Gp120 substitutions at “hot” positions associated with resistance to fostemsavir in naïve HIV-1 positive individuals

L. Lepore1, C. Fabrizz1, E. Millano1, N. de Gennaro1, A. Lagioia1, A. Volpe1, L. Scudeller1, A. Sancino1, G. Angaran0, L. Monn0

1Clinic of Infectious Diseases, University of Bari, Italy; 2Scientific Direction, Clinical Epidemiology Unit, IRCCS San Matteo Foundation, Pavia, Italy

BACKGROUND & AIM

Fostemsavir (FTR), prodrug of Temsavir, is a novel attachment inhibitor under investigation, targeting the HIV-1 gp120. It is active regardless of viral tropism and subtype, except for the CRF01_AE, group O and HIV-2. Up to now, there is no evidence of in vivo cross-resistance with other classes of antiretroviral drugs, therefore FTR has the potential to be used in highly treatable experienced population with unmet medical needs.

So far, some substitutions of the highly variable HIV-1 gp120 were found to be associated with an altered susceptibility to FTR.

The aim of our study is to investigate the presence of envelope (env) substitutions at “hot” positions associated with resistance to FTR in patients newly diagnosed with HIV-1 infection and to eventually correlate env substitutions according to HIV subtype and tropism (C/R).

METHODS

In this single-center study (2008-2017), gp120 env sequences from 409 patients (pts) with newly diagnosed HIV-1 infection were retrospectively analyzed. Clinical isolates were classified as either B and non-B subtypes (REGA-3 system). FTR was inferred with the gp2 algorithm (FPR 10%) and duration of HIV infection estimated based on the proportion of ambiguous nucleotides in RT/PR (e.g. 30.2% recent infection).

The frequency of the following mutations for FTR resistance was assessed: L116P (325 sequence), A204D (370 seq), S37H/M/T (382 seq), M42/L (282 seq), M34/I (238 seq), M47/I (11 seq). Other amino acid changes at the same positions were also recorded.

Variability at each amino acid position of gp120 in C1-C4 subdomains of a subtype B virus was also evaluated using Shannon entropy. Entropy of R5 virus sequences versus non-R5 viruses was compared by means of Entropy-2 tool.

RESULTS

Baseline characteristics of the enrolled pts (N=409)

- Age, median (IQR): 36.6 (7.8-94.8)
- Male, N (%): 346 (84.6%)
- Italians, N (%): 357 (87.3%)
- Infection < 1 year, N (%): 158 (45.6%)
- Acute infection, N (%): 23 (5.6%)
- Risk factor for HIV transmission, N (%): 368 (90.1%)
- Baseline CD4 cell count, cell/mm³ median (IQR): 354.0 (162.0-510.0)
- Baseline log10 HIV RNA, median (IQR): 4.92 (4.07-5.30)
- Coreceptor tropism, N (%): 331 (81.1%)
- Non-B strains, N (%): CRF01_AE, N

In descending order of frequency, mutations were S37H (9.4%), M42L (6.4%), M47I (2.9%), M47L (2.6%), S37H (1.5%), S37M (0.7%), and L116P (0.3%). A204D was never detected.

Frequency of gp120 mutations according to CRT

- Subtype B: HIV-1, within the group M is the most frequent subtype in the Americas, Western Europe and Australia.
- CRF01_AE: is the most frequent in our areas as a consequence of a recent outbreak among MSM.
- CRF02_AG: is the second most prevalent subtype circulating in Italy after subtype B.

Frequency of gp120 mutations according to subtype

For each subtype, entropy differences were determined only in C2, significance was observed in both populations, while for the other groups, it seemed that the entropy difference was significant only in one group compared to the other one.

No significant difference in the amino acid variability was observed for any of the substitutions previously studied, with the only exception of position 375 in the C3 domain where a significant variability was demonstrated in R5 viruses.

CONCLUSIONS

- Gp120 substitutions that may prejudice susceptibility to FTR were detected in different subtypes and in both R5 and non-R5 variants.
- Despite the great variability of gp120, the overall frequency of mutations for FTR resistance was low.
- In B subtype, the predominant mutation was S37H, whose role in reducing FTR efficacy is much less substantial than L116P, S37H and M42/L, which, conversely, were detected in a smaller proportion of subjects.
- We believe that FTR might be considered a promising therapeutic option for a large target of patients. It would be worthwhile to investigate a possible mutational potential reducing FTR efficacy in a larger scale.

References: