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Gammaglutamyltranspeptidase (gamma-GT) levels before treatment are predictive of Tipranavir interruption in ART multiexperienced HIV-1-infected patients

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ABSTRACT

The Italian Tipranavir EUP/EAP study was an observational study involving nine Italian centres that enrolled three class drug-experienced patients who consecutively entered the EUP/EAP TPV programs. The Cox model performed to assess the risk correlates of interrupting TPV included sex, age, HIV risk factors, HBV/HCV status, use of T20,CD4, HIV-RNA, ALT, γ-GT, cholesterol, triglycerides, glucose levels determination before starting TPV. The study enrolled 175 patients followed up for a median time of 30 weeks (range 3-68). TPV was interrupted by 46 patients (16 for intolerance, 14 for immuno-virological failure, four for disease progression – including two deceased – 12 for patient decision). The factors independently associated with treatment interruption for any cause were previous ART duration (OR 1.18, 95%CI 1.03-1.35, p=0.016 per each additional year) and γ-GT BL (grade 2 vs 0: OR 6.31, 95%CI 2.49-16.4, p< 0.0001). The γ-GT BL median level in the 16 patients who interrupted TPV for intolerance was 122 IU/L (range: 11-352). Both γ-GT and ALT were significantly increased at interruption compared to BL (p=0.041 and p=0.016 respectively, Wilcoxon test). A transient protective effect against γ-GT and TG increase was observed in patients receiving T20 with TPV (p=0.034 and p=0.027 respectively at week 12 in a Cox model assessing the risk of increasing one toxicity grade). γ-GT level seems to be relevant and more sensitive than ALT/AST level or HBV/HCV status in predicting the risk of TPV interruption. Unreported alcohol abuse could be considered a potential cofactor limiting the effectiveness and safety of TPV/RTV treatment.

Introduction

Despite the success of HAART in the treatment of HIV infection, treatment failure still occurs as a result of poor tolerability, lack of adherence, inadequate plasma drug level and the onset of drug resistant viruses. Such issues may limit options for further therapy, particularly for patients who experienced triple-drug class virologic failure and who may be at increased risk of death (3 year mortality rate, 15%) (1, 2). Therefore, newer agents with activity against drug-resistant HIV-1 are needed.

Tipranavir is the first of a new class of nonpeptidic PI (NPPI) that has demonstrated potent inhibitory activity against clinical HIV-1 and HIV-2 isolates in vitro and in vivo (3-5). TPV has a different structure from peptidic PIs, and therefore has a different susceptibility/resistance profile when compared with other PIs. Studies of clinical isolates have shown that TPV has activity against HIV isolates resistant to currently available PIs and that 16 to 20 protease gene mutations/polymorphisms may be required to confer reduced susceptibility to TPV (6, 7). Additionally, in the randomized evaluation of strategic intervention in multi-drug resistant patients with tipranavir (RESIST-1 and RESIST-2) studies, the efficacy of tipranavir/ritonavir in 1509 highly treatment-experienced HIV-positive patients is being assessed over 96 weeks. The results showed the durable superiority of TPV/r compared with other boosted-PI regimens in achieving viral load declines, in delaying treatment failure and increasing the CD4-positive T-lymphocyte (CD4) count. In addition, these studies showed that the safety profile of TPV/r was similar to that of the other ritonavir-boosted PI, despite the use of a larger daily dose of ritonavir in patients receiving tipranavir. Diarrhoea, nausea and fatigue were the most common clinical adverse events reported in both treatment

arms. Hepatic and lipid-related adverse events occurred at a greater frequency in the tipranavir/ritonavir arm, but were rarely a cause of discontinuation (8-11).

Considering the important role of this drug in the achievement of effective viral suppression in patients infected with multidrug-resistant strains who have limited treatment options, we analysed the causes of TPV discontinuation and the factors influencing TPV interruption in a cohort of Italian patients enrolled in the tipranavir expanded access program/emergency use program (EAP/EUP programs).

Methods

Patients were HIV-infected male and female adults enrolled in the tipranavir EAP/EUP programs (Boehringer Ingelheim Trial No 1182.16) in nine Italian centres. The study design was open label and non-randomised. Patients were required to be triple antiviral class experienced, including at least two previous PI-based regimens, who had failed or who were intolerant to other HIV-1 treatments. There were no restrictions on CD4 count or viral load. Patients with hepatitis were not excluded, provided they were stable and with no greater than grade 2 liver function test abnormalities at baseline. The study was designed and monitored in accordance with good clinical practices. Local institutional review boards of participating centres approved both EAP and EUP studies. Written informed consent was obtained from all study participants. Enrolled patients received tipranavir (TPV) 500 mg co-administrated with ritonavir (RTV) 200 mg, twice daily (b.i.d.) orally, plus at least two other NRTI/N(t)RTI and/or T-20.

The aims of the study were to allow for an early access to tipranavir and to evaluate the safety and tolerability to the drug. Safety evaluations were conducted after TPV/r initiation at one, two, three months, and every three months thereafter with clinical and laboratory valuations.

Differences between patients treated or not with T20 were tested by means of Mann-Whitney non parametric test and chi-square test. When evaluating the trend of hepatic and lipid parameters, Wilcoxon non parametric test was applied. Survival free from treatment interruption by any cause and by specific cause was analysed utilizing Kaplan-Meier methods and Cox regression models. Estimates of crude and adjusted relative risks were shown as hazard ratios (HR and AHR) with 95% confidence interval. All covariates taken into account in the analyses of risks of interruption by any cause and by immuno-virological failure were forced to enter the final regression model. Due to the low number of interruptions by intolerance, a step-forward selection was applied in the adjusted regression model. The software statistical package used for all the analyses was SPSS 14.1 (SPSS Inc. Headquarters, Chicago, Illinois).

Results

175 patients were enrolled in the study; T-20 treatment was associated in 89 (50.9%) of these subjects. Most patients were male, with a median age of 41 years. The distribution of risk factors was intravenous drug users or ex-intravenous drug users 38.3%, heterosexuals 36% and homosexuals 21.7%. 18.3% of patients were alcohol abusers; 93.7% of patients were HBsAg negative and 62.9% were HCV-Ab negative (Table 1).

Viro-immunologic characteristics and previous drug experience at baseline are summarized in Table 2. Median baseline CD4 cell count was 137 cell/mmc; median HIV-RNA was 4.7 log/cp. Patients were ART multiexperienced (median ART duration 10.2 years) and heavily PI experienced (median of 5 PI used in the previous ART treatments).

A summary of hepatic and metabolic parameters at baseline is presented in Table 3. Median AST and ALT was 34 U/L and 39 U/L, respectively; the median of gamma-GT was 57 U/L. Regarding the lipid panel the medians of total cholesterol, HDL cholesterol and triglycerides were 164 mg/dL, 36 mg/dL and 196 mg/dL, respectively.

Patients demonstrated a high treatment response rate: HIV-RNA was <50 cp/mL in 41.4%, 50.9% and 37.4% at six, 12, 24 months of treatment with tipranavir, respectively. A superior treatment response was reported with use of enfuvirtide: HIV-RNA undetectable in 42.6% with T-20 versus 40.4% without T-20, 56.3% versus 42.9%, 40.0% versus 33.3% at six, 12, 24 months of therapy; however, the difference between the two groups was not statistically significant (p=0.811, p=0.340 and p=0.520, respectively). The higher virologic response achieved was reflected in the observed immunologic response. There was an increase in CD4 cell counts at all time points, relative to baseline: medians of CD4 cell count at month six, 12 and 24 were 193 cell/mmc, 199 cell/mmc, 287 cell/mmc, respectively. Also in the analysis of CD4 cell counts use of T-20 was associated with higher response: median in CD4 cell count from 123 cell/mmc at baseline to 314 cell/mmc at month 24 with enfuvirtide use, and from 155 cell/mmc at baseline to 265 cell/mmc at month 24 without enfuvirtide; also in this analysis the difference between the two groups was not statistically sig-

Table 1: Population characteristics at baseline.

	Male	Female
Age (years)		
Median	41.65	39.79
Range (min-max)	22.04-65.64	18.20-47.11
Risk factors (%)		
IVDUs/past IVDUs	43.3	17.6
Heterosexual	26.2	76.5
Homosexual	27.0	-
Alcohol (%)	19.1	14.7
AIDS diagnosis (%)	53.2	35.3
HBsAg + (%)	5.7	2.9
HCV-Ab+ (%)	37.6	29.4

nificant (p=0.576, p=0.273 and p=0.659, respectively).

Hepatic and lipid parameters trend showed that AST and ALT medians did not significantly increase during tipranavir treatment, while gamma-GT increased at all time points (median gamma-GT 57 U/L, 95 U/L, 113 U/L, 136 U/L, 137 U/L, 171 U/L, 119 U/L at months one, three, six, nine, 12 and 24, respectively). Medians of total cholesterol, HDL cholesterol and triglycerides in our cohort of patients also failed to show a significant increase during therapy.

This study also analysed the causes of tipranavir interruption and the factors that may be involved in treatment discontinuation. At 12 months of therapy 26.3% (46 subjects) of patients interrupted tipranavir, while at month 24 63.5% (80 subjects) of patients interrupted therapy. The most important cause of tipranavir discontinuation was viro-immunologic failure (30.4% and 42.5% at months 12 and 24, respectively), followed by intolerance (34.8% and 20.0% at months 12 and 24, respectively) and lack of adherence (6.5% and 6.3% at months 12 and 24).

A multivariate analysis was performed to evaluate factors that could influence TPV interruption. At month 12, gamma-GT was the only factor influencing treatment interruption for any cause, with a p=0.047 and p=0.002 for grade 0 and grade 2 of gamma-GT, respectively (Table 4). At month 24, level of

Table 2: Viro-immunologic characteristics.

		Median	Range (min-max)
CD4 baseline	(cell/μL)	137	2-903
CD4 nadir	(cell/μL)	80	1-540
HIV-RNA	(log/copies)*	4.7	1.7-6.5
ART duration	(yrs)	10.2	3.5-18.0
NRTI used		6	2-7
NNRTI used		1	0-3
PI used		5	1-7
PI mutations		8	2-12

** at baseline*

Table 3: Metabolic parameters at baseline.

		Median	Range (min-max)
ALT	(UI/L)	39	8-259
AST	(UI/L)	34	8-227
g-GT	(UI/L)	57	7-578
Total cholesterol	(mg/dL)	164	71-408
HDL cholesterol	(mg/dL)	36	11-128
Triglycerides	(mg/dL)	196	32-1521
Glucose	(mg/dL)	88	48-2523

Table 4: Factors influencing TPV interruption (any cause); Multivariate analysis (Cox model).

			HR	95%CI	*p*
ART duration (per additional year)			1.18	1.03-1.35	*0.016*
g-GT	grade 1		2.06	0.84-5.09	0.116
	grade 2		6.37	2.48-16.4	*0.000*
	grade 3		6.42	1.00-41.3	*0.050*
ALT	grade 1		2.09	0.81-5.31	0.127
	grade 2		1.23	0.34-4.46	0.749
	grade 3		2.34	0.19-28.9	0.507
Glucose > 100mg/dL			1.48	0.52-4.21	0.466
Tg	150-199	mg/dL	0.45	0.12-1.72	0.242
	200-499	mg/dL	0.69	0.30-1.58	0.386
	> 500	mg/dL	1.16	0.30-4.41	0.833
Chol	200-239	mg/dL	1.50	0.49-4.63	0.479
	>240	mg/dL	1.38	0.38-5.09	0.626

Figure 1: Hepatic parameters (median values and range) at baseline and at TPV interruption due to intolerance.

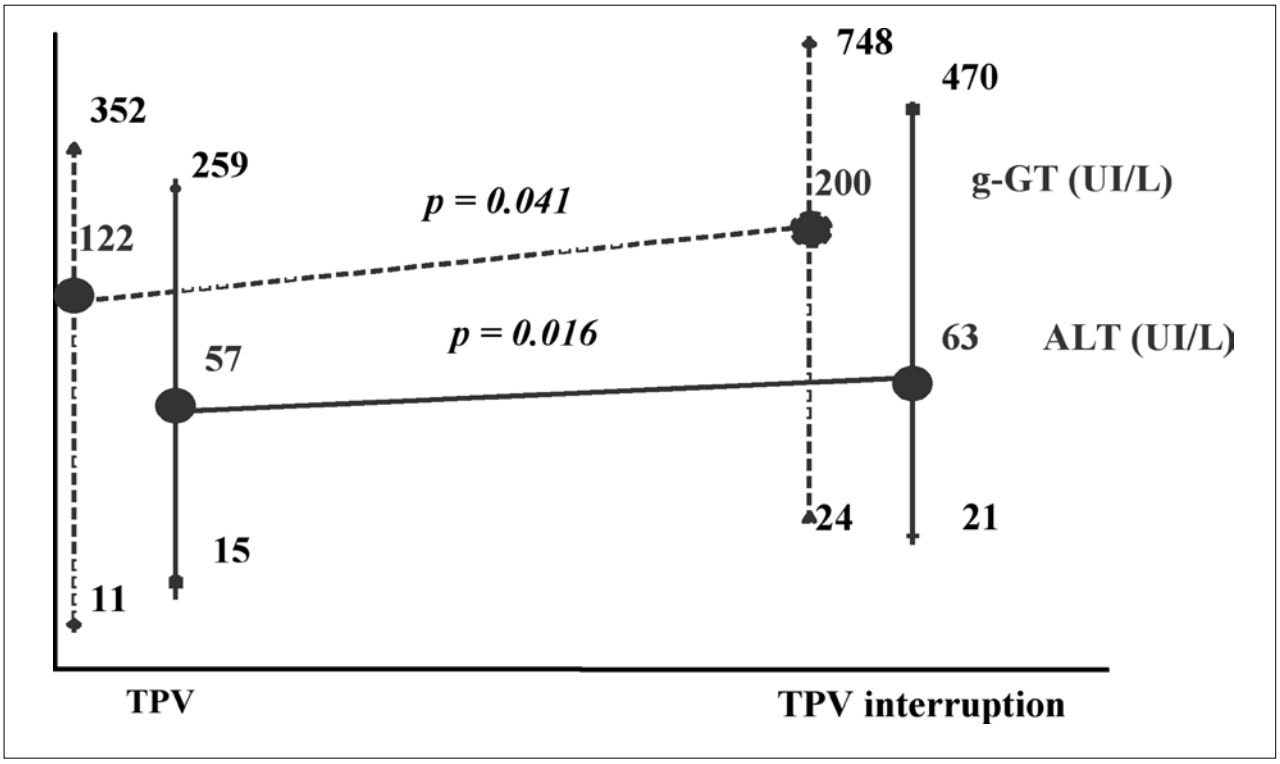
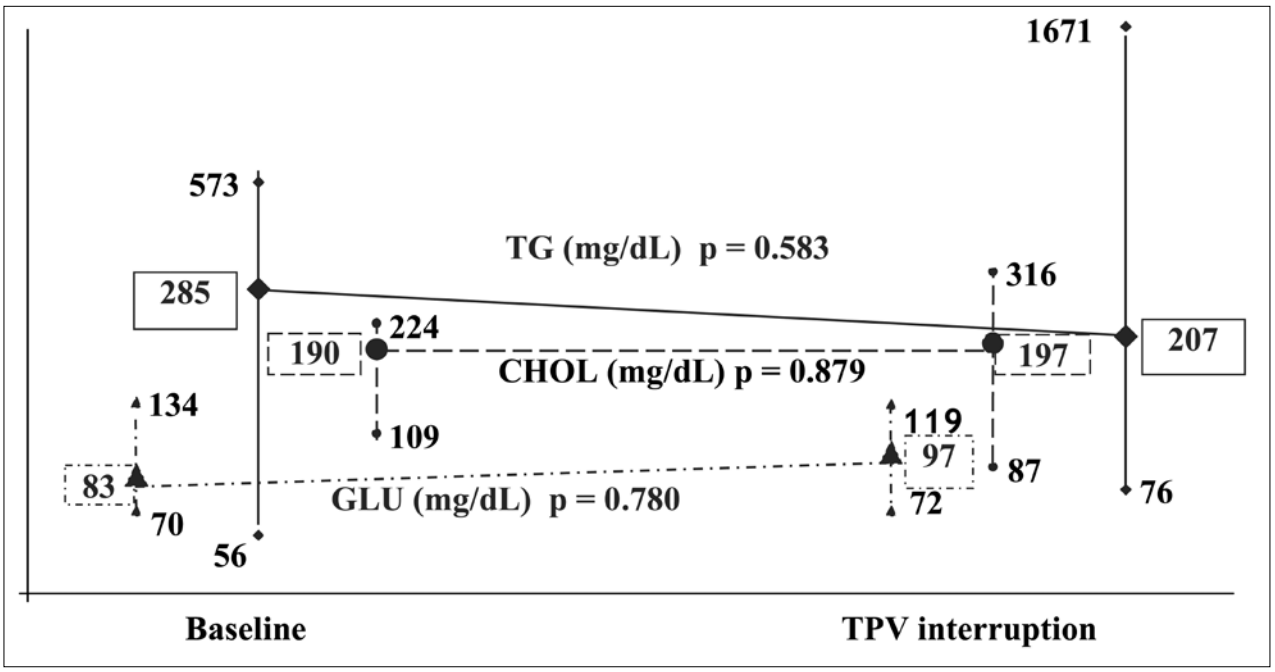


Figure 2: Metabolic parameters (median values and range) at baseline and at TPV interruption due to intolerance.



gamma-GT was not a significant covariate for treatment interruption due to failure. Lastly, a Wilcoxon test was performed to study the trend of hepatic and lipid parameters at baseline and at TPV interruption due to intolerance. We did not see a significant increase in lipid parameters (Figure 1), whereas there was a significant increase in median values of hepatic parameters (Figure 2).

Discussion

Current antiretroviral regimens for HIV-infected subjects have improved the durability of

treatment response. However, some patients experience viral load rebound, develop resistance to ARV drugs and CD4 cell count decline. For PI-experienced patients failing their therapy, treatment options that can offer a sustained clinical benefit may be limited. In this context the introduction of tipranavir into clinical practice enhances the choice of PIs for inclusion in second- and third-line regimens: tipranavir-ritonavir given the robustness of its genetic barrier to resistance, and represents an important option for patients infected with multidrug-resistant HIV strains who need a potent drug to build an affective treatment regimen (12, 13).

Complete virological suppression is the only proven way to achieve long-term clinical benefits. Therefore, the aim of therapy for all HIV-infected patients is to reach the virologic and immunologic response regardless of whether a patient is treatment-naïve or treatment-experienced. The results of this study confirm that tipranavir/ritonavir can achieve virologic suppression and improve immunological response in highly experienced and heavily PI-experienced patients, who showed low levels of CD4 cell count and HIV-RNA not suppressed at baseline. In our study the concomitant use of enfuvirtide was associated with a superior treatment response, both in virologic and immunologic parameters, although the results were not statistically significant, probably due to the low number of patients. The role of enfuvirtide in the efficacy of a therapy regimen containing tipranavir/ritonavir deserves further investigation.

Despite the efficacy of tipranavir/ritonavir (7-11), the use of this drug is limited in clinical practice by hepatic and lipid-related adverse events and by the early interruption of the treatment. Considering the important role of this drug in the achievement of effective viral suppression and immunological improvement, we analysed the causes of TPV discontinuation and the factors influencing TPV interruption.

The results of this study show that tipranavir is safe and relatively well tolerated in this multiple PI-experienced patient population: hepatic and lipid parameters do not significantly increase during therapy and are rarely the cause of study discontinuation, also in patients coinfected with viral hepatitis or alcohol abusers. The most common clinically significant laboratory abnormality was increased gamma-GT.

This study also analysed the causes of tipranavir interruption and the factors that may be involved in treatment discontinuation. The most important cause of TPV interruption in our cohort of patients was viro-immunologic failure, most probably due to the category of patients, more than intolerance.

Interestingly, in our analysis gamma-GT seems to be relevant in predicting the risk of TPV interruption within the first year of therapy: gamma-GT correlated *per se* with tipranavir interruption and high levels of gamma-GT during therapy predicted the risk of drug discontinuation in the early period of treatment, whereas gamma-GT did not influence drug interruption after the first year of tipranavir therapy. This finding suggests that clinicians could pay attention to the levels of gamma-GT more than AST and ALT level, or lipid parameters, or HBV/HCV status when they start therapy containing tipranavir/ritonavir.

One limitation of this study is the low number of trial participants. Although the patient population is sufficient to demonstrate the efficacy of the treatment containing tipranavir/ritonavir, it may not provide meaningful data on the safety of this therapy and factors that can predict drug interruption. In this analysis, the role of enfuvirtide in the tolerability of a therapy regimen containing tipranavir/ritonavir deserves further investigation.

In conclusion, although these findings are limited by the small number of patients, they should provide clinicians with evidence that the combination of tipranavir/ritonavir with an active optimised background regimen in antiretroviral-experienced patients plays an important role in the achievement of sustained viral suppression and immunological improvement- Moreover, this treatment proved safe in our cohort of patients with no significant increase in hepatic and lipid parameters, and relatively well tolerated, with a low number of patients interrupting therapy due to intolerance.

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