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CHARACTERIZATION OF BASELINE AND TREATMENT-EMERGENT RESISTANCE TO T-20 (ENFUVRTIDE) OBSERVED IN PHASE II CLINICAL TRIALS: SUBSTITUTIONS IN GP41 AMINO ACIDS 36–45 AND ENFUVRTIDE SUSCEPTIBILITY OF VIRUS ISOLATES

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BACKGROUND: The fusion inhibitor T-20 (enfuvirtide) is currently being tested in Phase III clinical trials at a dose of 90 mg twice daily. Substitutions in plasma HIV-1 gp41 amino acids (aa) 36–45 and enfuvirtide susceptibility of peripheral blood mononuclear cell (PBMC) coculture derived viruses from patients in Phase II studies were examined at baseline and during therapy. These studies provided the first opportunity to assess *in vivo* resistance to enfuvirtide.

METHODS: Baseline virus was examined for enfuvirtide-naïve patients from TRI-003, T20-206 and T20-208. Examination of genotypic and phenotypic changes during chronic enfuvirtide treatment was attempted for the 70 patients in T20-205 (50 mg dose), 52 patients in T20-206 (50, 75 or 100 mg doses) and 46 patients in T20-208 (75 or 100 mg doses). These patients received enfuvirtide as twice-daily self-administered subcutaneous injections along with oral antiretrovirals; data through 48 weeks are presented. The plasma HIV-1 gp41 ectodomain was sequenced and gp41 aa 36–45 were compared to the consensus sequence GIVQQNNLL. Enfuvirtide susceptibility was tested for PBMC cocultured isolates in a MAGI/cMAGI assay and the gp41 ectodomain of viruses with reduced susceptibility was sequenced.

RESULTS: At baseline, substitutions in gp41 aa 36–45 in plasma virus from enfuvirtide-naïve patients were infrequently observed (9/177 patients, 5.1%), excluding the N42S polymorphism (seen in 26/177 patients, 15%). In T20-205, the most common substitutions in plasma virus on treatment were G36D ($n=11$), G36S ($n=11$), V38A ($n=10$), N43D ($n=8$) and N42T ($n=6$). In T20-206 and T20-208, V38A ($n=8$), G36D ($n=4$)

and N43D ($n=4$) were most commonly observed. At the time of virological failure, substitutions in gp41 aa 36–45 were observed in plasma virus from 31/40 (78%) patients. Phenotypic susceptibility testing of baseline virus isolates showed a geometric mean EC_{50} of 0.020 $\mu\text{g/ml}$ ($n=118$, $SD=0.060$, range <0.001 to 0.480 $\mu\text{g/ml}$). Of these isolates, 114 (97%) fell within the mean EC_{50} plus 3 standard deviations. A greater than 10-fold decrease in susceptibility from baseline was observed in isolates from 21/74 (28%) patients with paired baseline and on treatment virus isolates. Sequence data was available for 19 of these 21 isolates and 18 (95%) harboured substitutions in gp41 aa 36–45.

CONCLUSION: Both the low incidence of substitutions in the gp41 aa 36–45 region at baseline, and the correlation between changes in this region on treatment and reduced susceptibility to enfuvirtide, support its importance as a principal determinant of enfuvirtide resistance. The majority of patients failing on treatment exhibited amino acid substitutions in gp41 aa 36–45 and PBMC virus isolates with reduced susceptibility to enfuvirtide also exhibited substitutions in this region. The role of other gp41 loci in determining resistance to enfuvirtide is unknown at present and is the subject of ongoing research.

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