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CASE REPORT

Efficacy of the anti-VZV (anti-HSV3) vaccine in HSV1 and HSV2 recurrent herpes simplex disease: a prospective study

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Background: The aim of this study was to evaluate the possibility of using the anti-varicella zoster virus (anti-VZV, also known as anti-HSV3) vaccine against orobuccal herpes simplex virus type 1 (HSV1) and genital herpes simplex virus type 2 (HSV2). This was suggested by study of the phylogenetic tree of members of the herpes virus family, which showed a close relationship between VZV (HSV3) and the HSV1 and HSV2 herpes viruses.

Methods: The present prospective study was conducted from January 2005 through January 2011. Twenty-four patients afflicted with HSV1 and HSV2 herpes recurrences over a period of years, numbering 6–8 and more recurrences per year, agreed to receive the anti-VZV vaccine. They were compared with 26 nonvaccinated patients presenting with herpes simplex diseases 2–5 times a year. All 50 patients were documented with anti-HSV1, anti-HSV2, and anti-VZV antibody serological testing.

Results: From 2005 through 2011, for the 24 anti-VZV vaccinated patients, the average number of herpes relapses decreased to 0, correlated with an increased anti-VZV antibody level and clinical recovery of all patients, whereas no improvement was observed for the 26 nonvaccinated herpes patients.

Conclusion: Data for the anti-VZV serological antibody levels tested before and after anti-VZV vaccination showed a significant ($P < 0.001$) increase among vaccinated patients. This suggests defective anti-VZV immune power in these patients. After 6 years of positive results for anti-VZV vaccine, this is a logical and fair hypothesis. We can now undertake a randomized study to confirm these findings.

Keywords: HSV1/HSV2 herpes prevention, anti-VZV (HSV3) vaccine, anti-VZV vaccine therapy

Introduction

The human HSV1 and HSV2 herpes simplex viruses and varicella zoster virus (VZV, also known as HSV3) are members of the subfamily *Alphaherpesvirinae* of the *Herpesviridae* family,[1] that were incorporated in 2009 into the new order *Herpesvirales*. As McGeoch et al[3] wrote, "morphologically herpes viruses are distinct from all other viruses". These viruses contain a large dsDNA genome, and are found in a large and varied number of hosts, including mammals, birds, reptiles, fishes, frogs, and oysters. They are characterized by a very brief lytic cycle,[3] and latency in epithelial cells, the sensory ganglia, and neurons.[4] Infections caused by HSV are nearly exclusively the result of local or regional spread by cell-to-cell transmission, involving cell-mediated immunity. HSV1, HSV2, and VZV possess related genetic expressions but with distinct recurrence frequencies.[5] This close genetic relationship led us to take a new clinical

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approach to the treatment of recurrent herpes simplex disease based on fundamental phylogenetic herpes virus analysis[1,2] (Figure 1).

The hypothesis of cross-reactivity based on the immunological power of the three herpes viruses (HSV1, HSV2, HSV3) was first proposed in studies in 1969 by Schmidt et al.[6] A study by Sadaoka et al[7] pointed to measurement of VZV-specific cell-mediated immunity. These two scientific teams, and many others, led the way to this prospective study.

In 2005, we observed two otherwise healthy teenagers suffering from relapses of orobuccal herpes disease following repeated varicella infection (chickenpox) beyond childhood. Their relapses were resistant to continuous prophylaxis, such as Zovirax® (or its generic acyclovir) or Zelitrex® (or its generic valacyclovir), administered discontinuously in low doses for several years. These clinical observations of repeated chickenpox during childhood followed by herpes disease for months or years suggested a possible relationship with an initial anti-VZV immune defect that preceded recurrent orobuccal herpes disease.

After one month of taking the usual medication at an effective dosage, the teenagers received anti-VZV vaccination. Thereafter, no further recurrences occurred. The relationship between chickenpox and recurrent herpes disease was thus established in these two teenagers, suggested that treatment with anti-VZV vaccine might be beneficial for patients with recurrent orobuccal herpes disease.

The aim of the present study was to establish whether a possible correlation exists between the serological HSV1, HSV2, and VZV antibody levels and the observed clinical results after anti-VZV vaccination. A suspected link between these orobuccal (HSV1) and genital (HSV2) herpes viruses and VZV might be revealed by the serological and clinical effects of the anti-VZV vaccine. Therefore, it was decided to follow up these interesting clinical observations in a larger number of herpes patients attending our medical practice.

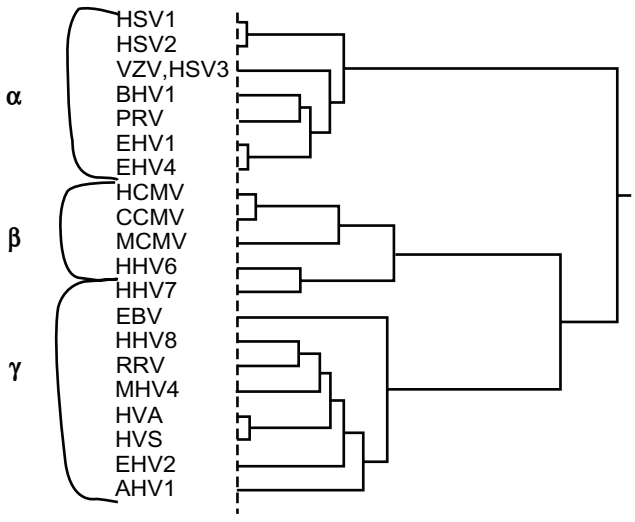

Figure 1 Phylogenetic tree of 20 members of the *Herpesviridae* family divided into three subfamilies, ie, *Alphaherpesvirinae*, *Betaherpesvirinae*, and *Gammaherpesvirinae*. Adapted from McGeoch et al.[1]

Materials and methods

Patient recruitment and inclusion criteria

Since 2005, among 50 patients with common herpes simplex disease diagnosed in dermatological consultation, the conditions for inclusion of patients in the present study was to perform anti-VZV vaccination as a therapeutic alternative, instead of the continuous anti-herpes prophylaxis by usual chemotherapy. Of these patients, 24 otherwise healthy and immunocompetent adults had suffered from recurrent herpes over the preceding 2–6 years, with at least 6–8 herpes relapses per year (Tables 1 and 2).

Primary and secondary outcomes

The patients were informed of the trial therapeutic approach, which was based on genetic analysis of the herpes virus family tree. The very close genetic relationship that exists between HSV1, HSV2, and VZV was explained in detail to the patients, all of whom provided their informed consent to participate in the therapeutic vaccine study. The 50 patients were immunocompetent without symptoms of hypertension or diabetes that would require medical treatment affecting general immunity. This was controlled at the time of the first consultation of any patient. A glycemia level and blood count were obtained, as well as a human immunodeficiency virus test (necessarily negative for this study). Anti-HSV1, anti-HSV2, and anti-VZV antibody levels were measured as a control reference before any antiherpes treatment for all patients.

Administration of the anti-VZV vaccine as a possible therapy was proposed as a substitute for classical antiherpes therapy to the 50 herpes patients, 24 of whom agreed to participate in the trial. The anti-HSV1, anti-HSV2, and anti-VZV antibody levels of the 26 nonvaccinated herpes patients served as reference controls for the 24 patients receiving the anti-VZV vaccine. One standard intradermal injection of anti-VZV vaccine was administered consistent with the dermatological requirement to stimulate skin cell-mediated immunity using the same anti-VZV vaccine (Oka Merck strain), being either Varivax® (sanofi-aventis, 0.5 mL/dose) or Varilrix® (GlaxoSmithKline, 0.5 mL/dose), as shown in Tables 3 and 4).

Table 1 Recurrences of herpes in female patients before and after anti-VZV vaccination

Patient	Age (years)	Time of consultation	Recurrences per year	Sites	Long-term therapy	Anti-VZV vaccine	Recurrences after anti-VZV vaccine
1	57	June 2006	>6	Orobuccal	Zovirax	2	0
2	37	July 2008	>12	Orobuccal	Zelitrex	1	0
3	25	February 2005	>8	Genital	Zovirax	2	0
4	47	February 2005	>12	Genital	Zovirax Zelitrex	2	Fleeting 1
5	68	January 2008	>8	Genital	Zovirax Zelitrex	3	0
6	71	March 2006	>10	Orobuccal	Zovirax	2	0
7	50	February 2005	>8	Orobuccal	Zovirax	4	0
8	40	June 2008	>6	Genital	Zelitrex	2	0
9	48	2006/02	>8	Orobuccal, genital	Zovirax, Zelitrex	1 + 1	0
10	33	2006/04	>6	Orobuccal	Zovirax	1	Fleeting 1
11	42	April 2005	>8	Orobuccal	Zovirax	1	0
12	32	March 2009	>10	Orobuccal	Valacyclovir	1	0
13	27	April 2009	>8	Orobuccal	Valacyclovir	1	0
14	53	February 2007	>8	Orobuccal, genital	Zovirax	1	0

After receiving the anti-VZV vaccine, the patients were requested to check their post-vaccination antibody levels. Of the treated and clinically cured patients (n = 24), only 12 agreed to have their HSV1, HSV2, and HSV3 antibody levels checked for 1–3 years after anti-VZV vaccination. The other vaccinated patients were still followed up by consultation and were cured and satisfied, but considered serological checks to be unnecessary (n = 12).

Patient follow-up consisted of comparing the clinical criteria of effectiveness with serological antibody levels. This involved comparison of anti-HSV1, anti-HSV2, and anti-VZV antibody levels in nonvaccinated patients (n = 26) with those in vaccinated patients (n = 24). Only one biological variable was significant, ie, the rise in anti-VZV antibody, which correlated well with the clinical efficacy of the anti-VZV vaccine against recurrent HSV1 and HSV2 herpes simplex disease.

Medication and assignments

Serological antibody titers were determined for each patient prior to conventional treatment for acute herpes infection using Zovirax (acyclovir) or Zelitrex (valacyclovir). Four to six weeks later, each patient received an intradermal anti-VZV vaccination after undergoing standard therapy.

Table 2 Recurrences of herpes in male patients before and after anti-VZV vaccination

Patient	Age, years	Time of consultation	Recurrences per year	Sites	Long-term therapy	Anti-VZV vaccine	Recurrences after anti-VZV vaccine
15	59	February 2008	4–6	Orobuccal, genital	Zelitrex	2	0
16	66	February 2007	4–6	Orobuccal	Zelitrex	2	0
17	66	April 2006	>6	Orobuccal	Zovirax	1	0
18	69	September 2005	>6	Orobuccal	Zovirax	2	0
19	54	February 2005	>6–10	Orobuccal	Zovirax	1	0
20	45	March 2005	>6	Genital	Zovirax	2	0
21	56	March 2006	>6	Genital	Zovirax	2	Fleeting 1
22	26	April 2009	>8	Orobuccal, genital	Zovirax	1	0
23	53	January 2010	>8	Orobuccal, genital	Valacyclovir	1	0
24	55	February 2009	>6	Orobuccal	Valacyclovir	1	0

Table 3 Comparison of HSV1, HSV2, and HSV3 antibody levels in the herpes control group (n = 26) and the recurrent herpes patient group (n = 24) before anti-VZV vaccination

	Ab levels in 26 controls Mean (median) ± SEM	Ab levels in 24 patients with recurrent herpes Mean (median) ± SEM	*P* value
Anti-HSV1 Ab level	3.38 (0.9) ± 1.029	3.171 (3.45) ± 0.3101	0.031
Anti-HSV2 Ab level	2.768 (0.9) ± 0.9173	1.581 (0.9) ± 0.279	0.1
Anti-HSV3 Ab level	0.69 (0.7) ± 0.069	0.79 (0.5) ± 0.083	0.4159

Note: The statistical analysis was performed using the Wilcoxon rank-sum test, and the *P* values are not significant.
Abbreviations: Ab, antibody; SEM, standard error of the mean; VZV, varicella zoster virus.

During this study, 24 patients (14 women, 10 men, mean age 51 [range 26–71] years) with recurrent herpes agreed to be vaccinated. Thirteen patients had orobuccal HSV1 herpes, six had genital HSV2, and five patients had orobuccal and genital herpes. Some patients were seropositive for both HSV1 and HSV2, even though recurrent herpes manifestations were limited to orobuccal herpes.

Factors that triggered relapses were identified in 20 cases, ie, menses in 12 women, and exposure to sun in eight men. All the women who participated in the study were on hormonal treatment for contraceptive reasons or as replacement therapy during menopause.

Following one anti-VZV vaccination, the mean annual number of herpes relapses decreased from 6–8 to zero. If requested by the patient, the anti-VZV vaccine was followed several months to one year later by a second injection, as recommended for children and proposed over ten years ago in the US. One dose of anti-VZV vaccine protected 76% of children, but 89%–99% were protected with two doses. The immune response is thus adequate with one dose.[8,9]

One year after the first vaccination, five women and five men who were clinically cured of recurrent herpes disease but feared relapses requested a second vaccination. One year after the first or second vaccination, a booster dose of anti-VZV vaccine was performed at the request of two clinically cured but very anxious female patients. The decision was made to comply with patient requests as long as vaccination was not harmful. Serological controls performed in these 12 patients after the first, second, or third injection showed that the level of anti-VZV antibody had greatly increased.

Clinical effectiveness was evaluated using the frequency of relapse at one, 2, and 5 years following vaccination, and by whether or not antiviral therapy was required. During this period, no herpes relapses were observed and no antiviral therapy was needed. Systematic serological measurements were performed in the 50 herpes patients in this study before any other treatment was given in order to be able to compare nonvaccinated herpes patients with those who were vaccinated with anti-VZV (Figure 2A and B).

Serological controls

Analyses of antibody levels prior to and after anti-VZV vaccination between 2005 and 2011 were determined by the Cerba and Biomnis laboratories, using the same enzyme-linked immunosorbent assay and electrochemoluminescence techniques. These laboratories use DiaSorin SpA kits to measure anti-HSV1, anti-HSV2, and anti-VZV titers, have standardized data based on the results of Sauerbrei et al,[10] and follow the interpolation of VZV assays based on standard curves, whereby a cutoff ratio of 0. 9/1 is correlated with 275/280 IU/mL.

For a healthy individual free of herpes, the standard serological HSV1/HSV2 antibody ratio is $<0.9/1$. In all our 50 herpes patients, the anti-HSV1 and anti-HSV2 antibody levels were expressed as a ratio > 1. A healthy herpes-free individual who has been exposed to chickenpox during childhood carries an anti-VZV antibody level expressed as

Table 4 Comparison of HSV1, HSV2 and HSV3 antibody levels in the herpes control group and the vaccinated herpes group after anti-VZV vaccination

	Ab levels in nonvaccinated herpes controls Mean (median) ± SEM	Ab levels in 12 herpes patients after vaccination Mean (median) ± SEM	*P* value
Anti-HSV1 Ab level	3.38 (0.9) ± 1.029	2.67 (2.8) ± 0.491	0.5073
Anti-HSV2 Ab level	2.77 (0.9) ± 0.917	1.63 (1.4) ± 0.337	0.9831
Anti-HSV3 Ab level	0.69 (0.7) ± 0.069	1.69 (1.4) ± 0.211	<0.0001

Notes: Statistical analysis was done using the Wilcoxon rank-sum test. The *P* value was significant at <0.001.
Abbreviations: Ab, antibody; SEM, standard error of the mean; VZV, varicella zoster virus.

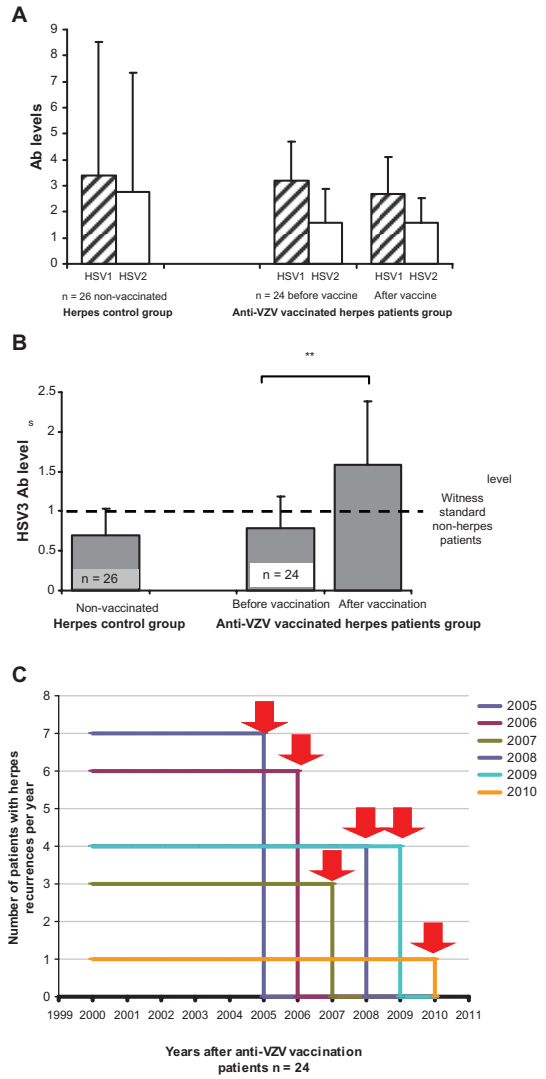

Figure 2 (**A**) Evolution of anti-HSV1 and anti-HSV2 antibody levels in 24 patients with recurrent herpes before and after anti-VZV vaccination. The *P* value is not statistically significant. Referring to Table 3, the values are expressed as the mean ± standard deviation and represent anti-HSV1 and anti-HSV2 antibody levels of the non-vaccinated herpes control group and the vaccinated herpes group before and after herpes anti-VZV vaccine. (**B**) Evolution of anti-VZV antibody levels before and after anti-VZV vaccination in patients with recurrent herpes. $^{**}P < 0.001$ is significant after anti-VZV vaccination (Wilcoxon's signed-rank test). Referring to Table 4, the values are expressed as the mean ± standard deviation and represent normalized anti-VZV antibody levels in the non-vaccinated herpes control group and in anti-VZV vaccinated patients before and after anti-VZV vaccination. (**C**) Efficiency of anti-VZV vaccination showing that herpes recurrences (at least eight per year) for all 24 patients decreased to zero after anti-VZV vaccination (highlighted by red arrow).
Abbreviation: VZV, varicella zoster virus.

a ratio > 4.5 or >1450 IU/mL. Anti-VZV antibody levels were generally low for all our herpes patients, and expressed as a ratio < 4.5 or <1450 IU/mL.

To compare anti-VZV antibody levels expressed either as a ratio or as IU/mL, all the data were normalized by dividing the anti-VZV antibody level by 4.5 when expressed as a ratio, and by 1450 when expressed as IU/mL. The serological sources of the data were the analyses of anti-HSV1, anti-HSV2, and anti -HSV3 antibody titers of the patients before and after anti-VZV vaccination.

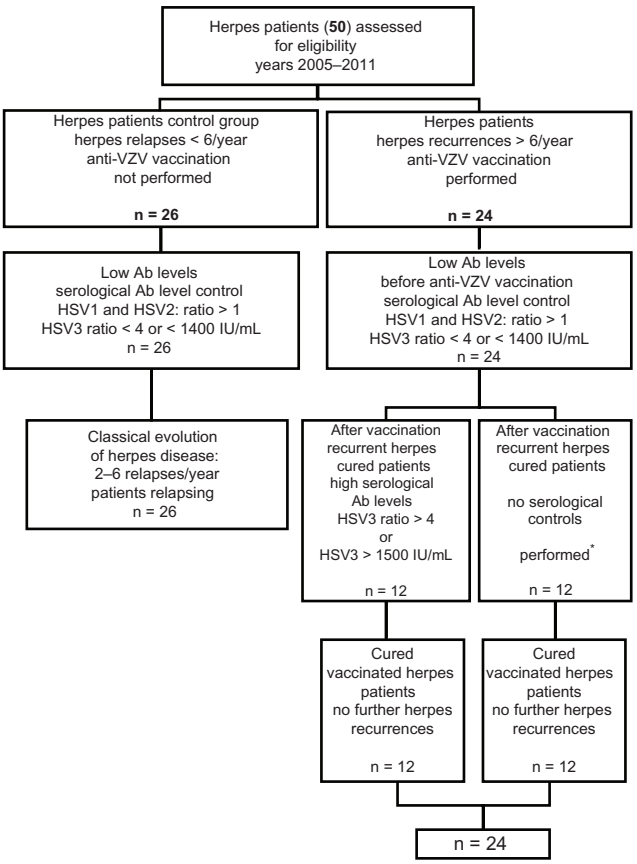

Figure 3 Flow chart for herpes patients at the time of analysis.
Note: *Twelve vaccinated patients who were clinically cured and satisfied refused to undergo further serological testing.

Results

In this study, of the 24 vaccinated patients who were cured, 11 received only one subcutaneous vaccination and showed complete recovery from herpes disease, as did the 13 patients who received a second or third anti-VZV vaccination. These patients were all free of recurrences of herpes simplex several years later.

In the control group of 26 patients who did not receive the anti-VZV vaccine, classical evolution of herpes disease was observed, ie, 2–6 relapses per year. Among the 24 patients which received the anti-VZV herpes vaccination, the annual number of recurrences fell to zero after the initial vaccination (Figure 2C).

Clinical follow-up of the vaccinated patients was by consultation at specified times over several years. A few patients reported a fleeting or prickling sensation or redness lasting a few hours, but in no case did this warrant standard anti-herpes treatment. With regard to side effects, erythema or

edema 4–5 cm in diameter that lasted 5–8 days (three cases) was detected at the injection site, but resolved spontaneously. Patients with recurrent herpes simplex disease typically require conventional antiviral treatment for an average of 150 days per year. After anti-VZV vaccination, this requirement decreased to zero (Tables 1 and 2, Figure 2C).

Before anti-VZV vaccination, the anti-VZV antibody titers of all the herpes patients (n = 50) was comparable, and the difference in the mean anti-VZV antibody level was not significant ($P = 0.416$, Wilcoxon's rank-sum test). After anti-VZV vaccination, the anti-VZV antibody titers of the 12 vaccinated patients who agreed to undergo further serological testing were significantly higher than the levels of the 26 nonvaccinated herpes patients ($P < 0.001$, Wilcoxon's rank-sum test). Anti-VZV antibody levels (Figure 2A) were increased by two-fold compared with the levels before vaccination. This increase was significant ($P < 0.001$, Wilcoxon's signed-rank test, Figure 2B). In healthy individuals, enhancement of anti-VZV antibody levels demonstrates the effectiveness of anti-VZV vaccination and its powerful role in protecting against herpes recurrences, although anti-HSV1 and anti-HSV2 antibody levels either remained stable or decreased slowly by a factor of 1.2.

These positive clinical results provide remarkable preliminary evidence of the efficiency of the anti-VZV vaccine as a cure for recurrent herpes disease. Two patients in this study are now described in more detail with regard to the relationship between herpes simplex disease recurrence and serological anti-VZV antibody immune deficiency.

Patient 1

For over ten years, this woman had suffered from recurrent genital HSV2 herpes resistant to low-dose acyclovir taken as ongoing conventional prophylaxis. She had neither the anti-HSV1 antibody nor the anti-HSV2 antibody, and had a very low level of anti-VZV antibody before receiving the anti-VZV vaccine. After anti-VZV vaccination, her HSV1 and HSV2 antibody levels increased slightly, but her anti-VZV antibody levels doubled, with no further herpes recurrences.

Patient 2

In 2006, a 65-year-old woman who had had herpes recurrences for many years received the anti-VZV vaccine, with no further relapses. In 2007, the patient successfully underwent surgery for abdominal cancer. This case is surprising because the patient would have had immune suppression for some time because of her underlying malignancy. Serological anti-VZV antibody titers, measured in 2006, 2007, and 2011, were very low. These VZV serological defects would appear to be linked to her immune depression as a result of having cancer and, for this reason, this patient was not included in the results, but was cured of recurrent herpes disease. This observation highlights the potent cell-mediated immunity acquired through the anti-VZV vaccine which persisted in spite of the emergence of cancer.

Discussion

In this study, we evaluated the immunological status of HSV1 and HSV2, two members of the large family of herpes viruses, and they appeared to be related to VZV. Our therapeutic decision-making with respect to recurrent herpes was based on these observations. The genetic link between VZV and the other herpes viruses of the order *Herpesvirales* can be considered a primordial event with an outcome specific to the immunogenetic human leucocyte antigen. This relationship must be taken into account within the framework of the phylogenetic tree of the herpes viruses[1] (Figure 1).

Herpesviridae comprises three subfamilies, ie, *Alphaherpesvirinae*, *Betaherpesvirinae*, and *Gammaherpesvirinae*. HSV1 and HSV2 are members of the *Alphaherpesvirinae* subfamily. They induce vesicles on the skin, and are most frequently expressed in the mouth or larynx and on the genital or rectal mucosa. However, they persist for months at the epidermal level surrounding the ends of peripheral nerves. Herpes viruses can also remain latent at the level of the nodes during the entire life of their host.[4] Among the members of the *Betaherpesvirinae,* HSV5 (human cytomegalovirus) is linked to lymphoproliferative disease and congenital malformation. Members of the *Gammaherpesvirinae* include HSV4 (Epstein–Barr virus), responsible for lymphoma, including Hodgkin's lymphoma and HSV8, which is linked to Kaposi's sarcoma.

The first anti-VZV vaccine was the "Oka strain" varicella vaccine produced by Takahashi et al.[11,12] This viral strain was isolated from typical vesicular varicella in an otherwise healthy child. The vaccine was used initially to prevent varicella in high-risk leukemic children.[12] The children all remained free of varicella after anti-VZV vaccination. Thus, the tolerance and the safety of the vaccine is considered excellent.[11,12]

Since the end of 2004, the anti-VZV vaccine has been used in France to prevent chickenpox in children, and to prevent shingles in immune-depressed or older individuals. Prior to the present study, this anti-VZV vaccine had never been used to prevent recurrent herpes infection. Nevertheless, studies exist on the anti-VZV vaccine, and its potential

pharmacodynamic properties has been speculated upon but not investigated.[13] In spite of the limited number of patients involved in the present study and the absence of a comparative placebo/vaccine randomized trial, our results demonstrate the remarkable efficiency of the anti-VZV vaccine in 24 patients suffering from recurrent herpes simplex disease.

Human beings encounter the VZV more often during childhood than later in life. In all patients with recurrent herpes, anti-VZV antibody titers are present but their levels are low. The anti-VZV vaccine, originally approved for children, has been used throughout the world since the 1980s. It is effective, harmless,[13] and well tolerated in immunocompetent children; however, the Oka VZV vaccine has been implicated in varicella in six immunocompromised patients.[14]

These findings warrant a second study involving a larger cohort with a control group in order to evaluate a possible placebo effect, although a report involving patients with HSV2 following classical herpes treatment with acyclovir or valacyclovir versus placebo showed no placebo effect.[15] The well tolerated anti-VZV vaccine induced a high increase in serological anti-VZV antibodies in parallel with clinical cure in patients. Anti-HSV1 and anti-HSV2 antibody levels vary slightly, increasing, decreasing, or remaining stable after administration of the anti-VZV vaccine with nonsignificant *P* values, and they may be considered residual "serological scars" of herpes disease.

The therapeutic effect of the anti-VZV vaccine on recurrent herpes disease might be attributed to a cell-mediated immune response, because T lymphocytes, CD8 cells, and natural killer cells are known to be involved in herpes.[16] If this hypothesis is correct, it would suggest immunological induction of cell-mediated cross-reactivity between HSV1, HSV2, and HSV3 due to specific VZV (HSV3) antigens. Subsequent polyclonal lymphocyte stimulation would then trigger the clinical anti-herpes efficiency observed here using the anti-VZV vaccine.[17]

In conclusion, the remarkable therapeutic effectiveness of the anti-VZV (anti-HSV3) vaccine in preventing recurrent herpes simplex disease due to HSV1 and HSV2 clearly demonstrates the efficacy of anti-VZV vaccination. In addition, our results suggest that cell-mediated cross-reactivity would be involved between HSV1, HSV2, and VZV, as demonstrated by the serological increase in anti-VZV antibody titers. A randomized trial with a larger cohort of patients has been initiated after this promising prospective study.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. McGeoch DJ, Dolan A, Ralph AC. Toward a comprehensive phylogeny for mammalian and avian herpes viruses. *J Virol*. 2000;74:10401–10406.
2. Davison AJ, Eberle R, Ehlers B, et al. The order *Herpesvirales*. *Arch Virol*. 2009;154:171–177.
3. McGeoch DJ, Rixon FJ, Davison AJ. Topics in herpesvirus genomics and evolution. *Virus Res*. 2006;117:90–104.
4. Favoreel HW. Immune evasion of alpha herpes viruses. *Verh K Acad Geneeskd Belg*. 2008;701:47–65. Dutch.
5. Giehl KA, Müller-Sander E, Rottenkolber M, Degitz K, Volkenandt M, Berking C. Identification and characterization of 20 immunocompetent patients with simultaneous varicella zoster and herpes simplex virus infection. *J Eur Acad Dermatol Venereol*. 2008;22:722–728.
6. Schmidt NJ, Lennette EH, Magoffin RL. Immunological relationship between herpes simplex and varicella-zoster viruses demonstrated by complement-fixation, neutralization and fluorescent antibody tests. *J Gen Virol*. 1969;4:321–328.
7. Sadaoka K, Okamoto S, Gomi Y, et al. Measurement of varicella-zoster virus (VZV)-specific cell-mediated immunity: comparison between VZV skin test and interferon-gamma enzyme-linked immunospot assay. *J Infect Dis*. 2008;198:1327–1333.
8. Gershon AA, Katz SL. Perspective on live varicella vaccine. *J Infect Dis*. 2008;197 Suppl 2:S242–S245.
9. Marin M, Meissner HC, Seward JF. Varicella prevention in the United States: a review of successes and challenges. *Pediatrics*. 2008;122:e744–e751.
10. Sauerbrei A, Färber I, Brandstädt A, Schacke M, Wutzler P. Immunofluorescence test for highly sensitive detection of varicella-zoster-virus specific IgG – alternative to fluorescent antibody to membrane antigen test. *J Virol Methods*. 2004;119:25–30.
11. Takahashi M, Otsuka T, Okuno Y, Asano Y, Yazaki T, Isomura S. Live vaccine used to prevent the spread of varicella in children in hospitals. *Lancet*. 1974;2:1288–1290.
12. Takahashi M. Current status and prospects of live varicella vaccine. *Vaccine*. 1992;10:1007–1014.
13. Kockler DR, McCarthy MW. Zoster vaccines live. *Pharmacotherapy*. 2007;27:1013–1019.
14. Galea SA, Sweet A, Beninger P, et al. The safety profile of varicella vaccine: a 10-year review. *J Infect Dis*. 2008;197 Suppl 2: S165–S169.
15. Fife KH, Warren TJ, Justus SE, Heitman CK. An international, randomized, double-blind, placebo-controlled, study of valacyclovir for the suppression of herpes simplex virus type 2 genital herpes in newly diagnosed patients. *Sex Transm Dis*. 2008;35:668–673.
16. Koelle DM, Corey L. Herpes simplex: insights on pathogenesis and possible vaccines. *Annu Rev Med*. 2008;59:381–395.
17. Ferenczy MW. Prophylactic vaccine strategies and the potential of therapeutic vaccines against herpes simplex virus. *Curr Pharm Des*. 2007;13:1975–1988.

Efficacy of the anti-VZV (anti-HSV3) vaccine in the treatment of HSV1 and HSV2 recurrent herpes simplex diseases: a prospective study

Names of the drugs used

I. Chemotherapy of Herpes diseases antibiotics and generics:
   1. **Zovirax**, generic: **Acyclovir** 200 mg × 6p/day × 6 days
   2. **Zelitrex**, generic: **Valacyclovir** 500 mg × 2p/day × 5 days

II. **Oka Strain Varicella Vaccine**: one dose 0.5 mL: two Laboratories:
   1. **Varivax** Sanofi Aventis Laboratory 0.5 mL/one dose Oka/Merck Strain
   2. **Varilrix** Glaxo Smith Kline Laboratory 0.5 mL/one dose Oka/Merck Strain