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Original Article

Evaluation of HLA-B*57:01 and its effect on antiretroviral therapy in patients with human immunodeficiency virus infection: Experience of a University Hospital

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Abstract

Aim: Before the decision to start abacavir (ABC), which is a member of the antiretroviral therapy (ART) combinations, the presence of the HLA-B*57:01 allele gene should be investigated in case of hypersensitivity to the drug.
In recent years, many clinics tend to conduct "treat now" policy for HIV therapy. We aimed to evaluate HLA-B*57:01 test results and its effect on the initiation time of ART, combination and changing of ART.

Materials and Methods: HLA-B*57:01 screening test was evaluated retrospectively in the HIV-infected patients admitted to Inonu University Faculty of Medicine Department of Infectious Diseases and Clinical Microbiology between January 2019 and December 2019.
Moreover, the time frame of HLA-B*57:01 tests were evaluated along with the HIV confirmation test completion time. It was evaluated whether there was any effect on the start of treatment and treatment change.

Results: Of the 47 HIV-positive patients 44 (93.6%) were male and 3 (6.4%) were female whose HLA-B*57:01 allele was screened. The mean age ± SD of these 47 patients was 37.7 ± 13.5 years. HLA-B*57:01 gene positivity was not detected in any of our cases.
After HLA-B*57:01 test detection, ten (21%) of these patients were treated with ABC sulfate plus dolutegravir sodium plus lamivudine. Five of the patients were naive patients, while the other five patients were treatment experienced.
HLA-B*57: 01 allele test completion time of the patients (mean ± SD) was 4.02 ± 2.35 days. HLA-B*57:01 completion time did not differ statistically in patients with and without treatment change (p=0.243).

Conclusion: HIV infected individuals should be started to treat with ART soon after their diagnosis. To detect the HLA-B*57:01 allele in genomic DNA is important in this period. The fact that this procedure can be performed in centers following HIV-infected patients will positively affect the process of starting treatment.

Keywords: Effect on antiretroviral therapy; HIV; HLA-B*57:01; prevalance

INTRODUCTION

Currently, morbidity and mortality associated with HIV infection are decreasing. At this point, it is important to initiate ART to all HIV-infected patients, including asymptomatic individuals, regardless of their CD4 count (1). In recent years, many clinics tend to conduct "treat now" policy, so they start the ART on the first encounter with the patient. By these strategies, the end of June 2019, 24.5 million (21.6 million - 25.5 million) people in the world are receiving antiretroviral treatment. New HIV infections have decreased by 40% since the peak observed in 1997 (2).

For the ART combinations, there are four classes of antiretroviral drugs typically used in early regimens. These are nucleoside (and nucleotide) reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and integrase strand transfer inhibitors (INSTIs) (3). ABC-lamivudine is one of the first-line NRTI combinations. However, drug hypersensitivity to ABC related to immunogenetically based susceptibility has been demonstrated (4). Therefore, HLA-B*57:01 should be investigated before treatment in patients with ABC combination regimens for ART treatment.

On the other hand, it is noteworthy that this gene allele is associated with the slow progression of HIV infection. HLA-B*5701 is reported to be effective in achieving and sustaining HIV viral load suppression (5). So, screening of HLA-B*57:01 has become interesting and important by studies in recent years. However, there are few reported data about HLA-B*57:01 allele prevalence in

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our country. We evaluated the results of the HLA-B*57:01 allele retrospectively in order to evaluate its effect on the initiation time of ART, combination and changing of ART.

MATERIALS and METHODS

HLA-B*57:01 screening tests performed in HIV infected patients, who visited the Inonu University Medical Faculty Infectious Diseases Clinic in Turkey, between January 2019 and December 2019 were evaluated, retrospectively. In these patients, demographic data, diagnosis times, verification test time, time to start treatment, those with treatment changes, and causes with treatment changes were evaluated. The data obtained from the hospital automation system were recorded in SPSS program. The statistical analysis was performed with IBM SPSS statistics version 25.0 for Windows (SPSS, Inc., Chicago, IL).

DNA isolation was performed in 200 microliters of automatic DNA isolation device from whole blood samples taken from the patients with 1-2 ml EDTA tube. Isolated patient DNAs were amplified by SSO-PCR, one of the molecular tissue typing methods, and then reverse hybridization was performed and analyzed by Lumineks device using SSO low resolution kit. PCR was performed on HLA-B*57:01 allele positive patients using SSP HLA-B*57:01 high resolution kit and SSP-PCR kit. After PCR, agarose gel electrophoresis was performed to determine whether the patient had the HLA-B*57:01 allele by looking at the HLA-B57 subgroup.

The present study was approved by the Inonu University Medical Faculty non-interventional Ethical Committee. (Approval no: 2020 /177).

RESULTS

Forty-seven HIV-positive cases with HLA-B*57:01 allele screened in our clinic were evaluated. Of the patients, 44 (93.6%) were male and 3 (6.4%) were female. The mean age ± SD of these 47 patients was 37.7 ± 13.5 years.

Table 1. HLA-B*57:01 conclusion and time to start treatment in patients with or without treatment changes

	Treatment Change		Day	p	z value
HLA-B*57: 01 completion time	Yes	Mean	5.00	0.243	-1.168
		Median	4.50		
		Minimum	2		
		Maximum	9		
	No	Mean	3.81		
		Median	4.00		
		Minimum	1		
		Maximum	11		

Gene positivity with HLA-B*57:01 was not detected in any of our cases. Ten (21%) of these patients were treated with ABC sulfate plus dolutegravir sodium plus lamivudine. Five of the patients were naive patients, while the other five patients were treatment experienced. Treatment was switched to ABC sulfate plus dolutegravir sodium plus lamivudine in five (10.6%) of the patients. The causes of the drug changes were drug side effects in two patients, insufficient drug efficacy in one patient, not able to access the drug in one patient, and physician decision in one patient.

HLA-B*57:01 allele test completion time of the patients (mean± SD) was 4.02 ± 2.35 days. HLA-B*57:01 completion time did not differ statistically in patients with and without treatment change (p=0.243) (Table 1).

DISCUSSION

Studies have reported that the incidence of the HLA-B*57:01 allele is lower in HIV-infected patients compared to the general population. It has been reported that the disease progresses more slowly and even stops progression, especially in people with allele positivity. The absence of HLA-B*57:01 allele in any of our patients may be due to the small number of patients. However, it can be attributed to the low prevalence in this patient group.

On the other hand, the cost-effectiveness of testing was investigated in several studies (6,7). The studies emphasized the need for further studies, but it was concluded that this test should be performed before ART containing ABC. In a study from the United Kingdom, the HLA-B*57:01 allele was examined over the last 10 years, and the use of ABC-containing combinations in HIV treatment revealed a significant reduction in hypersensitivity reactions. However, the treatment decision is said to be of the physician because of the potential for serious and even fatal reactions if it develops even if there is an allele negative (8).

It was reported that hypersensitivity reaction may develop with some differences due to the change in the prevalence of HLA-B*57:01 depending on societies and ethnicity (9,10). In a study of the HIV-positive patients from Northern Poland, the incidence was reported to be 5.8% in the Caucasus (11). In another prevalence study from Brazil, HLA-B*57:01 positivity was 19.9% in HIV infected patients (12).

However, there are few data in the literature about HLA-B*57:01 prevalence in our country. In the prevalence study of Deveci et al., HLA-B*57:01 allele positivity was reported in three of the 100 HIV-infected patients (13). In another study, Inan et al. have reported the results of HLA-B*57:01 allele ratios in HIV infected patients, respectively 1.1 to 4.8 % from two regions of Turkey (14).

On the other hand, HLA-B*57:01 allele-positive patients treated with ABC-free ART have been reported to have an undetectable viral load and less likely to experience a recovery of viral load (15). Therefore, allele positivity seems to be a hindrance to the use of ABC-containing regimens, but it seems to be more fortunate for patients in the treatment follow-up. The lack of gene positivity in our patients seems to be a convenience for starting ART

containing ABC. But this situation may be a disadvantage in the future process. Moreover, HLA-B*57:01 allele positivity is reported to be higher in individuals from the non-HIV-infected population. A Chilean reported study compared 300 blood donors who were not infected and 492 HIV-infected people from the community. HLA-B*57:01 allele positivity has been reported in 3.7% of the general population and 2.2% in the HIV-infected group (16). In the following studies, the evaluation of the HLA-B*57:01 allele in both HIV-infected patients and non-infected individuals in the community will provide more detailed information. However, the method should be evaluated in terms of cost-effectiveness.

Causes of change in antiretroviral therapy; Virological failure or treatment failure, drug toxicity is reported (17). On the other hand, the desire to switch to a more effective treatment regimen is shown as a reason for the change (18). We considered the treatment change in five (%10.6) patients. The factors that contributed to this were non-compliance with the previous treatment regimen, drug side effect (osteoporosis, thought to be due to the previous regimen in one patient, nausea in another patient) and the desire to move to a more effective treatment regimen. If the regimen containing ABC is considered during treatment change, it is important that the HLA-B*57:01 allele test is completed quickly. HLA-B*57:01 allele evaluation period in our hospital (mean ± SD) was 4.02±2.35 days. The time to request HIV verification test and start treatment (mean±SD) was 23.8 ±31.8 days. Looking at HLA-B*57:01, with or without treatment changes, did not cause any disadvantage at the start of treatment. However, we have the advantage to study HLA-B*57:01 screening test for one year. Previously, HLA-B*57:01 had been studied in the reference laboratory of the Public Health Institution, like most of centers.

HLA-B*57:01 allele, which has recently been investigated in our center, is important not only for the initiation of ABC-containing ART regimens, but also for the indication that the disease response to treatment may be good, so it is important to know it in the follow-up of HIV-infected patients.

CONCLUSION

Our study enrolled retrospectively, so we did not determine the number of patients. This is the limitation of study. It should be planned comprehensive studies by increasing the number of cases. On the other hand, it has been reported that waiting for HLA-B*57:01 results, studied in local immunogenotyping laboratory, did not cause a delay in treatment imitation. Hence, it is an informative study in terms of showing this point of view.

Conflict of interest : The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The present study was approved by The Inonu University Medical Faculty non-interventional Ethical Committee. (Approval no: 2020 /177).

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