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 (MGN1703, Mologen AG) adjunctive to cART functions as both a latency reversing agent and activator of cytotytic NK cells, potentially enhancing the elimination of infected cells (Vibholm et al, CID 2017).
- In this 2nd part of the trial, we assessed the safety profile of extended administration, analyzed HIV-specific T cell responses and measured time to rebound after treatment interruption.

Hypothized Mechanism
- Prolonged administration of lefitolimod augments HIV-specific CD8+ T cell cytotoxic activity and reactivates latent proviruses all together.
- This enhanced CD8+ T cell activity leads to killing of HIV-expressing cells, reducing the latent HIV-1 reservoir and increasing time to rebound.

Methods

Study Design and Analyses
- Phase IIb/III, open label, investigator-initiated clinical trial (NCT02443935).
- We enrolled 14 HIV-1 infected individuals, cART treated >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.
- HIV-specific immunity assessed by CD8+ T cell intracellular cytokine stain (ICS) for IFN-γ, TNF-α and IL-2.

HIV 1 DNA (total)
- Total HIV DNA from CD4+ T cells was assessed using ddPCR.

Outline of Study Design

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 for Lefitolimod (Wittig et al Crit. Rev. Oncol. Hematol. 2015, Vibholm et al, CID 2017).
- Lefitolimod was safe and well tolerated.

HIV-specific Immunity
- Analytical treatment interruption (ATI) until viral rebound occurred.
- Changes from baseline to specific time points were analyzed using Wilcoxon signed-rank test or paired t-test as appropriate.
- Data analyses and generation of graphs was performed using GraphPad Prism 6.0.

GraphPad PRISM 6.0.

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+ TEM responses.
- 4. Could be combined with other immune therapeutic agents and/or latency reversing agents to improve efficiency.