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Changes in CCR5+ cells and antigen-specific CD4+ T-cells during monotherapy with a CCR5 antagonist SCH532706 compared with combination therapy

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Background

CCR5 regulation appears important in Th1 cell recruitment to sites of inflammation/infection. HIV- and CMV-specific CD4+ T-cells are CCR5+. Maraviroc, a CCR5-receptor blocker licensed for HIV treatment, is associated with an increased incidence of upper respiratory tract and Herpes infections.

Methods

We investigated changes in CCR5+CD4+ and CD8+ T-cell subsets, plasmacytoid dendritic cells (PDC) and antigen-specific CD4+ cells in HIV (R5-tropic)-infected subjects given SCH532706 with ritonavir (/r) for 10 days, followed by a 15-day "washout" (day 11–25), and commencing combination antiretroviral therapy (cART) on day 25. Median decline in plasma HIV-RNA (VL) after 10 days of SCH532706/r vs. cART was -1.5 and -1.75 $\log_{10}$ copies/mL (p = 0.7, respectively. CD4+ cells specific for Mycobacteria tuberculosis and avium (M.TB, MAI), cytomegalovirus (CMV), Herpes simplex (HSV), HIV Gag, CCR5+ cell subsets, and PDC were measured at days 1, 3, 10 (phase 1); 20, 25 (phase 2); and 25, 28, 35 on cART (phase 3). Changes were analysed using the Mann-Whitney test. Changes in CCR5+ T-cell subsets were assessed by area-under-the-curve comparisons.

Summary of results

Ten males, with median 242 CD4+ (range 93–551), 783 CD8+ (range 353–1115) T-cells/μL, VL 4.5 $\log_{10}$ copies/mL (range 3.8–5.7), were enrolled. At baseline, 20% of CD4+ and 50% of CD8+ T-cells were CCR5+; CD4+ cells specific for M.TB, MAI, CMV, HSV, HIV Gag were 0.45%, 5.7%, 5.0%, 2.3% and 1.75%, respectively. Median changes in CD4+ T-cells during phases 1, 2, 3 were +16, -26, +28 cells/μL, respectively (1 vs. 3: p = 0.7); CD8+ T-cell changes were +91, -142, -71, respectively (1 vs. 3: p = 0.7). Relative to baseline, changes in CCR5+CD4+ T-cells for phases 1, 2, 3 were +22%, -24% and +24%, respectively (1 vs.3 p = 0.7). In contrast, CCR5+CD8+ T-cell changes were +33%, -13% and -10%, respectively (significant for phases 1 vs. 2 and 1 vs. 3; both p = 0.01). PDC increased during phase 1 compared to phases 2 (p = 0.02) and 3 (p = 0.04). Equivalent declines in percentages of M.TB-, CMV-, HSV-, and Gag-specific CD4+ cells occurred during phases 1 and 3. MAI-specific CD4+ cells declined on cART vs. SCH532706/r (p = 0.037).

Conclusion

CD4+ T-cell increases were modest on SCH532706/r and cART. CCR5+CD8+ T-cells and PDC increased substantially during receipt of the CCR5-antagonist, but not cART, suggesting alterations in trafficking due to CCR5

blockade. Declines in CMV, HSV and HIV Gag responses were equivalent during receipt of SCH523706/r and subsequent cART.