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Flexibility in the Administration Schedule of Varicella Vaccination in Healthy Adolescents and Young Adults

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SUMMARY **A clinical trial to assess the immunogenicity and reactogenicity of two doses of varicella vaccine (live attenuated Oka-strain, GlaxoSmithKline Biologicals), when either given 8 or 4 weeks apart in healthy seronegative adolescents and young adults, was conducted in Khon Kaen and Bangkok, Thailand. Contrary to seroconversion rates generally reported for this age group, in our study all subjects were already seropositive after the first vaccine dose. After the first vaccine dose, geometric mean titers (GMTs) for anti-varicella antibodies were 78.4 (median 64) for the adolescent group and 136.5 (median 128) for the young adult group. Six weeks after administration of the second dose, anti-varicella GMTs reached 331.7 (median 256) and 636.9 (median 512) for the adolescent and young adult groups, respectively, with a 4.2-4.7-fold increase from pre-vaccination titers. The difference in GMTs between post-dose I and dose II was statistically significant for each group. The reactogenicity after the first and second doses of vaccination was low: no varicella rash was seen, in either the shorter or longer schedule. GlaxoSmithKline Biologicals varicella vaccine (Varilix™) offered a high flexibility, administration possible at either 4 or 8 weeks interval, whilst eliciting good immunogenicity and good tolerability.**

Varicella (chickenpox) is generally considered benign. However, this disease may be severe and occasionally fatal in adults, in contrast to the mostly mild nature of this infection in otherwise healthy children. Although not frequent, the increased risk of secondary complications in adults such as pneumonia, encephalitis, and death, has been substantiated in population based surveys.[1,2] The peak and duration of the febrile period are more pronounced in adults, rash is frequent and more severe with a higher number of lesions, and it takes a longer time for clearing.[3,4] Complications include encephalitis in approximately 15/100,000 cases, which is seven times more common than in healthy children. Hospitalizations occur in 18/1,000 cases compared with only 1 to 2 per 1,000 childhood cases, which is nine times more frequent than in children. The case fatality rate is estimated to be 50/100,000 thus being 25 times more frequent than in children.[5-7] With the exception of varicella in infants, adulthood is the peak age-specific period for varicella morbidity.[5]

A seroprevalence study has indicated that one in three adolescents and young adults in Thailand lack natural immunity and are susceptible to varicella,[8] which is higher than reported from temperate regions where more than 90% of individuals are infected by the second decade of life.[6,9] A recent article has shown that those living in the lower altitude and warmer central and southern parts of Thailand are more prone to lack natural immunity against varicella-zoster virus (VZV), particularly in rural areas.[10] Even though the use of anti-viral therapy has shown the potential to decrease the morbidity and mortality of chickenpox in high-risk groups, the effectiveness of vaccination in preventing chickenpox and the savings on direct and indirect costs far outweigh a sole therapeutic approach. Varicella vaccination has been available in Thailand since 1997 but focused mainly on

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children. The purpose of this study was to assess the immunogenicity and reactogenicity of a two-dose regimen for healthy, seronegative adolescents and young adults when given at 4 and 8 week intervals.

MATERIALS AND METHODS

This study was conducted in Siriraj Hospital, Mahidol University and Khon Kaen University, Thailand. The written approvals of the Institutional Review Boards of the participating universities were received prior to the study start. Written informed consent was obtained from each participant or the participants' parent/guardian, respectively.

Study design

Healthy non-immune adolescents aged 13-16 years and young adults aged 17-21 years old were enrolled for this study. Prospects were excluded from the study if they had a clear history of clinical varicella or zoster infection, a history of exposure to varicella/zoster within the previous 4 weeks, were sensitive to neomycin, had a history of allergy or other serious adverse reactions to any previous vaccination, had received any blood products in the past 3 months, had an immunosuppressive condition or were on immunosuppressive therapy. Pregnant women were not enrolled in the study, thus females were required to have a urine pregnancy test prior to each injection and agree to avoid pregnancy during the study and to use an acceptable birth control method for 3 months after each injection.

Susceptibility to varicella was determined by antibody testing done at the Department of Microbiology, Siriraj Hospital, Mahidol University. The blood test was conducted within 10 days prior to the first vaccine dose. The original protocol was designed for an 8-week interval in both groups. However, in order to address the medical need for a shorter schedule, it was amended after study start to include a 4-week interval between dose 1 and dose 2. Since the 8-week adolescent group in Khon Kaen University was already ongoing, the amended protocol could only be applied to subjects in the young adult group from Siriraj Hospital. The same vaccine lot was used for both adolescent and young adult participants. Each individual received a single 0.5 ml subcutaneous injection of vaccine in the deltoid region at each visit.

Diary cards were provided to participants in both groups. They were asked to record on a daily basis temperature and any solicited local and systemic reactions for 6 days. In case of rash or if the subject felt hot or appeared ill, the subjects and/or parents/guardians were instructed to record body temperature and also measure the size/intensity of the local reaction at the injection site until it subsided. Participants were followed-up up to 42 days after the second injection.

Vaccine

Varicella vaccine used in this study was from a commercially and locally available lot provided by GlaxoSmithKline Biologicals, Rixensart, Belgium. Each dose of 0.5 ml of varicella vaccine contained live attenuated varicella (OKA strain) which retained a titer not less than $10^{3.3}$ plaque forming units (pfu) for 24 months or more, when stored at 2-8°C. The vaccines were labelled according to GCP recommendations.

Laboratory methods

Sera obtained within 10 days prior to the vaccination, were screened for varicella susceptibility by using a commercially available ELISA kit for varicella-zoster IgG detection (Enzygnost anti-VZV/IgG™; Behringwerke, Germany). The test was carried out according to the manufacturer's instructions and the results expressed in calculated arbitrary units. Serum samples taken post vaccination were stored at –20°C until they were tested for specific varicella antibodies at GlaxoSmithKline Biologicals' Laboratory, Rixensart, Belgium, by using an indirect immunofluorescence (IIF) commercial kit (Virgo® VZV IgG indirect immunofluorescent antibody test; Pharmacia, Sweden).

Statistical methods

Seroconversion rate and GMT with 95% confidence interval of anti-varicella antibodies were calculated for all time-points for which blood samples were taken. The GMTs after vaccine dose 1 were compared with GMTs after vaccine dose 2, using Wilcoxon's test. Fisher's exact test was used to compare safety/tolerability parameters of each solicited symptom after vaccine dose 1 with the incidence of symptoms after dose 2.

RESULTS

A total of 100 VZV seronegative adolescents (mean age 15.2 years) and 63 VZV seronegative young adults (mean age 19.1 years) were enrolled in this study. The adolescent group received the vaccine at 0 and 8 weeks while the young adult group received the vaccine at 0 and 4 weeks. The female to male ratio was 3:1 and 2:1 in the adolescent and young adult groups, respectively.

Immunogenicity

One hundred and fifty-three subjects (99 in the adolescents and 54 in the young adults) were el-

igible for the immunogenicity analysis. The reasons for the exclusion of 6 subjects in the young adult group from the immunogenicity analysis were protocol violation, 1 adolescent for non-compliance with the vaccination schedule and 2 with non-compliance with the blood sampling schedule.

All enrolled subjects were seronegative for varicella antibodies at the pre-vaccination screening and became seropositive upon completion of the vaccination course. Following the first vaccination, the GMTs at day 56 for adolescents and at day 28 for young adults were 78.4 (median 64) and 136.5 (median 128), respectively. The GMTs at 42 days after the second dose were 331.7 (median 256) for adolescents and 636.9 (median 512) for young adults, respectively. A significant difference between GMT values was observed between the two groups after dose 1 ($p = 0.0096$) and after dose 2 ($p < 0.001$) (Table 1).

Reactogenicity

Diary cards were obtained from the vaccinees. The vaccinees were requested to record both solicited and unsolicited symptoms reported over the 6-day follow-up period after each vaccine dose. However, any rash and other adverse event that occurred during the 42 days after dose 2 vaccination were recorded by vaccinees in both groups and reported to the investigator.

The majority of solicited local symptoms in adolescents, as well as young adults, were soreness, followed by redness and swelling graded as being associated with minimal discomfort. However, there was no statistically significant difference ($p > 0.05$) (Table 2). There was a total of 20 (1 in an adolescent 19 in young adults) solicited local symptoms with intensity grade 3, which was defined as preventing normal activity. Of these, the majority of the 14 symptoms was grade 3 redness, with only 1 case of grade 3 soreness reported. All solicited local symptoms resolved within day 6 follow up period.

Fever was the only general symptom that was solicited. The investigators determined this symptom to have a probable/suspect relationship to the study vaccine in 17.5% of the reported cases of fever in adolescents and 10.8% of the reported cases of fever were in young adults. Among them, 1% were defined as grade 3 fever (fever > 39.5°C) with one case occurring in each group.

During the follow-up period, 1 young adult reported a vesicular rash at the elbow on day 5 following dose 1 of the vaccine, which resolved on day 6. The event was determined by the investigator to be "unrelated" to the study vaccine. The second young adult subject reported an erythematous rash on day 2 following vaccine dose 1, which resolved on day 4. The investigator determined this event to be "probably" related to the study vaccine. There was no fever or other complication associated with either of these symptoms.

One serious event was reported during the course of the study. The subject developed high fever and headache one day after receiving the first dose of the study vaccine and was clinically diagnosed of having dengue hemorrhagic fever. The subject was hospitalized for three days and the events resolved on day 5 following dose 1. The subject also received the second dose of vaccine, which was well tolerated. Thus the event was defined as "not related" to the study vaccine.

DISCUSSION

Because of the potentially increased severity of natural varicella among adolescents and adults

Table 1 Seroconversion rate and geometric mean titer

Group	Timing	N	Seropositivity		GMT (range)	95 % CI	Median values
			n	%			
Adolescents*	Post I/Pre II	99	99	100	78.4 (8-1,024)	63.3 - 97.2	64
	Post-II	99	99	100	331.7 (16-4,096)	276.0 - 398.6	256
Adults#	Post I/Pre II	54	54	100	136.5 (4-4,096)	98.6 - 188.9	128
	Post-II	54	54	100	636.9 (32-4,096)	511.1 - 793.5	512

*adolescent group, two dose vaccination 8 weeks apart.
#adult group, two dose vaccination 4 weeks apart.
GMT= geometric mean titer, 95% CI = 95% confidence interval.
For the difference of GMTs (Wilcoxon's test) between the two groups (4 weeks (adults) and 8 weeks (adolescents): at post-I, p-value = 0.0096, at post-II, p-value < 0.001.

and the low seroconversion rate found after one dose of varicella vaccination in this age group.[11] the American Academy of Pediatrics Committee on Infectious Diseases recommended that healthy adolescents past their 13th birthday who are susceptible to varicella should be immunized against varicella by administration of 2 doses of vaccine 4 to 8 weeks apart.[12] This study confirmed the flexibility of administering the second dose of varicella vaccine at either 4 or 8 weeks apart. The GMT increase was 4.2-4.7-fold after the second injection either 4 or 8 weeks apart in both adolescent and young adult groups. This may support the need for administration of a second dose at this age. Kuter *et al.*[11] reported a higher titer when the second injection was administered at 8 weeks rather than 4 weeks, and indicated an age effect on the titer level with younger age groups having significantly higher GMTs than older age groups. This was, however, reversed in our study. The limited sample size of the young adult group in our study, and the overall age difference between subjects enrolled in the two studies could provide an explanation for the higher GMT as an occasional finding, however, a negative effect of acceleration of the schedule to the 4 weeks interval for our study vaccine can be excluded.

The rate of clinical reactions was mild but tended to be higher than those observed with childhood immunization. Although the vaccine was administered in the same way as in children, about 20-40% of adolescents and young adults in this study developed tenderness, swelling or redness at the injection site. However, occurrence of fever was comparable to that reported in healthy children and in adults in the previous report.[13] No statistically significant difference was noted in the incidence of redness, swelling, soreness or fever following the first and second injections in the groups receiving either the 4 or 8 week interval schedule in this study. This is in line with previous GSK Bio studies which reported the reactogenicity after the second dose was not higher than after the first dose.[14] In contrast, Kuter *et al.*[11] investigating a different varicella vaccine, found a greater incidence of mostly mild, short-lived erythema and swelling at the injection site after the second injection. However, there was a high incidence of grade 3 redness and swelling in the young adult group, which the investigator suspected to be caused by a too superficial route of injection at the first dose vaccination which was improved on the second dose. At the same time the incidence of grade 3 local side effects among the younger age group was very low. While routine administration of a second injection at 4 or 8 weeks was generally well tolerated, adults were found to have twice the chance of developing a vaccine-associated rash as healthy children.[15] Nevertheless, in this study, neither the adolescent nor the young adult group developed varicella-like rashes.

In conclusion, 2 doses of the varicella vaccine can be given at either 4 or 8 weeks apart, eliciting good antibody response and tolerability in adolescents and adults. Administration of two injections of the vaccine, 4 weeks apart, may be advisable, in situations where the vaccinee has a limitation of time.

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Table 2 Reactogenicity after vaccination with one and two doses

Symptoms	Intensity	Adolescent group*				Adult group#				Adolescent		Adult	
		Dose 1 (N = 100)		Dose 2 (N = 100)		Dose 1 (N = 100)		Dose 2 (N = 60)		All doses (N = 200)		All doses (N = 120)	
		n	%	n	%	n	%	n	%	n	%	n	%
Redness	Total	23	23.0	16	16.0	23	38.3	13	21.7	39	19.5	36	30.0
	Grade 3	0	0.0	0	0.0	12	20.0	2	3.3	0	0.0	14	11.7
Soreness	Total	34	34.0	31	31.0	25	41.7	23	38.3	65	32.5	48	40.0
	Grade 3	0	0.0	1	1.0	0	0.0	0	0.0	1	0.5	0	0.0
Swelling	Total	14	14.0	18	18.0	9	15.0	8	13.3	32	16.0	17	14.2
	Grade 3	0	0.0	0	0.0	4	6.7	1	1.7	0	0.0	5	4.2
Fever	Total	19	19.0	17	17.0	7	11.7	8	13.3	36	18.0	15	12.5
	Grade 3	0	0.0	1	1.0	1	1.7	0	0.0	1	0.5	1	0.8

*Adolescent group: two dose vaccination 8 weeks apart, $p > 0.05$
#Adult group: two dose vaccination 4 weeks apart, $p > 0.05$

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