Int J Physiol Pathophysiol Pharmacol 2022;14(4):262-266
www.ijppp.org /ISSN:1944-8171/IJPPP0142085

Original Article

Dose of ritonavir-boosted atazanavir for HIV patient: a reappraisal based on genetic polymorphism epidemiology in Southeast Asia

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Received January 28, 2022; Accepted June 29, 2022; Epub August 15, 2022; Published August 30, 2022

Abstract: Several anti-HIV medications are currently available and used in medical care for HIV-positive people all over the world. Drug resistance is a global problem that necessitates the development of a new treatment regimen to address it. In several countries, ritonavir (RTV)-boosted atazanavir (ATV) is now used. There is evidence that patients taking RTV-boosted ATV on a regular basis have a higher ATV exposure, increasing the risk of toxicity. A recent theory suggests that a smaller dose of ATV/r may be sufficient. In this article, the authors reevaluate the dose of ATV/r for HIV patients based on existing data on the genetic epidemiology of CYP3A5 6986 A > G. According to the research, the likelihood of an individual achieving the therapeutic range of ATV through concentrations in various ATV/r regimens differs depending on baseline sex and CYP3A5 6986 A > G type. With the exception of a normal dosing regimen for male subjects, all have a chance of reaching the therapeutic range of ATV through concentrations (overall probability greater than 1). As a result, the lowering of the ATV/r dose should be considered primarily for male HIV infected patients.

Keywords: Dose, ritonavir, atazanavir, HIV

Introduction

The human immunodeficiency virus (HIV) is a virus that targets the immune system of the body. Acquired immunodeficiency syndrome (AIDS) can develop if HIV is not treated. Following the first infection, a person may experience no symptoms or a brief period of influenza-like sickness. This is usually followed by a long period of incubation with no symptoms. As the infection progresses, it wreaks havoc on the immune system, raising the likelihood of common illnesses like tuberculosis, as well as other opportunistic infections and malignancies that are otherwise uncommon in people with healthy immune systems.

At present, HIV is still a main global public health problem [1]. Several countries still have a high infection rate. In Asia, HIV is still a major health problem in many countries [2, 3]. At present, several anti-HIV drugs are available and circulated in medical care for HIV infected cases worldwide. Drug resistance occurs worldwide, and there is a need for an updated new regimen to correspond with the situation [4]. Data collected at the national level can be used to improve HIV care and treatment and reduce the emergence of population-level HIV drug resistance, thereby enhancing the long-term efficacy and durability of available first- and second-line antiretroviral therapy regimens [4]. The ritonavir (RTV)-boosted atazanavir (ATV/r) regimen is currently used in many Asian countries where HIV prevalence remains extremely high. Because of RTV's pharmacoenhancing impact on ATV, a strong, clinically efficacious, and well-tolerated antiretroviral medication with high plasma concentrations and a sufficient genetic barrier to viral resistance was developed. In non-naive patients, the efficacy of ATV when combined with low-dose RTV was comparable to that of lopinavir/RTV [5].

There is evidence that patients receiving RTV-boosted ATV (ATV/r) on a regular basis have high atazanavir (ATV) exposure, which increases the risk of hepatoxicity [6, 7]. There is a new proposed idea that a lower dose of ATV/r might be sufficient. However, there is little pharmaco-

kinetic data on ATV/r in patients that can be used to alter doses. Essentially, sex is reported to be associated with drug clearance [6, 7]. Several factors are proposed as determinants for achieving the therapeutic range of ATV through concentrations [6]. In a recent publication from Thailand, several underlying genetic factors were studied, and it was found that the *CYP3A5* 6986 A > G had a significant effect on drug clearance [7]. In this report, the authors reappraise the dose of ATV/r for HIV patients based on available data on the genetic epidemiology of *CYP3A5* 6986 A > G.

Materials and methods

Study design

The aim of this study is to estimate the impact of *CYP3A5* 6986 A > G on drug clearance in several regimens of ATV/r for HIV patients. The setting is Indochina, a developing area in Asia, where there is a very high incidence of HIV and drug resistance is a common problem [4]. The inclusion criteria are reports with primary data derived from previously published articles on the focused topic of *CYP3A5* 6986 A > G and drug clearance of ATV/r for HIV patients. The publications that did not use the usual genetic polymorphism analysis technique or did not have complete data on genetic polymorphism and drug clearance of ATV/r were excluded.

Clinical modeling

For estimation, a clinical model was used. The model was developed based on the clinical probability rule. The primary data for modeling was derived from previous reports. The primary datasets included a) the data on allele frequency of *CYP3A5* 6986 A > G [8] and b) the data on clearance of drugs in different ATV/r regimens for HIV patient [9]. According to the primary data, the G allele frequency for CYP3A5 6986 A > G is 65% [9]. In terms of the primary data, HIV-positive people over the age of 15 who did not have any other infections were included. All cases involving non-Asian ethnics or people over 60 were excluded. There were a total of 544 HIV-positive cases, divided into two age-matched groups of both sexes.

Based on the primary data, the simulation was done based on the main variable (*CYP3A5* 6986 A > G type) and categorized by two group classifiers (ATV/r regimens and sex). Based on quoted data, the case with *CYP3A5* 6986 GG has a 7.1% lower clearance than those with an AA or AG genotype, and clearance was reduced by 10.8% for females [8]. Regarding regimens of ATV/r regimens, 3 regimens were assessed: a) standard dose (300/100 mg), b) 200/100 mg, and c) 200/50 mg. In the model, the decreased clearance was related to the dose to achieve the target therapeutic range of ATV. This means when there is an increased clearance, there will be a decreased gap in dose to reach the target therapeutic range of ATV.

Measurement outcome

The final measurement outcome in this study is the probability of a subject achieving the therapeutic range of ATV through concentrations in different regimens of ATV/r. Based on a previous efficacy study [8], the percentages of subjects able to achieve the therapeutic range of ATV through concentrations in different regimens of ATV/r for standard dose, 200/100 mg and 200/50 mg regimens were 40%, 70% and 70%, respectively. To assess the effects of *CYP3A5* 6986 GG and sex, the corresponding probability in different paths was used for joint probability calculation. In this study, the male patient without *CYP3A5* 6986 GG receiving the standard dose was assigned as wild type, probability 100%, for further probabilistic modeling.

Regarding modeling, the expected dose for each scenario was calculated by adding the reported interrelation with the wild type scenario (male patient without *CYP3A5* 6986 GG receiving a standard dose) to the starting dose of the wild type scenario. For example, the expected probability of a female patient without *CYP3A5* 6986 GG receiving a standard dose will be equal to the "probability of the wild type + reported interrelationship for a female patient without *CYP3A5* 6986 GG receiving a standard dose (which is hereby equal to an additional 10.8%)". The expected probability of a subject achieving the therapeutic range of ATV will then be calculated. The joint probability concept was used to calculate the expected probability. For the calculation, the route probability for the ATV/r regimen and CYP3A5 6986 GG were employed as particular factors. A male patient without CYP3A5 6986 GG receiving the standard dose was designated as wild type, with a probability of 100%, for subsequent probability modeling.

Table 1. Expected probability of subject to achieve the therapeutic range of atazanavir (ATV) through concentrations in different regimens of ritonavir-boosted atazanavir (ATV/r)

ATV/r regimen	Expected dose				Overall expected probability to achieve the therapeutic range of ATV**	
	With *CYP3A5* 6986 GG		Without *CYP3A5* 6986 GG			
	male	female***	male	female***	male	female***
standard dose*	107.1%	117.9%	100%	110.8%	0.96982	1.07134
200/100 mg	137.1%	147.9%	130%	140.8%	1.19982	1.35334
200/50 mg	137.1%	147.9%	130%	140.8%	1.19982	1.35334

*300/100 mg. **Expected probability is calculated based on joint probability principle. The path probability regarding ATV/r regimen and *CYP3A5* 6986 GG are used as specific factor for calculation. The primary assumption is using male patient without *CYP3A5* 6986 GG receiving standard dose is assigned as wild type, probability 100%, for further probability modeling. ***clearance is reduced by 10.8% for female [8].

Results

Primary data for mathematical modeling analysis

The primary data were reassessed to determine the gap dose required to achieve ATV's target therapeutic range. Regarding having *CYP3A5* 6986 GG type, the gap in dose to reach the target therapeutic range of ATV was reduced to 92.9% of normal. Regarding females, the gap in dose to reach the target therapeutic range of ATV was reduced to 89.2% of normal.

Mathematical modelling to derive overall expected probability to achieve the therapeutic range of ATV

Regarding *CYP3A5* 6986 GG, using the Hardy Weinberg genetic distribution principle, the calculated percentage of *CYP3A5* 6986, GG type was equal to 0.42. Hence, for *CYP3A5* 6986, in cases with and without GG, the specific path probability was equal to 42% and 58%, respectively.

These parameters were used to assign the path probability for further joint probability analysis. According to the study, the probability of a subject achieving the therapeutic range of ATV through concentrations in different regimens of ATV/r was different and varied according to background sex and *CYP3A5* 6986 A > G type (**Table 1**).

Discussion

In either pretreated or symptomatic patients with an AIDS-defining event, highly active antiretroviral therapy (HAART) is based on a combination of three or more antiretroviral agents from different antiretroviral classes, including two nucleoside reverse transcriptase inhibitors and at least one protease inhibitor, in either pretreated or symptomatic patients [5]. The majority of currently available protease inhibitors are given in combination with low-dose ritonavir, which acts as a pharmacoenhancer, increasing protease inhibitor plasma concentrations considerably. It is an azapeptide inhibitor of the HIV protease that is very effective [5]. The efficacy of ATV when paired with low-dose RTV in non-naive individuals is comparable to that of lopinavir/RTV. When compared to non-boosted atazanavir, the ATV/r is associated with better virologic control and immunological control, with no increased risk of side events except higher bilirubin. As a result, the ATV/r is the preferred technique of ATV prescription, and it is widely used currently in many countries [10].

The influence of genetic polymorphisms on plasma concentrations of ATV and RTV becomes an interesting issue in the current anti-HIV drug study [11-17]. The association between background genetic polymorphism and hyperbilirubinemia induced by ATV/r is also reported [18-20]. To optimize dose, researchers may look into the genetic polymorphism background. However, the test is expensive and might not be available in all settings. The consideration based on local genetic epidemiology can help decide on dose adjustment in general. In this study, the authors focus their interest on the ATV/r regimen. Here, the authors reappraised on using ATV/r based on local genetic epidemiology data in Indochina.

The effect of the examined genetic polymorphism, CYP3A5 6986 A > G, can be established in this study. The multiple CYP3A5 6986 A > G variants have varied effects, and there is a dis-

tinction between male and female HIV infected cases. Analysis can establish the influence of sex and CYP3A5 6986. Based on an overall analysis of the probability of a subject achieving the therapeutic range of ATV through concentrations, all but a standard dose regimen for male subjects have a chance of achieving the therapeutic range of ATV through concentrations (overall probability greater than 1). The findings of this investigation back up previous clinical observations obtained in our settings [8, 9]. Based on the clinical experiences from our settings [8, 9], it can be concluded that adjusting the ATV/r dose is required for effective and safe management of HIV-infected patients. Therefore, the adjustment of dose by reduction of ATV/r dose should be considered mainly for male HIV infected cases.

The key shortcomings of the current analysis include the lack of prospective data and inability to control confounding factors, such as the effects of other confounding factors (such as other concurrently used drugs [21]), due to the nature of clinical mathematical modelling studies. More prospective studies are required to look into the effects of numerous genetic variants that can change the therapeutic spectrum of anti-HIV therapies.

Conclusion

From this study, with the exception of male subjects on a standard dosage regimen, all have the potential to reach the therapeutic range of ATV via concentrations. As a result, ATV/r dose reduction should be considered primarily for male HIV patients. Other genetic polymorphisms, rather than CYP3A5 6986 A > G, may play clinical roles in real-life clinical practice. More research on the effects of other genetic polymorphisms, in addition to CYP3A5 6986 A > G, is needed.

Disclosure of conflict of interest

None.

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