HLA involvement in nevirapine-induced dermatological reaction in antiretroviral-treated HIV-1 patients

Sir,

Nevirapine is a non-nucleoside reverse transcriptase inhibitor used commonly in antiretroviral (ARV) treatment in India. Several studies have suggested and documented that HLA antigen plays a major role in this phenomenon. However, to our knowledge limited literature is available from India. Therefore, we investigated the role of HLA on nevirapine-induced rash among the antiretroviral treated HIV-1-positive infected individuals from India.

As per National AIDS Control Organization (NACO) under Ministry of Health and Family Welfare, the first regimen is given to patients in a combination of three drugs as follows: Stavudine+Lamivudine+Nevirapine (SLN); Stavudine +Lamivudine+Efavirenz (SLE); Zidovudine+Lamivudine+ Nevirapine (ZLN); and Zidovudine +Lamivudine+Efavirenz (ZLE). Currently, there are 26 antiretroviral (ARV) agents' divided into four classes: Reverse transcriptase inhibitors, protease inhibitors, entry inhibitors, and integrase inhibitors.[1]

Nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) with high antiretroviral efficacy.[1] NVP-based HAART regimens are widely used in resource-limited countries like India. Nevirapine is associated with hypersensitivity reactions (HSR) like fever, hepatitis, skin rash[1] with clinical complications. By a recent meta-analysis, approximately 50% of these were associated with rash. Several features of nevirapine hypersensitivity suggest that genetic factors may play an important role, and that nevirapine-specific antigens may trigger immunological response that is dependent on the CD4+T lymphocyte and CD8+T lymphocyte-related response of the patient.[2] Most nevirapine-associated hypersensitivity occurs within 14 to 21 days of drug administered and is more rapid and severe if re-challenged.[2] Therefore, we investigated the role of HLA on nevirapine-induced rash among the antiretroviral-treated HIV-1-infected individuals from India.

This case controlled study included a total of 40 HIV-1-infected patients who developed nevirapine-induced specific skin rash after treatment, and 40 HIV-1-infected patients who tolerated the drug were selected and compared The institutional Ethics committee's approval was obtained for the study. A clinical Performa, filled up for the patients with consent. For HLA from each patient 5 ml of peripheral blood in BD Sodium Heparin Vacutainer was collected by vein puncture. The HLA typing was done using specific HLA antisera by a two-stage microlymphocytotoxicity assay. The statistical analysis for the antigen gene frequency was carried out using the Chi-square test with Yates correction. The 95% confidence intervals were calculated for etiological fraction and preventive fraction. P values<0.05 were considered significant.

Clinically, among the nevirapine-induced rash cases we observed that all are positive for HIV-1. Most of the patients were females (52.5%) than males (47.5%), among nevirapine-induced skin rash-positive patients, 10% presented with Steven-Johnson syndrome, 7.5% had hepatitis, all patients had skin rash, while some had fever and pruritus. The distribution of HLA antigens among the nevirapine-induced hypersensitivity reactive HIV-1-positive patients is presented [Table 1]. Our results revealed a highly significant association of HLA B35 (OR: 3.378; P value 0.0032) with nevirapine-induced skin rash. Further, a significant HLA B7 (OR: 0.292; P value 0.0085); HLA B8 (OR: 0.272; P value 0.0825) and HLA B15 (OR: 0.272; P value 0.0825) were also found to be decreased significantly among the nevirapine-hypersensitive patients.

NVP-associated rash has been reported to be as high as 48% after the treatment with this inhibitor[6]. The rash associated with nevirapine is a distinct clinical and pathophysiological entity. Skin rash is the most common adverse drug reaction associated with NVP, and hypersensitivity reaction to NVP is

Table 1: Distribution of HLA antigens among the nevirapine-induced hypersensitivity in HIV-1-positive patients

HLA	NVP hypersensitivity	NVP tolerant	OR	EF	PF	95% CI	*P* value
	N = 40	N = 40					
	AF%	AF%					
B5	6.25	3.75	1.71				
B7	10.00	27.50	0.29		0.19	0.121-0.706	0.008
B8	3.75	12.50	0.27		0.08	0.072-1.032	0.082
B15	3.75	12.50	0.27		0.08	0.072-1.032	0.082
B17	17.50	11.25	1.70				
B35	35.00	13.75	3.38	0.35		1.541-7.405	0.003
B37	1.25	0.00	2.04				
B40	17.50	15.00	1.20				
B44	2.50	3.75	1.35				

AF-Allele frequency; OR-Odds ratio; EF-Etiological fraction; PF-Preventive fraction

rapid and severe when drug administration is suspended and re-challenged. NVP induced rash has been reported in 4.3-36% of adults[3] with prevalence for Thai HIV patients ranging from 6% to -21%.[4] In Sardinian population were HLA B14 and Cw8 was associated 26% developed NVP induced rash, in our study from India we found that NVP-induced rash was 2.14%, thus, reflecting the comparatively a high incidence of drug-related rash in Asians.[5] Recent studies have shown that hypersensitivity reactions to antiretroviral drugs are HLA-associated. HIV-infected Thai patients have a significant HLA Cw*04 allele association with nevirapine induced rash cases.[4] HLA B*3505 allele has been identified as a strong predictor for nevirapine-induced skin adverse reactions in Thai HIV patients.[6] This study shows that HLA B35 is significantly associated among the nevirapine-induced skin rash HIV-1 ARV-treated patients of India. Further, the molecular HLA characterization of these alleles will enlighten us on the immunological basis of the antiretroviral drug reactions.

Shankarkumar Umapathy, A. Pawar, S. Bajpai[1], A. R. Pazare[1], K. Ghosh

National Institute of Immunohaematology, 13th Floor, [1]Department of Medicine, ART Centre, KEM Hospital, Parel, Mumbai - 400 012, India

Address for correspondence:
Shankarkumar Umapathy, National Institute of Immunohaemtology, 13th Floor, KEM Hospital, Parel, Mumbai - 400 012, Maharashtra, India. E-mail: shankar2kumar@rediffmail.com

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