Highly Efficacious Novel Vaccine, Humoral Immunity, and Ocular Herpes Simplex Virus 1: Reality or Myth?

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Development of an efficacious vaccine against herpes simplex virus (HSV) is hindered by a lack of knowledge regarding which are the most important protective host immune responses that a vaccine needs to expand. Both antibody- and cell-mediated immunity (CMI) appear necessary for the control of HSV infection (1–3), but CMI may be more so since patients with defects in CMI have more severe recurrent HSV infections than those with impaired humoral immunity (4–6). In a *Journal of Virology* article by Royer et al. (7), they report the importance of humoral immunity against HSV infection. Moreover, a similar story to the present one was told recently by them in the *Journal of Immunology* (8). However, this is not a new concept, and many studies in the early 1980s showed the importance of antibody in mice against HSV infection, and we cite a few of them (9–13). Indeed, studies in mice can be used to show that almost any type of vaccine can protect them against HSV and all types of immune components can mediate protection. Unfortunately, none of this good news has been successfully translated to humans, where we still lack a vaccine evaluated as effective by an independent double-blind study.

The Carr group reported higher efficacy than a control vaccine against ocular HSV-1 infection when mice were immunized with an ICP0-null virus vaccine. The HSV-1 virus used lacked the replication-essential ICP0 gene, so growing it requires cells that make the missing ICP0 protein. Since no cells *in vivo* make ICP0, the virus is unable to replicate, acting more or less like an inactivated viral vaccine. These vaccines are less likely than replicating vaccines to induce a highly protective immune response against viral challenge. Some reasons include that the concentration of antigenic protein they contain is inadequate and the loss of immunogenicity of some proteins during the inactivation procedure. Replicating live vaccines can make abundant new proteins, which usually preserve the immunogenicity of all proteins. A practical problem with the Carr approach is producing sufficient virions to achieve acceptable immunogenicity, especially for human use. Other significant issues were the control vaccine chosen for comparison with their approach, along with the lack of stringency of their challenge approach. Thus, they compared their ICPO-null vaccine with an HSV-2 glycoprotein D (gD-2) subunit vaccine in an HSV-1 model of ocular infection. They rationalized the use of gD-2 subunit vaccine as a control because it was used as a vaccine against HSV-2 infection in a human phase III study (14). However, Belshe et al. (14) reported that “The gD-2 vaccine was not efficacious with regard to the primary endpoint, protection against genital disease caused by either HSV-1 or HSV-2 after two doses of vaccine. In fact, the overall vaccine efficacy was 20%.” Similarly, in two separate phase III studies using a gD-2 subunit vaccine (15), it showed no efficacy in men or HSV-1-seropositive women. Thus, even though the above human studies showed lack of efficacy against HSV-1 infection using gD-2 subunit vaccine, the authors chose to use gD-2 as their only

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control. This would seem to be an unwise choice. A better one would be to compare their vaccine with another HSV-1 formulation, such as a gD-1 formulation (16, 17) or better still an attenuated live vaccine. Why compare an HSV-1 vaccine against gD2 when HSV-1 gD (gD-1) would be the correct control or an even better control would have been another of many available mutants of HSV-1? Although HSV-1 and HSV-2 can cross-react antigenically and their genomes show approximately 80% sequence homology (18, 19), vaccines could still be highly specific. For example, gD-1 of HSV-1 and gD-2 of HSV-2 are 86% identical; however, a gD-1 subunit vaccine was more efficacious than a gD-2 vaccine against ocular challenge with HSV-1 in rabbits (20).

Despite numerous claims of successful HSV vaccines prior to 1990 and recent successes in animal models, no clinical, large-scale, double-masked HSV vaccine trials have been successful in reducing the incidence of primary or recurrent infections. In the 1930s, inactivated HSV was used in small open clinical trials with reported success (21). However, a placebo-controlled trial in 1964 illustrated the importance of appropriate controls as both the vaccine and placebo groups reported similar improvement (22). In the 1970s and 1980s, numerous large-scale clinical trials of various HSV-derived preparations were reported to show efficacy (23–26). However, these trials were performed in an open, rather than a masked manner, and controls were based either on historical information or on recollections of the subjects as to their previous disease patterns. When masked, placebo-controlled trials were done, none of the vaccines was judged to be efficacious. Similarly, the study by Royer et al. was performed without a proper control and used a very low dose of challenge virus. This would exaggerate the success of their candidate vaccine.

Finally, the authors did not explain why when natural infection with wild-type HSV does not protect against reinfection or reactivation and various preparations of HSV were not effective, a virus that cannot replicate without its complementing cell performs so well. One explanation for the high efficacy they reported is that the wrong positive control was used (i.e., gD-2 instead of gD-1) and they challenged their vaccinated mice with an extremely low dose of virus. Clearly the paper has many flaws, and the readers should be made aware of them.

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