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ATAZANAVIR FOR TREATMENT OF HIV INFECTION IN CLINICAL ROUTINE: EFFICACY, PHARMACOKINETICS AND SAFETY

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Abstract:
Introduction: Atazanavir (ATV) is a novel protease inhibitor that has been recently introduced into therapy of HIV infection. Currently there is little data on ATV therapy from daily practice.
Methods: In this retrospective study, we report on ATV efficacy and safety in clinical routine. Drug monitoring was performed consisting of unscheduled single measurements and a 4-hour-profile. Trough concentration of >80 ng/ml and peak concentration of 2000-6000 ng/ml were regarded as sufficient.
Results: Between May 2003 and April 2004, ATV treatment was started in 42 patients, mean observation time was 32 weeks (6-53). Mean age was 45.6 years, 38% had prior AIDS, viral load was undetectable in 73%. Important side effects were minor or moderate diarrhea (27%) and fatigue (15%). ATV was discontinued in 10% due to side effects or malignant diseases. No significant influence on mean values of cholesterol, triglycerides, liver enzymes, CD4-cell-count, and HI-viral load was seen. Virologic failure occurred in 13% of patients, all of them were PI-experienced. Pharmacokinetic data are available for 32 patients, all patients had sufficient trough levels. 30% with unboosted ATV and 21% with boosted ATV had peak plasma concentrations below the level defined as sufficient. Mean trough levels, plasma profile and AUC did not differ significantly between groups with nonboosted versus boosted ATV regimes but showed a wide inter-patient variability.
Conclusions: ATV treatment of HIV-infected patients with or without a RTV booster was safe and effective in clinical routine. Drug levels were sufficient in the majority of cases. The variability of pharmacokinetic results in our sample supports therapeutic drug monitoring in patients treated with ATV.
Key words: HIV; HAART; Atazanavir; therapeutic drug monitoring

INTRODUCTION

The introduction of protease inhibitors (PI) in 1995 was the starting point of the era of highly active antiretroviral therapy of HIV infection (HAART). In the following years, the widespread use of this substance group showed good virological and clinical efficacy, but also cumulative toxicity within in the treated patient population [5, 10]. The HIV-associated lipodystrophy syndrome (LDS) is a frequent complication of HAART and occurs in a substantial proportion of patients receiving a protease inhibitor [5]. It consists of peripheral lipoatrophy, central fat accumulation along with hyperlipidaemia and insulin resistance. It has been associated with an increase in the risk for cardiovascular disease [3, 6]. Atazanavir is a novel azapeptide protease inhibitor that promises advantages in terms of side effects and convenience. It is a compound with a once daily administration and favourable resistance profile, clinical efficacy, and little effect on serum lipid concentrations [7]. It is hoped that this improvement in the lipid profile translates to less lipodystrophy, although there is only little data to support this theory [8].

Atazanavir can either be administered 400mg once daily or 300mg with a ritonavir-booster of 100mg. The latter is the only approved dosage for Europe. ATV Plasma concentrations have been shown to exceed the IC50 value of wild type virus beyond the 24 hours dosing interval [2], although higher plasma concentrations may be needed to overcome low-level drug resistance. Therapeutic drug monitoring (TDM) is an instrument to individualize drug dosage currently under investigation in different clinical settings [1, 4].

The aim of the study was to summarize early experience of application of ATV including TDM in clinical routine.

METHODS

All patients who started Atazanavir from May 2003 until April 2004 in the outpatient unit of the Düsseldorf University Clinic were included into a retrospective analysis. Routine laboratory examinations including chemistry, CD4-cell count, and HIV RNA levels were determined, clinical data were collected by chart review. Baseline characteristics, adverse events, toxicities and laboratory results as well as co-medication were documented. Measurement of ATV and ritonavir plasma levels was conducted as an unscheduled blood sample and, subsequently, a scheduled four-hour pharmacokinetic profile. The pharmacokinetic profile was performed at least one month after starting ATV. At 8 a.m., after having taken the usual medication the day before and fasting overnight, five ml of plasma were drawn before and 1, 2, 3 and 4 hours after medication was administered with the patient´s breakfast.

ATV with a molecular weight of 801.94 g/mol, obtained as reference material in the sulfate-salt form by

the manufacturer, Bristol-Myers Squibb, New Brunswick, NJ, USA. A 86093 from ABBOTT, Abbott Park, IL, USA, was used as internal standard. The determination of ATV was done by gradient high performance liquid chromatography [9] with UV-detection at 215 nm and additionally by a photo diode array detection (Spectra System 6000 LP) with Chromquest Software, all parts from Thermo Separation Products, San Jose, CA, USA. With the described technique Atazanavir absorption maxima at 210, 250 and 279 nm were checked for peak purity. Therefore, any interference with nonnucleoside reverse transcriptase inhibitors or the other protease inhibitors, which could be determined simultaneously, was excluded. Linearity of detection was given for a minimum of 100 to a maximum of 7000 ng/ml. ATV target levels were defined as >80 ng/ml for trough level and 2000-6000 ng/ml for peak level concentrations.

Data are presented as mean ± standard deviation unless indicated otherwise. Comparison between subgroups or different time points was performed using paired or non paired t-test. Correlations were analysed by using the Pearson correlation coefficient. P-values less than 0.05 were considered as statistically significant. A correction for multiple testing was not performed.

RESULTS

In the investigational period from May 2003 to April 2004, ATV treatment was started in 42 patients. One patient was lost to follow up; the mean observation time was 32 (6-53) weeks; baseline characteristics are presented in Table 1.

Chronic hepatitis C and hepatitis B virus infection were each present in one patient. Reasons for switching to ATV were hyperlipidaemia (21 patients; 50%), lipodystrophy (13 patients; 31%), the wish for a more convenient therapy regime with less pills (12 patients; 29 %), diarrhea (9 patients; 21%) or other side effects under previous treatment (12 patients; 29%), and virological failure of HAART (4 patients; 10%), respectively (multiple options included). One patient received ATV as initial therapy.

Table 1. Baseline characteristics

Patient characteristics	Mean ± SD
Weight (kg)	72.6 (±13.9)
Body mass index (kg/m2)	23.03 (±3.89)
Age (years)	45.6 (±13.3)
Time since diagnosis of HIV (years)	7.87 (±4.6)
Observation period (weeks)	32 (±16)
CD4-cell count (cells/µl)	369 (±179)
HIV-1 RNA (copies /ml)	5954 (±21560)
HIV-1 RNA <50/µl	30 (73%)
AIDS	16 (38%)
Nadir <200 CD4 cells/µl	28 (67%)

All patients received ATV in combination with two (40 patients) or three (2 patients) standard nucleoside reverse transcriptase inhibitors (NRTI). Twenty-six patients (62%) started with Ritonavir-boosted ATV, sixteen with non-boosted ATV. Five patients were later switched from non-boosted to boosted ATV, four because of low ATV serum levels and one patient because of a detectable viral load despite adequate ATV serum levels. One patient was switched from boosted to non-boosted ATV because of gastrointestinal side effects.

ATV was generally well tolerated: common side effects were minor or moderate gastrointestinal disturbances as diarrhea and nausea (11 patients, 27%) or fatigue (6 patients; 15%). Three patients (7%) complained of jaundice. ATV was discontinued in four patients, in 1 case due to persistent ATV-associated hyperbilirubinaemia. The other cases, consisting of sleeping disorder, non-Hodgkin's lymphoma, and pleural adenocarcinoma, were not regarded as ATV-associated. Elevated bilirubin serum concentrations were seen in 40 (98%) patients and a grade 4 elevation in three (7%) patients without increase of other liver function tests. We found no significant association between bilirubin serum levels and atazanavir plasma concentrations.

Selected laboratory parameters are presented in Table 2. No relevant alteration of mean laboratory pa-

Table 2. Laboratory parameters, mean ±SD, *=p<0.05, **=p<0.001.

Parameter	Baseline	week 12	week 24	week 44
Total Cholesterol (mg/dl)	214.1 (±45.6)	196.4 (±39.5)	200.5 (±48.8)	217.7 (±46.9)
High density Lipoproteins (mg/dl)	48.1 (±13.3)	52.8 (±17.8)	50 (±14)	48.9 (±21.6)
Low density Lipoproteins (mg/dl)	145.9 (±40.3)	144.9 (±22.3)	151.4 (±40.7)	145.6 (±38.8)
Triglycerides (mg/dl)	262.8 (±180.5)	223.5 (±234.9)	272.6 (±188.4)	281.7 (±242.2)
Aspartat-Amino-Transferase (U/l)	14.8 (±6.4)	16.2 (±7.1)	23.8 (±15.4)	**16.2 (±6.02)***
Alanine-Amino-Transferase (U/l)	20.7 (±12.6)	25.8 (±21.8)	25.8 (±21.8)	24.78 (±16.5)
G-glutamyl-Transferase (U/l)	34.4 (±29.5)	39.7 (±60)	37.5 (±46.1)	21 (±10.1)
Alkaline phosphatase (U/l)	149 (±70.5)	159.3 (±77.8)	**172.9 (±57.8)***	155.4 (±64.2)
Total Bilirubin (mg/dl)	0.56 (±0.31)	**1.92 (±1.2)****	**1.77 (±0.86)****	**1.5 (±1.28)***
CD4 (cells/µl)	369 (±179)	357(±197)	343 (±203)	256(±106)
HIV-1 RNA (copies/ml)	5954 (±21560)	11011(±26863)	11682(±40655)	55(±12)

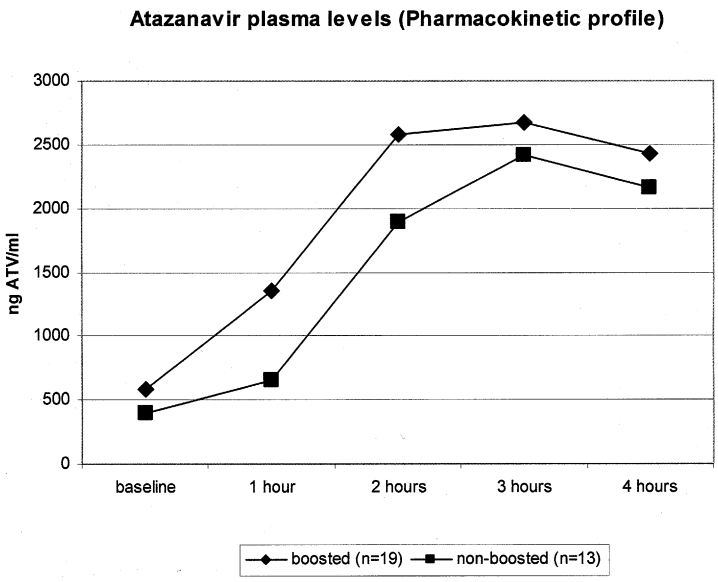

Fig. 1. Pharmacokinetic profile of ATV.

Table 3. Atazanavir and ritonavir plasma concentrations.

		ATV 300mg/ RTV 100mg	ATV 400mg	RTV
		(n = 19)	(n = 13)	(n = 19)
baseline	ng/ml (±SD)	583(±396)	431(±517)	144 (±92)
1 hour	ng/ml (±SD)	1356(±1243)	678(±620)	574 (±514)
2 hours	ng/ml (±SD)	2582(±1267)	1930(±1409)	847 (±503)
3 hours	ng/ml (±SD)	2676(±1290)	2408(±1278)	899 (±464)
4 hours	ng/ml (±SD)	2430(±1132)	2055(±1227)	833 (±378)
AUC	ng*h/ml (±SD)	8084(±3924)	5868(±3152)	2796 (±1336)

rameters except the discussed elevations of bilirubin levels was noted. Furthermore, mean HIV RNA plasma levels and CD4-cell count did not change significantly during ATV treatment. Of the 30 patients with undetectable HIV plasma levels (<50 copies/µl) at baseline, viral load increased in four patients (13%) in two consecutive determinations after 4-38 weeks. All of them were PI-experienced; two were switched to ATV from Lopinavir/rtv, one from Nevirapine and one from Indinavir. Two of those four patients were receiving non-boosted and two patients boosted ATV. Of seven patients with a detectable viral load at baseline and a follow-up period of at least 12 weeks, six achieved undetectable viral load.

The time course of drug concentrations of boosted as well as unboosted ATV is demonstrated in Figure 1. Unscheduled determination of ATV plasma levels was conducted in 30 patients and revealed plasma concentrations below the target trough level in two patients with normal plasma concentrations in the pharmacokinetic profile, suggesting adherence problems. A four hour pharmacokinetic profile was obtained from 32 patients, of which 19 received boosted atazanavir. All patients had a sufficient trough level. Four patients (30%) with unboosted ATV and four patients (21%) with boosted ATV had peak plasma concentrations below the target concentration of 2000-6000 ng/ml. Mean trough levels, the plasma concentrations at different measure points and the AUC did not differ significantly between groups with non-boosted versus boosted ATV regimes, as shown in Table 3. ATV plasma levels showed a wide inter-patient variability (>10-fold in peak levels). In three patients who were changed from non-boosted to boosted ATV, the AUC increased from 4770 ± 1313 to 6824 ± 3902 ng*h/ml.

Sixteen patients received Tenofovir (TDF), of which eight patients had a once daily therapy regime (six in combination with Didanosine and two in combination with Lamivudine). Tenofovir co-medication did not significantly decrease ATV plasma concentrations in boosted regimens, as compared in patients taking TDF vs. patients not taking TDF (AUC 7788±4268 vs. 8272 ± 2904 ng*h/ml).

Discussion

Atazanavir is a new protease inhibitor that has been recently introduced into clinical use. The aim of the study was to investigate the pharmacokinetics and safety of this compound after one year of routine application. The majority of our patients were switched to ATV from previous PI or NNRTI. The most important reasons for switching to ATV were side effects of previous HAART and the wish for more conve-

nient administration. ATV was generally well tolerated, although a mild increase in bilirubin was observed in almost all patients. The latter is rarely of clinical significance and led to discontinuation of ATV in only one patient without signs of liver toxicity. Other reasons for discontinuation were AIDS-defining events and non-HIV-related diseases that were not typical ATV-associated side effects. Apart from this, laboratory measurements revealed no further toxicity of relevance. Thus, ATV seems to be a safe PI with a convenient dosing frequency. However, in contrast to previous results, we found no relevant change of cholesterol, HDL, LDL or triglycerides after switching to ATV. The significance of this finding is limited by baseline lipid concentrations which were only marginally elevated and the lack of fasting state documentation at sampling time.

ATV treatment was immunologically and virologically effective in the majority of patients. In particular, 6 of 7 patients with detectable viral load at baseline and a follow-up period of at least 12 weeks achieved undetectable viral load with ATV-containing treatment. However, the risk of virological failure after switching to ATV even with undetectable HIV RNA plasma levels must be considered, particularly in protease inhibitor experienced patients. The percentage of virological failure in patients with undetectable HIV RNA at the time of switching to ATV was 13 %, both in patients receiving boosted and unboosted ATV.

ATV plasma concentrations indicate sufficient bioavailability of ATV alone and ATV boosted with Ritonavir 100mg once daily. ATV plasma levels showed a wide inter-patient variation, but exceeded the target trough concentrations in all patients. 30 % of cases with non-boosted and 21 % of patients with boosted ATV had peak concentrations below the target without association to virological response. The latter findings are arguments for perfoming therapeutic drug monitoring in clinical routine. ATV drug concentration can be safely increased with co-administration of 100mg Ritonavir once daily, few patients seem to experience additive side effects. In contrast to previous data [11], co-medication with Tenofovir was not associated with decreased ATV plasma levels or virological failure. Thus, Tenofovir may be a convenient combination partner in an ATV-containing once-daily regimen. An unresolved issue is the determination of validated target concentrations for trough and peak levels.

Our findings may be limited by the retrospective design of the study and the size of the observed cohort. However, they consist of unselected data possibly resembling daily practice of HIV-therapy. Thus, our conclusion is that ATV treatment in clinical routine shows good safety as well as tolerability. Moreover, ATV treatment within different HAART combinations is virologically and immunologically effective. The pharmacokinetic data suggest sufficient bioavailability of ATV in more than 70% of patients. In spite of a clear association of therapeutic drug monitoring with virological and toxic effects of protease inhibitors, there is significant inter-patient variability of pharmacokinetic results in literature [1]. As this is also the case in our study, the prognostic value of ATV-concentration measurement remains to be determined. However, our data indicate subgroups of patients that might benefit from therapeutic drug monitoring. We recommend ATV plasma concentration measurement particularly in PI-experienced patients, in regimens with non-boosted ATV, and in patients receiving other medication with potential drug interactions. This strategy may help to optimize the pharmacokinetic profile and thus therapeutic efficacy.

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