ABSTRACT

The approach to reach the functional cure in HIV-infected individuals is the development of T cell immune-based strategies able to sustain viral replication while promoting an immune response to clear residual virus and infected cells. We present a model combining the high-throughput screening of live cells to identify novel co-stimulatory antibodies that add the prime-boost vaccine regimen based on an in vitro UJI injection of two or more lentiviral vectors (ClinicalTrials.gov identifier: NCT02204842).

METHODS: The randomized, placebo-controlled trial enrolled 30 HIV-infected individuals on antiretroviral ART and aimed at comparing the safety, tolerability and immunogenicity of the therapeutic vaccine candidate at 3 incremental doses (0.59, 5.59 or 5.59 TLU) versus placebo. The vaccine regimen consisted of two lentiviral injections 8 weeks apart with non-replicable and self-instructing lentiviral vectors expressing for immunogenic regions of the HIV-1 gag, pol and nef proteins under the regulation of the 82-miroligand human receptor. Vaccine-induced HIV-specific T-cell in peripheral blood was characterized by intracellular cytokine staining in all participants, placebo included, before and after ART interruption and up to 24 weeks after the first injection.

RESULTS: With the lack of any serious adverse events in all 32 participants and no safety concerns related to the treatment, the clinical data confirmed safety and tolerance of the immunogenic regions of the HIV-1 gag, pol and nef proteins under the regulation of the 82-miroligand human receptor. Vaccine-induced HIV-specific T-cell in peripheral blood was characterized by intracellular cytokine staining in all participants, placebo included, before and after ART interruption and up to 24 weeks after the first injection.

CONCLUSIONS: This first-in-human study demonstrated the safety, tolerability and immunogenicity of a lentiviral-based therapeutic vaccine regimen. We are currently evaluating the impact of ART interruption on vaccination on CD4 T-cell levels, plasma viral load and viral reservoir of the induced immune response to optimize the design of the planned Phase II.

THE VACCINE TECHNOLOGY

Integrative recombinant lentiviral vectors developed by THERAVAX are opted from the HIV-1 NL-4.3 strain. They are non-replicative, non-pathogenic, and self-instructing (Figure 1). They are able to stimulate dendritic cells and non-dividing cells thanks to dubbed DNA Info, a VIR nucleotide sequence identified in 1999 at Pennsylvania Institute, which is functionalizing the native immune transduction of HIV. This sequence is measure for the viral ‘pre’ integration complex to cross the nuclear membrane of the non-dividing cell’s kit (3).

The ability of lentiviral vectors to transduce dendritic cells in a stable manner enables the presentation of antigens in an endogenous way to T cells, thereby allowing the first vaccine applications to be developed. The antigens encoded by THERAVAX’s therapeutic vectors are under the regulation of the THERAVAX patented human promoter (TMK-PROM) that is overexpressed in APC.

Furthermore, THERAVAX has developed an effluent prime-boost regimen that enables iterative injections of the same product. Thus, vaccines developed by THERAVAX allow the generation of a long-lasting immune response that is both strong and specific.

STUDY DESIGN & OBJECTIVES

This randomized, double-blind,安慰剂-controlled Phase I/II trial was conducted to compare the safety, tolerability and immunogenicity of therapeutic vaccine at 3 escalating doses (0.59, 5.59 or 5.59 TLU) versus placebo. A total of 32 patients HIV-1, ADEB Infected under highly active antiretroviral therapy (ART) were enrolled in 12 centers in France and Belgium. The vaccine trials enrolls HIV-1, ADEB sequences derived from Gag/p4/3 and and pol sequences from PolA. The prime-boost regimen consists in two or more lentiviral vectors expressing for the same target with 2 different envelopes (Figure 2).

RESULTS

Vaccine safety: Patients enrolled in safety was assessed before baseline from week -7 to week -2, after baseline to ART interruption at week 24 and after week 24 to week 36 or early termination. No serious adverse events has been reported. The distribution of treatment emergent adverse event incidence was globally similar in the four treatment groups, except that injection site pain occurred at a significantly higher rate in the highest dose.

Immunogenicity:

Figure 3: Candidate vaccine elicits strong CD4+ and CD8+ T-cell immune responses in F93 of all vaccinated patients.

Figure 4: Vaccine-induced HIV-specific CD4+ and CD8+ T-cell responses elicit polyclonal and multi-reactive immune responses.

Figure 5: Increased immune activation and cytokine release.

Figure 6: Sustained vaccine-induced CD4+ and CD8+ T-cell responses in most patients.

Figure 7: Change from baseline at week 2 to week 24 of frequency of Gag-specific, Pol-specific, or Env-specific antibodies. 

Figure 8: Change from baseline at week 2 to week 24 of frequency of Gag-specific, Pol-specific, or Env-specific antibodies. 

CONCLUSION

These clinical data for a first-in-human lentiviral-based therapeutic vaccine support the safety of lefetrovohin injections in a prime-boost regimen.

This novel candidate vaccine demonstrated elicitation of:

- Immune CD4+ T-cells and/or CD8+ T-cells specific to well-protected vaccine epitopes for Gag, Pol, and Nef.
- Polyclonal CD4+ and CD8+ T-cell responses with broad epitope-specific responses within the HIV-1 gag Env NL4-3.
- Broad CD4+ and CD8+ T-cell responses with multiple antigenic epitopes targeted.
- Sustained specific CD4+ and CD8+ T-cell responses beyond 24 weeks after the first injection, and
- dose-dependent immunogenicity with highest frequency of immune responses at the highest dose.