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Case Report

HLA-B*57:01 Allele Prevalence in People Living with HIV and the Effect of Allele Testing on the Frequency of Abacavir-Associated Hypersensitivity Reaction in HLA-B*57:01-Negative Subjects, Single Centre Experience, Saudi Arabia

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Abstract

Background: The presence of HLA-B*57:01 Allele is associated with a hypersensitivity reaction (HSR) to Abacavir (ABC). Several studies reported the relationship between this specific Human Leukocyte Antigen (HLA) and ABC HSR in various populations [1-4]. The study aimed to assess the prevalence of the HLA-B*57:01 Allele in people living with HIV in the Saudi population and the impact of allele testing on ABC hypersensitivity reaction. **Methods:** We conducted a retrospective cohort study among people living with HIV registered at East Jeddah Hospital, Saudi Arabia. Patients' blood samples were screened for HLA-B*5701 using the SybrGreen real-time PCR-melting method to identify the allele. **Results:** A total of 1545 HIV-infected patients were tested, of which 79.4% were male. All patients were Saudi, with a mean age of 37 years. The prevalence of HLA-B*5701 among HIV-I-infected Saudi patients was 1.7%. The prevalence among Arabs (92.6%) was higher than non-Arab (7.4%). Among the 378 patients given ABC, two individuals (0.5%) experienced ABC HSR. **Conclusion:** The prevalence of HLA-B*5701 among HIV-I-infected Saudi patients was lower than that in other Middle Eastern populations as well as Caucasians. Screening for HLA-B*5701 before initiating an ABC-containing antiretroviral therapy regimen may reduce the risk of HSR.

Keywords: HLA-B*57:01; Prevalence; People living with HIV; PLWHIV; Abacavir; ABC; Hypersensitivity reaction; HSR; Abacavir hypersensitivity reaction; ABC-HSR; Saudi Arabia

Introduction

Abacavir (ABC) is a nucleoside reverse-transcriptase inhibitor (NRTI) that has activity against the Human Immunodeficiency Virus (HIV).7 The USFDA approved its use in 1998. Studies showed that ABC is effective against HIV [8-11]. That, combined with its safety profile, fewer drug interactions, and favorable long-term toxicity profile, led to considering its use by all leading international guidelines as first-line therapy for HIV naïve patients [12,13].

Although usually well tolerated, some patients may experience an immunologically mediated, potentially life-threatening hypersensitivity reaction (HSR) associated with the class I MHC allele HLA-B * 57:01, which develops within the initial six weeks of therapy with Abacavir [5,6].

ABC-HSR is a multi-organ clinical syndrome.5,6 This reaction develops in 5% to 8% of patients studied in clinical trials when using clinical criteria for diagnosis, and it is the primary reason for the early discontinuation of ABC [3-5]. Symptoms of the hypersensitivity reaction are nonspecific, including combinations of fever, rash, constitutional, gastrointestinal, and respiratory symptoms that can become more severe with continued treatment [5,6].

Therefore, immediate and permanent discontinuation of ABC is mandated. Discontinuation results in a rapid reversal of symptoms. Rechallenging with ABC is contraindicated since it can result in a more severe, rapid, and life-threatening reaction [5,6].

A combination of altered drug metabolism and immune dysfunction, which is poorly understood, causes such a reaction [6].

Prospective screening of patients for HLA-B * 57:01 before commencing ABC therapy reduces the incidence of ABC-HSR significantly [1,2,5]. Therefore, international guidelines recommend screening patients before initiating an ABC-containing regimen [12,13].

The HLA-B*5701 allele is a genetic marker linked to hypersensitivity reactions to ABC [1-4]. The prevalence of the HLA-B*5701 allele has been widely studied in different populations.

The prevalence of HLA-B*5701 varies among different groups. The allele is present in approximately 5-8% of Caucasian populations, 1% of Asian populations, and less than 1% of African American populations. Individuals of African ancestry are less likely to experience ABC hypersensitivity compared to other ethnicities [7].

Our study is the first to estimate the prevalence of HLA-B * 57:01 among HIV-infected patients in Saudi Arabia.

Methodology

Study design

We conducted a retrospective cohort study from a single centre from December 2015 to September 2022.

Study population

We enroll PLWHIV aged 14 years or more, following at East Jeddah Hospital HIV Centre of Excellence. They were screened for HLA-B*5701 allele using SybrGreen real-time PCR-melting assay on blood samples.

Data collection

Epidemiological, demographic, and laboratory data were collected using electronic medical records.

Statistical analysis:

Data were entered into a Microsoft Excel sheet and then revised. The statistical analysis used IBM SPSS, version 26 (IBM Corporation, New York, USA). Data were statistically described frequencies, and valid percentages were used for categorical variables. For continuous variables, a normality test was performed. We reported variables that are continuous and normally distributed as mean and standard deviation (SD). At the same time, reporting variables that are continuous and non-normally distributed as median and interquartile range (IQR) plus minimum and maximum. We used Chi-square or Fisher's Exact test for categorical variables between the subgroups. Statistical significance was determined by considering p-values below 0.05.

Ethical considerations

We obtained approval through the research and ethical committee from the Jeddah Ministry of Health Institutional Review Board Ethics Committee. We maintained confidentiality through all research steps.

Results

A total of 1545 PLWHIV, of which 79.4% were male, were included in the study. All patients were Saudi, with a mean age of 37 years (SD?). Most of them were Arabs (94%), while 6% were of non-Arab ethnicities (Table 1).

The prevalence of the HLA-B*57:01 carriers was 1.7%, with a 95% CI of [1.09-2.40], among HIV-I-infected patients, as shown in Figure 1 and Table 2, with a higher prevalence among Arabs.

Three hundred seventy-eight (percentage?) patients who tested negative for the allele received an ABC-containing regimen. Two of them developed an HSR. With an incidence of 0.5% and a CI-95% of (-0.21 – 1.27).

Table 3 illustrates the HSR after the administration of the ABC-containing regimen.

Age (Years) (N=1545)	**Median (Range)**	36 (14-84)	
Parameters	**Category**	**Number**	**Percentage (%)**
Gender	Male	1226	79.4
	Female	319	20.6
Nationality	Saudi	1545	100
Race	Arab	1453	94.0
	Non-Arab	92	6.0
HLA	Negative	1518	98.3
	Positive	27	1.7
HIV1/HIV2	HIV1	1545	100
	HIV2	0	0
ART	Not ABC	1167	75.5
	ABC containing regimen	378	24.5
CD4 cell count (cells/mm^3) (N=1545)	<200	253	16.3
	200-499	570	36.9
	≥ 500	722	46.8
Viral load (copies/mL) (N=1545)	<40	698	45.2
	40-1000	150	9.7
	1001-10,000	142	9.2
	10,001-100,000	314	20.3
	>100,000	241	15.6
HLA: Human Leukocyte Antigen; HIV1/HIV2: Human Immunodeficiency Virus ½; ART: Anti Retroviral Therapy.			

Table 1: Demographic and laboratory characteristics of the patients (N=1545).

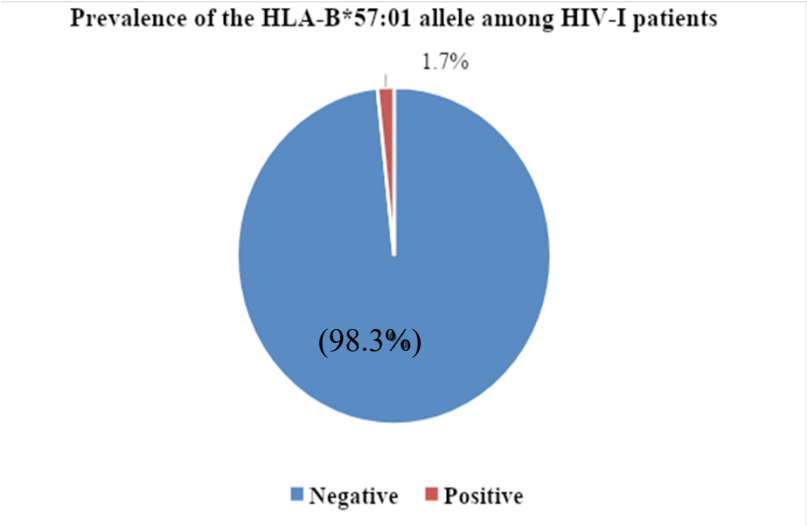

Figure 1: The prevalence of the HLA-B*57:01 allele among HIV-I patients.

Factors		HLA	
Categories		**Negative Number (%)**	**Positive Number (%)**
Age (Years)	≤35	733 (48.3)	16 (59.3)
	>35	785 (51.7)	11 (40.7)
Gender	Male	1207 (79.5)	19 (70.4)
	Female	311 (20.5)	8 (29.6)
Race	Arab	1428 (94.1)	25 (92.6)
	Non-Arab	90 (5.9)	2 (7.4)
HLA: Human Leucocyte Antigen.			

Table 2: HLA distribution among patients according to demographic characteristics.

ABC-c	**No HSR N (%)**	**HSR N (%)**
N = 378 patients	376 (99.5%)	2 (0.5%)
HSR among HLA-negative patients		
95% CI of HSR among negative HLA patients	0.5 [-0.21-1.27]	
N: number; (%): percentage; CI: confidence interval.		

Table 3: Occurrence of hypersensitivity reaction (HSR) in HLA-B 57:01 negative individuals receiving Abacavir-containing regimen (ABC-c).

Discussion

The HLA-B*57:01 allele prevalence in our population was 1.7%. This allele prevalence has been widely studied across various geographic regions, races, and ethnicities. In a study among Northeastern Brazilian HIV-infected patients, the frequency of HLA-B*5701 carriers was 3.1% [16]. Similarly, the prevalence reached 3.4% in a United States-based study [17].

In Europe, the overall estimated prevalence of the allele is higher than in the Americas, reaching 4.98%, which varies by region and country [18]. The frequency is lowest in Romania, at 1.4%, and highest in the Republic of Ireland, at 11.2%. Other countries with significant frequency include southern France at 6.9%, Northern Ireland at 7.5%, the UK at 4.55%, and the European part of Russia at 4.04% [1,13,18]. Additionally, HLA-B*57:01 allele prevalence among HIV-infected patients in Serbia was 8% [21].

In another study from Iran, the prevalence of the HLA-B*5701 allele among the Iranian patient population was 3.0% [15], comparable to the numbers from the Americas.

However, in the Eastern parts of Asia, the prevalence is much lower, particularly in Chinese Asians compared to non-Chinese Asians. A study from Hong Kong revealed that the prevalence of the HLA-B*57:01 allele was 0.5% among Han Chinese and 1% among non-Chinese Asians [23]. H. Zhang et al. confirmed the low prevalence of the allele among Chinese at 0.86% [24]. Nonetheless, in a study on HIV-infected children in Thailand and Cambodia, the prevalence of the HLA-B*57:01 allele was much higher than that of the Chinese. The allele prevalence was 3.4% in Cambodian children and 4.9% in Thai children [25].

The lowest recorded prevalence of the allele was in Africa, with a 0.1% prevalence across Central and Western African countries [26].

When stratifying for ethnicity, our study found that the HLA allele carrier was more prevalent among Arab patients (92.6%) than non-Arab patients (7.4%). The lower prevalence among non-Arabs could be attributed to their lower representation in our cohort. A study in the US reported that HLA-B*57:01 positivity was more prevalent in white individuals (85%) than African American individuals (15%) [17]. Another study in the UK reported a prevalence of 7.93% among Caucasianubjects and 0.26% among (see the previous comment) subjects [19]. Additionally, a Colombia study reported that the allele's prevalence was 4% for white individuals, 2.6% for individuals of mixed races (primarily mestizo), and 1.9% for Afro-Colombians [22].

Before initiating therapy containing ABC, international guidelines recommend testing for the existence of the HLA-B*57:01 allele to identify patients at risk of developing HSR [12,13]. White and Black HIV-positive US patients hypersensitive to ABC have been linked to the presence of the HLA-B*5701 allele [27].

In our population, among HLA-negative patients, the rate of HSR with ABC administration was 0.5%. Similarly, a study reported that testing for HLA-B*57:01 allele and enrolling exclusively HLA-B*57:01-negative subjects to receive ABC resulted in a suspected ABC HSR incidence of 0.5% [17]. There are very few reports in the literature of suspected ABC HSR in patients who test negative for HLA-B*57:01. The rare occurrence of ABC HSR in allele-negative individuals reflects the possibility of other immunologic risk factors not yet identified.

The diagnosis of ABC HSR is based on clinical symptoms [5,6]. It is important to note that a possible diagnosis can still be made even if other alternative diagnoses are plausible. Suppose the only symptom is a rash without other systemic signs including fever, respiratory or gastrointestinal symptoms, malaise, or myalgias. In that case, the patient is unlikely to have an underlying ABC HSR. However, if a patient develops a rash after starting ABC, monitoring them closely for the onset of systemic symptoms is recommended. On the other hand, because symptoms are non-specific and can involve different organ systems, ABC HSR may be missed and patients misdiagnosed, which would lead to severe adverse reactions and possibly death [6]. Suspected ABC HSR requires immediate discontinuation of ABC and close patient monitoring [5,6].

However, conducting more comprehensive studies would provide a better understanding of the prevalence of HLA-B*57:01 in Saudi Arabia.

Conclusion

The prevalence of HLA-B*5701 among HIV-1-infected patients in Saudi Arabia was low. Additionally, suspected ABC HSR is uncommon in individuals who test negative for HLA-B*57:01.

Although the prevalence of HLA-B*57:01 in our population is low, it is still cost-effective to check for the allele before starting an ABC-containing regimen to avoid the high morbidity associated with ABC HSR, which, in addition to its severe adverse effects on patients' health, would increase the cost of management.

Declarations

Author contributions: RA conceptualized and designed the study and drafted the manuscript. RA and AN carried out the statistical analysis. BM contributed to the study design. RA, AN, BM, SA, SK, AA, OA, AA, NA provided patients, contributed to their interpretation of data and critically revised the manuscript. All authors reviewed and approved the final manuscript.

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Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate: The study protocol was approved by the institutional review board of Ministry of health, Jeddah, Saudi Arabia. We confirm that all methods were carried out in accordance with relevant guidelines and regulations of Helsinki declaration. The informed con- sent was waived by the Research Ethics Committee of Ministry of health

Competing interests: The authors declare that they have no competing interests.

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