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Vacc-4x

AIDS Vaccine

HIV-1 immunotherapeutic composed of four water-soluble synthetic peptides (Vac-10, -11, -12 and -13) each corresponding to conserved domains on the HIV-1 p24 capsid protein and modified to improve immunogenicity

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Abstract

Vacc-4x is an HIV-1 immunotherapeutic comprised of synthetic peptides corresponding to conserved domains on the major core HIV-1 p24 capsid protein. Safety and tolerability have been confirmed in HIV-1-infected subjects following intradermal immunization schedules, with mild to moderate adverse events. As a therapeutic vaccination, it evoked strong, dose-dependent immune responses, with CD4+ and CD8+ T-cell proliferative responses and lower viral loads following a 14-week combination antiretroviral treatment (CART)-free period. Moreover, approximately 1.5 years after completing immunization, a significant proportion of patients had not returned to antiretroviral treatment. Vacc-4x is currently undergoing phase II clinical trials as a therapeutic vaccine for the treatment of HIV infection.

Introduction

Treatment regimens involving combinations of reverse transcriptase and protease inhibitors (three or more anti-HIV drugs), commonly referred to as highly active antiretroviral therapy (HAART) or by the more recent term combination antiretroviral treatment (CART), have revolutionized the treatment of human immunodeficiency virus type-1 (HIV-1) infection by markedly reducing morbidity and mortality (1), but several important factors limiting the therapeutic potential of HAART/CART are emerging, including drug resistance, tissue reservoirs, concerns about toxicity, noncompliance, high cost, limited availability in HIV-1-prevalent developing countries and unsustained viral suppression (2-4).

Therapeutic vaccination, by augmenting existing virus-specific immunity and/or eliciting *de novo* immune responses, may provide an important alternative or adjunct to HAART/CART. A number of different vaccine candidates have been tested in clinical trials, including recombinant protein vaccines, virus-like particle (VLP) vaccines, synthetic peptide vaccines, vaccines based on viral vectors and plasmid DNA vaccines, although these vaccination strategies have not been particularly successful to date (5-7).

Vacc-4x is an HIV-1 immunotherapeutic comprised of 4 water-soluble synthetic peptides (Vac-10, -11, -12 and -13), 20-27 amino acids in length, each corresponding to conserved domains on the major core HIV-1 p24 capsid protein, representing the native Gag regions with residues 186-204, 273-293, 288-308 and 359-378, respectively (8), and modified to improve immunogenicity. It is currently undergoing phase II clinical trials at Bionor Immuno as a therapeutic vaccine for the treatment of HIV infection.

Clinical Studies

An open phase I study was carried out in 11 HIV-1-infected subjects with or without antiretroviral therapy to assess the safety of and response to Vacc-4x immunization. Vacc-4x peptide solution (4 mg/ml intradermally; 0.1 mg of each peptide) was given as a total of 12 repeat immunizations conducted over a period of 28 weeks, together with intradermal granulocyte-macrophage colony-stimulating factor (GM-CSF; 30 μg). No serious adverse events were reported in any patient. At least one adverse event was reported in every patient (approximately 82% considered to be study-related), the majority of which were classified as mild to moderate. These included episodes of fatigue, vertigo and/or influenza-like symptoms after treatment in 5 patients, and the most frequent side effect was pain on injection, although the pain did not last for more than 5-10 min. All patients had a positive delayed-type hypersensitivity (DTH) response, indicative of cell-mediated immunity. Seven patients also showed weak antibody responses, but significant changes in HIV RNA or CD4+ cell counts were not observed (8).

A larger open, randomized phase II study was conducted over 52 weeks (with 4- and 14-week HAART/CART treatment interruption periods). This study involved high and low Vacc-4x peptide doses (0.3 and 0.1 mg of each peptide, respectively) administered over a period of 26 weeks as a total of 10 intradermal injections to non-AIDS HIV-1-infected patients (n=40; stable on

S.L. Davies. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

HAART/CART for a median of 4.5 years). In this trial, DTH testing carried out 48 h postimmunization indicated positive reactions to Vacc-4x antigens in approximately 90% of HIV-1-infected patients, with elevated DTH reactions seen in patients receiving higher doses of each peptide (0.3 mg) compared to those receiving lower doses (0.1 mg). DTH reactions correlated with Vacc-4x-specific CD4+ and CD8+ T-cell proliferative responses (detected in over 76% of subjects). Good safety and tolerability were also reported, with no serious adverse events (9, 10). Further observations indicated that HLA-A2 haplotype may influence the magnitude of the T-cell response to Vacc-4x. HLA-A2-negative patients exhibited a marked dose advantage, with superior overall DTH and proliferative responses, while dose-response relationships were not evident in HLA-A2-positive patients (10). Moreover, patients with a high DTH response showed lower viral load at 52 weeks than those with a low DTH response (9, 11). In these patients, recurrence of viremia during the 14-week HAART/CART interruption period was associated with significant decreases in proliferative responses to Vacc-4x peptides but sustained DTH reactions (9, 12, 13).

Extension of the 52-week study revealed that only 2 patients immediately resumed HAART/CART following the 14-week interruption. Approximately 1.5 years after completing immunization, 62% of patients still had not resumed antiretroviral treatment. Additionally, Vacc-4x-specific T-cell responses at 1.5 years were similar to those found after completing immunization. Overall, it appeared that the need to resume antiretroviral therapy depended on the level of Vacc-4x-induced cellular immune responses (14).

Source

Bionor Immuno AS (NO).

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