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ORIGINAL ARTICLE

Treatment response to unboosted atazanavir in combination with tenofovir disoproxil fumarate and lamivudine in human immunodeficiency virus-1-infected patients who have achieved virological suppression: A therapeutic drug monitoring and pharmacogenetic study☆

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protease inhibitor

Abstract *Background/Purpose:* Treatment response to switch regimens containing unboosted atazanavir and tenofovir disoproxil fumarate (TDF)/lamivudine guided by therapeutic drug monitoring in human immunodeficiency virus-infected patients is rarely investigated.
Methods: Consecutive patients with plasma human immunodeficiency virus RNA load < 200 copies/mL switching to unboosted atazanavir plus zidovudine–lamivudine (coformulated), abacavir–lamivudine (coformulated), or TDF/lamivudine > 3 months were included for determinations of treatment response, plasma atazanavir concentrations, and single-nucleotide polymorphisms of *MDR1*, *PXR*, and *UGT1A1* genes from 2010 to 2014. Treatment failure was defined as either discontinuation of atazanavir for any reason or plasma viral load ≥ 200 copies/mL within 96 weeks.
Results: During the study period, 128 patients switched to unboosted atazanavir with TDF/lamivudine (TDF group) and 186 patients switched to unboosted atazanavir with two other nucleoside reverse-transcriptase inhibitors (non-TDF group). There were no statistically significant differences in the distributions of single-nucleotide polymorphisms of *MDR1* (2677 and 3435), *PXR* genotypes (63396), and *UGT1A1*28* between the two groups. Recommended plasma atazanavir concentrations were achieved in 83.5% and 64.9% of the TDF group and non-TDF group, respectively ($p < 0.01$). After a median follow-up duration of 96.0 weeks, treatment failure occurred in 19 (14.9%) and 34 (18.3%) patients in the TDF group and non-TDF group, respectively ($p = 0.60$). Low-level viremia (40–200 copies/mL) before switch (adjusted hazard ratio, 2.12; 95% confidence interval, 1.12–4.01) and without therapeutic drug monitoring (adjusted hazard ratio, 2.08; 95% confidence interval, 1.16–3.73) were risk factors for treatment failure.
Conclusion: Switch to unboosted atazanavir with TDF/lamivudine achieves a similar treatment response to that with two other nucleoside reverse-transcriptase inhibitors in patients achieving virological suppression with the guidance of therapeutic drug monitoring.

Introduction

Protease inhibitors (PIs) boosted with ritonavir in combination with two nucleos(*t*)ide reverse-transcriptase inhibitors (NRTIs) are recommended antiretroviral regimens with good virological efficacy and a high genetic barrier to resistance.[1–3] Boosted atazanavir and darunavir are preferred for the initial treatment of human immunodeficiency virus (HIV) infection because each has demonstrated better lipid effects and tolerability than ritonavir-boosted lopinavir.[4–6] Despite being administered at a low dose (100 mg), ritonavir can lead to lipid disturbances, glucose intolerance, insulin resistance, liver enzyme elevations, gastrointestinal symptoms, and body fat abnormalities[7,8]; furthermore, the potential drug–drug interactions between ritonavir and nonantiretroviral medications may potentially lead to clinically significant adverse events.[9–11]

Randomized clinical trials have demonstrated similar virological efficacy between the switch regimens consisting of unboosted atazanavir and those consisting of boosted atazanavir in patients who had achieved suppression of HIV-1 replication after initial therapy with boosted atazanavir-containing regimens.[12–15] Regimens containing unboosted atazanavir may provide better efficacy in virological suppression and improvement of lipid parameters, compared with those containing other PIs such as boosted lopinavir, boosted or unboosted indinavir, boosted or unboosted saquinavir, and nelfinavir.[16] These issues were especially relevant to aging HIV-positive patients who are likely to have polypharmacy.[17]

Unlike other NRTIs, tenofovir disoproxil fumarate (TDF) is not recommended in combination with unboosted atazanavir because TDF may decrease atazanavir concentrations by 23–40%, although the mechanisms for this interaction remain unclear.[18–20] Lower plasma concentrations and higher interindividual variability due to the diverse distribution of genetic polymorphisms that are responsible for variations of atazanavir pharmacokinetics in different ethnic populations are the major concerns.[21] In the clinical setting, studies have revealed that coadministration with TDF was not associated with lower plasma exposure to unboosted atazanavir.[22,23] In terms of virological response, others studies have suggested that a combination of TDF with unboosted atazanavir may be safe in selected populations.[23–25]

In this study, we aimed to compare the treatment response to a switch regimen of unboosted atazanavir in combination with TDF and lamivudine versus regimens of unboosted atazanavir with two other NRTIs with the information provided with therapeutic drug monitoring (TDM) and pharmacogenetic investigations.

Methods

Study population

In this retrospective observational study, we included HIV-infected adults aged 20–65 years who switched to unboosted atazanavir plus two NRTIs after achieving

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