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LONGITUDINAL ANALYSIS OF RESISTANCE TO THE HIV-1 INTEGRASE INHIBITOR RALTEGRAVIR: RESULTS FROM P005 A PHASE II STUDY IN TREATMENT-EXPERIENCED PATIENTS

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BACKGROUND: Raltegravir (RAL) is the first licensed agent in a new class of antiretrovirals that inhibit integration. Understanding resistance and cross-resistance to these agents will become important in clinical practice but is still limited. Initial analysis from the Phase II trials of RAL and the mechanistically related integrase inhibitor elvitegravir suggest the potential for several resistance pathways, each involving multiple mutations with different effects on resistance and viral replication capacity. For RAL, two pathways characterized by signature mutations at either N155(H) or Q148(R/H/K) have been observed.

METHODS: We have followed up on these preliminary observations by performing a longitudinal analysis of resistance in patients with triple class resistant HIV-1 infection failing RAL in the Phase II study. Genotypic analysis was performed by population sequencing and identifying changes in the integrase coding region relative to the sequence prior to RAL treatment. Phenotypic analysis and evaluation of replication capacity was studied with site-directed mutants in a single-cycle infection assay.

RESULTS: Longitudinal genotyping and clonal analysis revealed a consistent preference for the Q148 pathway. Virus populations with mixed N155H and Q148H variants resolved to Q148H over time. Viruses with Q148 patterns, particularly G140S/Q148H, were generally stable while virus populations with N155H often switched to G140S/Q148H. In a subset of patients where the N155H viruses remained the majority population, additional mutations evolved over time. Although Q148H/R/K and N155H were observed to have similar effects on RAL susceptibility, Q148 variants with secondary mutations consistently displayed higher level resistance as compared with N155H variants with multiple mutations. The replication capacity of different combinations varied with Q148H/G140S being the least impaired.

CONCLUSIONS: These studies define four distinct evolutionary patterns for RAL resistance and provide evidence for ongoing selective pressure and a clear preference to evolve to pathways associated with higher level resistance. Whether differential effects on resistance and replication capacity associated with these patterns have consequences for clinical outcomes remains to be examined.

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