19-21 GIUGNO ROMA
UNIVERSITA' CATTOLICA DEL SACRO CUORE CENTRO CONGRESSI EUROPA
RESEARCH and CARE: FROM BENCH, TO BEDSIDE, TO COMMUNITY
Promosso da SIMIT
16° CONGRESSO NAZIONALE ICAR Italian Conference on AIDS and Antiviral Research
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POSTER 4 YOU ICAR 2024

Evaluation of resistance-associated mutations to nucleotide reverse transcriptase inhibitors in patients treated with tenofovir disoproxil/lamivudine/doravirine

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Introduction/Summary

- Doravirine (DOR) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for treatment in persons living with HIV (PLWH) in association with lamivudine and tenofovir disoproxil fumarate (DOR/3TC/TDF) as a single-tablet regimen (STR).
  This study aimed to evaluate the efficacy of doravirine-based regimens in PLWH with NRTI resistance-associated mutations (RAMs).

Methods

- A retrospective, monocentric cohort including virologically-suppressed (HIV-RNA < 50 copies/mL) patients switching to doravirine-based regimens was evaluated. Patients with no follow-up visits were excluded.

Results

- We analyzed a cohort of 69 PLWH, whose characteristics are summed in Table 1. A genotypic resistance test was available for 37 patients (53.6%) and 6 of them (16.2%) presented RAMs to NRTI.
  Six virological failures (VF) occurred in 24 months of follow-up (FUP). Four (66.7%) didn't have RAMs for NRTI or NNRTI, while 2 patients (33.3%) had M184V. One of them failed for lack of compliance and subsequently achieved virological suppression with the same regimen.
  No failures were detected in patients without a genotype test.
  The estimated risk of VF in one year was 25% in people with no RAM to NRTI and 50% in people with RAM to NRTI, with no significant differences between groups (p=0.321).
  The estimated probability of VF in one year was 0% for patients without the genotype and 3% for patients with an available historical genotype (p=0.027).
  Zenith viral load independently predicted VF (p=0.019). No other patient characteristics were associated with a higher risk of virological failures.
  After VF, no new RAMs were detected.

Conclusion

- Our study confirms the results of DRIVE-SHIFT Trial in which participants who received DOR/3TC/TDF for up to 48 weeks showed high rates of virologic suppression with low rates of virologic failure and discontinuation related to adverse effects. Also in the 144-week analysis of the DRIVE-SHIFT trial has been demonstrated the long-term efficacy of DOR/3TC/TDF in virologically suppressed adults who switched from a stable antiretroviral regimen that included a boosted PI, boosted elvitegravir, or an NNRTI.
  Similarly as in the DRIVE-SHIFT trial, because participants had been virologically suppressed for at least 6 months before enrollment, a treatment duration of 48 weeks after switching was considered important for evaluating the safety and tolerability of DOR/3TC/TDF and its durability in maintaining viral suppression [10]. Estimated probabilities of VF at 2 years of 3% for patients with available historical genotype (higher than patients with unavailable genotype) can be explained by the small size of the study sample.
  DOR is a safe and well-tolerated new NNRTI used in treatment switch without the development of resistance. In treatment-experienced individuals, DOR may be most beneficial to patients who wish to reduce pill burden or toxicity of other regimens. Its use in patients who previously had witnessed the development of mutations associated with NNRTI-resistance has not been fully validated, although initial clinical reports are encouraging. Our report confirms previous in vitro findings that DOR is active against HIV-1, despite the presence of NNRTI mutations based on the observed antiretroviral efficacy in a small number of participants. Doravirin, compared to the other NNRTIs, develops resistances much more slowly and rarely because it has a high genetic barrier.