Uncommon Association of T69 3-Base-Pair Insertion Plus Q151M Multidrug Resistance Mutations in Human Immunodeficiency Virus Type 1 Reverse Transcriptase

The reverse transcriptase (RT) Q151M complex which includes a cluster of five mutations (A62V, V75I, F77L, F116Y, and Q151M) and the codon 69 insertion are two independent multinaucleoside resistance (MNR) pathways. Up to now, Q151M and F116Y mutations were never found to be associated with a β3-β4 insertion (4, 5, 6, 7, 8).

To the best of our knowledge, this is the first report of the coselection of a T69 insertion with F116Y and Q151M mutations. The patient was a 41-year-old homosexual individual who began therapy with zidovudine (ZDV) in 1997 followed by a 12-month administration of combivir and then dideoxynosine (ddI) plus stavudine (d4T) for 24 months. HIV-1 RNA in plasma rose to 16,200 copies/ml in December 2001 (Fig. 1). Then, the patient received a triple therapy including tenofovir disoproxil fumarate (TDF), efavirenz (EFV), and lopinavir/r (LPV/r). The virus drug resistance was evaluated as previously described (5) from sequential plasma samples. The cDNA derived from plasma HIV-1 RNA was sequenced and cloned in PGEM-1 easy plasmid. The first investigated specimen (September 2000) showed a RT T69S-T insertion associated with nucleoside-associated mutations (NAMs) D67N, K70R, and K219Q. Under ddI-d4T treatment, Q151M and F116Y mutations appeared in December 2001 in the same genetic background consisting of the previous NAMs (D67N, K70R, and K219Q), plus the insertion evolving from T69S-T to T69T-T. In December 2001, the clonal analysis (100% of the 23 clones tested) of the plasma viral RNA revealed the colinearity of these genetic changes; the phenotypic analysis (recombinant virus assay antivirogram) showed reduced susceptibility to ZDV, ddI, dideoxycytosine (ddC), and d4T (with phenotypic susceptibility changes in the 50% inhibitory concentration [IC50] of 8.6, 6.7, 8.2 and 10.4, respectively), a normal susceptibility to 3TC and ABC (phenotypic susceptibility change in IC50 of 3.1 and 1.6, respectively), and a phenotypic susceptibility change in IC50 of 1.8 for TDF which might be clinically significant because the clinical cutoff for a reduced response to this compound is 1.4-fold (1, 2). After 5 months of a TDF-EFV-LPV/r regimen, plasma viral load decreased to <50 copies/ml and CD4 count increased to ≥400/mm³ until the end of the study.

Our clonal analysis showed that HIV-1 can acquire insertions and then multidrug resistance mutations in the same genome. Furthermore, sequencing of the bulk plasma HIV-1 RNA isolate of the 03/02 time point confirmed this double MNR genotype. It should be noted that this double MNR virus was associated with the cluster of NAMs D67N, K70R, and K219Q, classically associated with lower levels of resistance to TDF than mutations at positions 41, 210, and 215 (3).
The clinical consequences of this double MNR pattern, in particular how it could influence the virological response to nucleosides or nucleotide RT inhibitors, have yet to be determined. Interestingly, structural analysis based on molecular modeling of the RT, using the crystallized wild-type RT as template (data not shown), indicated that there was no steric clash between the side chains of the mutated residues suggesting that the Q151M/insertion 69 mutant may be functional. These data are consistent with the observed replication of the patient’s viruses and suggest that HIV-1 RT can accommodate this uncommon association of two MNR genotypes without loss of function.

REFERENCES


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