The HIV-1 maturation inhibitor bevirimat (BVM, MPC-4326) binds to Gag and specifically inhibits CA-SP1 processing. Recent clinical studies identified key baseline polymorphisms at Gag positions 369/370/371 in SP1 that correlated with variable patient responses. Polymorphisms at these 3 positions are found in ~30% of patients with clade B virus. Since the clade B consensus sequence differs from that of other clades, we examined the susceptibility of non-clade B isolates to BVM in vitro to determine which polymorphisms affect BVM activity in these other clades.

Methods: A panel of 25 non-clade B viruses was compiled with multiple representatives from each clade with global prevalence (>1% worldwide: clades A, C, CRF01_AE, CRF02_AG, D, G). The panel consisted of 10 isolates with known, distinct CA-SP1 genotypes and 15 randomly selected patient plasma samples from Switzerland. The complete gag-pr region from each isolate was amplified and cloned into a phLA-3 background. The bLaPeno replicon in vitro phenotyping assay, 6cFP2R (dual enhancement of cell killing in Phenotype Resistance), was used to quantify susceptibility to BVM. Fold-change (FC) in IC50 was compared to FC values for BVM-treated patient isolates and site-directed mutant controls.

Results: None of the 25 viruses in the test panel contained the wild-type QVT clade B consensus sequence at positions 369-371; nonetheless, 7/25 isolates (28%) were highly susceptible to BVM (FC <2). The included 3 viruses containing the clade A and CRF02_AG consensus sequence, QVQ. 9/25 isolates (36%) had intermediate susceptibility (FC 2-10), and 9/25 isolates (36%) fell into the least susceptible category (FC >10). Of the intermediate/least susceptible viruses, 1/18 contained V369A, V370M, or V373T polymorphisms, all of which are key polymorphisms in clade B.

Conclusions: Our analysis demonstrates that some, but not all, polymorphisms at Gag positions 369/370/371 in SP1 reduce the susceptibility of viruses to BVM in vitro. Specifically, the T371Q polymorphism that gives rise to the clade A and CRF02_AG consensus sequence, QVQ, appears to have no effect on BVM susceptibility. This suggests that, following more extensive testing, it may be possible to exclude the T371Q polymorphism from a future genotyping algorithm used to identify patients suitable for BVM treatment. Additional phenotyping and genotyping should help to further refine the genotyping algorithm for non-clade B patients.

Background

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