A Double-Blind Study of the Efficacy and Safety of the ICP10ΔPK Vaccine Against Recurrent Genital HSV-2 Infections

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A randomized double-blind trial to evaluate the safety of a novel recombinant virus, ICP10ΔPK, for reduction or prevention of recurrent herpes simplex virus type 2 (HSV-2) infection was carried out in public hospitals in Mexico City. Persons having a minimum of 5 documented herpetic recurrences in the previous year were randomized for vaccination. Patients were examined within 72 hours of lesion occurrence. If accepted into the study, the patient was inoculated subcutaneously in the upper deltoid muscle area at days 7, 17, and 28 after initiation of lesion occurrence. Recurrences were recorded by patient diary and physician examination.

During the observation period (extending from 10 to 180 days after the last booster dose), recurrences in the vaccine (V) group were prevented completely in 37.5% of the patients, whereas in the placebo (P) group, 100% of the patients had at least one recurrence (P=.068). Vaccinated patients had fewer recurrences (V, 1.58; P, 3.13 [P=.028]). The mean number of illness days was 10 for the vaccine group and 18 for the placebo group (P=.028).

Further studies to evaluate this vaccine and its dosimetry for the treatment of genital herpes infections appear warranted.

Nearly 45 million persons in the United States are infected with genital herpes.[1] Higher rates are estimated in other countries.[2] During pregnancy, infection is associated with spontaneous abortion, prematurity, and congenital neonatal herpes.[3] Herpes simplex virus type 2 (HSV-2) also has been shown to cause severe hyperproliferative lesions, and infection is associated with an increased risk of HIV infection and disease severity.[4,5] Approximately 50% of patients infected with HSV-2 experience periodic recurrent disease, resulting from reactivation of the latent virus and its replication in epithelial cells in the presence of preexisting virus-specific immunity. Infection with multiple HSV-2 strains that establish latency has been described, though its frequency is unclear.[6,7] Patients infected with multiple strains have not differed in the number or severity of recurrent episodes. Drugs currently used in the treatment of genital herpes infections are only partially effective at suppressing recurrences and do not prevent the shedding of virus.[8,9] Presently, there is no method of preventing recurrent disease, though a number of vaccines have been tested.[10,11] The advent of a therapy for the prevention of recurrences and viral shedding is highly desirable from the standpoint of patient management and epidemiologic studies.

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Recently, the concept that vaccination could be used for immunotherapy of HSV recurrent disease has gained renewed interest.[12-14] Accumulating evidence indicates that recurrent disease is associated with virus-specific helper T cell (T_H2) immune responses,[15-17] suggesting that the shift of virus-specific immune responses in favor of T_H1 might have immunoprotective potential. However, the design of therapeutic vaccines is complicated by the findings that both T_H1 and T_H2 responses are induced by HSV antigenic stimuli used for effective vaccination. Previous studies have shown that a recombinant HSV-2—in which the protein kinase domain of the multifunctional large subunit of the ribonucleotide reductase (RR1) has been deleted (known as ICP10ΔPK)—is innocuous in mice and guinea pigs at levels of 10^7 plaque-forming units (PFUs), while still being an effective vaccine in animal models.[18,19] A unique property of ICP10ΔPK is immunotherapeutic activity, which is likely due to its ability to elicit a predominant virus-specific T_H1 immune response.[20] In cutaneous and vaginal animal models, the ICP10ΔPK vaccine was shown to prevent nearly 90% of recurrences.[18,19] No harmful effects were noted in the course of these animal experiments or in the toxicologic studies performed on the vaccine. Based on these findings, a trial of ICP10ΔPK for safety and dosage (phases I and II) in human volunteers was desirable.

Methods

Vaccine Properties and Preparation—The protein kinase domain in the large subunit of viral RR1 is deleted in the recombinant HSV-2 mutant, ICP10ΔPK, which shares homology with a highly conserved cellular protein.[18] Therefore, this mutant lacks antigens that may be tolerogenic or induce autoimmunity. This virus is growth compromised in cultured cells, mice, and guinea pigs. In cutaneous and vaginal models of HSV-2 infection, ICP10ΔPK has prophylactic and therapeutic vaccine activity involving induction of a predominant HSV-specific T_H1 response, including CD8+ cytotoxic T cells.[20]

A standard sterile stock containing 2×10^5 PFU/mL, determined by plaque assay on Vero cells, was used for human vaccination as it was in earlier animal trials. Viral titers were stable for more than 2 years, as determined by plaque assay before and after completion of the vaccination program. Placebo was prepared in a similar manner, except with the omission of virus.

Study Participants and Design—Persons who were identified as having a genital HSV-2 infection with a minimum of 5 recurrences in the previous year (documented clinically by examination and history), and who ranged in age from 18 to 55 years, were recruited through advertisement in local newspapers, radio talk shows, and patient walk-ins at the investigators' sites. Local institutional review board or ethics committee, as well as the Mexican Ministry of Health, approved the study. Patients were considered for enrollment if they were (1) experiencing an active, confirmed episode less than 72 hours' old at the time of examination by the investigator; (2) in good general health, as determined by a current medical examination and laboratory tests, including pregnancy and HIV assays; and (3) willing and able to give informed written consent to the trial.

Patients were excluded if they were (1) pregnant or lactating women or women likely to become pregnant during the study period (except sexually inactive women; sexually active women whose partners had had vasectomies; or women who were willing to use a contraceptive method, including surgical sterility, oral contraceptive, implant of injectable systemic contraceptive, diaphragm with intravaginal spermicide, cervical cap, intrauterine contraceptive device, or condom with intravaginal spermicide); (2) known to be immunocompromised; (3) undergoing immune therapy; (4) unwilling to forego use of antiviral agents (either systemic or topical, including but not limited to acyclovir, valacyclovir, and famciclovir) for the duration of the trial; (5) diagnosed with significant medical or surgical disease that might result in hospitalization within 6 months; (6) experiencing malnutrition, blood dyscrasia, severe asthma, severe eczema, renal or hepatic impairment, chronic infection, drug or alcohol abuse, or cancer; (7) identified as having limited mental capacity, making the patient unable to give legal consent or information about the efficacy and side effects of the study vaccine; (8) using an experimental drug within 30 days before the initial visit; and (9) shown to have laboratory abnormalities on screening blood tests that would compromise the safety of the patient.

Written informed consent was obtained from all study participants before randomization. Subjects were assigned to a block randomization scheme, in which they received either vaccine (n=24) or placebo (n=8) identical to the active vaccine. Injections were given subcutaneously in the upper deltoid muscle area 7 days after the initiation of the presenting lesion, followed by additional injections at days 17 and 28. All subjects, investigators, and trial coordinators were blinded to treatment assignment. Subjects were followed for 6 months after their last injection. Both subjects and investigators

maintained records of lesions and adverse events. Subjects were asked to return to the physician when they experienced genital symptoms that needed to be examined. Then, the physician and patient scored both lesions and symptoms. Records were kept for both patient and physician assessment. A record of the number of days each episode lasted was kept in a patient diary. The episode was considered ended when all symptoms disappeared and at most only a scab remained.

Overall, both treatment groups were comparable in their baseline characteristics. (There were no statistically significant differences.) Patients in the test or vaccine (V) group were slightly older (3 years) and heavier (2 kg) than those in the placebo (P) group. There were more men enrolled in the vaccine group (V, 66.7%; P, 50.0%). More women in the vaccine group than in the placebo group were using a contraceptive method (V, 75.0%; P, 50.0%). Except for the medical history of genital warts found during the baseline physical examination (V, 58.3%; P, 50.0%), study patients were healthy subjects with only one sexual partner (V, 70.8%; P, 75.0%). A higher percentage of vaccinated patients reported previous sexually transmitted diseases (V, 54.2%; P, 25.0%). Of the vaccinated patients, 62.5% previously had taken a drug for herpes therapy.

All study subjects had experienced recurrent genital herpes for about 5 years, with approximately 8 to 10 episodes in the previous year lasting an average of 7 to 8 days.

Results

Tolerance for the ICP10ΔPK vaccine is reflected in the small number of side effects. No serious related adverse events occurred. For both treatment groups, the most frequently reported adverse reaction was headache (50.0%). This reaction was judged more frequently by the investigator to be treatment related in the placebo group (2 of 4 patients) than in the vaccine group (3 of 12 patients). The second most frequently reported adverse event was erythema at the site of injection (29.2%, n=7) in the vaccine group and mild myalgia (37.5%, n=3) in the placebo group. No deaths or hospitalizations related to the treatment occurred during the study. Contrary to the protocol-required use of an effective contraceptive method, one pregnancy occurred in the vaccine group because of failure of the patient to use contraceptives. Conception occurred in the second month after the last inoculation, and the mother successfully went to term without complication and delivered a healthy newborn infant who is now 1 year old. During the study, the mother had no recurrences.

In the observation period extending from 10 days after the last inoculation (allowing time for the immune response to develop) to 180 days thereafter, recurrent HSV-2 episodes were completely prevented in 37.5% (n=9) of vaccinated patients but in none (0%) of the patients given placebo (P=.068 for total episode comparison). Vaccinated patients had fewer recurrences (1.58) than patients in the placebo group (3.13, P=.028). During the entire observation period, the mean number of illness days was 10 in the vaccine group and 18 in the placebo group (P=.028). The severity of the observed recurrent herpetic episodes was reduced in the vaccine group, with symptoms being much milder than in the placebo group, as determined by both physician and patient assessment. This was expressed in a reduction of all symptoms. The incidence of symptoms for vaccinated and placebo groups was: vesicles (V, 12.5%; P, 62.5%), pain (V, 12.5%; P, 37.5%), and itching (V, 16.7%; P, 62.5%)(Table).

The number of recurrent episodes occurring after the treatment protocol was completed was significantly reduced in the vaccine group as compared with the placebo group. The mean number of recurrent episodes per month for the 24 vaccinated patients was significantly reduced when compared with that documented for the previous year (0.75–0.26, P<.001), while the number was only slightly changed in the placebo group (0.84–0.52, P=.188).

Comment

The ICP10ΔPK vaccine prevents recurrent episodes of cutaneous HSV-2 and HSV-1 lesions in previously infected guinea pigs and mice and is also effective against intravaginal HSV-2 infection in animal models.[18,19] Polymerase chain reaction and virus isolation studies indicated that ICP10ΔPK is compromised in its ability to establish latency in dorsal root ganglia and to reactivate from latency. Immunization with ICP10ΔPK dramatically reduced the frequency of ganglionic latency established by subsequent infection with HSV-2 and interfered with the reactivation of HSV-2 from latently infected ganglia.[18,19] Thus, the risk of establishing latent infections did not appear to be a complication of vaccination with this recombinant virus. Recent studies indicate that a major action of the ICP10ΔPK vaccine is to induce a virus-specific immune response that is primarily T_H1, thereby shifting the balance in favor of functions that stimulate rather than inhibit immunity.[20] Immunization with ICP10ΔPK increases the levels of CD8+ cytotoxic (killer) T cells that are responsible for lysing virus-infected cells and interferon gamma,

Local Signs and Symptoms of Herpetic Episodes Reported as Moderate or Severe During the Observation Period*

	Vaccine Group (n=24)	Placebo Group (n=8)
Signs and symptoms, %		
None	37.5	0
Vesicles	12.5	62.5
Erythematous ulcers	8.3	12.5
Dysuria	8.3	12.5
Pain	12.5	37.5
Hot or burning sensation	20.8	25.0
Itching	16.7	62.5

*Due to the small number of recurrences in the test group, these differences were not statistically significant. Moderate was defined as a symptom that was present but did not interfere with daily activity. Severe was defined as a symptom that was sufficiently disturbing that it interfered with daily activity.

which is not only a major T_H1 effector cytokine but also was shown to inhibit reactivation of latent HSV.[21]

Because of these successful animal studies, a trial utilizing human volunteers was initiated. The vaccine was well tolerated, and significant success was achieved under the studied experimental conditions. The minor side effects of inoculation with the ICP10ΔPK vaccine were characteristic of a delayed-type hypersensitivity, which is usually observed after inoculation with other biological vaccines. Incidences of headache and constitutional symptoms were the same in both the vaccine and placebo groups and were similar to those following the administration of a sugar pill.

Future research should be designed to perfect the dosage necessary to further reduce the frequency of recurrent episodes for longer periods and to test efficacy in a larger number of patients. This testing should be accompanied by an investigation of this vaccine's effect on asymptomatic virus shedding from lesional and nonlesional skin by polymerase chain reaction. Notwithstanding, the data from this group of patients indicates the recombinant vaccine resulted in specified statistically significant results and was well tolerated.

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