Tipranavir (TPV) genotypic Inhibitory Quotient (gIQ) predicts Early Virological Response to TPV-based salvage regimens

Poster 577

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BACKGROUND. Virological response to TPV-based regimen showed to be associated with number of mutations of the protease gene, use of enfuvirtide (T-20) and Inhibitory Quotient (IQ). The role of gIQ, simpler to derive than the latter, has not yet been investigated. ***Aim of our study was to evaluate the relationship between TPV gIQ and early virological response (EVR) to TPV-based salvage regimens.***

Material and methods. Patients (pts) placed on regimens containing 2 NRTIs +TPV/RTV 500/200 mg BID +/- T20 were prospectively studied. HIV-RNA (VL) and CD4+ cell count were recorded at baseline (BL) and at week 4, 8 and 12. TPV C_{trough} were measured at week 2, 4, 8, and 12 by a validated HPLC system. BL Genotypic resistance test and Virtual phenotype (Vph) were obtained. TPV mutation score with 21 mutations at 16 protease codons suggested by Valdez et al. (3rd IAS Conference on HIV Pathogenesis and Treatment; abstract WeOa0205) was used. TPV gIQ was calculated as the ratio between mean concentration of all available TPV C_{trough} and number of TPV-associated mutations. Optimized Background Score (OBS) was calculated as the number of active drugs according to BL Vph. EVR (HIV-RNA <50 cop/ml) at week 12 was assessed. Values were given as median [IQR].

Results. 27 multi-experienced pts were included. T-20 was associated in 14 (51.8%) subjects. BL VL and CD4+ cell count were 4.7 log [4.17-5.07] and 226 cells/mm³ [189-311], respectively. At week 12 VL decrease was -2.15 [-3.07;-0.43], 11 pts (40.7%) had VL<50 copies/ml, and CD4+ cell count increase was 8 cells/mm³ [-64; +61.5]. VL decrease was correlated to TPV gIQ (R=0.607, p=0.001) and not to TPV C_{trough} (R=-0.338, p=0.085), number of TPV mutations (R=0.364, p=0.062) OBS (R=-0.329, p=0.094), and T20 use (R=0.05, p=0.97). TPV gIQ was the only predictor of VL undetectability at week 12 by logistic regression analysis (p=0.026). The TPV gIQ value associated with 50% probability of being undetectable at week 12 (EC50) was 13000. At this time point, 7/9 subjects with a TPV gIQ>13000 had VL <50 cop/ml, whereas only 4/18 subjects with TPV gIQ<13000 had undetectable VL (X^2=7.6, p=0.011).

Conclusion. TPV gIQ showed to predict early EVR to TPV-containing salvage regimens better than TPV C_{trough} or TPV- associated mutations alone. A possible TPV gIQ cut off value (13000) for reaching VL undectability at week 12 was suggested. Further studies are needed in order to evaluate TPVgIQ as a new tool to optimise TPV-based salvage therapy.

PATIENTS AND METHODS

- Patients enrolled in 1182.16 study and administered with regimens containing 2 NRTIs +TPV/RTV 500/200 mg BID +/- enfuvirtide (T20) were prospectively evaluated.
- HIV-RNA (VL) and CD4+ cell count were recorded at baseline (BL) and at week 4, 8 and 12. TPV C_{trough} were measured at week 2, 4, 8, and 12 by a validated HPLC method.
- BL Genotypic resistance test and Virtual phenotype (Vph) were obtained.
  - TPV mutation score with 21 mutations at 16 protease codons suggested by Valdez *et al*. (3rd IAS Conference; abstract WeOa0205) was used: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, and 84V.
- TPV gIQ was calculated as the ratio between mean concentration of all available TPV C_{trough} and number of TPV-associated mutations.
- Optimized Background Score (OBS) was calculated as the number of active drugs according to BL Vph and to previous use of T-20 in failing regimens.
- Early Virological Response (HIV-RNA <50 copies/ml) at week 12 was assessed. Values were given as median [IQR]. Intention To Treat (ITT) Last Observation Carried Forward method (LOCF) was used. In this ITT approach, subjects who discontinued TPV before week 12 due to virological failure (VF) were considered as VF at 12 weeks
- Linear regression analysis was used to investigate the predictors of higher viral load decrease at 12 weeks.Logistic regreassion analysis was used to investigate the predictors of reaching VL<50 copies/ml at 12 weeks.
  - Graphic representation of TPV gIQ vs predicted probability of EVR was used to determine the EC50 for the gIQ.
  - ROC curve was also used to estimate a cut off value for TPV GIQ

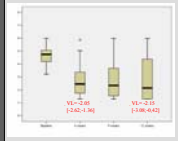
RESULTS

Population characteristics

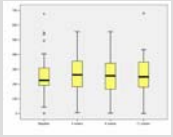
Total number of patients	27
Sex (male)	23 (85.18%)
Age (years) **Weight (kg)** **Height (cm)**	44 (38-49) 70 (60-76) 175 (170-180)
HCV co-infection	5 (18.5%)
Clinical Status (CDC 1993 classification) *A* *B* *C*	 14 (51.85%) 7 (25.92%) 6 (22.22%)
Pharmacological history N° of previous PIs *PIs with Virological Failure* N° of previous NRTIs *NRTIs with Virological Failure*	 5 (4-6) 4 (3-5) 6 (5-7) 6 (5-6)
Initial Regimen With T-20 OBS (T-20 included)	 14 (51.9%) 2 (1-3)
Baseline Immunovirology Log VL CD4 + cells/ml	 4.7 (4.17-5.07) 226 (189-311)

Immunovirological follow up

HIV-RNA



CD4+



- At 12 weeks, 11/27 (40.7%) subjects had a HIV-RNA < 50 copies/ml

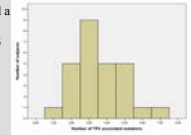
Pharmacokinetic analysis

- 70 plasma samples from 27 subjects were collected at different time points.
- At least 1 TPV C_{trough} was obtained for each subject (median [IQR]: 2 [1-3]).

	Week 2 mean (SD) *n*=17	Week 4 mean (SD) *n*=17	Week 8 mean (SD) *n*=18	Week 12 Mean (SD) *n*=18	Total Mean (SD) *n*=27
TPV C_{trough} (ng/ml)	39610 (20732)	33176 (20176)	27840 (19787)	26152 (14011)	**30760 (16821)**

Genotypic Resistance analysis

At baseline, subjects had a median [IQR] n° of TPV resistance mutations of 3 [3-5]



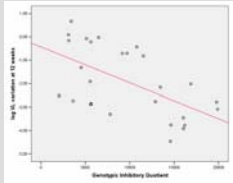
Genotypic Inhibitory Quotient

- Median [IQR] TPV gIQ was 9149 [5120-14626].

PK/PD analysis

Linear Regression Analysis

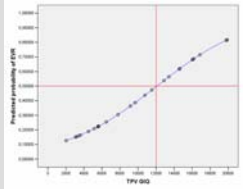
	Coefficient of Regression	*P value*
Mean C_{trough}	-0.3	*0.128*
TPV Mutations Score	0.359	*0.06*
TPV gIQ	**-0.573**	***0.002***
T-20 use	-0.005	*0.98*
OBS (T20 included)	-0.33	*0.09*



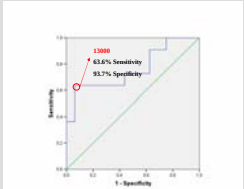
Logistic Regression Analysis

	OR [CI 95%]	*P value*
Mean C_{trough}	1.03 [0.98-1.09]	*0.17*
TPV Mutations Score	0.76 [0.42-1.38]	*0.38*
TPV gIQ	**1.21 [1.02-1.43]**	***0.026***
T-20 use	2.25 [0.46-10.8]	*0.31*
OBS (T-20 included)	2.56 [0.81-8.09]	*0.1*

Predicted probability of EVR vs TPV GIQ



ROC Curve for EVR



- At 12 weeks, 7/9 subjects with a TPV gIQ>13000 had VL <50 copies/ml, whereas only 4/18 subjects with TPV gIQ<13000 had undetectable VL (X^2=7.6, p=0.011)

CONCLUSIONS

- Our study was the first to evaluate TPV gIQ in the clinical setting.
- TPV gIQ showed to be a better predictor of both higher VL decrease and EVR to TPV-containing regimens than TPV C_{trough} or TPV- associated mutations alone. In our population, T-20 use was not shown to indipendently predict EVR, as opposite to previous study with TPV IQ. This could be partially due to limited sample size, bias of choice of patients to administer with T-20 and/or to unexpectedly found drug-drug interaction between T-20 and TPV (increase levels of the latter in case of co-administration, see poster 579).
- A TPV gIQ cut off value (13000) for the probability of achieving EVR was suggested. This cut off was obtained by both logistic regression analysis and ROC curve.
- Further studies are warranted in order to evaluate the usefulness of TPV gIQ as a tool for optimization of TPV-based salvage therapy and for prediction of sustained virological response over time.

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