Original Article

APOBEC3G POLYMORPHISM AND ITS IMPACT ON HAART RESPONSE AMONG HIV-1 IN MOROCCAN PATIENTS

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Abstract

APOBEC3G protein is a cytidine deaminase with strong antiviral activity acting as part of the antiviral innate immunity. It plays an important role in restricting intracellular HIV-1 replication. Two APOBEC3G allelic variants H186R rs8177832 and rs35228531 were shown to be associated with risk to HIV infection and also to the collapse of the immune system. Their polymorphism frequency differs depending on ethnic groups. Therefore, we aimed to investigate the allele and genotype frequency distribution of both SNPs among Moroccan healthy individuals and to assess its impact on the responsiveness to antiretroviral therapy among Moroccan HIV patients. In the present cross-sectional study, we enrolled 90 HIV patients confirmed and under HAART and 68 healthy individuals. Polymorphism for H186R and rs35228531 was performed using TaqMan®Drug Metabolism Genotyping Assay. The mutant allele frequency in healthy individuals was 17% for rs8177832 and 9% for rs35228531. The frequencies of mutated genotypes rs8177832 (GG) rs35228531 (TT) in healthy subjects were 4.41% and 1.96%, respectively. Regarding the impact of the polymorphism of these two genetic variants on the response to HAART, our results showed that both SNPs were not correlated to the response to antiretroviral therapy in the Moroccan population.

Keywords: APOBEC3G, SNPs, HIV-1, HAART response, genetic variation.

Introduction

The acquired immunodeficiency syndrome (AIDS) is a pandemic that is spreading quickly throughout the world. According to the UNAIDS 2020 report, 1,7 million people acquired HIV in 2019(1). In Morocco, HIV epidemic is heterogeneous, it remains low among general population (0.08%) but still concentrated in some key populations such as Sex Workers(1.3%), Men who have Sex with Men(5.7%) and people who inject drugs(7.9%)(2).

In2019, the National Aids Program reported more than 1 000 new HIV infections bringing up the number of people living with HIV in Morocco to 22 000(3). The introduction of Highly Active Antiretroviral Therapy (HAART) has substantially decreased the morbidity and mortality associated with HIV infection and then improving significantly the quality of life of patients (4–7). However, the infection persists with the increase of the rate of side effects among patients used antiviral molecules, and also the appearance of some resistance mutations may due to the lack of adherence to HAART protocol (8-9).

Several protein factors have strong impact to control significantly HIV infection and the dissemination of virions at the early stage of infection(10-11). Indeed, some of them act as restriction factors inhibiting different stages of the virus replication, like tetherine (BST-2), Apolipoprotein B mRNA editing enzyme, catalytic polypeptide -like 3G (APOBEC3G),the sterile alpha motif and histidine-aspartate domain1 (SAMHD1), and tripartite motif 5alpha (TRIM5α). The APOBEC3G is a human enzyme belongs to the multigene family of cytidines deaminases which is involved in RNA editing mechanisms (12-13). It is the most active deaminase with a strong inhibitory effect on replication by targeting RNA or DNA molecules produced during replication of retroviruses (14–16). However, the APOBEC3G action is overcome by HIV-1 accessory protein viral infectivity factor (pVif), a basic protein required for HIV-1 propagation and pathogenesis (17–20). The interaction between APOBEC3G and pVif is antagonistic (21-22).Therefore, in the absence of pVif, APOBEC3G is packaged into the budding retroviral virions leading to an excessive release of Cytidine (C) into Uridine (U) in transcribed viral RNA (23). Consequently, in the newly synthesized DNA strands, an hypermutation process turns the (G) into (A)(24–26). The HIV-1pVif neutralizes the antiviral activity of APOBEC3G before its incorporation into the newly produced virions predominantly by forming an E3 ubiquitin ligase with cullin 5 (Cul5), elongin B (EloB), elongin C (EloC) and core binding factor subunit beta (CBFβ) that targets it quickly for degradation by the ubiquitin-proteasome pathway (27–33). Parallel to its deamination activity, APOBEC3G, in a deaminase-independent manner, directly blocks reverse transcriptase (RT) elongation and interferes with proviral HIV-1DNA (34–37).

Several functional Single nucleotide polymorphisms (SNPs) located in APOBEC3G genomic region have been reported to affect the degree of G to A mutations and then the rate of HIV -1 disease progression (26- 27), (38–41). In fact, it has been suggested that in some ethnic groups, someAPOBEC3G variant were strongly associated with rapid progression to AIDS (38)(40)(42). However, such genetic association had not replicated in other populations (43- 44).The current work aims to study the polymorphism of two selected APOBEC3G SNPs rs8177832 and rs35228531in healthy Moroccan individuals and to assess its impact on AIDS progression and the responsiveness to HAART among HIV-1 infected patients.

Materials and methods

Study subjects

From January 2017 to July 2019, a total of 158 volunteers individuals were enrolled into two groups.The HIV-1 patients group comprised 90 individuals under HAART for more than 12 months, among them 57patients were classified as good responder to HAART and 33 patients assigned as non responders to HAART. Treatment response is defined as a restoring and/or a maintaining the number of TCD4 cells greater than 500 cells/$mm^3$and a plasma viral load undetectable or less than 50 copies/ml. On the other hand, therapeutic failure is defined asviral load greater than 1000 copies/ml determined by two consecutive measurements of the viral load andTCD4 count equal to or less than 250 cells / mm3 or persistence of a TCD4 count less than 100 cells / mm^3(45).

All the recruited HIV-1 positive cases were part of the active line of patients under monitoring in the Infectious Diseases service of the University Hospital IBN Rochd in Casablanca. Furthermore, 68 healthy volunteers individuals were recruited, as a control group, from the National Center for Blood Transfusion in Rabat. All of them were confirmed free from HIV-1, hepatitis B and Hepatitis C. Both groups were matched by sex and age.

T-CD4 Immunophenotyping

The immune status was assessed by TCD4 lymphocyte immunophenotyping using Fluorescence-Activated Cell Sorting (FACS) Calibur flow cytometer (Beckton Dickinson, USA), and the applied protocol for TCD4 count was the same as reported by the manufacturer (Beckton Dickinson, USA). Briefly, a three-color mAb combination is used to stain blood cells: anti CD3 / anti CD4 / anti CD45 coupled respectively to fluorescein isothiocyanate (FITC), to phycoerythrin (PE) and to PerCp for CD45. Sample acquisition was performed using a universal

template for obtaining both single-platform absolute counts and percentages of CD4 T cells. Scatter analysis was accomplished using Cell quest pro software (Becton Dickinson, USA).

HIV-1 Viral Load

The HIV viral load was carried out using a fully automated real time PCR testing system m2000rt (Abbott real Time HIV-1, USA) according to the manufacturer's instructions, with a detection threshold of 40 copies/ml).

DNA extraction and genotyping

Genomic DNA was carried out from EDTA anti-coagulated blood. Total genomic DNA was extracted from peripheral blood using the QIAamp DNA Mini Kit (QIAGEN, Hilden, Germany) according to the manufacturer guideline. The extracted DNA was quantitated by a Nanodrop spectrophotometer. Two SNPs of the APOBEC3G gene **rs8177832** (H186R) and **rs35228531** located in exon 4 and the extragenic region 3 ' respectively were investigated. The two SNPs were already studied in the context of susceptibility to HIV infection and AIDS progression (41-42),(46-47). The APOBEC3G polymorphism was then performed using a TaqMan®SNP Genotyping Assay Technology. First, all DNA samples were aligned to one equal concentration (between 1 and 20ng) using sterile water DNase free for dilution. PCR was performed in a total volume of 20µl with 10µl of Master Mix, 1µl of TaqMan®SNP genotyping assay(X20), 2µl of genomic DNA and 7µl of pure water. The conditions for PCR amplification of APOBEC3G variants were: initial denaturation at 95°C for 10 min, followed by 40 cycles of denaturation at 95°C for 15 s, annealing and extension at 60°C for 1 min. Cycling was performed on the thermocycler 7500 Fast System according to manufactuer's protocol and data analysed with the 7500 software 2.0.

Statistical analysis

The allele frequencies were calculated and fit to Hardy- Weinberg equilibrium by the chi-square test between HIV-1 cases and Healthy controls using Epi-Info softwareTM version 7.1.0.6 (CDC, Atlanta, 2012). Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each association between genotypes and HIV-1 infection. P-value<0.05 was considered as statistical significant. Pearson's correlation (Pearson's R) was used to assess a relation between TCD4 and VL in studied populations.

Ethical considerations

The study was approved by the Ethical Committee of the Faculty of Medicine and pharmacy, University Mohamed V, Rabat, Morocco (The approval N°72/16). A written informed consent was obtained from all participants.

Results

A total of 90 HIV-1 patients and 68 healthy controls were consecutively enrolled for the present study. The mean age of HIV-1 patients and healthy controls were 34.02 and 37.64 years respectively (Table 1)

Table 1. Demographic and biological data of HIV-1 patients and healthy controls.

Subject	HIV patients	Healthy controls
Number	90	68

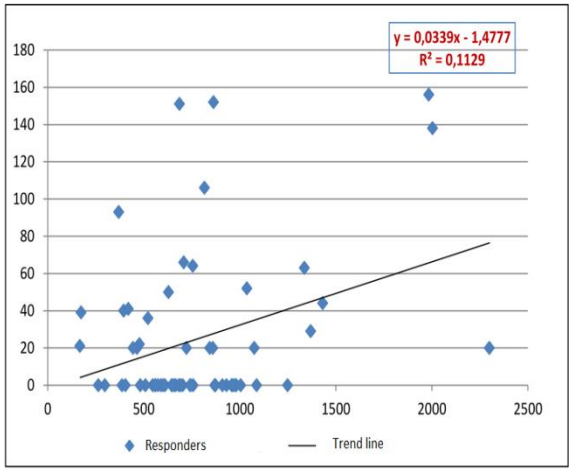
Females	47 (52.22%)	50 (73.52%)
Males	43 (47.77%)	18 (26.47%)
Mean age	34.02 (19-53)	37.64 (18-56)
CD4 count(cells/µl) - Responder group - Non responder group	 783 (168-2300) 504 (10-900)	
Viral Load (copies/ml) - Responder group - Non responder group	 Non detectable-156 168-1376 832	

Immuno-virological characterization of studied groups

Immuno-virological response to HAART was monitored by the assessment of the CD4 count and the quantification of the HIV VL. Patients recruited for this study were under treatment for at least 12 months. Results shown her after, matches the last determination of the VL and CD4. The ART responder group showed a VL comprising between 0 (undetectable) and 156 copies/ml. The arithmetic mean was equal to 25.05 copies/ml (95% confidence interval (CI): [14.32; 35.77]. The VL distribution tends towards an undetectable value, with a median equal to 0 copies / ml (95% CI: [0.00; 20.00]). From immunological stand point, the values of the CD4 count ranged between 168 and 2300 cells/ mm3 among the responder group. The arithmetic mean was equal to 783.30 cells / mm3 (95% CI: [676.88; 889, 71]. The median CD4 count value was 697 cells / mm3 (95% CI: [612.53; 841.61]).The analysis of the correlation of the two parameters (CD4 and VL) showed a wide dispersion of the clouds of values with a very low correlation index (r2 = 0.11) (Fig.1).

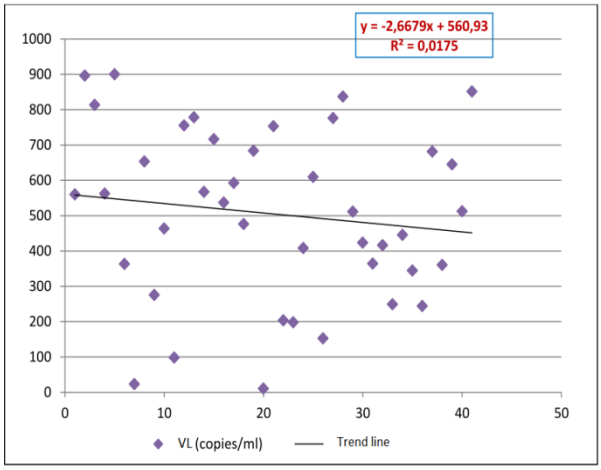
Among the group assigned as non-responder to HAART, the viral load values ranged from 168 copies/ml and a maximum value of 1,376,832 copies / ml. The arithmetic mean was 92,514 copies / ml (95% CI [21,176; 163,852]), and the median equal to 20,591 copies / ml (95% CI [6,332; 43 944]).The TCD4 count values comprised between 10 and 900 cells / mm3 with a mean equal to 504 cells / mm3 (95% CI: [428; 581]), The TCD4 median value was equal to 512 cells / mm3 (CI at 95%: [404; 645]).The correlation analysis of the VL and TCD4 count has a scattered appearance with a very low correlation index (r2 = 0.01). This indicates that the viral load and TCD4 count values in the group of patients not responding to antiretroviral therapy are discordant (fig.2).

Figure 1: Point cloud of viral load and TCD4 values among



Responders group to antiretroviral therapy (N=57)

Figure 2: Point cloud of viral load and TCD4 values among



Non responders group to antiretroviral therapy (N=33)

APOBEC3G polymorphism

All the studied groups were matched in age and gender. The genotype distributions of APOBEC3G SNPs (rs8177832 and rs35228531) polymorphisms in all studied groups were in the Hardy-Weinberg equilibrium (a calculated chi-square <theoretical chi-square (3.84)).Genotype and allele frequencies of the two APOBEC3G SNPs (rs8177832 and rs35228531) for both groups (HIV-1 patients and Healthy controls) are given in Table 2 and 3.

Table 2. Frequency distribution of APOBEC3G polymorphism in HIV-1 patients and healthy controls

APOBEC3G Genotypes	Healthy controls N=68 (n %)	Total HIV-1 patients N=88 (n %)	*p value*
AA	48 (70.59)	68 (77.27)	p>0.05
AG	17 (25.00)	19 (21.59)	p>0.05
GG	03 (4.41)	01 (1.14)	p>0.05
Allele			
A	113 (83)	155 (88)	p>0.05
G	23 (17)	21 (12)	p>0.05
CC	43 (84.31)	77 (87.50)	p>0.05
CT	07 (13.73)	10 (11.36)	p>0.05
TT	01 (1.96)	01 (1.14)	p>0.05
Allele			
C	93 (91)	164 (93)	p>0.05

T	09 (9)	12 (7)	p>0.05

N=Number of individuals, n= frequency of genotypes

Table 3. Frequency distribution of APOBEC3G polymorphism in HIV-1 patients (responders/Non responders)

APOBEC3G	HIV-1 patients		*p value*
Genotypes	Responders to HAART	Non responders to HAART	
	N=55 (n %)	N=33 (n%)	
AA	41 (74.55)	27(81.82)	p>0.05
AG	14(25.45)	19 (15.15)	p>0.05
GG	0 (0.00)	01 (3.03)	p>0.05
Allele			
A	96 (87)	59 (89)	p>0.05
G	14 (13)	07(11)	p>0.05
CC	52 (84.31)	25(80.65)	p>0.05
CT	05 (13.73)	05 (16.13)	p>0.05
TT	0 (0.00)	01 (3.23)	p>0.05
Allele			
C	109 (96)	55 (89)	p>0.05
T	05 (4)	07 (11)	p>0.05

N=Number of individuals, n= frequency of genotypes

Frequency of AA is common in both Control subjects and HIV-1 patients (70.59% *vs* 77.27%) while the frequency of GG was low among both the healthy group and HIV-1 patients under HAART (4.41% *vs* 1.14%). The wild type allele A is slightly higher in infected patients compared to healthy controls (88% *vs* 83%). Moreover, the wild type (CC) was found also common in both Control subjects and HIV-1 patients (84.31% *vs* 87.50%) while the rare allele T was found to be 9% in healthy controls and 7% among HIV patients.The analysis of APOBEC3G rs8177832 and rs35228531 genotyping showed no statistical difference between HIV-1 patients and healthy controls for each genotype (AA, AG and GG) or (CC, CT and TT) frequencies distribution.

The genotype frequency distribution of bothrs8177832 GG and rs35228531 TT was respectively similar between Healthy controls and Non responders group (4.41% *vs* 3.03%) (1.96% *vs* 3.23%) while they were totally absent in HIV-1 Responders group (0.0%).The overall distribution of allelic and genotypic frequencies shows no significant difference between all the studied groups, with a p> 0.05. According to our results, both of SNPs are probably not associated with HIV infection and antiretroviral therapy response among Moroccan population.

Discussion

APOBEC3G has been characterized by a large number of polymorphisms (SNPs) which could have several levels of anti-retroviral activity among populations (39) and could also play significant role in HIV-1 diversity among African populations where the prevalence of HIV-1 is still increasing (48). Our work aimed at describing genetic variations at two APOBEC3G lociH186R rs8177832 and rs35228531, their association with HIV infection and their impact on the antiretroviral therapy response among HIV Moroccan patients.

Viral load and TCD4 cell counts during the follow up of HIV-1 patients under HAART are the key measures to assess their response to treatment. In our study, among both HAART responder group and Non Responders, we found respectively a low correlation index between the two parameters (r2 = 0.11) and (r2 = 0.01) but this positive correlation still strong in Responders compared to Non-responder group. Responding to HAART depend on the host immunity, compliance with the treatment and the absence of drugs resistance(49).

There is a clear difference in the distribution of APOBEC3G genotypes and alleles in different ethnic groups. In the present study, the frequency of the minor allele 186R of APOBEC3Gwas found 17%among healthy individuals which was higher compared to that found among Europeans (5%)(38), Western Indians(22)and Europeansa from Brazil (4.16%)(39),Europeans Americans (38) and Caucasian population (3%)(50).On the other hand, it remains low compared to Pakistanians (42.95%)(40), Zimbabwean populations (40%)(51), African-American (37%)(38) and South African (30%)(42).Our minor allele G frequency was nearly comparable with Brazilians (11.63%) but it has not yet been identified among North Indians and Asian populations(52).

The allele frequency distribution of the second SNP rs35228531 has not been widely studied since his identification by Reddy et al. 2010. The mutated allele (T) was found low among the Moroccan population (9%) when compared to Burkina Faso (43.5%)(41) but still slightly similar to the south African females (7.3%)(42).

In our study, presence of both G and T minor alleles of APOBEC3G in Healthy group suggests that there are minor variations in Moroccan population that we should not overlook. Indeed, due to its geographical position, Morocco is considered as migratory crossroads for the Euro-African flows. Native Africans are recognized by high levels of genetic diversity within and between populations(53) and historical migration events across the continent would be at the origin of genetic admixture thus the relatively high allele frequencies of SNPs observed could be certainly explained by the existence of a little genetic mixing process between Moroccan and African populations.

The APOBEC3G polymorphism have been implicated in differential outcomes of HIV infection and disease progression(26)(38). In our study, through SNPs distribution evaluated we noticed that both G and T minor alleles were 12% and 7% respectively and were not significantly different from that found among Healthy controls (17% and 9%). Moreover, statistical analysis of data showed that there was no significant variation neither of APOBEC3G rs8177832 AA, AG and GG (70.59% *vs* 77.27%; 25% *vs* 21.59%; 4.41% *vs* 1.14%; $p>0.05$)nor rs35228531 CC, CT and TT (84.31% *vs* 87.50%; 13.73% *vs* 11.36%; 1.96% *vs* 1.14%;$p>0.05$) between the healthy controls and HIV-1 patients as shown in table 2 and the genotyping results analysis of two SNPs did not appear to be related to HIV-1 infection ($p>0.05$).The H186R mutation that has been reported in the literature to be associated with accelerated progression to AIDS in HIV-1 African Americans(38) and in South African cohort infected with HIV-1 subtype C (42) was at a low frequency (1.14%) in HIV-1 Moroccan patients. Furthermore, in Caucasus, the rs8177832 variant found no linked to HIV infection (50) and in a study from French cohort, it showed no significant association with disease progression(54). Similarly, Li *et al.*(55)reported the distribution of H186R among 483 HIV-1 positive and 493 HIV-1 negative men from China and no association found with HIV susceptibility. Moreover, in the Argentinian population, the activity of H186R reported having no impact on HIV disease progression (56) and recently in West India, Singh *et al.*(39), H186R was neither linked with risk of HIV acquisition nor its progression among 153 HIV-1 patients and 156 healthy individuals. However, theAPOBEC3G rs8177832 variant was associated with more rapid HIV-1 disease progression and CNS impairement in Children(27) and individuals with H186R AA genotypes in Pakistan were genetically predisposed to get HIV-1 infection(40). Additionally, in Burkina Faso, Compaore *et al.*(41) studying among 336 seropositive and 372 seronegative subjects, the H186R distribution and reported that the G allele displays a protective effect against HIV-1 infection among the homozygous GG carriers. In the same study, the minor allele T frequency for the SNP

rs35228531 was 32.8% in HIV-1 infected patients, it had also a protective profile and its carriage reduced greatly the risk of being infected with HIV-1(41).

Since its introduction in Morocco in 2000, the HAART was available and free of charge for all HIV patients. Therapeutic success/failure after antiretroviral drugs administration is related to several factors. It has been proposed that APOBEC3G by inducing hypermutations in HIV-1 may contribute to viral diversity which can be at the origin of antiretroviral escape leading to a viral failure (57–59). Since the genetic variations in APOBEC3G have been reported influencing HIV infection outcomes, it's still debated if they could interfere on the HAART responsiveness(59). Indeed, regarding the impact of both SNPs studied among HIV-1 Moroccan patients on HAART response, genotyping results showed that the distribution of mutated GG and TT genotypes is relatively similar in Controls and Non responders group while they were untraceable among Responders group. The statistical analysis revealed that both of SNPs seem to be not related to the HAART response ($p>0.05$).R. Da Silva *et al*, 2017 evaluated the distribution of SNPs in APOBEC3G (rs3736685, rs2294367) among 264 HIV-1 infected subjects and 256 unexposed-uninfected individuals from Northeast Brazil and looked for a possible association with therapeutic success/failure of the antiretroviral treatment. They found no association between APOBEC3G polymorphism with antiretroviral therapy virological failure except rs2294367 GC genotype who was associated with delayed VL suppression during treatment (59). On the other hand, Neogi *et al*, 2013 showed that APOBEC3G-hypermutation was significantly associated with the use of treatment in Indian patients who failed HAART(57).

Despite the discordant outcomes reported in several previous studies, the polymorphism of the APOBEC3G gene seems influencing the HIV infection parameters (TCD4 and plasma VL) as well as the profiles of progression to AIDS stage of disease in different populations. The variability of results obtained throughout the world about the SNP polymorphism associations with HIV disease progression can be owed to the design of the studies, the genetic background of the studied population, the anthropomorphic characteristics (Age, Sex) of populations, the root of HIV transmission, the duration of the infection and the duration of the treatment.

Conclusion

To our knowledge, this is the first study held in Morocco investigating the polymorphism of APOBEC3G among Moroccan population and its impact on the antiretroviral therapy response among HIV-1 patients. The lack of associations of APOBEC3G SNPs polymorphism studied with response to HAART among HIV-1 positive patients cannot rule out the association of these SNPs with progression to AIDS and HAART response. Being aware that our study has limitations such as the small sample size and the single use of two APOBEC3G SNPs during allelic discrimination but it provides epidemiological evidence for the presence of the APOBEC3G polymorphism in Moroccan population. Thus, further investigations with larger sample size are under process to assess the association of such a polymorphism with HIV-1 infection susceptibility and disease progression taking into account the patients who are under HAART.

Competing interest

The authors declare no competing interest.

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