Nussenzweig: Clinical Trial of Broadly Neutralizing anti-HIV Antibodies

OVERVIEW

Recent evidence lends support to the idea that broadly neutralizing antibodies might play an important role in vaccine design because they can protect macaques from infection, and because anti-HIV antibodies were the only significant, positive correlate of protection in the recent RV144 trial.

Despite their potential importance to vaccine design and development, little was known about the molecular composition of the human anti-HIV antibody response until single cell antibody cloning techniques were developed to characterize IgGs from the sera of HIV-infected individuals with broadly neutralizing activity. Initial studies revealed that neutralization breadth can be accounted for by combinations of antibodies and by a few highly potent antibody clones that target different viral envelope epitopes, such as the CD4 binding site (3BNC117) and the base of the V3 loop (10-1074).

When tested in in vitro TZM-bl assays, both 3BNC117 and 10-1074 showed neutralizing activity against > 90% of all HIV-1 isolates tested, and combinations of antibodies could achieve greater than 99% coverage of all strains at IC80 concentrations below 50 ng/ml. In vivo neutralizing activity at low antibody concentrations has been demonstrated in humanized mice, using HIV-1, and in rhesus macaques, using 2 different tier 2 SHIVs. 3BNC117 and 10-1074 are 10-50X better at protecting against SHIV infection than VRC01, the most advanced clinical candidate to date. These results suggest that 3BNC117 and 10-1074, alone or in combination, might have utility in immune prophylaxis of HIV acquisition in humans. Further potential of these antibodies has recently been demonstrated for therapy of HIV infection. Passively administered combinations of potent human monoclonal antibodies controlled established infection in humanized mice for prolonged periods of time. Moreover, during chronic infection in humanized mice, even a single monoclonal antibody could control infection when the viral load was initially suppressed by anti-retroviral therapy. Similar results have been obtained in macaques chronically infected with two different tier 2 SHIVs (SHIVAd8 and SHIV162P3). To date, 19 macaques infected for 1-3 years have been treated with 3BNC117 and or 10-1074. Viral loads ranged from 103-105, and in all but one case, viremia became undetectable within 7 days. Viremia remained controlled for an average of 4-6 weeks or as long as antibody levels were maintained, however 20% of the animals remained aviremic even after antibody levels became undetectable. The 1 animal that did not respond had high levels of endogenous broadly neutralizing antibodies before therapy and likely harbored resistant HIV-1 variants before treatment.

These experiments suggest that broadly neutralizing monoclonal antibodies may be powerful tools for both the prevention of HIV-1 acquisition and the treatment of established infection. The proposed clinical trials are designed to support both clinical indications for each antibody alone, or in combination.

The objectives of the proposed research are to evaluate the safety, tolerability, pharmacokinetics/pharmacodynamics and in vivo antiretroviral effects of two highly neutralizing anti-HIV monoclonal antibodies when administered to HIV-uninfected and HIV-infected individuals in three proof-of-concept phase 1 studies: (1) A dose-escalating single infusion study of 3BNC117 alone, (2) A dose-escalating single infusion study of 10-1074 alone, and (3) A single infusion study of the combination of 3BNC117 and 10-1074, at the dose level selected in (1) and (2). The long-term goal is to develop the antibodies for two potential clinical indications: prevention of HIV acquisition in healthy HIV-1-uninfected individuals at risk for HIV infection, and adjunct therapy of HIV-1-infected individuals.

Grant at a Glance

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Grantee Institution
Rockefeller University, New York, USA

Project Title
Clinical Trial of Broadly Neutralizing anti-HIV Antibodies

OPPID
1092074

Grant Award
Up to $19.1 million, awarded October, 2013

Collaborating Institutions
- Brigham and Women's Hospital, USA
- Beth Israel Deaconess Medical Center, USA
- Weill Cornell Medical Center, USA
- University of Cologne, Germany
- Military HIV Research Program, USA
- National Cancer Institute, USA
- Celldex Therapeutics, USA
- Vaccine Research Center, USA

RESEARCH OBJECTIVES

1.) Conduct a phase 1 study with 3BNC117 mAb in three target populations (HIV-uninfected, HIV-infected who are viremic, and HIV-infected on ART with suppressed viremia).

2.) Conduct a phase 1 study with 10-1074 mAb in three target populations, as in Objective 1.

3.) Conduct a phase 1 study with the combination of 3BNC117 and 10-1074 mAbs in three target populations, as in Objectives 1 and 2.

PROGRESS

1.) The first subject in the the Phase 1 study of 3BNC117 (objective 1) was enrolled in February of 2014. As of October of 2016 dose escalation to 30mg/kg in both HIV-uninfected and HIV-infected subjects has been completed with 30 subjects enrolled. To date the antibody is safe and well tolerated. Safety data as well as virologic data continues was collected. A single injection of 3BNC117 reduced viral loads transiently. The antibody treatment not only blocked free virus from infecting new cells, it also accelerated the clearance of infected cells. We were able to demonstrate that therapeutic antibody treatment enhanced infected individuals' humoral response against the virus. Thus, neutralizing antibodies may be a promising therapy as well as prophylaxis for HIV-1 because of their potential to reduce the viral reservoir.

2.) As of October 2016 the FIH clinical trial of 10-1074 (Objective 2) in HIV negative and positive participants is fully enrolled with 33 participants. Dosing is complete in all participants. Clinical activities are complete in all US sites with follow up continuing at the University of Cologne Hospital in Germany. To date the antibody is safe and well tolerated.

3.) As of October 2016, 6 participants are enrolled in the combination trial of 3BNC117 and 10-1074. The trial is continuing enrollment and dosing in the US and Germany.