Available online at www.sciencedirect.com
SCIENCE DIRECT®
Vaccine 23 (2005) 2395–2398
Vaccine
www.elsevier.com/locate/vaccine

Development of a therapeutic vaccine for HSV-2

Nancy A. Hosken *

Corixa Corporation, 1900 9th Avenue, Suite 1100, Seattle, WA 98101, USA

Available online 13 January 2005

Abstract

A therapeutic vaccine for genital herpes is clearly needed. Vaccines recently developed for HSV-2 in humans have been aimed at eliciting $CD4^+$ T cell responses and neutralizing antibody responses to two HSV-2 glycoproteins (gB and gD). These vaccines have had no therapeutic effect against HSV-2 in human clinical trials. To enable development of an efficacious vaccine, Corixa Corporation has made a major effort to identify novel antigens that can be recognized by human HSV-2-specific $CD8^+$ and $CD4^+$ T cells. Corixa Corporation's proprietary adjuvants and delivery systems, when combined with appropriate antigens, may allow the development of an effective therapeutic vaccine for HSV-2.
© 2004 Elsevier Ltd. All rights reserved.

Keywords: Herpes; Therapeutic; Vaccine

Recurrent genital herpes is a disease of major public health importance that causes significant morbidity and psychosocial distress [1]. Herpes simplex virus type 2 (HSV-2) is responsible for the majority of recurrent genital herpes disease [1]. An estimated one-fifth (>45 million persons) of the United States adult population is infected with HSV-2 [1]. The rate of new HSV-2 infections has been estimated as up to 1.0 million per year [2]. The increase in HSV-2 prevalence in the adult population correlates with an increase in the incidence of neonatal herpes [4], a disease that is frequently lethal. The prevalence of HSV-2 infection has increased substantially in the past two decades, despite the availability of anti-viral drugs, such as Acyclovir, to treat the disease [1]. Long-term ("suppressive") anti-viral drug therapy reduces the frequency and severity of recurrences and the frequency of viral shedding in infected persons and also reduces the risk of transmission to uninfected persons [3]. However, it can have compliance problems and can diminish HSV-specific immune responses [5], possibly resulting in less effective control of HSV by the immune system. Antiviral drug treatment may therefore be most effective when combined with therapeutic vaccination. The magnitude of the public health problem posed by HSV-2, and the failure of antiviral drugs to prevent its spread, points to a clear need for a safe and effective therapeutic vaccine.

Ideally, a therapeutic vaccine would eradicate latent HSV-2 infection; however, this is likely an impractical objective. A more practical goal is a therapeutic vaccine that would elicit immune responses capable of eliminating clinical recurrences and viral shedding. At minimum, a therapeutic vaccine should reduce the frequency, severity and duration of clinical recurrences and reduce viral shedding in order to impact transmission. Any vaccine for HSV will require an excellent safety profile.

Nearly all HSV-2 seropositive persons reactivate virus from the sacral nerve ganglia [1], which enervates an extensive anatomic area that includes the genitalia. HSV replication and shedding at epidermal or mucosal surfaces is usually associated with the appearance of vesicular lesions; however, virus may be shed in the absence of clinical symptoms [1,6]. HSV-2 transmission usually occurs by direct contact during periods of viral shedding [1]. Individuals with a clinical history of HSV-2 infection are therefore counseled to avoid such contact when viral lesions are present, but may be infectious even when lesions are absent [1,6]. Many individuals have not had clinically recognized primary HSV-2 infection, but have had sub-clinical or asymptomatic recurrences and can shed infectious virus and transmit it to others [1]. Therefore, a therapeutic vaccine will need to reduce both symptomatic

* Present address: ZymoGenetics, Inc., 1201 Eastlake Avenue East, Seattle, WA 98102, USA. Tel.: +1 206 428 2734; fax: +1 206 442 6608.
E-mail address: hoskenn@zgi.com.

0264-410X/$ – see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2005.01.017

and asymptomatic viral shedding to prevent transmission of HSV-2.

While a therapeutic vaccine is clearly needed, its development has historically been challenging. Early vaccines were clinically ineffective and/or poorly immunogenic in humans and their development has been abandoned (see [7] for a historical review). Modern vaccines in clinical trials have focused on two approaches: (1) subunit vaccines using a limited set of viral antigens (gB and gD) or (2) live vaccines comprised of either attenuated or replication-incompetent virus (most recently reviewed in [8]). All of these vaccines were at least partially protective in animal models of HSV-2 infection; however, none was therapeutically effective and most were poorly immunogenic in human clinical trials [8]. Only one vaccine has been protective in Phase III clinical trials [9]; however, because protection was limited to acquisition of symptomatic recurrences this vaccine may not significantly impact viral transmission. The general failure of prior vaccines suggests the need to test other viral antigens and delivery systems, particularly those capable of eliciting $CD8^+$ T cell responses. A successful therapeutic vaccine may require different antigens, adjuvants or delivery systems than previously tried. It is worth considering that the immune mechanisms that control viral shedding and clinical recurrences may be different from those that protect against HSV-2 infection. Consistent human immune correlates of viral shedding and clinical recurrences have not yet been identified, but would greatly aid the rational design of HSV vaccines.

Antibodies have been suggested to protect against primary HSV-2 infection and to reduce maternal-fetal transmission of HSV-2 [1]. However, evidence that antibodies may be important for controlling recurrences is lacking. Recurrences are no more frequent or severe in humans with immunoglobulinemia [1]. Furthermore, vaccines that elicited strong antibody titres (equivalent to or surpassing those elicited by natural infection) have not been therapeutically effective in clinical trials [1,7]. This suggests that to be effective, a therapeutic vaccine will need to elicit virus-specific cellular immune responses.

A role for both $CD4^+$ and $CD8^+$ T cells in protecting against HSV infection has been suggested in both human and animal studies (most recently reviewed in [10]). Both $CD4^+$ and $CD8^+$ T cells specific for HSV have been detected in animals and humans after infection with HSV-2. Immunodepletion studies in mice have demonstrated the ability of T cells to protect against genital HSV-2 disease [10]. Additionally, vaccines capable of eliciting cellular immune responses have been shown to protect against HSV-2 disease in rodents [10]. Beta-2-microglobulin gene-deficient mice are more susceptible than wild-type mice to HSV [10]. Depletion of infiltrating $CD8^+$ T cells abolishes control of HSV replication in explanted murine ganglia [10]. Humans with defects in cellular immunity are known to be susceptible to frequent and severe recurrences [1,10]. In humans, HSV-2-specific $CD4^+$ and $CD8^+$ T cells are present at higher frequencies in recurrent viral lesions than in PBMC [11]. Lastly, the lack of correlation between antibody responses and protection noted for a vaccine recently reported to be protective in human clinical trials suggests that cellular immune responses may have been responsible for the observed protection [9].

The mechanisms by which HSV-specific T cells may control HSV-2 remain unclear, but may include production of cytokines (e.g. IFN-γ) and destruction of HSV-infected cells (most recently reviewed in [10]). HSV-specific $CD4^+$ T cell responses with a T helper 1 (Th1) phenotype are associated with resistance to HSV infection in animal models [10]. The observed protective role of IFN-γ against HSV in mice varies depending on the strain of mice, the method of inhibition of IFN-γ function, and the route of infection with HSV. IFN-γ and IFN-γ-receptor gene-knockout mice have been shown to be more susceptible than wild-type mice to HSV infection [10]; however, IFN-γ may have a limited role in relation to other factors. Good therapeutic efficacy in rodent models has required the use of potent Th1-promoting adjuvants, such as MF59 plus a muramyl dipeptide derivative MTP-PE, in subunit vaccines [10]. The MF59/MTP-PE-containing subunit vaccine unfortunately had unacceptable local and systemic reactogenicity, which prevented its evaluation in Phase III clinical trials [7]. Interferon levels produced by lymphocytes stimulated with HSV-2 antigen have been suggested to correlate with the frequency of clinical recurrences in HSV-2 infected humans [10,12]. Treatment of HSV-2 infected APC with IFN-γ been shown to prevent viral inhibition of antigen-presentation to Class I-restricted, $CD8^+$ T cells [10]. Both Th1-type $CD4^+$ T cells and $CD8^+$ T cells are able to produce significant amounts of IFN-γ when stimulated with HSV antigen plus APC [10,12]. Th1-type $CD4^+$ T cells may also support the development of HSV-2-specific $CD8^+$ T cell responses. Thus, a vaccine designed to elicit both $CD8^+$ T cell and Th1-type $CD4^+$ T cell responses to HSV-2 is the most likely to have a significant positive clinical effect in humans.

Corixa aims to develop a therapeutic vaccine for HSV-2 by defining the optimal combination of HSV-2 antigens, adjuvant and delivery-system needed to elicit therapeutically effective and comprehensive immune responses. When this effort began, a limited set of $CD4^+$ T cell antigens had been described and no $CD8^+$ T cell antigens were known. We therefore made a major effort to identify novel HSV-2 antigens and to characterize their immunogenicity in order to define those antigens most suitable for inclusion in a vaccine [14,15].

Antigens for $CD8^+$ T cells were expression-cloned using both standard COS cell transfection methods and a novel retroviral transduction of autologous B-LCL method [16]. HSV-2 specific $CD8^+$ T cell clones were derived primarily from lesion-infiltrating lymphocytes from HSV-2 seropositive subjects. Retroviral expression-cloning entailed preparation of HSV-2 genomic fragment expression-libraries in retroviral vectors. Infectious retrovirus was produced and used to stably transduce LCL expressing the appropriate Class I HLA molecules for T cell recognition of antigen. Retrovirally transduced LCL were screened by co-culture

Download English Version:

https://daneshyari.com/en/article/2411078

Download Persian Version:

https://daneshyari.com/article/2411078

Daneshyari.com