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Phase I study of a candidate vaccine based on recombinant HIV-1 gp160 (MN/LAI) administered by the mucosal route to HIV-seronegative volunteers: The ANRS VAC14 study☆

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Summary One goal of HIV vaccination is to achieve high mucosal levels of specific secretory IgA (SIgA). In order to elicit specific SIgA antibodies against human immunodeficiency virus type-1 (HIV-1), a vaccine must be administered by the mucosal route, to the nasal or vaginal mucosa for example.

We report here the results of the first phase I, randomized, open-label trial designed to assess the mucosal tolerability and immunogenicity of a candidate vaccine (recombinant protein HIV-1 gp160MN/LAI with or without DC-Chol adjuvant) administered by the nasal or vaginal route. Thirty-four female volunteers with a mean age of 46 years were vaccinated. There were 465 adverse events, of which 65 were considered related to the vaccine. No severe adverse events were related to the vaccine, and no difference

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in terms of tolerability was observed between the sites of vaccination or between the vaccine formulations. None of the volunteers reported that study participation affected their intimate or broader social relationships.
No anti-gp160 activity was found between week 4 and week 48 in serum, saliva, or cervicovaginal and nasal secretions.
These results show that a mucosal HIV vaccine can be well tolerated when administered by the nasal or vaginal route.

Introduction

Sexual intercourse is the most common risk factor for human immunodeficiency virus transmission, and the genital and rectal mucosae are major HIV entry sites [1—4]. Achieving vaginal and rectal mucosal protection with a parenterally administered HIV vaccine is proving difficult [1,5]. In contrast, mucosal (rectal, nasal, oral, or vaginal) vaccination can generate high levels of HIV-1-specific secretory IgA (SIgA) at mucosal sites [6]. Initial HIV candidate vaccines were based on HIV-1 envelope protein, which possesses many epitopes that elicit neutralizing antibodies (V3 loop, CD4-binding sites, 2F5, B12, 2G12) and T-cell responses. Immunization with recombinant envelope protein subunits such as gp160 has proved safe in healthy HIV-seronegative volunteers and has been shown to induce neutralizing antibodies and T-cell proliferative responses but only weak HIV-1-specific cytotoxic T lymphocyte (CTL) responses [3,5,7,8]. The immunogenicity of gp160 can be improved by using an adjuvant such as DC-Chol, which increases permeation of the nasal epithelium and facilitates systemic delivery of the vaccine antigen [9].

The intestinal mucosa is both a major site of HIV replication and the site where CD4+ T cells are depleted early after infection. In Rhesus macaques the gastrointestinal and vaginal mucosae are also the main initial sites of simian immunodeficiency virus (SIV) replication. Early after intravaginal inoculation of macaques, SIV is restricted to endocervical tissue and does not disseminate to the systemic circulation [2]. Other animal studies [10—14] suggest that antibodies contribute to resistance to mucosal infection by HIV-1. Indeed, (1) mucosal vaccination of macaques with inactivated SIV protects against both mucosal and systemic SIV challenge; (2) passive immunization with 2F5 antibodies protects macaques from mucosal SIV challenge; (3) vaginal application of anti-gp120 b12 antibodies protects monkeys from vaginal SIV challenge; (4) anti-HIV-1 IgA isolated from mucosal secretions of HIV-infected patients can block HIV transcytosis; and (5) neutralizing IgA has been detected in highly exposed HIV-seronegative sex workers [15,16].

In this phase I randomized trial, we compared the tolerability and immunogenicity of recombinant oligomeric gp160MN/LAI administered by the nasal or vaginal route, with or without DC-Chol adjuvant.

Patients and methods

Trial design

This phase I, randomized open-label trial was designed to assess the mucosal tolerability of a candidate HIV vaccine. It took place in two hospitals in Paris, France. Randomisation was centralised in a Clinical Trials Unit (INSERM U593) using a computer-generated list of random numbers. The volunteers were allocated to one of the following four vaccine strategies at a 1:1:1:1 ratio: (1) gp160 alone by the nasal route, (2) gp160 alone by the vaginal route, (3) gp160+DC-Chol by the nasal route, (4) gp160+DC-Chol by the vaginal route.

Study population

The study population consisted of HIV-1-seronegative women volunteers who were selected through a uniform screening process specifically designed for HIV vaccine clinical trials by the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) [17—19]. Volunteers aged between 21 and 55 years were eligible for enrolment in this trial if they had not reached menopause or if they were postmenopausal and had been using the same hormone replacement therapy for at least 6 months, together with a contraceptive method, and without metrorrhagia. Volunteers were not eligible for inclusion if they had antibodies to hepatitis B (HBV) or C virus; if they refused mucosal testing or engaged in behaviors carrying a high risk of HIV-1 infection; if they had a history of hysterectomy, colpectomy, metrorrhagia or any vaginal disease; if they had received antibiotics 10 days before the enrolment examination; if they had received a vaccine within the month before the first candidate vaccine administration or would require vaccination during follow-up; or if they were pregnant.

Each volunteer gave her written informed consent to the study. The volunteers were informed that there was no evidence that the vaccine product had any protective effect against HIV infection, and that they might even become more susceptible to infection. They were also informed of the potential psychological and social consequences of HIV seropositivity due to the development of anti-gp160 antibodies. The volunteers were given a tamperproof identification card and the number of a telephone hotline. The protocol was approved by the Ethics Committee of Pitié-Salpêtrière Hospital (Paris, France) and by the ANRS Institutional Review Board.

Follow-up, clinical and laboratory evaluations, and endpoints

Clinical, biological and virological data were collected at a screening visit 4 weeks before randomisation, then on the