Neurology Asia 2017; 22(2) : 113 – 116

HLA-B*1502 and carbamazepine induced Stevens-Johnson syndrome/toxic epidermal necrolysis in Indonesia

[1,2]Herlyani Khosama, [1,3]Astri Budikayanti, [4]Amy Hui Ping Khor, [5]Kheng Seang Lim, [4]Ching-Ching Ng, [6]Indra G Mansyur, [7,8]Alida Harahap, [3]Teguh AR Ranakusuma, [5]Chong Tin Tan

[1]Biomedical Sciences, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia; [2]Department of Neurology, Faculty of Medicine University of Sam Ratulangi/Prof RD Kandou Hospital, Manado, Indonesia; [3]Department of Neurology, Faculty of Medicine, University of Indonesia/RSUPN Cipto Mangunkusumo Hospital, Jakarta, Indonesia; [4]Genetics and Molecular Biology, Institute of Biological Sciences, Faculty of Science, University of Malaya, Kuala Lumpur, Malaysia; [5]Division of Neurology, Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [6]Department of Medical Biology, Faculty of Medicine, University of Indonesia;[7] Eijkman Institute, Indonesia; [8]Departement of Clinical Pathology, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia.

Abstract

Background & Objective: Association between HLA-B*1502 and carbamazepine-induced Steven-Johnson syndrome/toxic epidermal necrolysis (CBZ-SJS/TEN) was reported in many Southeast Asian populations but not in Indonesian. The purpose of this study was to evaluate the association between HLA-B*1502 andCBZ-SJS/TEN in an Indonesian population. *Methods*: Patients with history of CBZ-SJS/TEN are recruited as cases and those who tolerated CBZ as controls. HLA-B typing was performed. *Results*: We recruited 14 cases with CBZ-SJS/TEN and 53 controls. Positive HLA-B*1502 was found in 8 (57.1%) cases and 14 (26.4%) controls (OR 3.7, 95% CI 1.09-12.61, p=0.035). *Conclusion*: HLA-B*1502 is associated with CBZ-SJS/TEN patients in Indonesian.

Keywords: Carbamazepine induced Steven-Johnson syndrome/toxic epidermal necrolysis, hypersensitivity, HLA-B*1502, Indonesia.

INTRODUCTION

Carbamazepine (CBZ) is widely used in Indonesia for focal epilepsy, neuropathic pain and bipolar disorders. However, CBZ is a common drug causing Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), a life threatening drug hypersensitivity. The mortality rate of SJS is 1-5% and 25-35% for TEN. Up to 50% of patients with TEN who survive will have life-long sequelae.[1] An Indonesian study reported a higher mortality rate among those with SJS and TEN (7.69% and 36.36%, respectively).[2]

According to the European SCAR registry (EuroScar), the two commonest drugs causing severe cutaneous adverse reaction (SCAR), such as SJS and TEN, are CBZ and allopurinol.[3] Incidence of SJS/TEN caused by CBZ and phenytoin in Southeast Asia was reported to be 26%, significantly higher than the Europe population (12%).[4]

In 2004, Chung *et al*.[5] reported a strong association between CBZ-induced SJS/TEN (CBZ-SJS/TEN) in Taiwan. This association between HLA-B*1502 and CBZ-SJS/TEN was also reported in other Asian countries such as China[6,7], Hong Kong[8], Thailand[9,10], and Malaysia.[11,12] However, the association between HLA-B*1502 and CBZ-SJS/TEN in Indonesian population is not available.

Indonesia is the most populated country in Southeast Asia, and third in Asia, with 260 million population. Although it is ethnically very diverse, with around 300 distinct ethnic groups, most Indonesians are descended from Austronesian-speaking peoples with the largest ethnic group, Javanese, comprising 42% of the population. In

Address correspondence to: Herlyani Khosama, Department of Neurology, University of Sam Ratulangi/Prof RD Kandou Hospital Manado, Indonesia. Tel (O): 62-431-834323, Email: h.khosama@gmail.com

this study, we aimed to determine the association between HLA-B*1502 and CBZ-SJS/TEN in Indonesian population.

METHODS

Subject

Patients with CBZ-SJS/TEN were recruited from the Hasan Sadikin Hospital in Bandung (2 cases), Prof RD Kandou Hospital in Manado (2 cases) and Cipto Mangunkusumo Hospital in Jakarta (10 cases). This study was approved by the Ethics Committee of the University of Indonesia (No: 198/UN2.F1/ETIK/2014). Written informed consent was obtained prior to participation. The diagnosis of SJS, SJS-TEN overlap and TEN was made by dermatologists based on diagnostic criteria by Roujeau *et al*. and severe cutaneous adverse reactions (SCAR) study classification by Batsuji-Garin *et al*.[13,14] The cases with either SJS, SJS-TEN overlap or TEN were grouped together as SJS/TEN. The causal relationship between CBZ and SJS/TEN was determined based on ALDEN score of 6 and above. CBZ tolerant controls were patients on CBZ for at least 3 months without hypersensitivity reactions. All controls were recruited from Cipto Mangunkusumo Hospital, Jakarta. A total of 6 ml of venous blood sample was obtained from each subject for HLA typing.

Genotyping

Genomic deoxyribonucleic acid was isolated from peripheral blood, using qiagen midi kit. HLA-B typing using sequence specific oligonucleotide (SSO) method, with LABType SSO DNA (One Lambda, USA). The DNA amplification, hybridization and labelling were done according to instruction from the kit. The alleles were read using Luminex 200 and were analyzed using HLA fusion 2.0 software.

Association between HLA-B*1502 and CBZ-SJS/TEN was tested using Fisher's exact test, with $p<0.05$ considered as significant.

RESULTS

We recruited 14 cases of CBZ-SJS/TEN and 53 tolerant controls. Two cases were diagnosed as TEN, one as SJS/TEN overlap, and the rest as SJS. More than half of the subjects (56.7%) were male. The median age was 33.5 years old (11-76 years old). Most subjects were Javanese (29.9%), followed by 22.4% Sundanese, 11.9% Padangnese, 6.0% Bataknese, 3.8% Chinese. Others were of Acehnese, Ambonese, Minahasanese, Maduranese, Torajanese, Dayaknese and Rajangnese origin.

*Association between HLA-B*1502 and CBZ-SJS/TEN*

Eight out of 14 cases (57.1%) had HLA-B*1502 alleles, as compared to 26.4% (14 out of 53) in control group (OR 3.71; 95% CI, 1.09-12.61, p= 0.035). The sensitivity of HLA-B*1502 testing in related to CBZ-SJS/TEN was 57.14% and the specificity was 73.58%.

Ethnic subgroup analysis was performed. In Javanese subgroup, 3 out of 4 (75.0%) cases were HLA-B*1502 positive as compared to 4/13 (30.8%) in control group (OR 9.75, 95% CI, 0.78-121.84, p=0.08). In Sundanese subgroup, 2/4 cases were HLA-B*1502 positive, as compared to 2/11 (18.2%) in control group (OR 4.5, 95% CI 0.37-54.16, p=0.24). In Padangnese group, the only case (100%) was HLA-B*1502 positive, as compared to 2/7 (28.6%) in control group (OR 6.4, 95% CI 0.19-225.81, p=0.29).

Association between other HLA-B alleles and CBZ-SJS/TEN

The other HLA-B alleles frequency of both cases and controls is shown in Table 1. The commonest HLA-B alleles besides HLA-B*1502 were HLA-B*1513 and HLA-B*3505. None of these HLA-B alleles showed significant association with CBZ-SJS/TEN.

DISCUSSION

This study showed that HLA-B*1502 is associated with CBZ-SJS/TEN in Indonesian population. However, HLA-B*1502 was only found in 57% of the cases, lower than those reported in other Southeast Asian countries, such as Malaysia (75%)[11], Thailand (88-100%)[9-10] and Vietnam (89.5%).[15] It could be due to confounding factors, including other HLA alleles. However, none of the other HLA-B alleles in our study were found to have significant association with CBZ-SJS/TEN.

Indonesia is ethically diverse but HLA-B*1502 was found to be a common allele among the major ethnic groups including Javanese, Sundanese and Padangnese. Although ethnic subgroup analysis did not showed significant association between HLA-B*1502 and CBZ-SJS/TEN limited by small sample size, the overall significant result support the use of HLA-B*1502 as a screening tool for CBZ-SJS/TEN in Indonesia.

Table 1: HLA-B alleles frequency in CBZ-SJS/TEN and tolerant group.

Allele	Cases n(%)	Control n (%)	p	OR (CI 95%)
HLA-B*1502	8 (57.14%)	14 (26.41%)	0.035	3.71 (1.09-12.61)
HLA-B*1513	3 (21.43%)	7 (13.21%)	0.447	1.79 (0.40-8.06)
HLA-B*1521	2 (18.18%)	4 (7.55%)	0.440	2.04 (0.33-12.49)
HLA-B*1525	0	3 (5.66%)	0.651	0.50 (0.02-10.20)
HLA-B*15297	1 (7.14%)	0	0.136	11.89 (0.46-308.42)
HLA-B*15301	0	3 (5.66%)	0.065	0.50 (0.02-10.20)
HLA-B*1501	0	1 (1.89%)	0.910	1.23 (0.05-31.22)
HLA-B*15357	0	1 (1.89%)	0.910	1.23 (0.05-31.22)
HLA-B*15387	0	1 (1.89%)	0.910	1.23 (0.05-31.22)
HLA-B*1525	0	3 (5.66%)	0.065	0.50 (0.02-10.20)
HLA-B*0705	0	1 (1.89%)	0.910	1.23 (0.05-31.22)
HLA-B*0753	1 (7.14%)	0	0.136	11.89 (0.46-308.42)
HLA-B*0752	0	1 (1.89%)	0.910	1.23 (0.05-31.22)
HLA-B*0818	0	1 (1.89%)	0.910	1.23 (0.05-31.22)
HLA-B*1301	0	2 (3.77%)	0.828	0.71 (0.03-15.64)
HLA-B*1342	0	1 (1.89%)	0.910	1.23 (0.05-31.22)
HLA-B*1801	1 (7.14%)	2 (3.77%)	0.594	1.96 (0.165-23.34)
HLA-B*1802	1 (7.14%)	3 (5.66%)	0.835	1.28 (0.12-13.36)
HLA-B*1851	0	1 (1.89%)	0.910	1.23 (0.05-31.22)
HLA-B*1867	0	1 (1.89%)	0.910	1.23 (0.05-31.22)
HLA-B*2706	0	6 (11.32%)	0.358	0.25 (0.013-4.75)
HLA-B*3101	0	2 (3.77%)	0.828	0.71 (0.03-15.64)
HLA-B*3501	2 (14.29%)	0	0.053	21.4 (0.97-474.19)
HLA-B*3505	3 (21.43%)	10 (18.87%)	0.830	1.17 (0.28-5.00)
HLA-B*3508	0	1 (1.89%)	0.910	1.23 (0.05-31.22)
HLA-B*3565	0	1 (1.89%)	0.910	1.23 (0.05-31.22)
HLA-B*3802	0	2 (3.77%)	0.828	0.71 (0.03-15.64)
HLA-B*3901	1 (7.14%)	0	0.139	11.89 (0.46-302.72)
HLA-B*4001	0	5 (9.43%)	0.430	0.30 (0.02-5.83)
HLA-B*4006	1 (7.14%)	0	0.139	11.89 (0.46-302.72)
HLA-B*40194	0	1 (1.89%)	0.910	1.23 (0.05-31.22)
HLA-B*4101	0	1 (1.89%)	0.910	1.23 (0.05-31.22)
HLA-B*4403	0	6 (11.32%)	0.358	0.25 (0.01-4.75)
HLA-B*5101	0	2 (3.77%)	0.828	0.71 (0.03-15.64)
HLA-B*5102	1 (7.14%)	4 (7.55%)	0.959	0.94 (0.10-9.17)
HLA-B*51186	0	1 (1.89%)	0.910	1.23 (0.05-31.22)
HLA-B*5201	0	2 (3.77%)	0.828	0.71 (0.03-15.64)
HLA-B*5250	0	1 (1.89%)	0.910	1.23 (0.05-31.22)
HLA-B*5601	1 (7.14%)	0	0.139	11.89 (0.46-302.72)
HLA-B*5602	0	1 (1.89%)	0.910	1.23 (0.05-31.22)
HLA-B*5701	0	3 (5.66%)	0.065	0.50 (0.02-10.20)
HLA-B*58:01	0	5 (9.43%)	0.430	0.30 (0.02-5.83)

Some previous studies reported association between other HLA-B75 family (e.g., HLA-B*1521, HLA-B*1508, HLA-B*1511 and HLA-B*1518) and CBZ-SJS/TEN. For example, HLA-B*1511 in Korea[16], HLA-B*1508 in India[17] and Japan[18], and HLA-B*1521 in Thailand.[10] In this study, HLA-B*1521 was found in 2 cases (14.3%) and 4 controls (7.6%) but the difference was not statistically significant. HLA-B*1508, HLA-B*1511 and HLA-B*1518 were not found in the cases.

This study is limited by small sample size especially in the ethnic subgroups.

In conclusion, this study showed that HLA-B*1502 is associated with CBZ-SJS/TEN in Indonesian population.

ACKNOWLEDGEMENTS

We would like to thank all the participants in this study. We would also like to thank Dr. Fitri Octaviana, Dr. Suryani Gunadharma, Dr. Donny Hamid, Dr. Nurhayana Lubis in the patient recruitment. Part of the study is funded by the University of Malaya under High Impact Research from Ministry of Higher Education research funds (reference no.:UM.C/625/1/HIR/MOHE/MED/45).

DISCLOSURE

Conflict of Interest: None

REFERENCES

1. Harr T, French LE. Toxic epidermal necrolysis and Steven-Johnson syndrome. *Orphanet J Rare Dis* 2010; 16(5)39.
2. Suwarsa O, Yuwita W, Dharmadji HP, Sutedja E. Steven-Johnson Syndrome and toxic epidermal necrolysis in Dr. Hasan Sadikin General Hospital Bandung, Indonesia from 2009-2013. *Asia Pac Allergy* 2016; 6:43-47.
3. Mockenhaupt M, Viboud C, Dunant A, et al. Steven-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risk with emphasis on recently marketed drugs. The EuroSCAR study. *J Invest Dermatol* 2008; 128:35-44.
4. Lee HY, Martanto W, Thirumoorthy T. Epidemiology of Stevens-Johnson syndrome and toxic epidermalnecrolysis in Southeast Asia. *Dermatol Sinica* 2013; 31:217-20.
5. Chung WH, Hung SI, Hong HS, *et a*l. Medical genetics: A Marker for Stevens-Johnson syndrome. *Nature* 2004; 428:486.
6. Wu XT, Hu FY, An DM, *et al*. Association between carbamazepin-induced cutaneous adverse drug reactions and the HLA-B*1502 allele among patients in central China. *Epilepsy Behav* 2010; 19:405-8.
7. Wang Q, Zhou JQ, Zhou LM, *et al*. Association between HLA-B*1502 allele and carbamazepin-induced severe cutaneous adverse reaction in Han people of Southern China mainland. *Seizure* 2011; 20:446-8.
8. Man CBL, Kwan P, Baum L, *et al*. Association between HLA-B*1502 Allele and antiepileptic drug-induced cutaneous reaction in Han Chinese. *Epilepsia* 2007; 48(5):1015-8.
9. Tessaneeyakul W, Tiamkao S, Jantararoungtong T, *et al*. Association between HLA-B*1502 and carbamazepin induced severe cutaneous adverse drug reaction in Thai population. *Epilepsia* 2010; 51(5):926-30.
10. Locharernkul C, Loplumlert J, Limotai C, *et al*. Carbamazepin and phenitoin inducedSteven-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. *Epilepsia* 2008; 49(12):2087-91.
11. Chang CC, Too CL, Murad S, Hussein S. Association of HLA-B*1502 with carbamazepin induced toxic epidermal necrolysis and Steven-Johnson Syndrome in Malaysia population. *Int J Dermatol* 2011; 50(2):221-4.
12. Khor AHP, Lim KS, Wong SM, Tan CT, Ng CC. HLA-B*1502 allele association with carbamazepin-induced severe cutaneous reaction in Malaysian Indian, a pooled-sample analysis and meta-analysis. *Epilepsia* 2014; 55(11):e120-124.
13. Bastuji-Garin S, Rzany B, Stem RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome and erythema multiforme. *Arch Dermatol* 1993; 129(1):92-6.
14. Roujeau JC, Stern RS. Severe adverse cutaneous reaction to drugs. *N Engl J Med* 1994; 331: 1272-85.
15. Nguyen DV, Chu HC, Nguyen DV, *et al*. HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in Vietnamese. *Asia Pac Allergy* 2015; 5(2):68-77.
16. Kim SH, Lee KW, Song JW, *et al*. Carbamazepin-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. *Epilepsy Res* 2011; 94:213-7.
17. Mehta TY, Prajapati LM, Mittal B, *et al*. Association of HLA-B*1502 allele and carbamazepin-inducedSteven-Johnson Syndrome among Indians. *Indian J Dematol Venereol Leprol* 2009; 75:579-82.
18. Ikeda H, Takahashi Y, Yamazaki E, *et al*. HLA class I marker in Japanese patients with Carbamazepin induced cutaneous adverse reations. *Epilepsia* 2010; 51:297-300.