Retrovirology

Poster presentation

Vicriviroc (SCH 417690) Distribution from the Gut to Gut-Associated Lymphoid Tissues (GALT) and to Peripheral Lymphoid Tissues Following an Oral Dose

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Background

Vicriviroc (SCH 417690) inhibits HIV-1 infection by blocking the viral CCR5 co-receptor. Early HIV replication is associated with rapid depletion of CCR5+ CD4 T lymphocytes that predominate in gut-associated lymphoid tissue (GALT), an important site of early establishment of HIV infection. Given the rapid absorption of oral Vicriviroc, appreciable drug exposure to GALT is predicted, potentially protecting this important component of the immune system.

Materials and methods

An oral 5 mg/125 μCi/kg dose of ^{14}C-labeled Vicriviroc was administered to rats and drug concentrations determined by autoradiographic techniques at various timepoints up to 168 hr.

Results

Vicriviroc rapidly permeated the gut wall resulting in appreciable drug exposure to GALT. The rank-order in cumulative Vicriviroc exposure was GALTl > ymph node ≥ lungs > blood, although exposure to GALT<spleen. GALT drug concentrations up to 48 hr were 10- to 10^3-fold higher than the targeted IC90 concentration (IC90 = 6 nM). Differences in cumulative drug exposure between GALT and other tissues was the result of differences in both the observed peak drug concentration and in clearance rates from the individual tissues.

Conclusion

Results suggest that high and sustained Vicriviroc concentrations in GALT can be achieved by as little as a single oral dose, which may prevent viral replication in these tissues and reduce the depletion of CCR5+ CD4 T lymphocytes.