was observed and the spread of varicella in the paediatric ward at Siriraj Hospital was stopped.[22]

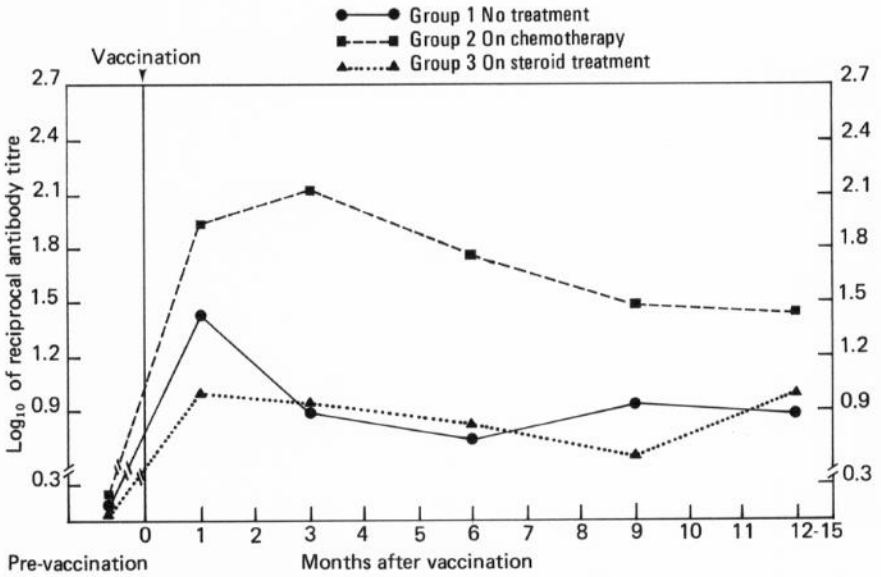

Fig. 1 Antibody response in 42 vaccinees after live attenuated OKA-strain varicella vaccination as measured by immune adherence haemagglutination test (IAHA), showing the geometric mean titre in each group.

Table 4 Varicella skin test in vaccinees after vaccination with VZ vaccine.

Group*	No. of patients tested	VZ skin-test-positive after vaccination (%) (No. positive/No. tested)		
		1 month	6 – 7 months	9 – 12 months
1	7	60 (3/5)	33.3 (2/6)	0 (0/6)
2	18	50 (6/12)	33.3 (4/12)	0 (0/10)
3	2	0 (0/2)	0 (0/2)	100 (1/1)
Total	27	50	31.5%	6.2

*1 = no treatment; 2 = on chemotherapy; 3 = on steroid treatment

DISCUSSION

A live, attenuated VZV vaccine, designated as the OKA strain, was developed by Takahashi and has been studied in clinical trials in Japan since the early 1970s.[4,15] Since then, this vaccine has been studied extensively both in Japan and the United States along with another VZV strain, referred to as KMcC, which was developed in the United States.[5,6,23] The rationale for using this vaccine, in contrast to other viral vaccines, was to immunise immunocompromised children since there was increasing evidence of severe and stormy clinical effects with a mortality rate of about 10 per cent in leukaemic children who contacted chickenpox as well as in those with neonatal varicella.[1,2,5,23]

Table 5 Immune status prior to vaccination and immune response after vaccintion in seven vaccinees who developed clinical varicella. (Underlying diseases: No. 1-6 = acute leukaemia in remission; No. 7 = myeloproliferative disorders).

No.	Age (yrs)	Sex	I.P.* (day)	Severity	Day after vaccination	DHST†	VZ skin@ test	Antibody titre☆	
								CF	IAHA
1	8	F	41	mild	0	pos**	....	<8	<2
					46	....	neg**	<8	16
					98	....	....	32	512
					230	....	neg	8	128
					480	....	neg	8	128
2	5	M	25	mild	0	pos	....	<8	<2
					35	....	neg	32	256
					98	....	....	32	32
					270	....	neg	<8	8
					462	....	....	<8	8
3	3½	M	16	mild	0	neg	....	<8	<2
					30	....	....	32	256
					90	....	neg	32	128
					197	....	neg	8	128
					480	....	neg	8	32
4	3½	M	17	moderate	0	neg	....	<8	<2
					40	....	neg	32	2,048
					112	....	....	32	256
					210	....	neg	16	128
					457	....	neg	8	64
5	10	F	21	moderate	0	pos	....	<8	<2
					27	....	neg	<8	<2
					198	....	pos	16	32
6	7	M	34	severe	0	pos	....	<8	<2
					35	....	neg	<8	<2
					178	....	pos	64	1,024
					450	....	pos	32	256
7	6	M	30	mild	0	pos	neg	<8	<2
					34	....	neg	16	32
					168	....	neg	16	8

*I.P. = Incubation period = first day of skin rash after vaccination
†DHST = delayed hypersensitivity skin test prior to vaccination
@Varicella zoster skin test
☆Reciprocal serum dilution
CF = Complement fixation test
IAHA = Immune adherence haemagglutination test
**pos = positive, neg = negative

After it was found that the vaccine was immunogenic and caused no side effects in normal children, vaccination of immunocompromised children was investigated especially in those with acute lymphocytic leukaemia.[4-9] The majority of leukaemic children were immunised in conjunction with a suspension of anticancer chemotherapy starting from one week before vaccination and continuing for one week after vaccination.[8,9] When it was apparent that there was no serious adverse reaction, vaccination was performed without discontinuing chemotherapy, since such a procedure is preferable from the point of view of treating acute leukaemia and for immediate vaccination in urgent cases when varicella occurs in a children ward with high-risk susceptibilities.[10-14] Over 90 per cent of the vaccinees in both groups developed antibody to VZV with minimal complications after vaccination, although the clinical reactivity rate (rash or fever) was 71 per cent in leukaemic patients without suspending chemotherapy.[10,23] The results of these previous studies suggested that immediate use of attenuated varicella vaccine

without suspension of chemotherapy may be safe and effective in children with acute leukaemia or other malignancies if they are immunologically not in an extremely suppressed condition. In the present study, 33 children with acute leukaemia, Hodgkin's disease, nephrotic syndrome and other diseases were given a live attenuated varicella vaccine without suspending the administration of immunosuppressive agents in an attempt to stop the spread of varicella in the ward.[22] The cell-mediated immunity in these patients prior to vaccination was not markedly suppressed which was an effect similar to that observed in the previous report.[16] After vaccination, seven of these 33 patients (21.2%) developed clinical varicella but the symptoms in most cases were not troublesome, fever was mild and only countable vesiculopapular skin lesions were found, except in one patient with acute leukaemia who had severe systemic symptoms compatible with disseminated varicella. Ha *et al* also found severe varicella symptoms in a child with lymphosarcoma after vaccinating the young patient without first suspending chemotherapy.[10] It is not clear whether the clinical varicella observed in our patients was caused by vaccination or natural infection since there were several cases of varicella in the paediatric ward at the time of vaccination; attempts to determine whether the virus was derived from the vaccine or the wild type, were unsuccessful. Ozaki *et al* noted that vaccination of acute leukaemic children shortly after they had been exposed to varicella in a children ward but without suspending chemotherapy modified the clinical varicella so that only mild symptoms appeared, whereas the unvaccinated patients succumbed to severe varicella with one case proving fatal.[11] All children with mild and moderate varicella symptoms in our study demonstrated antibody to varicella at the time of the appearance of clinical varicella but no detectable antibody was found in the severe cases. This indicated that antibody may have modified the course of varicella symptoms in our patients. Baba *et al* noticed that skin reaction to varicella antigen became positive as early as five days after vaccination, 7-9 days before the appearance of neutralising antibody; this early appearance of cellular immunity after vaccination seems to be correlated with the prevention of the spread of varicella in the hospital.[21] This observation is in agreement with our findings that all seven patients who developed clinical varicella had a negative skin test to varicella antigen at the time of the appearance of skin rashes, but that the varicella skin test later became positive in two cases.

In the present study, the measurement of the antibody response by the IAHA test is far more sensitive than the CF test as described in detail elsewhere.[19] The seroconversion rate by the IAHA test after varicella vaccination in patients with acute leukaemia and lymphoma without first suspending chemotherapy (93.3%) was comparable with that of normal children (75%), but it was significantly lower in patients who received long-term steroid therapy (50%, $p < 0.05$). These findings suggested that the majority of patients with acute leukaemia and lymphoma are able to produce antibody after vaccination in spite of the continuation of chemotherapy, but that those who received steroid treatment have poorer antibody response. However, the seroconversion rate in our study was lower than that of the previous studies of the same OKA strain of varicella vaccine in Japan.[23] Izawa *et al* immunised children with acute leukaemia or other malignancies using a live varicella vaccine during a two-week period when anticancer chemotherapy was suspended and found that there was a 100-per-cent seroconversion rate with persistence of neutralising antibody lasting for at least two years after vaccination.[8] Later, Ha *et al* vaccinated children with acute leukaemia and other malignancies without suspending anticancer therapy and also obtained almost 100-per-cent seroconversion.[10] The lower seroconversion rate in our study may be due to the difference in the sensitivity of methods used to detect varicella antibody since we used IAHA methods; neutralisation test (NT) was used in the previous studies.[19]

Development and persistence of VZV-specific cellular immunity following vaccination is crucial to the success of varicella vaccination. Using VZV-specific lymphocyte proliferation following immunisation of healthy children, Arbeter *et al* demonstrated specific cellular immune responses to varicella virus antigens in almost 100 per cent of the vaccinees.[7] A similar result was obtained when varicella skin test was used to evaluate cellular immune responses in normal children after vaccination with varicella.[20,21] In patients with acute leukaemia and other malignancies, Ha *et al* observed that skin test reaction to varicella antigen was positive at six weeks after vaccination in all the children examined, but no long-term follow-up information was reported.[10] In our study, however, only 50-60 per cent of the patients showed positive varicella skin test at four weeks after vaccination and the percentage with positive varicella skin test decreased progressively at six and 9-12 months after vaccination. Since only a small number of patients were evaluated in our study for cellular immunity by varicella skin test, no definite conclusion could be established. Long-term follow-up of vaccinees will give a more complete understanding of the duration of cellular immunity and the relationship of cellular immune mechanisms to the protection from natural infection and prevention of vaccine virus reactivation.[23] In this study, three leukaemic patients had been exposed to natural varicella at home

or in their class rooms five months, six months, and one year after vaccination respectively. All were free from any varicella symptoms. The experience with the OKA strain of varicella vaccine in Japan and our additional data support the conclusion that the lyophilised, live attenuated varicella vaccine (OKA strain) is sufficiently safe and immunogenic in leukaemic children and those with other underlying diseases even without suspending the administration of immunosuppressive agents at the time of vaccination. In addition, live-attenuated varicella vaccine was found to be effective for preventing the spread of the disease in the paediatric ward.

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