

Atazanavir Ctrough is associated with efficacy and safety: definition of therapeutic range

Gonzalez de Requena D., Bonora S, Canta F, Marrone R, D'Avolio A, Scindra M, Milia MG*, Di Garbo A*, Sinicco A, and Di Perri G.
 Department of Infectious Diseases, University of Torino, Italy and *Amedeo di Savoia Hospital, Torino, Italy

INTRODUCTION

Outcome of atazanavir (ATV)-containing regimens showed to be related to the number of protease inhibitor (PI)-associated mutations (PRM) and to plasma drug exposure, expressed as genotypic inhibitory quotient (GIQ).

Moreover, ATV Ctrough appeared to drive total (TB) and unconjugated bilirubin (UB) elevations.

However, no ATV plasma thresholds of efficacy and safety have been yet determined.

MATERIAL AND METHODS

*Patients from the ATV Expanded Access Program were prospectively evaluated. All they began an ATV (± RTV) based regimen.

*HIV RNA levels (viral load), T CD4+ cell counts, and total (TB) and unconjugated bilirubin (UB) levels were recorded at baseline, week 4, and week 12.

*Baseline genotypic resistance was assessed using an automatic sequencer. Interpretation of drug resistance mutations was performed according to latest IAS-USA guidelines (October 2004). Changes at positions L10F/IRV, K20M/R, L24I, D30N, V32I, L33F, M36I, M46I, I47V/A, G48V, I50V, I50L, F53L, I54V/L/A/M/T/S, L63P, A71V/T, G73S, V77I, Y82A/F/I, I84V, N86D/S, and L90M, were considered as Protease Inhibitors Resistance Mutations (PRM).

*ATV concentrations were measured in plasma from blood extracted before morning dose (Ctrough), at week 4 and week 12 by a validated SPE-HPLC method. Limit of quantification of this method was 10 ng/ml

*Genotypic Inhibitory Quotients (GIQ) was calculated as ATV Ctrough/ number of PI-associated mutations ratio.

*Virological response at week 12 was defined as viral load of < 50 copies/mL or viral load decrease > 2 logs.

*Increase of unconjugated bilirubin > 2 mg/dL, was considered as safety cut-off.

CONCLUSIONS

plasma concentrations and GIQ. Linear regression analysis was used to analyse the relationship between continuous variables. Pearson Chi Square Test was used to explore the association between categorical variables. U-Mann Whitney test was used to compare between ATV Ctrough and both efficacy and safety has been demonstrated

- Maintaining ATV plasma concentrations between 150-850 ng/ml should result in a high rate of virological response (85.7%) associated to a low incidence of bilirubin elevations (both TB and UB) above 2 mg/dL at 12 weeks
- In patients with different previous PI experience and selection of PI-associated mutations, the use of GIQ > 60 could optimise the efficacy threshold by individualising the lower limit of this range. Therefore, ATV therapeutic range could be a tool for TDM.
- Further studies to evaluate this therapeutic range over a longer follow up are warranted

Baseline Characteristics of Total Population

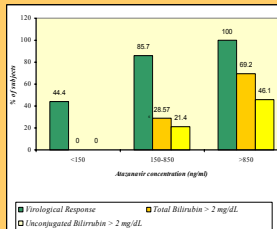
| | N (%) |
|--------------------------------------|------------------|
| Total number of patients | 38 |
| Sex (male) | 25 (65.8) |
| Age (years) | 40 (38-46) |
| Weight (kg) ¹ | 70 (52-86) |
| Height (cm) ¹ | 170 (165-174) |
| UCY selection | 19 (50) |
| Cause of inclusion | |
| Compliance | 7 (18.4) |
| Virological Failure | 9 (23.7) |
| Outpatient | 11 (28.9) |
| Other toxicities | 11 (28.9) |
| N° of previous regimens ² | 5 (13.1) |
| N° of previous PIs ² | 1 (0.5) |
| PI naive | 14 (36.8) |
| N° of previous NRTIs ² | 6 (15.8) |
| PIs with <50 copies/ml | 8 (15.8) |
| VI in PI with >50 copies/ml | 21000 (114-2975) |
| CD4 + cells/ml ¹ | 316 (217-429) |

Virological outcome

| | 4 weeks | | 12 weeks | |
|-----------------------|-----------|-----------------------|-----------|-----------------------|
| | N (%) | Δ log VL median (IQR) | N (%) | Δ log VL median (IQR) |
| RESPONDERS | 27 (71) | | 29 (80.6) | |
| BE VL <50 copies/ml | 23 | -2.31 (-2.78; -1.24) | 24 | -2.77 (-3.3; -1.3) |
| BE VL <50 copies/ml | 4 | | 5 | |
| NON RESPONDERS | 11 (28.9) | | 7 (19.4) | |
| BE VL <50 copies/ml | 9 | -0.8 (-1.4; 0.04) | 0 | 0.23 (-0.23; 0.44) |
| BE VL <50 copies/ml | 2 | | 7 | |

Immunological outcome (CD4+ cells/ml)

| | Baseline | 4 weeks | 12 weeks |
|----------------|---------------|---------------|---------------|
| Total | 322 (202-423) | 354 (228-451) | 370 (196-554) |
| Responders | 306 (247-440) | 382 (246-534) | 370 (278-555) |
| Non Responders | 86 (21-401) | 133 (80-373) | 142 (56-373) |



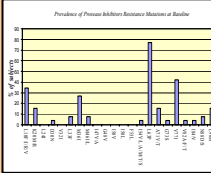
RESULTS

Virological Outcome Predictors

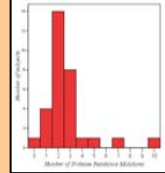
Genotypic analysis

Genotypic Resistance Test was performed in 20/38 (50.4%) of subjects. All baseline, median (IQR) number of PRM was 2 (2-3).

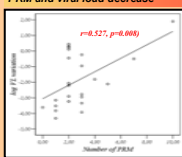
Prevalence of PRM



N° of PRM and distribution



Correlation between number of PRM and viral load decrease



*In subjects with VL <50 copies/ml at Baseline, a good correlation was found between viral load variation and n° of PRM

*78.3% of subjects with ≤5 PRM responded to therapy at 12 weeks, whereas no one (0%) responded with more than 5 PRM (p<0.2; p=0.07)

Pharmacokinetic analysis

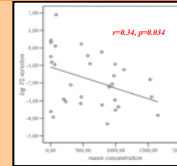
Descriptive

| | N | 4 weeks* ng/ml | 12 weeks* ng/ml | Mean (std. Dev)** ng/ml |
|---------------------|----|-------------------|--------------------|----------------------------|
| Total | 38 | 473 (84-934) | 328 (62-970) | 512 (82-977) |
| ATV 400 mg | 13 | 232 (17-439) | 138 (24-607) | 204 (24-668) |
| ATV > 300 mg/100 mg | 25 | 796 (339-1015) | 807 (114-1061) | 790 (391-994) |

*Median (IQR)

Correlation between VL decrease and ATV Ctrough

*In subjects with VL <50 copies/ml at baseline, a good correlation was found between viral load variation and mean ATV Ctrough



ATV Ctrough and Virological Response

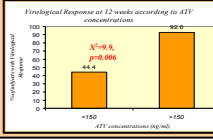
*ATV Ctrough was significantly higher in subjects with VR than in those not responding to therapy at 12 weeks

| | N | 4 weeks** ng/ml | 12 weeks** ng/ml | Mean (std. Dev)** ng/ml |
|----------------|----|--------------------|---------------------|----------------------------|
| Total | 38 | 473 (84-934) | 328 (62-970) | 512 (82-977) |
| Responders | 29 | 607 (313-994) | 39 (-5-80) | 790 (278-994) |
| Non Responders | 7 | 74 (-5-474) | 803 (131-1166) | 74 (-5-474) |
| P value** | | 0.014 | 0.023 | 0.007 |

*U-Mann Whitney Test. **Median (IQR)

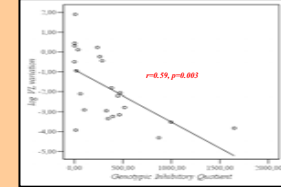
*ROC curve test provided an ATV Ctrough cut off of 150 ng/ml for the prediction of Virological Response at 12 weeks (sensitivity 86.2%, specificity 71.4%)

*ATV Ctrough > 150 ng/ml was confirmed as an independent predictor of VR in univariate logistic regression analysis (OR [95%CI]: 5.6 (2-108.8), p=0.005)



Genotypic Inhibitory Quotient

Correlation between VL decrease and GIQ



GIQ and virological outcome

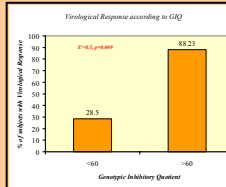
| | N | Median (IQR) |
|----------------|----|----------------|
| Total | 24 | 296 (29-468) |
| Responders | 17 | 396 (194-544) |
| Non Responders | 7 | 8.4 (2.5-23.7) |
| P value** | | 0.002 |

*U-Mann Whitney Test. **Median (IQR)

*GIQ was significantly higher in subjects with VR than in those not responding to therapy at 12 weeks

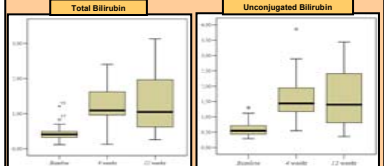
*ROC curve test provided a GIQ cut off of 60 for the prediction of Virological Response (sensitivity 88.2%, specificity 71.4%)

*GIQ > 60 was confirmed as an independent predictor of VR in univariate logistic regression analysis (OR [95%CI]: 18.7 [2.08-170.2], p=0.009)



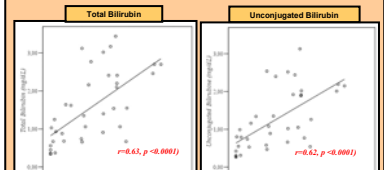
Safety analysis and Predictors

Variation on Bilirubin (Total and unconjugated) serum levels over time



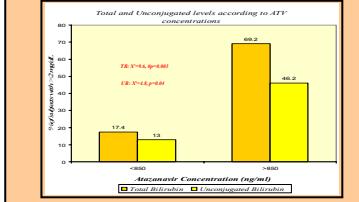
At 12 weeks, Total Bilirubin and Unconjugated Bilirubin serum levels >2 mg/dL were found in 35% and 24.3% of subjects.

Correlation between Bilirubin (Total and Unconjugated) serum levels and ATV Concentrations



*A good correlation was found between TB and UB serum levels at 12 weeks and mean ATV Ctrough

*ROC curve test provided a cut off of 850 ng/ml for the prediction of both TB and UB elevations above 2 mg/dL (sensitivity 69.2% and 68.7%, specificity 62% and 74.1%, respectively)



*ATV Ctrough > 850 ng/ml was confirmed as an independent predictor of TB and UB serum levels > 2mg/dL at 12 weeks in univariate logistic regression analysis (OR [95%CI]: 10.88 [2.16-52.7], p=0.004; and 5.7 [1.11-29.2], p=0.036, respectively)