

PHARMACOKINETIC AND PHARMACODYNAMIC DETERMINANTS OF VIROLOGICAL RESPONSE TO ENFUVIRTIDE-BASED REGIMENS



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ABSTRACT

Background: ENF, the first compound of HIV fusion inhibitors, has been mainly used as a component of rescue treatment in multi-experienced patients (pts). In phase II studies ENF showed dose-related efficacy, but no data are currently available in the clinical setting. Therefore, aim of our study was to evaluate PK/PD determinants of virological response to ENF-based regimens.

Methods: Multi-experienced pts starting an ENF-based regimen were prospectively enrolled. HIV-RNA levels and CD4+ cell counts were recorded at baseline, week 4 (W4) and week 12 (W12). HIV-1 genotypic resistance and Virtual Phenotype (VPh) were also obtained at baseline. Optimised Background Score (OBS) was defined as the number of active drugs associated to ENF given by VPh. A complete ENF concentration-time curve (area-under-the-curve, AUC) was determined at week 2 (W2) and ENF C_{trough} were measured at W4 and W12. A validated HPLC method was used. Predictors of viral load (VL) decrease were determined by linear regression analysis. Predictors of viral suppression (HIV-RNA <50 copies/ml, VS) were evaluated by logistic regression analysis (backward method).

Results: Thirty-eight pts were included. At baseline, median (IQR) VL and CD4 cell count were 5.16 log (4.7-5.5), and 49 (19-109) cells/ml. Median (IQR) VL decrease was -0.59 (-2.1 to -0.21), and -0.41 (-1.69 to -0.15) at W4 and W12, respectively. Median (IQR) CD4+ cell count increase was 61 (12.3-86) cells/ml at W4, and 35.5 (4.75-88.5) cells/ml at W12. Multivariate analysis showed that ENF AUC, number of PIs in OBS, and the presence of LPV in OBS were independently associated with VL decrease at W4, whereas only OBS was associated with VL decrease at W12. VS at W12 was reached by 15.2% of pts. OBS and W12 ENF C_{trough} were independently associated with VS at W12 (p=0.04; and p=0.07, respectively). Moreover, W12 ENF C_{trough} > 2200 ng/ml and OBS > 2 were associated to VS at W12 (χ²=5.96, p=0.035, and χ²=6.3, p=0.012, respectively).

Conclusions: Efficacy of ENF-based regimens in multi-experienced pts has previously shown to be related to OBS. Our data showed that also ENF plasma exposure is independently associated to virological response at W12. Moreover, a C_{trough} cut off of virological efficacy (> 2200 ng/ml) was found. Therefore, therapeutic drug monitoring could be a useful tool to optimise efficacy of ENF-containing regimen in multi-experienced subjects.

BACKGROUND

Enfuvirtide is the first compound of new class of anti-HIV compounds, the fusion inhibitors. It has been mainly used as a component of rescue treatment in multi-experienced patients, such as in TORO studies.

We previously showed an inter-individual variability of plasma concentration in the clinical setting comparable to as reported for some PI (nelfinavir, lopinavir). Moreover, median trough concentration lower than reported in clinical trial was found.

In phase II studies enfuvirtide showed a dose-related efficacy, as it is for other antiretrovirals. However, no data of pharmacokinetic/pharmacodynamic (PK/PD) relationship in the clinical setting has been yet obtained.

Therefore, aim of our study was to evaluate PK/PD determinants of virological response to enfuvirtide-based regimens

PATIENTS AND METHODS

Multi-experienced patients starting a salvage enfuvirtide-based regimen (in association to 1 or 2 boosted PI, 2 or 3 NRTIs, and in 18% plus a NNRTI) were prospectively enrolled in two centres of Northern Italy.

HIV-RNA levels and CD4+ cell counts were recorded at baseline, week 4 (W4) and week 12 (W12). HIV-1 genotypic resistance and Virtual Phenotype (VPh) were also obtained at baseline. Optimised Background Score (OBS) was defined as the number of active drugs associated to enfuvirtide given by VPh.

In Table 1 characteristics of patients are reported.

A complete enfuvirtide concentration-time curve (area-under-the-curve, AUC) was determined at week 2 and enfuvirtide C_{trough} were measured at week 4 and week 12. A validated HPLC method was used.

Statistical analysis was performed using NCSS software. Receiver Operative Characteristics curve (ROC curve) was employed to found cut-offs for enfuvirtide plasma concentration for achievement of viral suppression. Pearson Chi Square Test was used for categorical variables. Predictors of viral load (VL) decrease were determined by linear regression analysis. Predictors of viral suppression (HIV-RNA <50 copies/ml, VS) were determined by logistic regression analysis (backward method).

Table 1: Characteristics of study population

	Median (range)
Age	45 (31-61)
N° previous NRTI	6 (5-9)
N° previous NNRTI	1 (1-2)
N° previous PI	5 (4-7)
Months on ARV therapy	95 (15-136)
N° active drugs in OB	2 (0-2)
N° of PIs in OB	0 (0-2)
LPV (%)	33%
N° of NRTI in OB	1 (0-3)
N° NNRTI in OB	0 (0-1)
N° Protease Inhibitors	8 (1-14)
N° NAMS	5 (0-7)
T CD4+ (cells/ml)	49 (1-332)
HIV-RNA (log)	5.16 (3.77-6.00)

RESULTS - 1

Thirty-eight pts were included. At baseline, median (IQR) VL and CD4 cell count were 5.16 log (4.7-5.5), and 49 (19-109) cells/ml.

Median (IQR) VL decrease was -0.58 (-2.1 to -0.21), and -0.41 (-1.69 to -0.15) at week 4 and week 12, respectively (Table 2, Figure 1). Median (IQR) CD4+ cell count increase was 61 (12.3-86) cells/ml at week 4, and 35.5 (4.75-88.5) cells/ml at week 12 (Table 2, Figure 2).

	Median	Max	Min
Δ VL at week 4 (log)	-0.58	-3.37	0.48
Δ VL at week 12 (log)	-0.41	-3.05	0.3
Δ CD4+ at week 4 (cells/ml)	61	-52	349
Δ CD4+ at week 12 (cells/ml)	35.5	-60	337

Table 2: Median (range) variation of HIV-RNA and T CD4+ cells count as compared to baseline (38 patients)

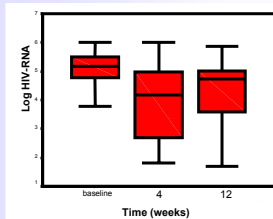


Figure 1: Median log HIV-RNA (38 patients)

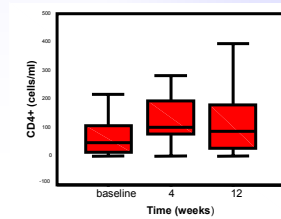


Figure 2: Median CD4+ cells count (38 patients)

Multivariate analysis showed that enfuvirtide AUC, number of PIs in OBS, and the presence of LPV in OBS were independently associated with VL decrease at week 4 (Table 3, Figure 3), whereas only OBS was associated with VL decrease at week 12 (Table 4).

	Univariate analysis p-value	Multivariate Analysis p-value
N° of drugs (no OBS)	ns	
OB score TOTAL	0.0017	0.026
OB score PI	0.012	ns
OBS NRTI	ns	
OB score NNRTI	0.012	ns
N° protease inhibitors	0.07	ns
N° NAMS	0.019	ns
LPV in OB score	0.015	0.004
Baseline LogVL	ns	
Baseline CD4	ns	
T20 C _{trough} (2 weeks)	0.07	ns
T20 AUC (2 weeks)	0.016	0.0085
T20 Cmax (2 weeks)	ns	

Table 3: Predictors of ΔHIV-RNA at week 4 (linear regression analysis).

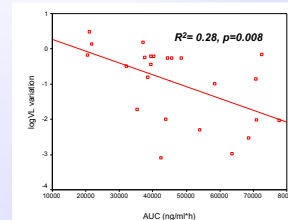


Figure 3: Correlation between AUC and ΔHIV-RNA at week 4.

RESULTS - 2

	Univariate analysis p-value	Multivariate analysis p-value
N° of drugs (total)	ns	
OBS	0.0093	0.03
N° of PIs in OBS	0.08	ns
N° of NRTI in OBS	ns	
N° of NNRTI in OBS	ns	
N° protease inhibitors	ns	
N° NAMS	ns	
LPV in OB score	0.06	ns
Baseline LogVL	ns	
Baseline CD4	ns	
T20 C _{trough} (2 weeks)	ns	
T20 AUC (2 weeks)	ns	
T20 Cmax (2 weeks)	ns	
T20 C _{trough} (1 month)	ns	
T20 C _{trough} (3 months)	ns	

Table 4: Predictors of ΔHIV-RNA at week 12 (linear regression analysis).

Viral suppression (HIV-RNA <50 copies/ml) at week 12 was reached by 15.2% of pts. In logistic regression analysis (Table 5) OBS was independently associated to viral suppression at week 12 (p=0.04) while week 12 enfuvirtide C_{trough} did not result statistically significant, although borderline (p=0.07).

ROC curve test provided an enfuvirtide C_{trough} cut off of 2200 ng/ml for the prediction of virological suppression at week 12 (sensitivity 100%; specificity 62.5%; Figure 4).

Moreover, week 12 enfuvirtide C_{trough} > 2200 ng/ml and OBS > 2 were associated to viral suppression at week 12 (χ²=5.96, p=0.035, and χ²=6.3, p=0.012, respectively).

Table 5: Predictors of HIV-RNA <50 copies/ml at week 12 (logistic regression analysis).

	Univariate analysis p-value	Multivariate analysis p-value
OBS	0.3	0.07
C _{trough} T20	0.09	0.04
OBS	0.03	0.04
N° of PIs in OBS	0.1	ns
N° of NRTI in OBS	0.6	
N° of NNRTI in OBS	0.22	
LPV in OBS	0.2	
N° protease inhibitors	0.34	
N° NAMS	0.2	
Baseline LogVL	0.1	ns
Baseline CD4		

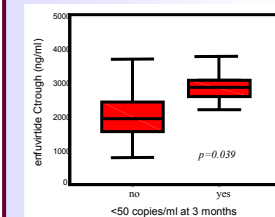


Figure 4: Difference in median enfuvirtide C_{trough} according to viral suppression at month 3.

CONCLUSIONS

Sustained efficacy of enfuvirtide-based regimens in multi-experienced patients has been known to be related to residual activity of companion drugs (OBS).

Our data showed that also the degree of enfuvirtide plasma exposure can affect early therapeutic outcome, being AUC independently associated to virological response at week 4. Such a trend (p=0.07) was found also for C_{trough} according to achievement of viral suppression at week 12.

Moreover, an enfuvirtide C_{trough} cut off (> 2200 ng/ml) of virological efficacy at week 12 was found.

Virological response at week 12 has recently been shown to be predictive of long-term outcome of enfuvirtide-based regimens: monitoring of enfuvirtide plasma concentrations could be an additional tool to optimise therapeutic efficacy.

Therefore, our study, although it has limited sample size and follow up, pointed out that further evaluations of PK/PD of enfuvirtide are warranted.