BIKEN JOURNAL Vol. 23 89–94, 1980

PRELIMINARY REPORT

PREVENTION OF VARICELLA IN URGENT CASES BY PASSIVE TRANSFER OF VACCINE-INDUCED IMMUNITY[1]

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(Received February 6, 1980)

For the purpose of preventing spread of infection to high risk children whose immunities were severely impaired by intensive chemotherapy or for some other reason, when cases of varicella occurred in a children's ward or in a family, healthy adults (mothers and a doctor) were immediately given live varicella vaccine, blood was collected from these adults 5 to 7 days after vaccination and the whole blood or plasma including the buffy coat was transferred into the high risk children. Subsequently the children showed little or no clinical reaction, and follow-up studies by the neutralizing test and skin test with varicella antigen indicated that inapparent or subclinical varicella infection occurred in them and that their immunity to varicella was lasting. Skin tests with varicella antigen showed that booster reaction occurred in adults with a previous history of varicella as early as 5 to 7 days after vaccination. The cellular immunity thus induced in the donors may have played a role in preventing a clinical reaction in the high risk children. Thus passive transfer of vaccine-induced immunity seems a convenient and effective method for preventing infection in subjects whose immune capacities are severely impaired.

Recently a live varicella vaccine has been developed and its efficacy in vaccination to normal children and children with underlying diseases has been reported (Takahashi et al., 1974; Asano et al., 1977; Ueda et al., 1977;

1 This work was supported in part by grants from Ministry of Education, Science and Culture and Children's Cancer Association of Japan.

Baba et al., 1978). Successful vaccination of children with acute leukemia or other malignancies in the stage of remission has also been reported (Izawa et al., 1977; Ha et al., 1980). However, there is no convenient method for protection against varicella in subjects whose immunity is extremely impaired. This report describes the effect of passive transfer of fresh blood or plasma with the buffy coat from normal adult donors who had been vaccinated immediately after exposure of those subjects to varicella.

CASE REPORT

Case 1. A patient in a children's ward developed vesicles on Aug. 22, 1977 and was diagnosed as having varicella on Aug. 24. In the same room there was 10 months old baby girl with lymphosarcoma (M.F.) who had just completed intensive therapy with Vincristin, Predonisolon, Cyclophosphamide, 6 MP and Methotrexate. Nineteen children in the ward were examined by the varicella skin test and 11 children including patient M.F., gave a negative reaction.

TABLE 1. *Transferable vaccine-induced immunity in a 10-month-old child with lymphosarcoma 11 days after exposure to varicella*

Date	Donor (mother)		Recipient (patient)	
	NT antibody titer	Skin reaction with varicella antigen	NT antibody titer	Skin reaction with varicella antigen
Aug. 22. 1977	—	—	Contact with varicella	
Aug. 24. 1977	8	$\frac{7\times7^{a}}{13\times15}$	< 4	$\frac{0}{1\times1}$
Aug. 26. 1977	Booster vaccination		—	—
Sep. 2. 1977	32	—	Transfusion	
Sep. 20. 1977	16	$\frac{0}{24\times17}$	8	$\frac{0}{10\times13}$
Nov. 4. 1977	—	—	4	—
Dec. 26. 1977	16	—	< 4	$\frac{3\times3}{10\times10}$
Feb. 3. 1978	16	—	4	$\frac{5\times5}{10\times10}$
Mar. 8. 1978	16	—	< 4	$\frac{4\times4}{10\times10}$
May. 17. 1978	—	—	< 4	$\frac{8\times8}{14\times14}$
Aug. 25. 1978	—	—	16	—
Oct. 6. 1978	—	—	128	—
Dec. 20. 1978	16	—	32	$\frac{4\times4}{15\times15}$
Jul. 26. 1979	—	—	32	—
Aug. 29. 1979	—	—	16	—

[a] mm diameter.
Numerator: diameter of induration.
Denominator: diameter of erythematous change.

The 10 children were immediately vaccinated on Aug. 26 (5,000 PFU/dose), but as M.F. was severely immunocompromised, she was not vaccinated. The mother of M.F. (25 years old, healthy) was vaccinated and 7 days later, 200 ml of fresh blood from the mother was transfused into M.F. No symptoms of varicella developed in the 10 children or in patient (M.F.) after blood transfusion. Test of neutralizing (NT) antibody and the skin reaction with varicella antigen were carried out at intervals for 2 years on patient M.F. and her mother, and the results are shown in Table 1. The NT antibody titer in patient M.F. rose temporarily after transfusion but decreased to an undetectable level 4 months after transfusion. However, the skin test reaction was positive 18 days after transfusion and has been persistently positive since then. Thirteen months after transfusion, the NT antibody titer rose abruptly to a high titer, suggesting that the occurrence of inapparent varicella infection just previously. The follow-up results suggest that although contact-infection from the index-case occurred in the patient, clinical symptoms were prevented by passively transferred immunity.

Case 2. T.I. and K.I. were 5 year-old identical twins. They showed severe clinical manifestations after inoculation of smallpox and DPT (Diphtheria, Pertussus, Tetanus) vaccines, and they were suspected to be immunodeficient. On Jan. 4, 1978, T.I. developed numerous vesicles with a high temperature of 39.7°C and on Jan. 7, he was diagnosed as having varicella. Both twins had suffered severe mumps infection with a temperature of over 39°C for 3 days and parotitis for more than 10 days just before the varicella infection and they were in bad condition. Therefore we decided to carry out passive transfer of vaccine-induced immunity, and accordingly mother (35 years old) and a doctor (39 years old) whose blood types were compatible with that of K.I., were immediately vaccinated. Five days after vaccination (Jan. 12), blood was taken from these adults and transferred to K.I. and his sister (7 years old) as follows: 400 ml of blood from the doctor was drawn directly into a plastic bag containing 40 ml of ACD (acid-citrate dextrose). The bag was centrifuged at 1,000 rpm for 20 min in a refrigerated centrifuge. Approximately 240 g of immune plasma including the buffy coat, was collected and immediately transferred to K.I.

In the same way, 200 ml of blood was taken from the mother and centrifuged at 3,000 rpm for 40 min and approximately 130 g of pure plasma was collected in another bag and immediately transferred to the twin's sister (J.I.). After vaccination a booster reaction was observed in both of the donors by the skin test with varicella antigen (Table 2).

TABLE 2. *Immune response of adult donors who received booster varicella vaccination*

Date	A doctor (39 years old)		Mother (33 years old)	
	NT antibody	Skin test with varicella antigen	NT antibody	Skin test with varicella antigen
1978 1 : 6	16	$\frac{7\times7}{15\times16}$	64	$\frac{9\times5}{18\times18}$
1 : 7	Booster vaccination		Booster vaccination	
1 : 17	32	$\frac{11\times11}{25\times30}$	64	$\frac{15\times15}{30\times28}$

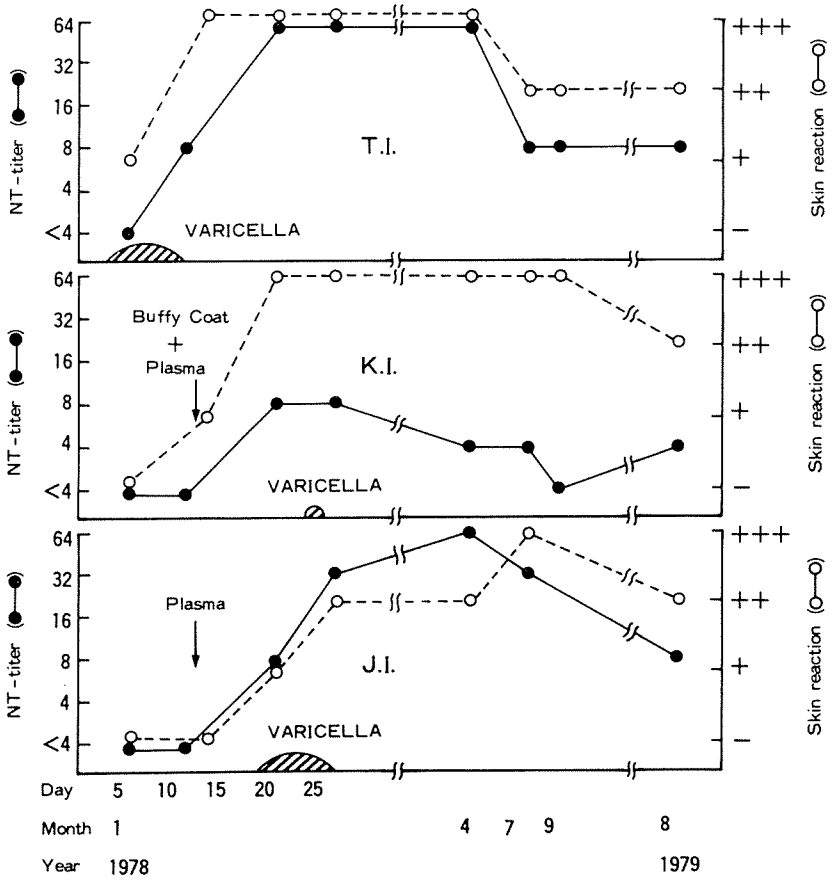

FIGURE 1. Follow-up of neutralizing (NT) antibody and skin reaction with varicella antigen in the varicella index case (T.I.) and the contacts that received passive transfer of vaccine-induced immunity (K.I. and J.I.)

On Jan. 21, the sister (J.I.) developed about 20 vesicles, which became innumerable with a temperature of 38°C after 3 days. K.I. developed only 3 vesicles without fever. The results of an immunological follow-up on the 3 children are shown in Fig. 1. Although the NT antibody titer of K.I. (recipient of plasma including the buffy coat) was lower than that after natural varicella infection (T.I.) and moderate varicella infection (J.I.), the intensity of skin reaction with varicella antigen in K.I. was comparable with that in T.I. and J.I.

We observed an early booster reaction after vaccination by the varicella skin test in several other adults who had a history of varicella: 4 of 5 vaccinated adults showed a boostered skin reaction 4 to 7 days after vaccination, as shown in Table 3.

Varicella may be severe, or even fatal in children who are receiving large doses of steroid and in children with leukemia or other malignancies. In such children after exposure to varicella, immediate administration of zoster immune globulin (ZIG) (Brunell et al., 1972; Judelsohn et al., 1974) or zoster immune plasma (ZIP) (Geiser et al., 1975; Balfour et al., 1977; 1979) has been reported to be effective in preventing or modifying the clinical course of varicella infection. But ZIG

TABLE 3. *Early booster reaction after vaccination in the skin test with varicella antigen in adults with history of varicella*

Case	Age	Sex	Before vaccination (7 days before vaccination)		After vaccination		
			NT antibody titer	Skin reaction	NT antibody titer	Skin reaction	Days after vaccination
I. K.	23	F	16	5×5 / 10×11	32	20×20 / 40×37	7
K. H.	20	F	4	4×5 / 10×12	4	10×10 / 54×45	5
M. T.	20	M	8	6×6 / 11×11	16	9×9 / 21×18	7
T. W.	26	M	32	9×9 / 20×20	32	10×10 / 34×30	4
S. K.	20	F	16	7×9 / 18×18	8	6×6 / 20×20	5

Vaccine dose: 1,000 PFU/person

and ZIP are not readily available, especially in large quantity. Vaccination is safe and effective in such cases when they are in remission or are not severely immunocompromised. However, there is still no convenient measure for urgent cases whose immunity is severely damaged.

We have previously reported that the skin test reaction with varicella antigen became positive in children as early as 5 days after vaccination (Baba et al., 1978), indicating that cell-mediated immunity to V-Z virus was induced very early after vaccination. Taking advantage of this early response, in this study we transferred urgently vaccine-induced immunity to the severely immunocompromised children who were exposed to varicella. For this purpose we vaccinated normal adult donors immediately, during the incubation period of the immunocompromised children, and took blood from them 5 to 7 days after vaccination. Then we transferred the fresh blood or plasma including the buffy coat fraction to the immunocompromised children. A patient with lymphosarcoma just after completion of intensive chemotherapy was prevented from developing clinical varicella by receiving this treatment on day 11 after exposure. In addition, the efficacy of this method was confirmed by giving vaccine-induced immune plasma including the buffy coat fraction to a child suspected of being immunodeficient 8 days after his twin brother developed. A sister of these twins, who had received a pure vaccine-induced immune plasma fraction developed moderate varicella symptoms although she was not immunodeficient. Too few cases were tested to draw any conclusions, but it seems probable that in these cases, transfer of cellular immunity in whole blood or the buffy-coat fraction played a major role in preventing clinical varicella. Definite stimulation of the skin test reaction with varicella antigen was observed 5 to 7 days after vaccination in donor adults and we have noticed similar early stimulation in several other cases (Table 3). Thus passive transfer of vaccine-induced immunity may be convenient and useful as an emergency measure for preventing clinical varicella in severely immunocompromised patients.

REFERENCES

Asano, Y., Nakayama, H., Yazaki, T., Kato, R., Hirose, S., Tsuzuki, K., Ito, S., Isomura, S., Takahashi, M. 1977. Protection against varicella in family contacts by immediate inoculation with varicella vaccine. Pediatrics 59: 3–7.

Baba, K., Yabuuchi, H., Okuni, H., Takahashi, M. 1978. Studies with live varicella vaccine and inactivated skin test antigen: Protective effect of the vaccine and clinical application of the skin test. Pediatrics 61: 550–555.

Balfour, H. H., Groth, K. E., MuCullough, J., Kalis, J. M., Marker, S. C., Nesbit, M. E., Simmons, R. L., Najarian, J. S. 1977. Prevention or modification of varicella using zoster immune plasma. Am. J. Dis. Child. 131: 693–696.

Balfour, H. H., Groth, K. E. 1979. Zoster immune plasma prophylaxis of varicella: a follow-up report. J. Pediatrics 94: 743–746.

Brunell, P. A., Gershon, A. A., Hughes, W. T., Harris, D. R. Jr., Smith, J. 1972. Prevention of varicella in high risk children: A collaborative study. Pediatrics 50: 718–722.

Geiser, C. F., Bishop, Y., Myers, M., Jaffe, N., Yankee, R. 1975. Prophylaxis of varicella in children with neoplastic disease: Comparative results with zoster immune plasma and gamma globulin. Cancer 35: 1027–1031.

Izawa, T., Ihara, T., Hattori, A., Iwasa, T., Kamiya, H., Sakurai, M., Takahashi, M. 1977. Application of a live varicella vaccine in children with acute leukemia or other malignant diseases. Pediatrics 60: 805–809.

Judelsohn, R. G., Meyers, J. D., Eillis, R. J., Thomas, E. K. 1974. Efficacy of zoster immune globulin. Pediatrics 53: 476–480.

Ha, K., Baba, K., Ikeda, T., Nishida, M., Yabuuchi, H., Takahashi, M. 1980. Application of live varicella vaccine to children with acute leukemia or other malignancies without suspension of anticancer therapy. Pediatrics 60: 46–50.

Takahashi, M., Otsuka, T., Okuno, Y., Asano, Y., Yazaki, T., Isomura, S. 1974. Live vaccine used to prevent the spread of varicella in children in hospital. Lancet II: 1288–1290.

Ueda, K., Yamada, I., Goto, M., Nanri, T., Fukuda, H., Katsuta, M., Otsuka, T., Takahashi, M. 1977. Use of a live varicella vaccine to prevent the spread of varicella in handicapped or immunosuppressed children including MCLS (Muco-Cutaneous Lymphnode Syndrome) patients in hospitals. Biken J. 20: 117–123.