title

Efficacy and safety of boosted atazanavir in HIV-infected, ARV-naive patients – results from 48/96 weeks Castle study

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summary

Antiretroviral regimens based on human immunodeficiency virus-1 protease inhibitors are the cornerstone of combination antiretroviral therapy because of their antiviral efficacy and high genetic barrier. Protease inhibitor – containing regimens are complicated by a number of side effects, mainly diarrhea, dyslipidemia, an increased risk of myocardial infarction, diabetes and lipodystrophy. Atazanavir (ReyatazTM) is the first, originally designed as once-daily HIV-1 protease inhibitor that offers a more convenient and safer PI-containing management of HIV infection. The antiviral efficacy of atazanavir has been proven in both treatment-experienced and treatment-naïve patients. In July 2008 boosted atazanavir has received registration for use in antiretroviral-naïve HIV-infected population. This specific registration was based on results from 48 weeks of the Castle (BMS AI424138) study.

key words

boosted atazanavir, atazanavir/ritonavir, HIV-1 protease inhibitor, antiretroviral therapy, ARV, HIV-1, once-daily regimen

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Introduction

Antiretroviral (ARV) regimens based on human immunodeficiency virus-1 (HIV-1) protease inhibitors (PI) are the cornerstone of combination antiretroviral therapy (cART) because of their antiviral efficacy and high genetic barrier. PI-containing regimens are complicated by a number of side effects, mainly diarrhea, dyslipidaemia, an increased risk of myocardial infarction, diabetes and lipodystrophy. ATV (ReyatazTM) is the first, originally designed as once-daily HIV-1 protease inhibitor that offers a convenient and safer PI-containing cART. The use of atazanavir has been associated with less hyperlipidaemia and diarrhea than other drugs in the same class (1). Atazanavir like the other PIs is a substrate of the subunit CYP3A4 of the P450 cytochromes and can be boosted with low dose of ritonavir to increase plasma concentration. In Poland atazanavir has been registered boosted with 100mg of ritonavir, once daily (2). However in USA it is also registered in unboosted dosing, therefore in clinical practice atazanavir is very often used as an ritonavir – sparing, PI-based therapeutic option (3).

In terms of antiviral activity *in vitro* and susceptibility ATV is one of the most potent drugs in HIV-1 protease inhibitor class, having EC50 (50% effective concentration) of 3-5 nM and an EC90 of 9-15 nM against a variety of HIV-1 isolates in different cell types. Atazanavir has activity against HIV-1 Group M subtype viruses A, B, C, D, AE, AG, F, G, and J isolates in cell culture. It has also activity against HIV-2 isolates (EC50 of 1.9 to 32 nM0 (2).

Due to very fast absorption ATV reaches the peak serum concentration 2.5 hours after dosing. Its bioavailability depends on gastric pH. Therefore in the presence of food, exposure measured as the area-under-the-curve (AUC) can be raised by 70% in comparison with the fasting state. Atazanavir should therefore be administered with food. (4). Atazanavir is 86% protein bound (5) and the trough plasma levels when ATV 300 mg is given in combination with ritonavir 100 mg in HIV-1-infected patients average 709 ng/mL (30-60 times the protein binding-adjusted EC50) (6). Metabolism of ATV in the liver leads to the production of three metabolites – none of them inhibits the P450 cytochrome system or has anti-HIV-1 activity. The plasma half-life of ritonavir boosted ATV is 11 hours. The Cmin and AUC are respectively 5- and 3-fold higher than when the drug is administrated boosted with ritonavir (in comparison to dose of 400 mg q.d., without boosting). The main way of elimination is biliary – 79% of the drug is recovered in the feces, therefore dose adjustment for renal insufficiency is unlikely to be required. In comparison with healthy subjects, a 42% increase in the AUC has been observed in patients with hepatic impairment (2). In subjects with severe hepatic impairment ATV/r has not been studied and therefore is not recommended (7). In antiretroviral treatment naive patients, the I50L substitution, sometimes in combination with an A71V change, is the signature resistance substitution for atazanavir. The N88S substitution has been rarely observed in patients with virologic failure on atazanavir treatment. In clinical studies N88S by itself does not lead to phenotypic resistance to atazanavir or have a consistent impact on clinical efficacy (2).

The antiviral efficacy of atazanavir has been proven in both treatment-experienced and treatment-naïve patients (3). In July 2008 boosted atazanavir has received registration for use in antiretroviral-naïve HIV-infected population. This specific registration was based on results from 48 weeks of the Castle (BMS AI424138) study (9).

Castle study – design and results

The aim of the CASTLE study was to compare the clinical efficacy of atazanavir/ritonavir once-daily and lopinavir/ritonavir twice-daily, given in combination with once-daily, fixed-dose tenofovir and emtricitabine, in treatment-naive HIV-1-infected patients. It was open-label, randomized, multicentre non-inferiority study (with non-inferiority margin Δ 10%, 95%CI). Patients participating in this study were recruited from 134 centers (29 countries in Euorpe, Asia, Africa, North and South America). The eligibility criteria for the participation in the study were: HIV-1 infection, age >18 years, no previous history of antiretroviral therapy (naïve), HIV-1 RNA ≥5000 copies/mL. Patients were randomized 1:1 to receive either atazanavir 300mg plus ritonavir 100 mg once daily, or lopinavir/ritonavir 400/100 mg, each with tenofovir/emtricitabine fixed dose (300/200 mg) once daily. Patients were also stratified by HIV RNA level at baseline: below 100 000 copies/mL or 100 000 copies/mL or greater and geographic region.

The primary endpoint used in this study was the proportion of patients with HIV RNA <50 copies/mL at week 48 of therapy. The principal analysis is based on confirmed virological response (CVR), non-completer equals failure (NC = F), intend–to–treat (ITT). Supportive analysis includes: time to loss of virologic response (TLOVR–ITT) and virologic response observed cases (VR-OC, OT – on treatment). Secondary endpoints were: 1/ the proportion of patients with HIV RNA <400 copies/mL at week 48; 2/ the proportion of patients with HIV RNA <50 copies/mL at week 96; 3/ changes from baseline in absolute CD4 count through weeks 48/96; 4/ HIV RNA reduction (log) by week 48; 4/ resistance profiles; 5/ virologic failures; 6/ genotypic and phenotypic testing; 7/ adverse events (AEs); 8/ changes in fasting lipids – fasting lipid National Cholesterol Education Program (NCEP) shifts and ratios (9,10).

In Castle study 883 HIV-infected, treatment-naive patients were randomised: 440 patients to ATV/ RTV group and 443 to LPV/r – treated arm. Selected baseline characteristics of patients is summarized in table 1. There were relatively high percent of women participating in the study (31% in both arms), patients were advanced in HIV infection: 48% had CD4 cell count <200 cells/mm^3, 51% had HIV RNA >100000 copies/mL. Study data show that antiviral efficacy of once-daily atazanavir boosted with ritonavir is non-inferior to twice-daily ritonavir-boosted lopinavir, both in combination with tenofovir/emtricitabine (FD, once-daily) for the treatment of antiretroviral-naive HIV-1-infected patients over 96 weeks. At weeks: 48 and 96 similar percent of patients in each arm had HIV RNA <50 copies/mL (principal ITT analysis, CVR, NC = F), confirmed by the supportive analyses (TLOVR ITT, VR-OC, OT). Detailed results of proportion of subjects achieving primary and secondary virologic endpoints are in table 2. Response rates achieved according to baseline HIV RNA (<100 000 and ≥100 000 copies/mL) are presented in table 3. The association between virologic response and baseline CD4 cell count was performed as *post hoc* analysis for both regimens. At week 48 lower virologic response was associated with lower baseline CD4 cell count in LPV/r treated patients (p = 0.0085), but not in ATV/RTV treated subjects. At week 96 the response rates for ATV/RTV were maintained across all CD4 strata. There was no specific trend in virologic response for either arm. For patients starting therapy with CD4 cell count bellow 50 cells/mL response rate was 78% in ATV/RTV arm compared to 58% in LPV/r group (Table 4). This reduced response rate in