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IMMUNE RESPONSE INDUCED BY LIVE ATTENUATED VARICELLA VACCINE AND SHORT TERM FOLLOW-UP ON IMMUNITY OF THE VACCINATED CHILDREN

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Live attenuated varicella vaccine (Oka strain, 500 to 750 PFU) was inoculated into 234 children with various underlying diseases. Varicella-zoster virus (VZV) specific immune adherence hemagglutination antibody developed in 95% of initially seronegative subjects. VZV specific cellular immune responses were detected in 91% of subjects within 6 weeks after vaccination. A preliminary survey of 46 vaccinated normal-risk subjects during the first and the third year revealed excellent protection with the exception of one case who had not shown any antibody response at the fourth week.

INTRODUCTION

Infections due to varicella-zoster virus (VZV) in immunologicaly handicapped subjects are often life-threatening, although the primary infection, chickenpox, is generally mild in normal children. We initiated use of live attenuated varicella vaccine from 1978. In five hospitals, over 200 subjects with various underlying illnesses were inoculated until 1983. The main purpose of the vaccination was to prevent the spread of varicella infection which had occurred unpredictably among hospitalized children in wards. Normal susceptible subjects were also inoculated with this vaccine, upon request. In this report, we describe the humoral and cellular immune responses of these subjects after administration of the vaccine, and some preliminary results supporting the protective efficacy of the vaccine.

MATERIALS AND METHODS

For each patient 500 to 750 PFU of the Oka strain of varicella vaccine (Takahashi et al., 1975) was employed. The patient's VZV specific antibody response was determined by the immune adherence hemagglutination (IAHA) method. Their VZV specific cellular immune response was measured by the lymphocyte transformation test, as has been previously described (Kumagai et al., 1980a, b).

RESULTS

As shown in Table 1, 234 children with various underlying diseases received the vaccine. The numbers of patients who were vaccinated during on-going immunosuppressive treatment are indicated in parentheses. Among 5 patients with ALL, adverse reactions including

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TABLE 1. *Diseases and the number of subjects who received varicella vaccine*

Diseases	Cases
Malignance	
ALL	5 (5)[a]
AML	1 (1)
Lymphoma	1 (1)
Neuroblastoma	1 (1)
Renal disease	
Nephrose	22 (15)
Nephritis	7 (3)
Neuromuscular	
CP	26
Epilepsy	5
PMD	19
WH	4
Others	22
Metabolic disease	14
Allergy	7 (3)
Others	28 (1)
Normal subjects	28 (1)
Total	234 (30)

( )[a] Cases with immunosuppressive therapy.

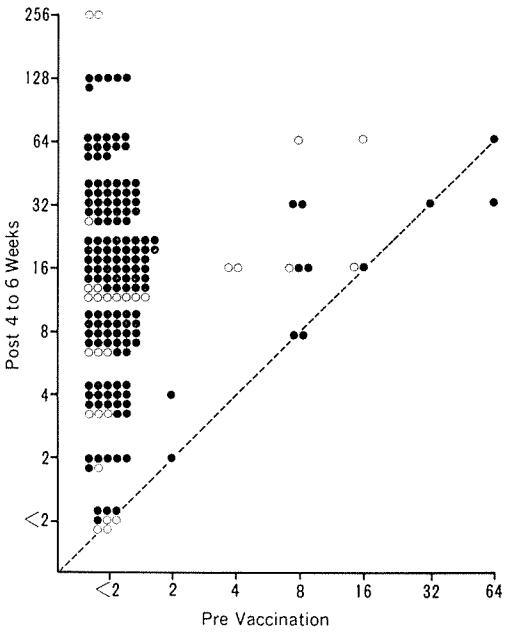

FIGURE 1. Development of VZV specific IAHA antibody following administration of live attenuated varicella vaccine. Solid circles indicate normal subjects and open circles indicate subjects who were receiving immunosuppressive drugs.

a small to moderate numbers of vesicles were observed in 3 patients during the 18th and 28th day after vaccination. These patients were severely immunosuppressed due to induction therapy for their original diseases. A few vesicles were also observed in 4 cases with nephrotic syndrome at 10 to 20 days following vaccination. They were also receiving a moderate dose of predonisolon. However, since these subjects received varicella vaccine as an emergency measure, it was difficult to decide whether these reactions were actually due to the vaccine; particularly, in 3 cases who had the reaction within 2 weeks after vaccination.

The response of VZV specific IAHA antibody 4 to 6 weeks after vaccination are shown in Fig. 1. Patients under immunosuppressive or anti-leukemic therapy are indicated by open circles. Antibody responses were observed in 95% of 165 initially seronegative subjects and the geometric mean antibody titer was $2^{3.8}$ in these subjects. In general, the antibody response did not seem to be influenced by a minimum dose of immunosuppressive drugs if these patients were in remission. However, 4 patients with severely immunosuppressed conditions failed to respond to vaccination at the fourth week. This clearly indicates the importance of immunological evaluation for such patients prior to vaccination.

The antibody titers measured during the first and third years compared to those at 4 to 6 weeks after vaccination, are shown in Fig. 2. The average antibody response of $2^{3.0}$ during this period was slightly lower than that of $2^{3.8}$ at the fourth or sixth week. However, 4 cases showed a significant increase in antibody activity, suggesting the presence of a boosting effect of the VZV immunity. Indeed, 1 of these 4 cases had a history of household exposure to varicella a half year after vaccination.

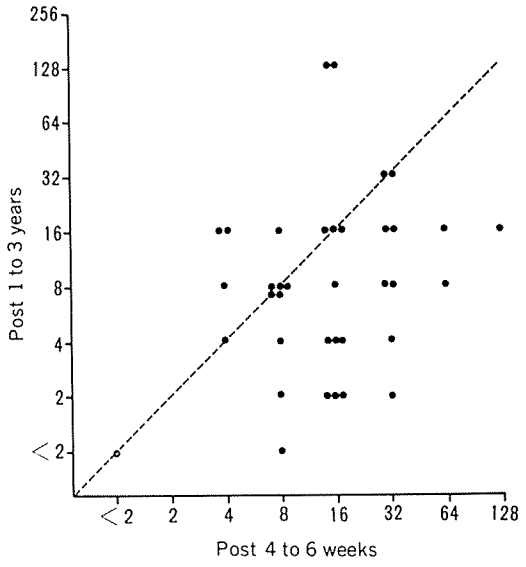

FIGURE 2. Titers of VZV specific IAHA antibody 1 to 3 years after administration of live attenuated varicella vaccine, as compared to those of the antibody 4 to 6 weeks after the vaccination.

Cases who had VZV infection after vaccination are shown in Table 2. The three cases at the top were subjects who were followed in our hospital due to their underlying diseases. The first case, T.S., had vesicles 18 days after vaccination, and also had herpes zoster after 7 months when he received anti-leukemic therapy against a relapse of leukemia. The second case had been receiving standard maintenance therapy. No antibody response at the fourth week was detected in this patient. The third case was also rsceiving therapy against a relapse of malignant lymphoma when she was exposed to varicella in the hospital. The fourth case was detected in our preliminary survey aimed at measuring the degree of protection in 46 vaccinated subjects. The patient had cerebral palsy as an underlying disease and had not shown any antibody response at the fourth week after vaccination.

VZV specific cellular immune responses as measured by in vitro lymphocyte transformation are shown in Fig. 3. The responses of these subjects were arranged according to their antibody activity both at the second week and at the fourth or sixth week. Although the in vitro proliferative response in some subjects appeared to be transient, 91% of these 77 subjects showed a significant cellular immune response of more than 3 with stimulation index during these periods. It is interesting to note that a number of patients showed a significant response at the second week, at which time IAHA antibody had not been detected in the serum. Such an early celluar immune response appears to be related to the unique character of the vacaine which makes it employable as an emergency measure to prevent nosocomial spread of varicella.

DISCUSSION

Nosocomial infection with varicella often disturbs the daily medical care of hospitalized patients. Such a common procedure of preventing the spread of virus infection as isolation of the initial case is not effective for this disease. We used this vaccine largely as an emergency measure, and were able to prevent

TABLE 2. *VZV infection in vaccinated subjects*

Patients	Age	Illness	IAHA antibody		Varicella (V) or Zoster (Z)	Interval
			Pre	4 weeks		
T. Sugiura	5 yr	ALL	<2	64	Z	7 mo
N. Abe	10 yr	ALL	<2	<2	V	2 yr & 6 mo
K. Takeda	8 yr	ML	<2	8	V	3 yr
N. Kasahara	4 yr	CP	<2	<2	V	11 mo

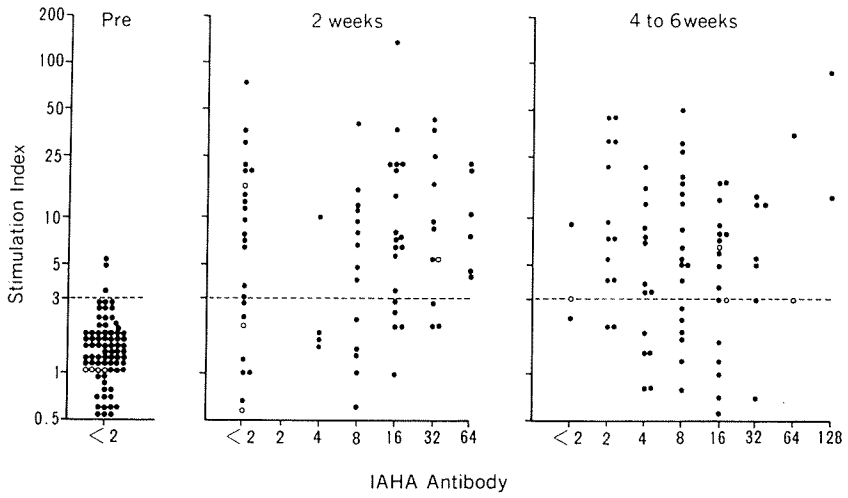

FIGURE 3. Lymphoproliferative response to VZV in vitro following administration of live attenuated varicella vaccine, as arranged according to individual VZV specific IAHA antibody.

the spread of varicella in the wards of every hospital involved. The rapid development of VZV specific cellular immunity as well as of VZV specific antibody seemed to be attributable to this early effect, as has been previously described (Asano et al., 1975; 1977; Kumagai et al., 1980a, b).

Inadvertent administration of the vaccine to severely immunosuppressed patients, however, resulted in occurrence of a few subjects with a moderate degree of varicella rash. This clearly indicates the importance of immunological evaluation of such patients prior to vaccination (Izawa et al., 1977).

VZV specific antibody activity developed in 95% of initially seronegative subjects at the fourth or sixth week after vaccination. Although mean antibody activity at 1 to 3 years was slightly lower than that of the initial level, a small number of subjects exhibited a rise in VZV antibody activity, suggesting the presence of a boosting effect of VZV immunity. However, the presence of a few normal-risk subjects who failed to show any antibody response may suggest the necessity for increasing the vaccine dose to more than 700 PFU. Revaccination of subjects who have to receive continuous immunosuppressive therapy should also be considered.

Our preliminary survey of 46 vaccinated children 1 to 3 years after vaccination detected 11 cases with definite exposure to the infection. Except for one case who showed no antibody response at the fourth week, none of the subjects had any evidence of varicella during this period. Live varicella vaccine is quite effective in protecting susceptible children from the infection and can be employed with minimum risk as long as caution is exercised with regard to the immunological condition of the subjects who receive the vaccine.

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