Seeking Suppression in HAVARTI: Viremia & T Cells
After Vedolizumab & ATI in HIV/ART

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Introduction

Anti-α4β7 integrin primed monoclonal antibody (mAbs) treatment in macaque-SIV infection model of AIDS has demonstrated alteration in cellular infection in gut mucosa and protection from SIV infection upon intravaginal challenges (Byrareddy, 2014). Lately, anti-α4β7 has produced sustained SIV remission of viremia in the same model (Byrareddy et al., 2016). If an analogous anti-α4β7 humanized mAb (vedolizumab) has such biological activity in human HIV infection, then this may point to a strategic new path towards biomedical HIV prevention and treatment.

HAVARTI is a dose-ranging pilot study of vedolizumab in healthy HIV+ ART-treated (HIVART) adults. Participants receive seven infusions beginning 6 weeks before and extending to 14 weeks after ATI. The aims of the pilot study are to assess the safety and tolerance of vedolizumab and to assess dose-related plasma viremia kinetics in ATI and the potential for sustained plasma HIV suppression in humans. Medium-TERM ACT allows for assessment of the natural history of viral rebound under the influence of vedolizumab, with characterization of post-rebound kinetics of plasma viremia and immunity.

Methods

Eight healthy HIV+ adults on ART for 2-10 years had vedolizumab given 3 times in 6 weeks before, and 4 times in 14 weeks after ATI, at 300mg/dose in Group 1 (4 units) and 150mg/dose in Group 2 (4 units). Monthly follow-up for adverse events (AE), plasma viremia (pVL) and T cell count outcomes informed clinical judgement for ART retreatment.

Participants were recruited from HIV clinics at The Ottawa Hospital and were enrolled sequentially into dose groups. Baseline characteristics of participants in Groups 1 and 2 are presented in Table 1. Group mean values for age, nadir CD4, pre-ART CD4 and ART duration were similar in both groups. There were few participants with a history of severe hepatitis after ART failure, none had sustained CD4 cell count <350 cells/µL. Reversal of CD4:CD8 ratio was observed in PBMCs and rectal mucosa during ART. CD4:CD8 ratios were higher in Group 1 than Group 2 after vedolizumab and ATI. Results of CD4 & CD8 T cell counts from rectal mucosal biopsies are shown in Figure 3. Highlighted participants (yellow lines) did not trigger ART-restart criteria before final biopsies (week 48) and had more preserved CD4 T cell subsets in rectal mucosa at week 24.

Table 1: Baseline Characteristics

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<tr>
<th>Group</th>
<th>Baseline CD4 (cells/µL)</th>
<th>Mean Nadir CD4 during ATI (cells/µL)</th>
<th>Mean CD4 during ATI (cells/µL)</th>
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<tbody>
<tr>
<td>Group 1</td>
<td>350 ± 100</td>
<td>79 ± 10</td>
<td>191 ± 10</td>
</tr>
<tr>
<td>Group 2</td>
<td>150 ± 70</td>
<td>57 ± 7</td>
<td>107 ± 7</td>
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Plasma viral load rebound occurred in all participants in both groups by 6 weeks after ATI (study week 12). No participant had sustained suppression of viremia; 1 participant in Group 1 had non-sustained suppression < 40 copies/mL in two consecutive measurements. Mean rebound pVL for Group 1 was lower than proximate pre-ART pVL by 1.21 log10 copies/mL at post-ART week 6. For Group 2, post-ART week 6 rebound pVL reached 0.26 log10 copies/mL higher than proximate pre-ART pVL. Post-rebound pVL were maintained at levels below pre-ART values throughout ATI (by 1.17 log10 copies/mL in Group 1, and 0.82 log10 copies/mL in Group 2). Rebound pVL doubling time was calculated from week 2 (imputing ±40 to 39 copies/mL to week 6) at 7.67 ± 4.41 days for Group 1, and 2.58 ± 0.79 days for Group 2. Local historical controls for pVL rebound in ATI from the placebo group of an HIV therapeutic vaccine trial had a calculated rebound viremia doubling time of 3.4 ± 1.3 days using during this interval, and post-ATI peak pVL was greater than proximate pre-ART level (Angel et al., 2011, data not shown).

Discussion & Conclusion

There appears to be a biologically significant effect of vedolizumab on pVL rebound kinetics, which may be both dose- and exposure-related in comparing higher-dose Group 1 with lower-dose Group 2: There is much longer doubling time (12 mean 7.62 vs 2.57 days, p=0.057), lower peak rebound pVL relative to pre-ART (by mean 1.47 log10), and longer time to rise in pVL after vedolizumab infusions (mode 3 vs 1 months). Limitations include inter-individual variation and small numbers. Strengths include coherence of a biologically large apparent effect and dose-relatedness of pVL rebound dynamics, kinetics, and breakthrough. Deeper biological study in these cases, further data from more cases, high CV dosing and/or longer duration needed to confirm significant activity of vedolizumab in pursuit of pVL suppression after ATI.

References

