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EDITORIAL COMMENTARY

Vaccination to Reduce Reactivation of Herpes Simplex Virus Type 2

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(See the major article by Bernstein et al on pages 856–64.)

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"A therapeutic herpes simplex vaccine is a journey of a thousand miles that begins with a single step." —Modified from Lao-Tzu

Herpes simplex virus type 2 (HSV-2) is associated with primary and recurrent genital herpes, disseminated disease or encephalitis in neonates, and severe disease in immunocompromised patients [1]. HSV-2 is also associated with an increased risk of acquisition and transmission of human immunodeficiency virus (HIV). More than 400 million persons are infected with HSV-2 worldwide, and there is no treatment to eliminate the virus.

A therapeutic vaccine that reduces symptomatic disease, shedding, and transmission would be a major advance, both for patients and as a public health measure to reduce spread of the virus to uninfected individuals. Although such a vaccine is not yet available, suppressive therapy for infected persons with once-daily oral valacyclovir has been shown to achieve all of these endpoints [2].

Despite attempts to develop prophylactic and therapeutic HSV-2 vaccines for >70 years, no vaccines have been licensed [3]. In this issue of *The Journal of Infectious Diseases*, Bernstein and colleagues [4] report their results of a phase 1/2 trial of an HSV-2 vaccine containing 2 polypeptides, derived from HSV-2 glycoprotein D (gD) and ICP4 protein, in Matrix M2 adjuvant. Volunteers with 3 to 9 HSV-2 recurrences per year were immunized with 10 μg, 30 μg, or 100 μg of HSV-2 polypeptides in adjuvant (vaccine), polypeptides without adjuvant, or placebo. Three doses of vaccine were given 3 weeks apart and patients were followed for 1 year after the last vaccination. The primary endpoints were safety and tolerability. Whereas the highest frequency of the most common systemic adverse events (myalgia and fatigue) was in the vaccine group, the differences among the groups (vaccine, vaccine without adjuvant, placebo) were not significant. Solicited grade 3 or 4 adverse events were more common in the vaccine group.

Virus neutralizing antibody titers were highest in persons receiving the highest dose of vaccine, whereas HSV-2-specific T-cell responses were highest in those receiving the 2 lower doses of vaccine. Persons receiving the 2 highest doses had reduced shedding rates (52% reduction with the 30-μg dose and 31% reduction with the 100-μg dose) immediately after the last vaccine dose compared with baseline (before vaccination). At 6 months after the last vaccine dose, shedding was still significantly lower in the group receiving the 30-μg dose, but not in the 100-μg dose group; however, at 1 year neither group had significantly lower shedding, although there were fewer subjects providing swabs at this time. Lesion rates were also significantly reduced in the 2 highest-dose groups immediately after the last dose of vaccine; at 6 months after vaccination, lesion rates were significantly lower in the 30-μg dose group, but not in the 100-μg dose, group. At 1 year after vaccination, lesion rates were not significantly lower for either of the 2 highest-dose groups.

Some of the unexpected results reported in this study will need to be verified in future studies. It is surprising that subjects who received 100 μg of vaccine had a reduced clinical response at 6 months, in terms of the vaccine's effect on shedding and lesion formation, compared with those receiving 30 μg of vaccine. In addition, there was an inverse correlation between T-cell responses and dose of the vaccine. The lack of correlation between the level of T-cell responses and clinical responses might indicate that (1) the T-cell response measured in this study is not the appropriate measure of cellular immunity important for protection, (2) HSV-2–specific T-cell exhaustion was present in these subjects, or (3) circulating T cells do not reflect the T-cell response at the site of reactivation. As the authors point out, the minimum shedding rate observed in any of the groups after vaccination—6.4% immediately after the last dose of the 30-μg vaccine—is in the same range (4%–6%) as persons receiving once-daily suppressive valacyclovir [5]. However, 6 months after vaccination, shedding in the 30-μg vaccine group rose to 8%. Thus, to achieve an

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effect similar to suppressive valacyclovir, additional doses of vaccine might have to be given more often than every 6 months. While once-daily valacyclovir reduces the quantity of virus shed and HSV-2 transmission [2], the authors do not report the quantity of virus shed in vaccine recipients in this study, and it is unknown whether this vaccine would reduce transmission. Finally, HSV type 1 (HSV-1) has now become the leading cause of primary genital herpes in women in some high-income countries. Although genital recurrence rates are lower for HSV-1 than for HSV-2, it is unknown how an HSV-2 vaccine would perform to reduce recurrences of genital herpes due to HSV-1.

Three other HSV-2 therapeutic vaccines are in phase 1/2 or 2 clinical trials. First, a vaccine consisting of synthetic peptides derived from HSV-2 complexed with heat shock protein 70 in saponin adjuvant elicited virus-specific HSV-2 CD4 and CD8 T cells in a phase 1 trial [6]. A phase 2 trial of this vaccine was recently completed; the primary outcome was the HSV-2 shedding rate after vaccination compared to baseline [7]. The study showed a 15% reduction in HSV-2 shedding after the initial vaccination, and before the administration of the booster injection [8]; however, the full results have not yet been reported. Second, DNA vaccines that encode for 1 or 2 HSV proteins in Vaxfectin adjuvant were tested in a phase 1/2 trial [9]. Although neither the monovalent nor the bivalent vaccine met the primary endpoint of viral shedding rate reduction from baseline, a 57% reduction was observed in lesion rates compared with baseline for the bivalent vaccine at 9 months, together with an increase in HSV-specific T cells [10]. A phase 2 trial was initiated using the bivalent DNA vaccine in Vaxfectin with a primary outcome of lesion recurrences [11]. Third, a DNA vaccine, containing 2 plasmids that express full-length HSV-2 gD and ubiquitin-fused truncated gD2 induced cell-mediated immune responses, but not detectable neutralizing antibody responses, in HSV-seronegative subjects [12]. This vaccine is now in a phase 1/2a clinical trial in HSV-2 seropositive adults with safety, antibody, and cell-mediated immune responses as the outcomes [13]. Finally, a DNA vaccine containing 4 HSV-2 antigens from immediate-early genes in a particle-mediated epidermal delivery device was tested in a phase 1 trial in persons with recurrent genital herpes; the results of this study have not yet been reported [14].

Why has it been so difficult to develop a vaccine to prevent HSV-2 disease? Because HSV directly infects mucosa in the female genital tract and, subsequently, nerve endings in axons that transport the virus to dorsal root ganglia, antibodies and immune cells need to be situated at the mucosa where infection begins. Thus, measurement of antibodies and cellular immunity in the blood does not necessarily indicate what immune effectors are present at the mucosal site. Patients with genital herpes reactivate virus on 20% of days [15]. Thus, while their immune system is being repeatedly exposed to replicating virus, and neutralizing antibody is present in serum and T cells are present in the mucosa [16], the virus is still able to reactivate and be shed. Therefore, a successful vaccine must improve upon the natural ongoing antigen exposure that these patients experience. There is a precedent for improving upon nature through the use of vaccines that have improved antigenicity over wild-type virus [17].

Currently, there are effective therapeutic vaccines to prevent reactivation of a herpesvirus in humans. Both a live attenuated [18] and a subunit [19] zoster vaccine have been effective in phase 3 clinical trials. Although varicella zoster virus (VZV) and HSV are both alphaherpesviruses, they differ markedly in their propensity to reactivate. Persons infected with VZV do not have frequent asymptomatic or symptomatic reactivations, unlike herpes simplex. Unlike VZV, HSV has evolved to reactivate frequently and has a much larger repertoire of genes that evade host immune responses. Thus, a therapeutic HSV vaccine is more challenging to develop than a comparable vaccine for VZV.

While the first vaccine trials for HSV began decades ago, only a small number of vaccines have been tested in the clinic, and the protective immune responses needed for a therapeutic vaccine are unknown. A recent workshop convened at the National Institutes of Health [20] reported several recommendations to remedy this problem, including adaptive clinical trial designs [21] to increase testing of more vaccines, and developing a laboratory infrastructure to determine immune correlates of protection from disease, shedding, or infection.

What other approaches might be tried to reduce shedding and transmission of HSV-2? As valacyclovir does not completely prevent transmission [2], and high-dose valacyclovir (3 g daily) does not eliminate shedding [5], newer antivirals with different mechanisms of action than acyclovir, such as helicase-primase inhibitors [22, 23], might be more effective or have an added or synergistic effect in combination with valacyclovir. It is also possible that combined vaccine and suppressive therapy would be beneficial. The HSV-2 therapeutic vaccine study of Bernstein et al [4] is an important step in a long journey toward an effective therapeutic HSV-2 vaccine.

Notes

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