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Review

Long-term clinical studies of varicella vaccine at a regional hospital in Japan and proposal for a varicella vaccination program

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ABSTRACT

In 1974, a live varicella vaccine (Oka strain) was developed in Japan for the prevention of varicella. It has been commercially available since 1987 for the voluntary vaccination program, in which children over the age of 1 year with no history of previous varicella infection receive a single dose. From before approval up to the present, we have been carrying out long-term studies in healthy children at a regional hospital to assess the immunogenicity, safety, and efficacy of the varicella vaccine. This vaccine is very safe, and serious adverse reactions have not been observed since the year 2000 when it changed gelatin-free. In the past three studies, seroconversion was detected in around 95% of subjects by the immune adherence hemagglutination (IAHA) test, and this high rate was considered to indicate good immunogenicity. Breakthrough varicella is observed in approximately 20–30% of children who receive a single dose of the vaccine, but most cases are mild.

Although recent vaccination has generally been effective, the IAHA test has shown that immunogenicity is somewhat lower than was previously demonstrated. The sensitivity of the IAHA test has been shown to be adequate when compared with the neutralization test, so the current testing system is sufficient for the maintenance of immunity levels. An additional vaccination increased the IAHA antibody level in subjects who failed to seroconvert after a single dose vaccination. According to another clinical study, additional varicella vaccination at 3–5 years after the initial vaccination achieved stronger immunogenicity.

Because it is administered as part of the voluntary vaccination program, the varicella vaccination coverage rate has remained low in Japan, with no sign of a decrease in the number of varicella patients. We consider that implementation of routine varicella vaccination program based on the Preventive Vaccination Law would be the most effective approach for improvement of the coverage rate. Along with this, introduction of a two-dose schedule would also be desirable. In addition to decreasing the prevalence of characteristic breakthrough varicella infection, the vaccination coverage rate would also be expected to improve with a two-dose schedule due to an increase in opportunities for vaccination.

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1. Introduction

In 1974, a live vaccine (Oka strain) for the prevention of varicella was developed in Japan by Takahashi et al. [1]. Varicella-zoster virus (VZV) was isolated from a young varicella patient whose family name was Oka and was subjected to attenuation by serial passage in human embryonic lung cells, guinea pig embryo cells, and human diploid cells. Then extensive studies were conducted in Japan, as well as in Europe and the United States, which provided comprehensive data on the safety and efficacy of this vaccine. In 1985, the Oka strain was selected by the WHO as the most desirable attenuated live varicella vaccine strain [2]. Today, all varicella vaccines used worldwide to immunize approximately 32 million people annually contain the Oka strain. In 1984, this vaccine was approved in several European countries (the first approval worldwide) for use in high-risk children. In Japan, the vaccine was approved in September 1986 and it has been commercially available since March 1987 (Varicella Vaccine Live Attenuated "BIKEN", The Research Foundation for Microbial Diseases of Osaka University). In Japan, vaccination against VZV infection is not included in the routine vaccination program specified by the Preventive Vaccination Law. Instead, the vaccine is administered at the request of an individual or a child's legal guardian as part of the voluntary vaccination program. Vaccination under the routine program is basically free to participants, but varicella vaccine is not free and each vaccine is responsible for the cost. Persons over one year old without a history of varicella are eligible for vaccination, and they receive a single subcutaneous injection of 0.5 ml [containing at least 1000 plaque-forming units (PFU) of the virus].

We have investigated the efficacy, safety, and other related issues of varicella vaccination in healthy children at a regional hospital in Japan over an extended period. We summarize of these results in this review article and discuss our proposal for a nationwide varicella vaccination program.

2. Pre-approval studies on the varicella vaccine

Clinical trials performed during development of the varicella vaccine were mainly focused on high-risk children [3–7], representing a difference from other vaccines for which clinical trials were mainly performed in healthy individuals. Therefore, it was confirmed that the vaccine could be administered to patients who were likely to develop complications of VZV infection, including those with acute leukemia or solid tumors and those with steroid therapy for nephrotic syndrome. The package insert listed test results that were used as the criteria for vaccination.

A clinical trial of varicella vaccination in healthy children was carried out by our team at Showa Hospital, which was later amalgamated with Konan Kosei Hospital [8]. A strong antibody response was obtained with a seroconversion rate of 98.4% (253/257) by the immune adherence hemagglutination (IAHA) test. During observation periods ranging from 6 months to 4 years, 10 out of 253 vaccines (4.3%) contracted breakthrough varicella. While 6 of the 10 subjects seroconverted, seroconversion was not observed in the other 4 subjects. Clinical features of breakthrough varicella were mild in 100% of the former group and 75% of the latter. Problems with breakthrough varicella have been apparent since the initial development of this vaccine.

3. Safety of the varicella vaccine

Varicella vaccine is considered to be very safe. According to the results we have obtained so far [8–11], there have been no cases of anaphylaxis, generalized rash, or other serious adverse reactions due to vaccination, with the only mild reactions being feverish ($\geq$37.5 °C) and/or having mild rash. However, anaphylaxis caused by an allergic reaction to gelatin used as a stabilizer was occasionally reported by other investigators after varicella vaccination [12]. Sensitization to gelatin contained in diphtheria–tetanus–acellular pertussis vaccine that was administered prior to the varicella vaccine was found to be the cause of such anaphylaxis [13]. Therefore, gelatin has been removed from varicella vaccine used in Japan since January 2000, and there have been no reports of serious anaphylaxis following vaccination since then (Table 1) [10].

4. Immunogenicity of varicella vaccine

As the assay for anti-VZV antibody, IAHA test is used in Japan, whereas a glycoprotein-based enzyme-linked immunosorbent assay (gpELISA) is commonly used in the United States. Our previous study showed that the IAHA antibody titer was generally consistent with the neutralizing antibody titer [14], the gold standard for antibody measurement [15], suggesting that the IAHA test is adequate for measuring anti-VZV antibody.

The vaccine is sufficiently immunogenic, with a very high IAHA seroconversion rate of 93.6–98.6% [8–10]. In a survey conducted between 2005 and 2008 [11], however, the IAHA seroconversion rate was only 86.1% (192/223), which was slightly lower than the rates obtained in the previous studies. Thus, immunogenicity of this vaccine should carefully be monitored in the future.

In recent years, the viral titer of the commercial varicella vaccine has been 42,000–67,000 PFU per dose [16], which is more than 5 times higher than that at the time of its development and approximately 50 times higher than the product standard listed in the package insert (1000 PFU/dose or more). We compared a group of 20 subjects who received 0.1 ml (containing 2600–6400 PFU) of the current vaccine (containing an amount of virus similar to that in the full dose at the time of development) with a group of 23 subjects who received the normal dose (containing 13,000–32,000 PFU). It was demonstrated that the seroconversion rate of the former group (25.0%: 5/20) was lower than that of the latter group (76.2%: 16/21) ($p < 0.01$), while the two groups showed no significant difference in the incidence of adverse reactions (Fig. 1) [17]. Thus, it seems that the current viral titer, which greatly exceeds the product standard for this vaccine, is actually required to maintain adequate immunogenicity. We also found that giving an additional dose of the vaccine to subjects who failed to show seroconversion resulted in a high seroconversion rate and high antibody titer, possibly due to a booster effect.

5. Efficacy of the varicella vaccine

Occurrence of breakthrough varicella in children who had been vaccinated was observed in the early clinical trials [8], and it is widely known to occur at a slightly higher frequency than those in subjects vaccinated with other live vaccines. A post-marketing survey showed that 21% of vaccines developed varicella, usually within four years after vaccination (Table 2) [9]. In Japan, the reported prevalence of breakthrough varicella after vaccination ranges widely from 6.2 to 12.3% [18] up to 34.2% [19]. Most cases of breakthrough varicella are mild.

The preventive effect of varicella vaccine was estimated to be 75% in the survey conducted by us [9]. For comparison, the preventive effect of single-dose vaccination with the Oka/Merck strain in the USA was reported to be 79–88% for all types of varicella, including mild disease, and 95–100% for moderate to severe disease [20–24].

According to a survey of vaccine-preventable diseases conducted in Aichi prefecture from 1994 to 1998, hospitalization for varicella was relatively common (654 patients) and accounted