Causative drugs and HLA-B polymorphism in drug-induced Stevens-Johnson syndrome - toxic epidermal necrolysis: A study in five hospitals in Jakarta

Anesia Tania,[1] Evita Halim Effendi,[1] Inge Ade Krisanti,[1] Yulia Ariani[2]

[1]Department of Dermatology and Venereology, Faculty of Medicine Universitas; [2]Department of Biology, Faculty of Medicine Universitas, Indonesia

Abstract

Stevens-Johnson syndrome and toxic epidermal necrolysis is a very rare but life-threatening form of cutaneous drug eruption. In recent years, several countries in Asia had succeded in preventing carbamazepine induced SJS/TEN by screening for HLA-B*15:02 before prescribing carbamazepine. This study aimed to acquire data regarding causative drugs and HLA-B allele polymorphism in SJS/TEN patient in Jakarta. We acquired data from 5 referral hospitals from March 2015 to March 2017. Subject fulfilling the inclusion and exclusion criteria was interviewed and blood sample was taken for DNA extraction. The DNA was examined with PCR SSOP and Luminex technology for high resolution HLA-B typing. We studied 22 subjects. The median age was 45,4 years old (14-74). The most common causative drug in this study is carbamazepine. HLA-B*15:02 and HLA-B*18:01 were the most common allele in all subjects. HLA-B*15:02 was found in five (72%) out of seven subjects whose condition was caused by carbamazepine. The most common causative drug of SJS/TEN in five hospitals in Jakarta is carbamazepine, with five (72%) out seven subjects had HLA-B*15:02 allele.

Introduction

Adverse drug reaction caused a significant number of morbidity and mortality in the world. Cutaneous eruption is the most common form of adverse drug reaction. RegiSCAR had proposed the term *severe cutaneous adverse reactions* (SCAR) for a rare and severe form of cutaneous eruption that has a high rate of morbidity and mortality, unpredictable and most often caused by drug.[1] Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) is a very rare but life-threatening form of cutaneous drug eruption. SJS/TEN inicidence varies among countries, from 1-9 per million populations per year. Until recently, there is no data regarding the incidence of SJS/TEN neither in Indonesia nor in Jakarta. Eventhough this is a rare occurrence; the mortality rate could reach 50%, especially in the case of TEN. [2]

SJS/TEN most often caused by drugs. However, causative drugs vary among countries. The most common drug in the Europe is allopurinol, meanwhile Southeast Asian countries reports carbamazepine as the most common culprit. Data in Indonesia is still lacking and mostly hospital-based. Hasan Sadikin hospital in Bandung reports 55 patiens during 2009-2013. Moehammad Hoesin Hospital in Palembang reports 43 patients during 2006-2008. The most common causative drug from both studies is paracetamol. [3,4] These findings are quite interesting, because paracetamol is deemed as a low-risk drug for SJS/TEN and suspicion mostly perceived as protopathic bias. [5]

Recently, management of SJS/TEN is focused on prevention, by acknowledging a certain population who are more vulnerable to certain adverse drug reaction. One of the most vastly studied factors is the role of genetic. HLA gene, particularly HLA-B, had a very high rate of polymorphism, reaching 16.251 allele in various populations in 2015. Allele frequency and haplotype from HLA locus is highly differ in each population and influenced by ethnical groups. [6] Chung et al.[7] (2004) reported a strong association between HLA-B*15:02 and carbamazepine–induced SJS/TEN in Han Chinese. However, these association was not reproduced in some other population.[8] This finding had greatly affected the management of SJS/TEN. Several countries, especially in Asia, had implemented a rule to screen HLA-B*15:02 before starting carbamazepine. This regulation had successfully decreased the number of carbamazepine-induced SSJ/TEN cases. [9] Unfortunately, this regulation has yet to be implemented in Indonesia due to lack of data. Indonesia population consists of more than 200 million people, thus even condition with such low incidence could produce a high number of cases and need to be prevented.[10] This study aimed to provide SJS/TEN data in Jakarta from five referral centers regarding causative drugs and HLA-B polymorphism.

Materials and Methods

This cross-sectional study was performed in Cipto Mangunkusumo hospital, Persahabatan hospital, Fatmawati hospital, Koja hospital, and Tarakan hospital. The sampling method is total sampling of all recorded SSJ/TEN patients in all five hospitals from March 2015 to March 2017. Subject fulfilling the inclusion and exclusion criteria was interviewed and their blood sample was taken for DNA extraction. The causative drugs were reexamined using algorithm of drug causality for epidermal necrolysis (ALDEN) through interview, medical record, drug receipts or communication with previous medical personnel. The DNA was examined with PCR SSOP and Luminex technology for high resolution HLA-B typing.

The ethical committee of Faculty of Medicine Universitas Indonesia and the local ethical committee in each hospital approved this study. Subjects received thorough explanation regarding the objective, result and potential harm of the study. All subjects signed a written informed consent.

Correspondence: Anesia Tania, Department of Dermatology and Venereology, Faculty of Medicine Universitas, Jl. Radin Inten II no 91, Duren Sawit, Jakarta, Indonesia.
Tel.: +6281294502692
E-mail: anesiatania@gmail.com

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Results

We found recorded data of 105 SJS/TEN patients (ICD L51.1 dan L51.2). However, after evaluation with the inclusion and exclusion criterias, only 22 patients (21%) could be included in the study. The clinical profile of the subject is displayed in Table 1. Most subject are female with median age of 44,5 (14-74) years old.

Causative drug of SJS/TEN in subjects

Most subjects received polipharmacy when the eruption occurred, thus we used ALDEN and only included subjects with probable or very probable score. The most common causative drug in subjects is anticonvulsant, especially carbamazepine (32%). Other anticonvulsant, lamotrigine, was also found in 14% of subjects.

HLA-B polymorphism according to the causative drug

The most common HLA-B allele in this study population is HLA-B*15:02 (36%), followed by HLA-B*18:01 (32%). Five subjects (72%) with carbamazepine-induced SJS/TEN had HLA-B*15:02. Findings of HLA-B allele according to causative drug are listed in Table 2.

Discussion

There were 105 SJS/TEN patients in five hospitals in Jakarta during 2015-2017. All hospitals included in this study are referral hospitals in five regions of Jakarta. Cases of severe drug eruption, especially SJS/TEN, are usually referred to referral center on each region. According to national survey in 2015, Jakarta has a population of 10 million people.[10] This gave an estimated incidence rate of 5 cases per million people per year in Jakarta, higher then some other countries in Asia. This should inspire medical personnel to be more aware and active in the management of SJS/TEN, especially for prevention measures. From 105 patients, we could only include 22 patients in this study. Most common reason of exclusion is incomplete data in medical record to reconfirm the diagnosis and cause. A great number of patients had also lost to follow-up and could not be contacted. Epidemiological data regarding number of cases and drug causality is very important in the management and prevention of adverse drug reaction. Further studies will require consensus regarding diagnosis criteria, algorithm to decide the causative drug and case-reporting method to be implemented all over the country.

The most common causative drug in this study is carbamazepine (32%). Carbamazepine is regarded as a high-risk drug in causing SJS/TEN, especially in Asia.[11] In Europe, carbamazepine only caused 5-6% of SJS/TEN cases, but in Taiwan it caused 25-33% of cases in 2009.[7] Previous reports in other cities in Indonesia had not found carbamazepine as the most common cause. [3,4] This difference could be caused by the retrospective means of data collection, different algorithm used to decide the causative drug and protopathic bias. We also found a trend of prescribing

Table 1. Sociodemographic characteristic of the subject.

Sociodemographic characteristic	N	Persentase (%)
Gender		
Male	10	45
Female	12	55
Age (year old)		
<20	2	9
21-45	8	36
45-60	9	41
>60	3	14
Occupation		
None	6	27
Housewife	11	50
Student	2	9
Office job	2	9
Physical work	1	5
Education		
None	2	9
Elementary school	1	5
Junior high school	6	27
Senior high school	6	27
College	7	32
Status		
Single/divorced	4	18
Married	18	82

Table 2. Hla-b polymorphism according to the causative drug

Drugs	Allele hla-b 1	Allele hla-b 2
Carbamazepine	Hla-b*15:02	Hla-b*15:02
	Hla-b*15:02	Hla-b*52:01
	Hla-b*15:21	Hla-b*38:02
	Hla-b*15:02	Hla-b*35:05
	Hla-b*15:02	Hla-b*18:01
	Hla-b*18:01	Hla-b*35:05
	Hla-b*15:02	Hla-b*18:01
Cephalosporine	Hla-b*18:01	Hla-b*38:01
	Hla-b*35:05	Hla-b*51:02
	Hla-b*15:02	Hla-b 40:01
	Hla-b*40:01	Hla-b*51:01
Nevirapine	Hla-b*18:01	Hla-b*40:01
	Hla-b*15:02	Hla-b*15:02
	Hla-b*13:01	Hla-b*15:02
	Hla-b*44:03	Hla-b*44:03
Lamotrigine	*Unreadable*	*Unreadable*
	Hla-b*15:13	Hla-b*18:01
	Hla-b*07:05	Hla-b*15:21
Ciprofloxacin	Hla-b*18:01	Hla-b*58:01
	Hla-b*35:01	Hla-b*44:03
Cotrimoxazole	Hla-b*15:21	Hla-b*46:01
Natrium diclofenate	Hla-b*38:01	Hla-b*58:01

carbamazepine in a mixed form for common pain management, thus complicating the investigation of causative drug.

This study found 36% of the subjects had HLA-B*15:02. Yuliwulandari et al. reported HLA-B*15:02 allele frequency of 11,2% in normal population of Javanese and Sundanese. The frequency of HLA-B*18:01 allele in this study is also higher than the common population (6,33%).[12] This is an interesting finding, although this could be explained by the mixed race of the subjects with this allele (Kaukasian and Pakistan).

In this study, five subjects (72%) with carbamazepine-induced SJS/TEN had HLA-B*15:02. This is higher than study by Herlyani (2017), which found 57% subjects with carbamazepine-induced SJS/TEN had HLA-B*15:02.[13] In Taiwan Han Chinese population, HLA-B 15:02 was found in 100% patients with carbamazepine-induced SJS/TEN.[7] In Malaysia, with more racially diverse population similar to Indonesia, HLA-B 15:02 was found in 80% patients with carbamazepine-induced SJS/TEN [14]. This difference showed that the association between genetic and clinical manifestation is also influenced by the etnic and race. Further studies with more subjects grouped by ethnic and case-control method should be performed to determine the role of HLA-B*15:02 and other gene in SJS/TEN for Indonesia patients.

Conclusions

There were 105 recorded SJS/TEN patients in five hospitals in Jakarta during 2015-2017. However, only 22 patients could be included in the study. Retrospective data collection is vital for epidemiology study, especially for adverse drug reaction. We should implement a consensus regarding diagnosis criteria, algorithm to decide the causative drug and case-reporting method. The most common causative drug of SJS/TEN in this study is carbamazepine, with five (72%) out seven subjects had HLA-B*15:02 allele. Further study should be performed to determine the role of HLA-B*15:02 and other gene in SJS/TEN for Indonesia patients.

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