Lettera all'Editore

Letter to the Editor

Pharmacokinetic exposure and virological efficacy of a reduced atazanavir dose

Analisi farmacocinetica ed efficacia virologica di atazanavir a dosaggio ridotto

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The Ctrough of atazanavir associated with the highest probability of virological response and the lowest probability of increase in unconjugated bilirubin is considered to be between 150 ng/mL and 850 ng/ml [1-3] This therapeutic range was defined in a group of highly therapy-experienced patients treated with boosted atazanavir regimens [4].

However, no relationship was observed between atazanavir plasma trough concentrations and antiviral response in patients with no evidence of protease inhibitors mutations [1, 5].

We report our experience in 6 patients on a reduced atazanavir dose and on their first antiretroviral regimen, naïve to protease inhibitors (PI) and with no PI resistance mutations. Sex, age, body weight, body mass index, Ctrough of atazanavir, months on reduced dose of atazanavir, lymphocytes TCD4 and HIV-RNA levels at baseline and at the last visit in the Outpatient Department of the Infectious Diseases Unit, University of Verona are reported in table 1.

All the mono-infected patients (negative serology for Hepatitis B and hepatitis C viruses) were taking an NRTI backbone (3 abacavir/lamivudine, 1 tenofovir/emtricitabine, 1 zidovudine/lamivudine, 1 zidovudine/didanosine) with atazanavir 300 mg.

Ritonavir was taken, for few days at the beginning of HAART, and then stopped for gastrointestinal side effects without disclosing to us. When they revealed it we performed therapeutic drug monitoring.

Atazanavir plasma concentrations were measured using a validated HPLC assay at Antiretroviral drugs' Clinical Pharmacology laboratory at "Amedeo di Savoia" hospital in Turin [6]. All the patients were taking atazanavir in the morning , on full stomach, and blood samples were taken after a mean of 24 hours from the last doses.

The samples were centrifuged at 2500-3000 rpm and stored at -20°C in freezer. Only one patient was taking an other drug without interactions with atazanavir (levetiracetam).

Pharmacokinetic analysis gave values of Ctrough for atazanavir below the suggested minimum target trough concentration (150 ng/mL) for all six patients (Table 1).

We did not change the atazanavir doses in any of the six patients, and after a mean of 22 months (range 20-24 months) from the pharmacokinetic analysis, all the patients continued to have an undetectable plasma HIV-RNA (<50 copies/mL).

The suggested cut-off level was generated in an observational cohort of whom only 33% were protease inhibitors naïve, and indeed other researchers have failed to validate it [4, 5, 7]. The main source of data on the exposure-response relation of atazanavir in treatment naïve patients was the BMS-089 study, where unboosted atazanavir was compared with atazanavir 300 mg plus ritonavir 100 mg [8].

The results of this latter study supported a higher efficacy of the concentration range ob-

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Table 1 - Sex, Age, body weight, body mass index, Ctrough of atazanavir, months of HIV-RNA suppression on reduced dose of atazanavir, and HIV-RNA level at last follow-up visit.

Patient	*Age/sex*	*HAART regimen and dosage*	*Body Mass Index*	*Body weight (kg)*	*Ctrough of ATV (ng/mL)*	*Months of HIV-RNA suppression on reduced dose*	*HIV-RNA at last visit (copies/mL)*
1	44/M	Abacavir/lamivudine 600/300 mg once daily, atazanavir 300 mg once daily	26	75.200	112	25	<50
2	47/M	Abacavir/lamivudine 600/300 mg once daily, atazanavir 300 mg once daily	23	70	41	27	<50
3	40/M	Tenofovir/emtricitabine 245 mg/ 200 mg once daily	21	65.200	93	26	<50
4	58/M	Zidovudine 300 mg twice daily, didanosine 400 mg once daily, atazanavir 300 mg once daily	23	72	57	51	<50
5	41/F	Zidovudine/lamivudine 300/ 150 mg twice daily, atazanavir 300 once daily	19	56	81	44	<50
6	46/M	Abacavir/lamivudine 600/ 300 mg once daliy, atazanavir 300 mg once daily	23	64	0	21	<50

served with a booster of ritonavir, but they did not support the specific cut-off of 150 ng/mL [8]. These results, even if in a small cohort, also confirm previous studies that questioned relationship between plasma levels and efficacy of other antiretroviral drugs [9, 10].

We cannnot try any conclusion due to the paucity of the sample but the long-lasting suppression of plasmatic HIV RNA confirm that further studies are warranted to assess the correct minimum target trough concentration of atazanavir and its correlation with virological efficacy, even if atazanavir unboosted should not be considered the first choice for treatment-naïve patients.

Keywords: Atazanavir, Ctrough, pharmacokinetics, virological response, HIV, HAART.

RIASSUNTO

We report our experience of reduced atazanavir dose in 6 HIV-infected patients on their first antiretroviral regimen, naïve to protease inhibitors and with no PI resistance mutations. In spite of plasmatic trough concentrations of atazanavir below the suggested minimum effective level in all of them, virological suppression (HIV-RNA <50 copies/mL) was obtained and persisted in all patients for a fairly long time.

Despite the paucity of cases, this lends weight to the clinical importance of atazanavir MEC which is still being debated.

SUMMARY

Nel lavoro abbiamo descritto la nostra esperienza in merito al trattamento di 6 pazienti sieropositivi per HIV-Ab, naïve *al trattamento antiretrovirale, senza mutazioni di resistenza per i PI, che al loro primo regime HAART assumevano una dose ridotta di atazanavir. Nonostante il riscontro in tutti i pazienti in studio di una concentrazione plasmatica di atazanavir (C trough) inferiore al livello minimo consigliato, si è ottenuta una duratura soppressione virologica (HIV-RNA<50 c/ml) per un lungo periodo di tempo. Pur considerando la scarsità numerica dei casi, ciò supporterebbe il dibattito ancora in corso sulla rilevanza clinica della MEC di atazanavir.*

REFERENCES

[1] Winston A., Bloch M., Carr A., et al. Atazanavir trough plasma concentration monitoring in a cohort of HIV-1-positive individuals receiving highly active antiretroviral therapy. *J. Antimicrob. Chemother.* 56, 380-387, 2005.

[2] Colombo S., Buclin T., Cavassini M., et al. Population pharmacokinetics of atazanavir in patients with human immunodeficiency virus infection. *Antimicrob. Agents Chemother.* 50, 3801-3808, 2006.

[3] Smith D.E., Jeganathan S., Ray J. Atazanavir plasma concentrations vary significantly between patients and correlate with increased serum bilirubin concentrations. *HIV Clin. Trials* 7, 34-38, 2006.

[4] Gonzalez de Requena D., Bonora S., Canta F., et al. Atazanavir Ctrough is associated with efficacy and safety: definition of therapeutic range. In Program and Abstarcts of the 12th Conference on Retroviruses and Opportunistic infections, Boston, 2005, Abstract 645.

[5] Cleijsen R.M., van de Ende M.E., Kroon F.P., et al. Therapeutic drug monitoring of the HIV protease inhibitor atazanavir in clinical practice. *J. Antimicrob. Chemother.* 60, 897-900, 2007.

[6] D'Avolio A., Baietto L., Siccardi M., et al. An HPLC-PDA method for the simultaneous quantification of the HIV integrase inhibitor raltegravir, the new nonnucleoside reverse transcriptase inhibitor etravirine, and 11 other antiretroviral agents in the plasma of HIV-infected patients. *Ther. Drug Monit.* 30, 662-669, 2008.

[7] La Porte C.J.L., Back D.J., Blaschke T., et al. Updated guidelines to perform therapeutic monitoring for antiretroviral agents. *Reviews in Antiviral Therapy*. 3, 3-14, 2006.

[8] Malan D.R., Krantz E., David N., et al., 089 Study Group. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naïve patients. *J. Acquir. Immune Defic. Syndr.* 47, 161-167, 2008.

[9] Langmann P., Weissbrich B., Desch S., et al. Efavirenz plasma levels for theprediction of treatment failure in heavily pretreated HIV-1 infected patients. *Eur. J. Med. Res.* 7, 309-314, 2002.

[10] Lopez-Cortes L.F., Ruiz-Valderas R., Marin-Niebla A., Pascual-Carrasco R., Rodriguez-Diez M., Lucero-Munoz M.J. Therapeutic drug monitoring of efavirenz: trough levels cannot be estimated on the basis of earlier plasma determinations. *J. Acquir. Immune Defic. Syndr.* 39, 551-556, 2005.