Effect of 24 Weeks TLR9 Agonist Therapy on CTL Responses and Viral Rebound During ATI

Lina K. Vibholm1, Giacomo Frattari1, Mariane H. Schleemann1, Rikke Olesen1, Mathias Lichterfeld2, Anni Winckelmann1, Christina V. Konrad1, Vibeke Klastrup1, Thomas A. Raab-Johnson1, Manuel Schmidt3, Bughardt Weng3, Lisa J. Bronge-Paul4, Paul V. Denton4, Thomas Tolstrup4, Ole S. Søgaard4

1Aarhus University Hospital, Aarhus, Denmark, 2Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, USA, 3Mologen AG, Berlin, Germany, 4Freie Universität Berlin, Berlin, Germany

Introduction

Background
- The latent HIV reservoir impedes the development of an HIV cure.
- A proposed HIV eradication strategy is the “shock and kill”, where latently infected cells are stimulated to resume HIV transcription.
- These interventions alone do not impact reservoir size due to inefficient immune-mediated elimination of antigen-producing cells.
- We have shown that 4 weeks treatment with the TLR9 agonist lefitolimod (MSN1703, Mologen AG) adjunctive to cART functions as both a latency reversing agent and activator of cytotoxic NK cells, potentially enhancing the elimination of infected cells (Vibholm et al., CID 2017).

Hypothesis
- Prolonged administration of lefitolimod augments HIV-specific CD8+ T cell cytotoxic activity and reduces latency proviruses, reducing the latent HIV-1 reservoir and increasing time to rebound.

Objectives

- 1. Safety
- 2. HIV-specific T cell responses
- 3. Time to rebound after interruption of cART

Methods

Study Design and Analyses
- Phase IIb/IA, open label, investigator-initiated clinical trial (NCT02443935).
- We enrolled 14 HIV-1 infected individuals, cART treated 5-12 months.
- Lefitolimod (60 mg s.c.) was administered twice weekly for 24 weeks while participants remained on cART.
- Analytical treatment interruption (ATI) until viral rebound occurred (two consecutive plasma HIV RNA >5000 c/mL).
- Prior to the ATI, participants were randomized to either 1) stop cART or 2) stop cART while continuing with Lefitolimod for 4 weeks.
- Blood samples for immunological and virological analyses were collected at baseline, 12 weeks, 24 weeks and at time of rebound.
- Total HIV DNA from CD4+ T cells was assessed using ddPCR.
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- HIV-specific immunity assessed by CD8+ T cell intracellular cytokine stain (ICS) for IFN-γ, TNF-α and IL-2.
- Statistical analyses: Data analyses and generation of graphs was performed using GraphPad Prism 6.0. Changes from baseline to specific time points were analyzed using Wilcoxon signed-rank test or paired t-test as appropriate.

Results

Safety
- Lefitolimod was safe and well tolerated.
- During 24 weeks of treatment and additional 6 – 22 weeks of ATI, a total of 139 drug-related adverse events (AEs) were registered.
- The types of drug-related AEs were similar to previously reported a total of 139 drug-related adverse events (AEs) were registered.

HIV-1 DNA (total)
- Time to Rebound

HIV-Specific Immunity
- Activation of CD8+ T cells

Conclusion
- Prolonged 24 weeks adjunctive TLR9 agonist therapy with Lefitolimod:
  1. Was safe and well tolerated.
  2. Enhanced HIV-specific CD8+ T cell responses.
  3. Allowed us to observe increased time to rebound in an individual with strong polyfunctional HIV-specific CD8+ T cell responses.
  4. Could be combined with other immune therapeutic agents and/or latency reversing agents to improve efficiency.