BACKGROUND

Vpu is a HIV-1 encoded membrane protein with multiple regulatory functions that enhance HIV-1 replication fitness and promote innate immune evasion in multiple cell types including monocytes. BIT225 inhibits HIV-1 replication in myeloid cells in vitro. BIT225 has been studied in patients with chronic HIV-1 infection receiving antiretroviral therapy (ART).

METHODS

- A randomized, placebo controlled, double-blind, Phase 2 study of 100mg and 200mg BIT225 in individuals infected with HIV-1 commencing ART (males and females, aged 18-85yrs, viral load >5,000 copies/mL; CD4 count >100 cells/mm3, ART naïve).
- Participants were recruited from two sites in Thailand, treated with BIT225 or placebo in addition to ART (Atripla) for 12 weeks.
- Individuals were randomized 2:1 (BIT225:placebo).

MARKERS OF VIRAL REPLICATION AND IMMUNE FUNCTIONS WERE INVESTIGATED

RESULTS

Thirty-six patients were enrolled. Plasma HIV-1 RNA levels declined with similar viral decay kinetics in all cohorts over the 12 week study period. In contrast, significant changes were observed for multiple immune markers between the placebo and BIT225 cohorts (200mg cohort only shown). Levels of the monocyte activation marker sCD163 showed significantly greater reduction from baseline (P<0.05, general linear model, two-way ANOVA) in the 200mg BIT225 treated cohort compared to ART alone over the 12 week treatment period. There was a statistically significant increase in activated CD8+, CD4+ cells, and NK cells in the BIT225 cohort. There was a transient statistically significant increase in plasma IL-21 production in the first 3 weeks of BIT225 therapy. There were no significant changes to plasma TNF-alfa, IL-6, and interferon-gamma in either cohort over the treatment period.

The Vpu inhibitor BIT225, in combination with Atripla® promotes innate immune restoration in ART naïve participants infected with HIV-1.

REFERENCES

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The elevated NK cell numbers over the treatment period observed in the BIT225 cohort compared to placebo cohort, suggests enhanced NK cell recruitment and activation to eliminate HIV infected cells. This may be mediated via Vpu-related cell-signaling mechanisms. It is possible that there has been restoration of non-neutralizing antibody immune function.

The transient but statistically significant increase in plasma IL-21 is a unique finding in the BIT225 treatment cohort. ART and BIT225 treatment increase IL-17 production (results not shown). This data together supports restoration of Th17 cell number and perhaps function to restore the gut related immune barrier. The IL-21 data may also indicate that Th1 cell functions are being restored. Th1 cells produce IL-21 and are involved in neutralizing and non-neutralizing antibody mediated immune functions.

CONCLUSIONS

The addition of BIT225 to ART resulted in unique stimulation of multiple arms of the innate immune system. The increased numbers of CD8+, CD4+ and NK cells are consistent with enhanced recognition of HIV-1 infected cells. Vpu has been associated with reducing cell surface expression/function of numerous cellular proteins/receptors involved in viral antigen presentation to CD4+, CD8+ T cells and NK cells. The production of IL-21 by Th1, Th17, and/or NK cells is a unique immunological consequence of addition of BIT225 to ART and offers the potential for treatment targeting different HIV-1 compartments during standard therapy. The T cell, NK cell, sCD163 and IL-21 data together suggest that the addition of BIT225 to ART stimulates antigen presentation as well as T cell and NK cell priming, and may result in changes to the immune system similar to that of long term non-progressors.

BIT225's immune modulating effects may have utility in improving HIV-1 induced chronic immune activation outcomes and aid in future eradication strategies.

ADDITIONAL KEY INFORMATION

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Acknowledgements

- Clinical trial participants
- ACLIRES staff and management
- Staff associated with the studies at HIV-NAT, Thai Red Cross AIDS Research Centre and Chiang Mai University Hospital.