Shaping CTL Immunodominance With Conserved HIV Vaccines After Early Treatment (BCN01)

B. Mothe1,2,3, C. Manzardo4, P. Coll2,3, Sara Morón1, L. Dorrell1, B. Clotet1,2,3, J. Martinez-Picado1,4,5, T. Hanke6 and C. Brander1,2,3 for the BCN01 study group*

1Iriscia AIDS Research Institute-HIVACAT, Badalona, Spain; 2Fundació Lluita contra la Sida, Badalona, Spain; 3Universitat de Vic-Central de Catalunya, Unic-UCC, Spain; 4Hospital Clinic-IDIBAPS, Barcelona, Spain; 5Nuffield Dept. Medicine (NDM), University of Oxford, UK; 6CREA, Catalonia, Spain; 7The Jenner Institute, Oxford, UK

Background

Therapeutic T-cell vaccines targeting the most conserved regions of the HIV-1 proteome have the potential to enhance host immune control and facilitate clearance of the latent reservoir. HIVconsv vaccines (Fig 1) vectored by chimpanzee adenovirus (ChAdV63) and modified vaccinia virus Ankara (MVA) have been shown to induce high levels of effector T cells in healthy individuals (HIVCORE02 trial; Borthwick, 2014).

Fig 1. Schematic representation of HIVconsv Immunogen

Methods

BCN01 (NCT01712425) is a phase I, multicenter trial to evaluate the safety, immunogenicity and impact on the latent reservoir of a combined ChAdV63-MVA.HIVconsv vaccine in early-treated individuals (<6m from HIV-1 infection, n=24) who initiated TDF/FTC/RAL 1w after diagnosis. (Table 1)

Table 1. Population Characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median Age at T ini (range)</th>
<th>Sex ratio (men/female)</th>
<th>HIVconsv</th>
<th>T ini (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age at T ini (range)</td>
<td>32 (19-67)</td>
<td>1:1</td>
<td>12/12</td>
<td>12/12</td>
</tr>
</tbody>
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Results

1. Patients Characteristics, Immune Recovery and Viral suppression dynamics are consistent with an early treated HIV+ population (Integrase-Inhibitor based ART)

Fig 2. Flow Chart of Study Design

2. Local and systemic events after vaccination occurred in 22/24 individuals, mostly severity grade 1-2 and transiently (48 hours). Local pain was more often reported with MVA than ChAdV63 vaccination.

3. HIVconsv induced responses over vaccination. 22 individuals (92%) mounted de-novo HIVconsv-specific T cell responses during vaccination (not detectable before cART initiation). Responses were increased in 50% of participants after ChAdV63 prime and in 100% of participants after MVA booster vaccination.

4. Change in dominance patterns of HIV responses. No significant expansion of T-cells targeting HIV-1 regions outside the vaccine insert was noted, reflective of an effective shift of CTL immunity towards conserved regions (58%)

5. 30% of patients developed anti-HIVconsv antibodies, peak levels of which were observed 6-8 weeks after T ini. Median peak to baseline antibody responses were 1.9fold.

6. No reactivation observed during vaccination.

7. Reservoir decay (proviral DNA) was equal in all groups

Conclusions and Future work

Heterologous prime/boost vaccination with ChAdV63 and MVA.HIVconsv was a safe strategy to induce new and/or shift pre-existing immune response towards conserved regions of HIV-1 in a cohort of early-treated individuals. Reservoir decay during first year of early-ART was not further impacted by HIVconsv vaccinations.

This is the first therapeutic vaccine trial able to demonstrate a refocusing of the CTL immunodominance patterns that is conserved regions of HIV-1 and may provide the base for effective kick and kill strategies (Roll-over study BCN20-1, ROM 02618674, enrolling 2016)

*Members of the BCN01 study group

- Hospital Clinic-IDIBAPS, Barcelona, Spain (C. Manzardo, M. Torrella, J. Ariza, I. Calafat, J. Martínez-Picado, V. Montaner, M. Ariza, J. de la Torre)
- Hospital Clinic-IDIBAPS, Barcelona, Spain (P. Coll, D. Massot, J. de la Torre, M. Alcalá, M. Lloveras)
- University of Vic-Central de Catalunya, Unic-UCC, Spain (I. C. Calafat, F. Blancho, A. Huidobro, N. Serrano)
- Hospital Clinics+:<NAME>; Hospital Clinics+;<NAME>; Hospital Clinics+;<NAME>; Hospital Clinics+;<NAME>;<NAME>; Hospital Clinics+;<NAME>;
- Hospital Clinic-IDIBAPS, Barcelona, Spain (C. Manzardo, M. Torrella, J. Ariza, I. Calafat, J. Martínez-Picado, V. Montaner, M. Ariza, J. de la Torre)

Funding: This study has been partially funded by AVA14004 and Fundación Globalalia. The authors have no conflicts of interest.