Poster H-1999
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PREDICTIVE VALUE OF DRUG LEVELS, HIV GENOTYPING, AND THE GENOTYPIC INHIBITORY QUOTIENT (GIQ) AT DIFFERENT TIME-POINTS ALONG 48 WEEKS USING A SQV/RTV SALVAGE THERAPY

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Introduction

- PI plasma levels often are close to IC_{50} values of WT viruses when administered without ritonavir (RTV) boosting.
- Boosting their levels with RTV may overcome low-level of resistance in multitreated patients with mutations at either RT and/or PRO genes.

Objectives

- To evaluate the response to SQV/RTV-based regimen in heavily pretreated patients.
- To examine the impact of drug levels, genotypic and phenotypic resistance, as well as GIQ, on the response to a SQV/RTV-based salvage therapy.

Patients

- A total of 20 clinical centers from Spain participate at the FORTOGENE study.
- 139 HIV+ adults experiencing virologic failure after receiving multiple PI (no SQV) regimens were included.
- All began SQV-SGC 1000 mg BID/RTV 100 mg BID as a part of a multicentre, prospective trial.

Methods

- Virological response was measured by a decrease in viral load >1 log and/or <50 HIV-RNA copies/ml.
- The immunological benefit was considered as a median of increase in CD4+ cell counts.
- All patients were examined genotypically at baseline using ABI 3100 DNA automated sequence (Applied Biosystems).
- HIV genotyping baseline was assessed according to www.iasusa.org rules.
- Phenotypic resistance was performed at ViroLogic™.
- SQV trough plasma levels were measured at week 12 using HPLC.

Results

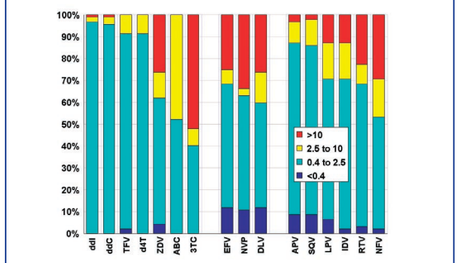
- 139 patients were included in the study.
- A total of 54 patients discontinued therapy prematurely: 1 death, 22 lost to follow-up, 14 voluntary withdrawal, 12 complaining of GI symptoms, 2 liver toxicity, 1 lipodystrophy, and 2 treatment simplification.
- The mean plasma HIV-RNA before beginning SQV/RTV was 4.3 log c/ml and the mean CD4 count was 350 cells/µl.

TABLE 1 BASELINE CHARACTERISTICS OF PATIENTS

No. of patients	139
Gender (%)	
Male	76
Female	24
Risk factor (%)	
Intravenous drug user	58.8
Heterosexual	25
Homosexual	15.2
Others	1
Length of antiretroviral therapy (months)	52
Length of treatment with PIs (months)	28
Baseline plasma HIV-RNA (logs)	4.3
Baseline CD4 count (cells/ml)	350

- HIV drop >1 log occurred in 68.3% of patients on treatment at 1 year (ITT, 41.7%).
- Moreover, 60% reached <50 c/ml at 1 year.
- The median CD4 gain was +81 cells/ml.
- At baseline, the median number of mutations was 4 at the RT and 3 at the PRO.
- In the univariate analysis, VR was higher in subjects with ≤5 PRO resistance mutations at baseline (73.3% vs. 40%, p=0.02).
- Most patients experiencing virological failure accumulated primary PI mutations associated with SQV or RTV resistance (48, 90, 84, 46) and/or at codon 184 in the RT gene.
- Baseline phenotypic fold resistance to SQV was significantly associated with VL reductions (p=0.029).
- The antiretroviral fold resistance of viral isolates from PI-experienced HIV-1-positive individuals with no prior exposure to SQV is shown in Figure 1.

FIGURE 1 FOLD-RESISTANCE



- SQV C_{min}>0.1 mg/ml was significantly associated with VR (p=0.003).
- VR was seen in 77.1% of patients with GIQ>0.04 but only in 18.2% of patients with lower GIQ (p=0.001).
- A positive strong correlation at 12, 24, and 48 weeks was found between GIQ and VL reductions (r=0.43, p=0.004).
- The mean decrease of plasma VL was higher in patients with GIQ>0.04 (-2.1 vs -0.3, p<0.0001).
- In the multivariate analysis, ≤5 PRO resistance mutations and SQV C_{min}>0.1 mg/ml were independently associated with virologic response.

TABLE 2 Predictive value of HIV genotyping and saquinavir (SQV) drug levels on the virologic response to a SQV/ritonavir salvage combination (multivariate analysis).

Variable	OR	CI (95%)	p
≤5 PRO resistance mutations	7.1	1.3-36.1	0.02
SQV plasma level >0.1 mg/ml	12	1.9-74.5	0.008

Conclusions

- A significant VR at 48 weeks occurs in more than 2/3 of patients on RTV/SQV salvage therapy.
- Drug levels seem to be the main predictor of viral response at week 12 (early response).
- At week 24 (intermediate response), the impact of HIV-1 genotyping is the highest, suggesting that viral response in those taking the drugs is highly dependent of the presence of resistance mutations.
- Nevertheless, when we integrate both parameters into GIQ it provides a more accurate predictor of VR at any time point, indicating the dependency of VR on the interaction between SQV plasma levels and baseline resistance mutations.

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