Effect of Infusion of Broadly Neutralizing Antibody VRC01 on HIV Plasma Rebound

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Abstract

Background: Recent advances in immunogen and antibody cloning technologies have led to the isolation of several highly potent and broadly neutralizing HIV-specific antibodies (bnAbs) from B cells of infected individuals. VRC01 has proven to be effective in neutralizing diverse strains of HIV in vitro and in animal models and has the capacity to suppress plasma viremia in infected individuals. However, the ability of VRC01 to suppress plasma viral rebound in HIV-infected patients following cessation of antiretroviral therapy (ART) remains unclear.

Methods: An exploratory, open-label clinical trial was conducted to examine the effect of passive transfer of VRC01 on plasma viral rebound following discontinuation of ART in HIV-infected individuals who initiated treatment during the acute-early phase of infection and who suppressed plasma viremia ≥3 years with CD4+ T cell count > 400 cells/μL at enrollment. Subjects received VRC01 (400mg/kg) 3 days prior to and 14 and 28 days following interruption of ART, and monthly thereafter for up to 6 months. Levels of plasma viremia and VRC01 were measured at day 7, 14, 3, 7, 14, 21, and 28 and briefly thereafter. In addition, the capacity of VRC01 to block the infection of culture cells by vRNA of VRC01-resistant HIV-1 isolates was evaluated in the study participants at the time of plasma viral rebound.

Results: Ten subjects were enrolled in the study. Mean duration of ART was 10.6 years. Mean CD4+ and CD8+ T cell counts at baseline were 796 and 768/mm^3, respectively. Multiple failures of VRC01 were safe and well-tolerated. Ten of ten subjects experienced plasma viral rebound (>40 copies/mL) between 11-86 days (median 39) following cessation of ART; 9 subjects reinitiated ART per protocol.

Conclusions: While multiple infusions of VRC01 were safe and well-tolerated, the majority of patients experienced plasma viral rebound despite adequate plasma levels of antibody. Therefore, therapeutic strategies involving passive transfer of bnAbs may require a combination of Abs and/or resistance prescreening in order to achieve sustained virologic control in HIV-infected individuals upon withdrawal of ART.

Background and Rationale

- Plasma viremia rapidly rebounds in virtually all HIV-infected individuals upon cessation of therapy.
- The burden of taking daily medication necessitates a continued search for effective treatment alternatives.
- HIV-specific bnAbs can neutralize emerging HIV, block cell-to-cell spread of HIV, and facilitate the clearance of plasma virus and HIV-infected cells.
- This study evaluates the safety and tolerability of multiple doses of VRC01 as well as the effect on viral rebound following discontinuation of ART.

Materials and Methods

Study Population: HIV-infected individuals who initiated ART during the chronic phase of infection (Table 1). Study Design: A single-arm, open-label study was designed to examine the effect of VRC01 on plasma viral rebound in HIV-infected individuals following an analytical treatment interruption (ATI).

Study Agent: VRC01 is a recombinant human IgG1 directed against the CD4-binding site of HIV gp120.

Pharmacokinetic analyses: Measurement of VRC01 plasma concentrations were performed using the anti-idiotypic mAb SC5.

HIV neutralization: Multiple infectious HIV isolates were obtained from anonymized commercial samples to assess for in vitro neutralization of VRC01. The viral isolates were pre-incubated with human IgG, VRC01, 3BNC117, 10-1074, or PGT121 (100μg/mL) for 30 minutes and added to TZM-bl cells. Following a 2-day incubation period, cells were lysed and the viral infectivity was quantified by measuring luciferase activity.

Treatment Phase: VRC01 was administered on day 0 and ART discontinued on day 3. Subsequent virologic follow-up occurred at week 2, 4, and every 4 weeks thereafter until week 24 for a total of 8 doses.

Reinitiation of ART: The subject was instructed to restart ART if any of the following criteria were met: 1) ≥30% decline in baseline CD4 cell count, 2) detectable CD4 cell count ≥<350 cells/μL, 3) sustained plasma viral load ≥10,000 copies/mL, 4) any HIV-related symptoms, or 5) pregnancy.

Results

Figure 1: Plasma viremia in study participants following discontinuation of ART

Figure 2: Levels of plasma viremia and VRC01 in study participants

Table 1: Demographic and immunologic profiles of HIV-infected individuals

<table>
<thead>
<tr>
<th>HIV-Infected Individuals</th>
<th>Pre-Infusion</th>
<th>Post-Infusion</th>
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<tbody>
<tr>
<td>CD4+ T cell count (cells/μL)</td>
<td>587 ± 123</td>
<td>326 ± 78</td>
</tr>
<tr>
<td>CD8+ T cell count (cells/μL)</td>
<td>768 ± 142</td>
<td>768 ± 142</td>
</tr>
<tr>
<td>Plasma viral load (copies/mL)</td>
<td>&gt;40,000</td>
<td>&lt;400</td>
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</tbody>
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Conclusions

- Multiple infusions of VRC01 were safe and well-tolerated.
- The majority of patients experienced plasma viral rebound following discontinuation of HAART despite adequate plasma levels of antibody.
- Pre-existing and rapid emergence of VRC01-resistant HIV likely contributed to plasma viral rebound.
- Therapeutic strategies involving passive transfer of bnAbs may require a combination of Ab and/or resistance prescreening in order to achieve sustained virologic control in HIV-infected individuals upon withdrawal of ART.

References