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The Members of the VZV-AD study group

Safety, reactogenicity, and immunogenicity of live attenuated varicella vaccine in children between 1 and 9 years of age with atopic dermatitis

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Abstract *Introduction:* Infection with varicella-zoster virus (VZV) is known to facilitate secondary bacterial infection, which is cause for particular concern in children with atopic dermatitis. This 2-year study assessed the safety, reactogenicity, and immunogenicity of a live attenuated Oka strain varicella vaccine (Varilrix, GlaxoSmithKline Biologicals) in 160 children aged 1–9 years with atopic dermatitis randomized to vaccination at the start of either the 1st or 2nd study year (VAR-1Y and VAR-2Y, respectively). Mean scores for atopic dermatitis

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(SCORAD) at baseline were 19.3 ± 11.1 and 26.0 ± 10.4 in the two groups, respectively. *Results:* Varicella vaccination did not adversely affect the severity of atopic dermatitis, with analysis of variance (ANOVA) confirming equivalence for the change in SCORAD index from baseline to week 8 between vaccinated and unvaccinated subjects. Within-group comparison of post-vaccination changes in SCORAD index from baseline to week 8 and month 12 in the VAR-2Y group showed a greater reduction in mean SCORAD scores following vaccination in year 2 than in year 1 when subjects were unvaccinated. Overall, SCORAD indices fell by approximately 10 points in both study groups over the 2 years of follow-up. Varicella vaccination was well tolerated, with no children withdrawn due to adverse events. Injection site redness was the most frequent solicited adverse event, occurring in 17.1% of subjects. Seroconversion rates were 94.3% at week 8 and 88.9% at month 12. In all, 43.6% of vaccinees reported at least one varicella contact during the course of the study. However, none developed varicella infection after vaccination over the 2 years of follow-up. *Conclusion:* In summary, vaccination with a live attenuated varicella vaccine appears safe and effective in children with atopic dermatitis.

Keywords Children · Atopic dermatitis · Varicella infection · Varicella vaccine · Reactogenicity

Abbreviations ANOVA: Analysis of variance · ANCOVA: Analysis of covariance · ATP: According to protocol · PFU: Plaque-forming units · SAE: Serious adverse event · SCORAD: SCORing Atopic Dermatitis · VAS: Visual analogue scale · VZV: Varicella-zoster virus

Introduction

Atopic dermatitis is a chronic inflammatory skin disorder affecting 10–20% of young children worldwide [17, 18]. Viral skin infections, such as varicella-zoster virus (VZV) infection (chickenpox), tend to be more severe in children with atopic dermatitis [18, 30, 33, 34]. Available data show

no difference in the specific antibody response to VZV between subjects with atopic dermatitis and healthy controls [29]. Even in children with otherwise healthy skin, secondary bacterial infections are common complications of varicella infection [3]. However, the frequency of secondary bacterial infection is higher in children with atopic dermatitis, presumably due to the high rate of colonization of the skin with *Staphylococcus aureus* and other bacterial species in these subjects [12, 16].

Recognition of varicella as a significant cause of morbidity and mortality has led to an increasing number of countries adopting universal childhood varicella vaccination programs. Recommendations for varicella vaccination in healthy children currently exist in the United States, Canada, Australia, Uruguay, Brazil, Qatar, several countries in Asia (including Taiwan, Korea, and India), Spain, and most recently Germany and Italy [1, 2, 4, 6, 9, 19, 21, 22, 26, 28]. According to data from the United States, the annual incidence of varicella infections has fallen significantly since the introduction of routine childhood immunization against varicella in 1995 [5]. Significant reductions in varicella-related complications and varicella-related mortality have also been reported [7, 23, 25]. As the course of varicella infection tends to be more severe in children with underlying atopic dermatitis, it seems reasonable to assume that varicella vaccination may be particularly beneficial in this population. However, data to support varicella vaccination in children with atopic dermatitis are lacking, presumably due to concerns that exposure to the vaccine may exacerbate the underlying condition.

Varilrix is a live attenuated Oka strain varicella vaccine [GlaxoSmithKline (GSK) Biologicals, Rixensart, Belgium], which has been shown to be well tolerated, immunogenic, and highly protective against varicella infection in healthy children [8, 13, 20, 24, 32, 33]. The present study was undertaken to assess the safety, reactogenicity, and immunogenicity of this varicella vaccine in children with atopic dermatitis. Disease severity was assessed using the SCORing Atopic Dermatitis (SCORAD) index [10, 14, 27]. This is an established method for the clinical assessment of atopic dermatitis and for monitoring disease severity in clinical trials.

Materials and methods

Subjects

Healthy male or female children aged 1–12 years with a history of atopic dermatitis (duration ≥ 1 year) who had experienced an acute flare of atopic dermatitis within the past 6 months with no acute flare or apparent progression of atopic dermatitis in the past month were eligible for study entry. Children with a SCORAD index >40 or any other concomitant skin condition with the potential to complicate assessment of the effects of vaccination were excluded. Other exclusion criteria included: previous VZV infection or VZV vaccination; use of topical and systemic corticosteroids, immunosuppressive agents, or UV therapy within 4 weeks of study entry; lymphocyte count less than $1,200/\text{mm}^3$; known systemic hypersensitivity to neomycin;

Table 1 Summary of key procedures and assessments in the two study groups. *IIF* indirect immunofluorescence

VAR-1Y	Year 1				Year 2	
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	
	Week -4	Day 0	Week 8	Month 12	Month 12	
SCORAD	X	X	X	X	X	
Serology (IIF)	X		X	X		
Varicella vaccination ^a		X				
Diary cards (solicited local & general symptoms)		X	X			
Adverse events		X	X			
Serious adverse events	X	X	X	X	X	

VAR-2Y	Year 1			Year 2		
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Week -4	Week 8	Month 12	Day 0	Week 8	Month 12
SCORAD	X	X	X	X	X	X
Serology (IIF)			X		X	X
Varicella vaccination ^a				X		
Diary cards (solicited local & general symptoms)				X	X	
Adverse events				X	X	
Serious adverse events	X	X	X	X	X	X

^aSubjects received a single dose of Varilrix administered subcutaneously in the upper arm

a history of allergic or other adverse reactions after previous vaccination or known allergy to any vaccine component; vaccination with another live vaccine [e.g., measles, mumps, rubella (MMR)] within 1 month prior to study entry; blood transfusion and administration of standard or specific immunoglobulins within 3 months prior to study entry or at any time during the course of the study; administration of salicylates within 30 days prior to or 6 weeks following vaccination; and application of allergens (hyposensitization) 2 weeks before or after vaccination. The study was approved by the independent Ethics Committees of each participating center and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from the parents/guardians of each child prior to study entry.

Study design and vaccine

This was a prospective, open-label, randomized, parallel group study conducted over a period of 2 years at 13 centers in Germany. The children received sequential numbers in a chronological order at the first screening visit (week 4). Eligible children were randomly allocated to receive varicella vaccination either in the 1st year of the study about 4 weeks after enrollment (VAR-1Y) or in the 2nd year about 13 months after enrollment (VAR-2Y). Allocation of subjects to treatment groups (VAR-1Y or VAR-2Y) was based on a randomization list and was observer independent. Each dose of the varicella vaccine used (Varilrix) contained at least 2,000 plaque-forming units (PFU) of attenuated Oka strain varicella virus cultured in human diploid cells. The vaccine was administered as a single dose by subcutaneous injection in the upper arm. Subjects with no detectable VZV-specific antibodies 8 weeks after vaccination were offered revaccination 3–6 months later. Key study procedures and assessments are summarized in Table 1.

Assessment of reactogenicity and safety

The severity of atopic dermatitis was assessed at each clinic visit using the SCORAD index [10, 14]. The following clinical criteria were assessed: (A) the total extent of the affected area, (B) the total intensity of key symptoms of erythema, edema or papulation, oozing or crusting, excoriation, lichenification and dryness, each rated on a scale of 0 (absent) to 3 (pronounced), and (C) the total severity of subjective symptoms (itching and insomnia), each rated using a visual analogue scale (VAS) ranging from 0 (absent) to 10 (severe). The SCORAD index was calculated using the following formula (maximum score 103): $\text{SCORAD index} = A/5 + (7 \times B)/2 + C$. In order to minimize an observer bias in SCORAD assessment, all investigators underwent training, prior to this study, at two separate meetings in Würzburg. Parents/guardians documented the occurrence of solicited local (pain, redness, and soreness at

the injection site) and general (fever) symptoms on diary cards during the 6 days following vaccination in both study groups. Fever was defined as a rise in rectal temperature to either $\geq 38.0^\circ\text{C}$ (moderate fever) or $> 39.5^\circ\text{C}$ (high fever). The occurrence of rash was solicited for 8 weeks following vaccination. Unsolicited adverse events occurring within 8 weeks of vaccination were also recorded and causality to vaccination assessed by the local investigator. Information on serious adverse events (SAEs) was collected during the entire study period.

Serology

Blood samples were collected 4 weeks prior to administration of the study vaccine and 8 weeks and 12 months after vaccination in both study groups. Anti-varicella antibody titers were determined by indirect immunofluorescence (IIF) [35] at GSK Biologicals, Rixensart using a commercial assay (Virgo, Hemagen Diagnostics, Inc., Columbia, MD, USA). Titers were expressed as the reciprocal of the last positive dilution. Samples which showed no fluorescence or barely visible fluorescence at the starting dilution (anti-varicella antibody titer < 4 dilution $^{-1}$) were considered seronegative. Seroconversion was defined as the appearance of antibodies (anti-varicella antibody titer > 4 dilution $^{-1}$) in the serum of subjects who were seronegative prior to vaccination. The number and source of varicella contacts was recorded at each visit to permit evaluation of vaccine effectiveness.

Statistical methods

All analyses were performed on according-to-protocol (ATP) cohorts. The primary study endpoint was the difference in the change in SCORAD index from baseline to week 8 between vaccinated subjects in the VAR-1Y group and unvaccinated subjects in the VAR-2Y group. This was an equivalence study based on the null hypothesis that clinically relevant differences in SCORAD index will exist between vaccinated and unvaccinated children with a history of atopic dermatitis. Two-sided 90% confidence intervals (CI) were calculated by analysis of variance (ANOVA) for the difference in the change in SCORAD index between the two study groups. The null hypothesis was rejected (i.e., equivalence was proven) if the upper limit of the two-sided 90% CI for the difference between the two groups was ≤ 10 . This corresponds to the upper limit of a one-sided 95% CI. Changes in SCORAD index from baseline to week 8 and month 12 were also compared by analysis of covariance (ANCOVA) before and after vaccination in the VAR-2Y group. Solicited and unsolicited adverse events were analyzed by relative frequencies. Seroconversion rates and two-sided 95% CI were generated based on the development of VZV-specific antibodies (anti-varicella antibody titer > 4 dilution $^{-1}$) at 8 weeks and 12 months after vaccination. For seroconversion rates and reactogenicity, data from the two study groups were pooled.

Results

Demographics

A total of 160 children were randomized into this study (80 in each study group). Of these, 111 children completed the study, 66 in the VAR-1Y group and 45 in the VAR-2Y group. None of the subjects who failed to complete the study withdrew due to adverse events. In all, 133 children were included in the ATP cohort for the primary analysis of the SCORAD index (63 in the VAR-1Y group and 70 in the VAR-2Y group). Reasons for exclusion from this cohort included failure to receive the study vaccine ($n=10$), noncompliance with the study schedule ($n=5$), missing SCORAD data ($n=4$), initial seropositivity or unknown antibody status ($n=3$), varicella infection ($n=3$), and initiation of corticosteroid therapy ($n=2$). Demographic characteristics for the ATP cohort for the analysis of SCORAD were comparable between the two study groups (Table 2).

In all, 117 subjects were included in the ATP analysis of reactogenicity (70 in VAR-1Y and 47 in VAR-2Y) and 98 in the ATP analysis of immunogenicity (63 and 35 in the two groups, respectively). The demographic characteristics of the ATP cohorts for analysis of reactogenicity and immunogenicity were generally comparable between the two study groups, with the exception of age. In both cohorts, subjects in the VAR-1Y group were significantly older than those in the VAR-2Y group [3.3 ± 1.6 vs 2.7 ± 1.6 years ($p=0.011$) and 3.2 ± 1.5 vs 2.7 ± 1.8 years ($p=0.031$), respectively].

Analysis of SCORAD

The severity of atopic dermatitis was found to differ significantly between the two study groups at baseline, with mean SCORAD indices of 19.3 ± 11.1 at day 0 in the VAR-1Y group and 26.0 ± 10.4 at week -4 in the VAR-2Y group ($p<0.001$). The SCORAD index at week 8 was virtually unchanged from baseline in vaccinated subjects in the VAR-1Y group (20.1 ± 13.6). A marked improvement in

disease severity was seen in unvaccinated subjects in the VAR-2Y group over this period of time, resulting in a difference in change in SCORAD index from baseline to week 8 between the two study groups of 6.7 ± 1.8 (90% CI: 3.7, 9.7) (Table 3). This was presumably due to the higher mean SCORAD index at baseline in the VAR-2Y group (regression to the mean phenomenon). Equivalence between the two study groups was confirmed, since the upper limit of the 90% CI was ≤ 10 points. An additional ANCOVA adjusted for SCORAD index at baseline was performed to account for the significant difference in baseline disease severity between the two study groups (Table 3). The difference in the change in SCORAD index from baseline to week 8 between the VAR-1Y and VAR-2Y groups obtained by ANCOVA was 4.7 ± 1.8 points (90% CI: 1.7, 7.8), also supporting equivalence between the two study groups.

Within-group comparison of post-vaccination changes in SCORAD index from baseline to week 8 and month 12 in the VAR-2Y group with corresponding data from the 1st study year when subjects were unvaccinated supports the results of the primary analysis. For both comparisons, the upper limit of the 90% CI was ≤ 10 points indicating that varicella vaccination had no clinically relevant effects on the severity of atopic dermatitis (Table 4). Indeed, greater reductions in SCORAD index from baseline were seen at both time points following vaccination in year 2 than in year 1 when subjects were unvaccinated.

The change in SCORAD index in both study groups over the 2 years of follow-up is shown in Fig. 1. No detrimental effects of vaccination were seen in either treatment group, with SCORAD indices decreasing by approximately 10 points in both groups over the course of the study (-8.5 ± 12.1 in the VAR-1Y group and -9.7 ± 9.0 points in the VAR-2Y group).

Safety and reactogenicity

The live attenuated varicella vaccine used in this study, Varilrix, was found to be safe and well tolerated in children with atopic dermatitis. No subjects were withdrawn from this study due to adverse events. The overall frequency of adverse events (solicited and unsolicited symptoms) was

Table 2 Baseline demographic characteristics (ATP cohort for analysis of SCORAD)

	VAR-1Y	VAR-2Y
No. of subjects	63	70
Age (years)		
Mean $\pm$ SD	3.2 $\pm$ 1.5	3.2 $\pm$ 1.9
Range	1.1–8.3	1.0–9.0
BMI (kg/m ²)		
Mean $\pm$ SD	15.7 $\pm$ 1.5	16.2 $\pm$ 2.3
Range	12.3–20.3	13.1–30.8
Gender		
% female	50.8	50.0
Race		
% White/Caucasian	100.0	97.1

Table 3 Change in SCORAD index from baseline to week 8 in the 1st year of study in the VAR-1Y and VAR-2Y groups (ATP cohort for analysis of SCORAD). ANOVA analysis of variance, ANCOVA analysis of covariance (SCORAD at baseline as single covariate), LS_{Mean} least squares mean, SE standard error

	VAR-1Y ($n=63$)	VAR-2Y ($n=70$)	Difference
ANOVA			
LS _{Mean} $\pm$ SE	0.85 $\pm$ 1.33	-5.84 $\pm$ 1.26	6.69 $\pm$ 1.83
(90% CI)	(-1.35, 3.05)	(-7.93, -3.75)	(3.66, 9.72)
ANCOVA			
LS _{Mean} $\pm$ SE	-0.19 $\pm$ 1.30	-4.90 $\pm$ 1.23	4.71 $\pm$ 1.84
(90% CI)	(-2.35, 1.97)	(-6.95, -2.86)	(1.67, 7.76)

Table 4 Change in SCORAD index from baseline to week 8 and month 12 in the 2 years of study in the VAR-2Y group (ATP cohort for analysis of reactogenicity). *LSMean* least squares mean, *SE* standard error. Analysis of covariance with SCORAD at baseline as single covariate

	Year 1 (n=47)	Year 2 (n=47)	Difference
Week 8–baseline ^a			
LSMean±SE	−2.80±1.12	−4.10±1.21	1.30±1.85
(90% CI)	(−1.89, 2.11)	(−6.13, −2.07)	(−1.82, 4.41)
Month 12–baseline ^a			
LSMean±SE	−0.72±1.04	−6.88±1.11	6.16±1.69
(90% CI)	(−2.47, 1.03)	(−8.74, −5.02)	(3.31, 9.01)

^aBaseline: week −4 in year 1 and day 0 in year 2, respectively

50.4%. Table 5 shows the relative frequency of solicited local and general symptoms following vaccination. Injection site redness was the most frequent solicited local symptom, occurring in 17.1% of subjects. Transient fever following vaccination was seen in 10.3% of subjects. Fever was documented as moderate in nine and as high in three vaccinees and lasted for 1–3 days. Rash occurred in 16.2% of subjects and was most frequently characterized by erythema (8.5%), itching (7.7%), allergic reaction such as urticaria or maculopapular exanthema (6.0%), and excoriation (5.1%). No cases of rash were associated with the development of vesicles. The relative frequency of unsolicited adverse events was 35.0%. However, none of these events were considered to be causally related to vaccination. Six SAEs were reported, none of which were considered causally related to vaccination. Two of these SAEs specifically affected the skin. These were exacerbation of eczema occurring 35 days after vaccination and secondary infection of atopic dermatitis 215 days after

Table 5 Relative frequencies of solicited local and general symptoms following vaccination (ATP cohort for analysis of reactogenicity, n=117)

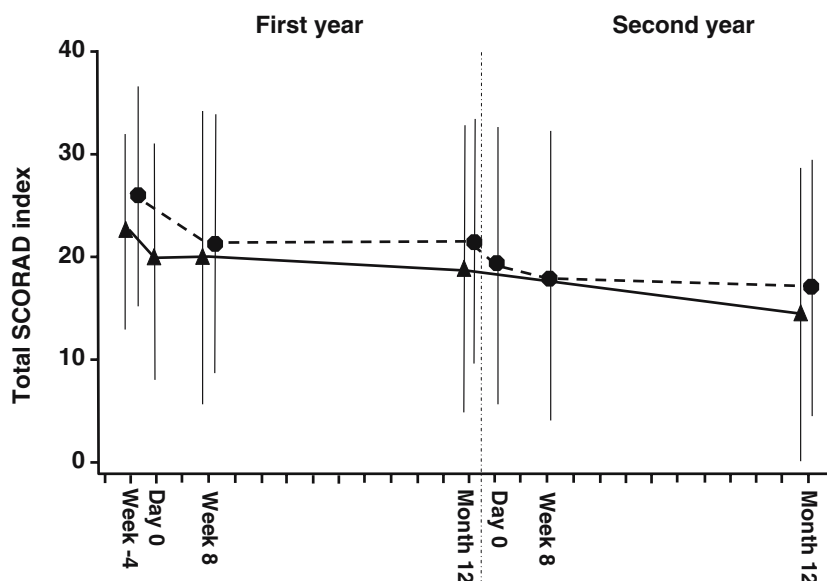
	Frequency	
	n	%
Local symptoms		
Redness	20	17.1
Soreness	11	9.4
Swelling	7	6.0
General symptoms		
Fever	12	10.3
Rash	19	16.2

vaccination. Neither event was considered related to vaccination and resolved after 27 and 4 days, respectively.

Immunogenicity

Prior to vaccination, all subjects were seronegative for VZV-specific antibodies (anti-varicella antibody titer <4 dilution^{−1} measured by IIF). In all, 94.3% (95% CI: 81.1–98.1) of subjects were seropositive for anti-VZV antibodies 8 weeks after vaccination, with 88.9% (95% CI: 80.0–94.8) remaining seropositive 12 months after vaccination. Sero-conversion rates were lower in children aged ≤3 years than in those aged >3 years at both time points, but the differences were not statistically significant [89.3% vs 100% at week 8 ($p=0.06$) and 85.7% vs 92.3% at month 12 ($p=0.49$)]. Geometric mean anti-VZV antibody titers were 98.4 (95% CI: 72.4–133.7) at week 8 and 49.9 (95% CI: 31.8–78.3) at month 12. In all, 43.6% of vaccinees reported at least one varicella contact during the course of the study, most frequently in the household (27.4%) and/or during daycare (21.4%). However, no study participants developed varicella infection after vaccination.

Fig. 1 Change in SCORAD index over the 2 years of study in the VAR-1Y (▲—▲) and VAR-2Y (●—●) groups (ATP cohort for analysis of reactogenicity)



Discussion

The clinical benefits of routine childhood immunization against varicella infection are increasingly well documented [7, 23, 25]. As the course of varicella infection tends to be more severe in children with atopic dermatitis, it seems reasonable to assume that varicella vaccination may be particularly beneficial in this population. However, while German guidelines advocate vaccination of children with atopic dermatitis against varicella [9] and atopic dermatitis is not considered a contraindication to vaccination in US guidelines [4], data to support the use of live attenuated varicella vaccine in this patient population are lacking.

This is the first study to specifically evaluate the safety and reactogenicity of vaccination with a live attenuated varicella vaccine in children with atopic dermatitis. Results show varicella vaccination to have no clinically relevant effects on the severity of atopic dermatitis assessed using the SCORAD index. The SCORAD index has been shown to be a reliable tool for the assessment of disease activity [31]. Changes in disease severity from baseline to week 8 were found to be statistically equivalent between vaccinated and unvaccinated subjects. Changes in disease severity from baseline to week 8 and month 12 were also found to fulfill the definition of equivalence before and after vaccination in the control group of children who were not vaccinated until the beginning of the 2nd study year. Indeed, greater reductions in SCORAD index were seen at both time points following vaccination in the 2nd year in this group than during the 1st year when subjects were unvaccinated. Overall, SCORAD indices fell by approximately 10 points in both study groups over the 2 years of follow-up, indicative of clinically relevant improvement in disease severity.

Improvements in the severity of atopic dermatitis have been previously reported following natural VZV infection in subjects with atopic dermatitis [11, 15], with available data indicating that this may be due to conversion of the CD4 T-cell profile from a Th2 to a Th1 phenotype [11]. It is possible that exposure to a live attenuated varicella vaccine could induce a similar phenotypic switch, which may have contributed at least in part to the improvements in the severity of atopic dermatitis seen following vaccination in this study. However, additional research is clearly required to confirm this hypothesis.

The live attenuated varicella vaccine was found to be highly immunogenic in children with atopic dermatitis, with seroconversion rates of 94.3% at 8 weeks after vaccination and 88.9% at 12 months. This is in keeping with the results of previous studies in healthy children, in which the average seroconversion rate following primary vaccination with this live attenuated varicella vaccine was 98.6% [20, 33]. Importantly, no cases of varicella infection were reported in vaccinated subjects over the 2 years of follow-up in this study despite 43.6% of vaccinees having close varicella contact during this time. Data from other studies also support the effectiveness of this varicella vaccine for the prevention of chickenpox in vaccinated cohorts [24, 32]. Injection site redness was the most

frequent solicited symptom occurring after vaccination in this study. Results of previous studies confirm that this live attenuated varicella vaccine is well tolerated in children [8, 13, 20], with no differences in relative frequencies of solicited local and general symptoms compared with placebo seen in controlled trials [13, 20].

In summary, results of this study show vaccination with a live attenuated varicella vaccine to be safe and effective in children with atopic dermatitis. In our study, we observed even an improvement in disease severity following vaccination. While this is largely attributable to the fact that infantile-onset atopic dermatitis tends to improve with age in the majority of children, varicella vaccination does not appear to lead to any exacerbation in the severity of atopic dermatitis. Nevertheless, it is still advisable to postpone vaccination in a child with acutely exacerbated eczema.

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