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LIVE ATTENUATED VARICELLA VACCINE IN CHILDREN WITH LEUKEMIA IN REMISSION

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One-hundred-ninety-one children with acute leukemia in remission for at least one year were immunized with 1 or more doses of live attenuated varicella vaccine. All were susceptible to varicella prior to vaccination. The only significant side effect was mild to moderate rash, seen especially in children with maintenance chemotherapy temporarily suspended for one week before and one week after vaccination. Children with rash were at some risk (10%) to transmit vaccine virus to varicella susceptibles with whom they had close contact.

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Twenty-two vaccinees subsequently had household exposures to varicella or zoster. The attack rate of clinical varicella in these vaccinees was 18%, significantly lower than the attack rate of approximately 90% known to occur in varicella susceptibles with household exposures. All cases of clinical illness were extremely mild, with an average of about 50 vesicles, and few systemic complaints. In this study varicella vaccine was 80% effective in preventing varicella in children with leukemia and completely effective in preventing severe varicella in this high-risk group.

INTRODUCTION

Live attenuated varicella vaccine was developed by Takahashi and his colleagues in 1974. Studies in Japan in normal (Takahashi et al., 1974; Asano et al., 1977) and immunocompromised (Izawa et al., 1977; Sakurai et al., 1982; Gershon, 1980) children have shown that the vaccine is safe and that it induces antibody and cellular immunity (CMI) to varicella-zoster (VZ) virus. Little has been known, however, of the protective effect of this vaccine in children with underlying acute leukemia (ALL). Mild cases of varicella have been observed in Japanese vaccinees (Sakurai et al., 1982), and it seems possible that immunity to VZ virus may not always persist after immunization. We therefore undertook a large collaborative study of varicella vaccine in children with ALL in remission. We wished to observe as many vaccinees as possible with household exposures to varicella to study the protective efficacy of the vaccine. In order to optimize potential household exposures to varicella in vaccinees, one requirement for receipt of varicella vaccine was that one or more other household members be susceptible to varicella. Since it is well known that the attack rate of varicella in susceptibles with household exposures is extremely high, 80 to 90% (Ross et al., 1962), we predicted that it would be possible to determine the protective efficacy of varicella vaccine if there were 10 to 20 household exposures among vaccinees.

STUDY POPULATION

Children with ALL in remission for at least 1 year with varicella susceptible siblings or parents were offered varicella vaccine. Other prerequisites for entry were a positive response of lymphocytes in vitro to at least one mitogen (pokeweed mitogen or phytohemagglutinin), a peripheral blood lymphocyte count of at least 700/cu mm, no prior history of varicella, and no detectable serum VZ antibody.

Children were immunized with 1,000 plaque forming units of Oka vaccine subcutaneously. They were examined daily by their parents for 2 months after immunization, and by a physician if they appeared to have any adverse reactions to the vaccine. Blood for immunologic studies was obtained every 1 to 2 months.

A control group of children with ALL who had experienced natural varicella was followed for the incidence of relapse of ALL and development of zoster.

IMMUNOLOGIC STUDIES

Antibody to VZ virus was measured by the fluorescent antibody to membrane antigen (FAMA) assay (Williams et al., 1974). CMI to VZ virus was measured by lymphocyte transformation (Gershon, 1980), and expressed as a stimulation index (SI). A FAMA titer of $\geq 1:4$ and an SI of ≥ 3 is usually considered to indicate immunity to varicella.

STUDIES ON VZ VIRUS

These were performed by isolating the virus from lesions, purifying the viral nucleocapsids on density gradients, isolating the viral DNA,

and subjecting the DNA to restriction endonuclease analysis. A distinctive profile of wild type and vaccine type virus is evident at the ABC fragments using the restriction endonuclease Bgl 1 (Martin et al., 1982).

RESULTS

One-hundred-ninety-one children were immunized, 53 off chemotherapy and 138 with chemotherapy suspended. All vaccinees had VZ FAMA titers of $<1:2$ prior to immunization. Twenty-four of 191 (13%) had a VZ SI of >3 prior to immunization. These were felt to be false positive lymphocyte stimulation tests because they were seen in young children with no history of varicella who had siblings who were susceptible to varicella. Their FAMA titers were also $<1:2$. A seroconversion by FAMA occurred in 156/191 (82%) after 1 injection of vaccine. Of 79 children given a second dose of vaccine, VZ antibody was detectable in 75/79 (95%). Loss of detectable VZ antibody was noted in 2/28 (21%) of children off chemotherapy and in 13/28 of children with chemotherapy suspended, 12 to 18 months after the first dose of vaccine. A second dose of vaccine was therefore instituted routinely for two reasons. One was to increase the chances of seroconversion and the other to induce a stronger immune response that might induce better persistence of VZ antibody. A boost in the VZ antibody response was noted in 63/69 (93%) who received a second injection of vaccine.

A relapse in leukemia occurred in 25 (13%) of vaccinees and in 4/51 (8%) of controls. These differences are not significantly different ($p>.25$ by chi square analysis employing Yates' correction.) No vaccinee has developed zoster; one of the 51 controls has developed zoster.

There were no serious side effects attributable to varicella vaccine. The most common side effect of vaccination was development of rash from 1 to 6 weeks after immunization. After the first dose, 2/53 (4%) of children off chemotherapy and 49/138 (36%) of children with chemotherapy suspended had rash. Rashes were less common and less extensive after the second dose of vaccine, in which the overall incidence was 9/79 (11%). No rash was severe, although in three children it was serpentine, lasted up to 1.5 months, and resembled a mild form of bilateral zoster. This rash was not termed zoster, however, because prior to beginning the study, zoster had been defined as a unilateral dermatomal rash occurring at least 3 months after varicella vaccination. Seven children had rashes with 50–100 vesiculopapular lesions that resembled a very mild form of varicella. Chemotherapy was continued despite these rashes. Most rashes appeared about 1 month after immunization, after VZ antibody or CMI had already developed. Vaccinees manifesting rash usually developed higher FAMA titers than vaccinees who did not have rash.

There was evidence of spread of vaccine virus to 4/129 (3%) of susceptible siblings with whom the vaccinee had household contact. In each instance of spread, the vaccinee had manifested a rash. Transmission to siblings occurred about 3 weeks after exposure to the vaccinee with rash. Two siblings had very mild varicelliform rashes with a seroconversion, and 2 had silent seroconversions. VZ virus was isolated from 1 sibling with rash; it was vaccine type by restriction endonuclease analysis. VZ vaccine type virus was also isolated from 2 other vaccinees with rashes.

Additional undesirable side effects in leukemic vaccinees, most of whom were receiving chemotherapy, included fever to 40 C lasting for up to 4 days in 10, swelling and erythema at the injection site in 7, upper respiratory tract symptoms in 2, mild transient thrombocytopenia with purpura in 3, and severe headache lasting for several weeks in 1. In the absence of a control group it is difficult to know which of these reactions truly related to the vaccine and which were coincidental.

EXPOSURES TO VZ VIRUS

Documented household exposures to VZ virus occurred in 22 vaccinees, 2 to 24 months after immunization. There were 19 exposures to varicella and 3 exposures to zoster. Four of the exposed children developed a mild case of chickenpox, with an average of about 50 vesicular lesions. In 3 cases a virus isolate was obtained from vesicular lesions; it was identified as wild type in each instance. Although each of these vaccinees also had fever up to 40 C for 1 to 3 days, the disease was considered to be mild. The overall attack rate for clinical varicella was 4/22 (18%). If only exposures to varicella are counted, the attack rate was 4/19 (21%). One of the 4 had no detectable VZ antibody at the time of exposure, so she was passively immunized with varicella-zoster immune globulin (VZIG).

Exposures to friends with varicella occurred in 39 vaccinees. In two of these vaccinees mild clinical varicella developed, with less than 50 vesicular lesions. One child with no known exposure to VZ virus also developed mild clinical varicella (Gershon et al., 1984a, b).

In 6/7 cases of clinical varicella VZ FAMA antibody was detected in serum (average titer 1: 8) at the time of exposure. There was a positive VZ SI in 5/7 (mean 29) at exposure in vaccinees who developed varicella.

DISCUSSION

This study of 191 children with ALL in remission confirms those from Japan in which the vaccine was found to be safe in these high risk children. In our study, the only significant side effect was rash, and no rash was considered severe. There was, however, a 10% incidence of spread of vaccine virus from vaccinees with rash to others with whom they had close contact. Therefore it is important that vaccinees with rash avoid close contact with varicella susceptible immunocompromised individuals.

In contrast to studies in Japan, we administered 2 doses of vaccine routinely. Most children who were given a second dose manifested a booster response; we feel that a second dose provides extra protection to these high risk children. A second dose of vaccine also seemed to be important to ensure that a seroconversion had taken place in some of these immunocompromised children. The need for a second dose became more apparent in later stages of the study when, due to more intensive chemotherapy for ALL, vaccinees were less likely to manifest a seroconversion after 1 dose of vaccine than those who were vaccinated early in the study.

Neither two doses of vaccine nor the presence of VZ antibody at exposure protected vaccinees completely from clinical varicella. In all probability the reason these children were not totally protected is that they had deficiencies in cellular immunity. Normal children who have received varicella vaccine appear to have more complete protection from clinical disease. Seroconversion therefore seems to be important mainly as a marker that an immunologic response to VZ virus has taken place.

The mild character of varicella in vaccinees who developed it attests to the immunologic protection conferred by VZ vaccine. The usual course of varicella in leukemics is much more severe, and it is fatal in about 10% of cases (Feldman et al., 1975). The character of varicella in immunized children with ALL was milder than that seen even in normal children in which the average number of vesicles is 250–500 (Ross et al., 1962).

While the vaccine did not confer complete protection to children with ALL, the attack rate after household exposure was only 18% (21% if only exposures to varicella are counted). Varicella susceptible individuals with household exposures have a clinical attack rate of 80 to 90%. These differences in attack rate (19% or 21% vs 80% or 90%) are statistically significant ($p<.01$ by Fisher's exact two tailed test). The lower attack rate in vaccinees is further evidence for the efficacy of varicella vaccine in children with ALL.

In future studies it is planned to determine for how long the immunity to varicella conferred by vaccine lasts. In the study so far, the average interval between vaccination and exposure was 9 months. In the future vaccinees will also be carefully followed for development of zoster.

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