Tuberculosis 93 (2013) 270–274

Contents lists available at SciVerse ScienceDirect

Tuberculosis

journal homepage: http://intl.elsevierhealth.com/journals/tube

HOST GENETICS OF SUSCEPTIBILITY

Antituberculosis drug-induced hypersensitivity syndrome and its association with human leukocyte antigen

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ARTICLE INFO

Article history:
Received 25 July 2012
Received in revised form
18 October 2012
Accepted 22 October 2012

Keywords:
Antituberculosis drugs
Hypersensitivity syndrome
Human leukocyte antigen
Genetic association

SUMMARY

Antituberculosis drug (ATD)-induced hypersensitivity syndrome (HSS) is a serious adverse reaction to ATDs, but much remains to be determined regarding its characteristics and genetic risk factors. In this study, we have collected cases of ATD-induced HSS and their clinical features, and investigated the associations of ATD-induced HSS with human leukocyte antigen (HLA). Subjects with ATD-induced HSS and ATD-tolerant controls were recruited through analysis of a multicenter adverse drug reaction registry in Korea. HLA allele frequencies were compared between subjects with ATD-induced HSS ($n = 14$) and two control groups: ATD-tolerant controls ($n = 166$) and the general population ($n = 485$). The number of enrolled subjects with ATD-induced HSS ($n = 14$) was comparable to those of patients with HSS induced by other common drugs such as allopurinol during the recruitment period. The frequency of Cw*0401 was much higher in the cases (50.0%) compared with ATD-tolerant controls (12.7%, $Pc = 0.0204$, OR = 6.90) and the general population (12.8%, $Pc = 0.0132$, OR = 6.82). Our results suggest that ATD is an important causative agent inducing HSS with distinct clinical features. The strong association of Cw*0401 with the risk for ATD-induced HSS suggests immunological involvement in the development of this syndrome.

1. Introduction

Severe cutaneous adverse reactions (SCARs) such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are often life-threatening and involve severe and generalized cutaneous reactions accompanied by systemic manifestations.[1] Hypersensitivity syndrome (HSS) is a distinct type of SCAR that has also been referred to as drug-induced hypersensitivity syndrome (DIHS) or drug reactions with eosinophilia and systemic symptoms (DRESS).[2] HSS is characterized by fever, skin eruptions, internal organ involvement, and peripheral blood eosinophilia.[3] Although the pathomechanisms of HSS are not yet well understood, a growing body of evidence suggests that immune mechanisms play key roles in the development of HSS.[4]

An important advance in HSS research is the strong associations between specific human leukocyte antigen (HLA) alleles and these reactions.[5] The B*5801 allele is strongly associated with allopurinol-induced HSS,[6,7] and B*5701 increases the risk for abacavir-induced hypersensitivity reactions similar to HSS.[8,9] In addition, A*3101 is significantly associated with carbamazepine-induced hypersensitivity reactions, including HSS.[10–12] As these associations are not only phenotype-specific but also drug-specific, the HLA alleles associated with HSS may differ depending on the causative agent.

Specific drugs, including anticonvulsants, allopurinol, and antibiotics, have been frequently associated with HSS,[13] exhibiting clinical features that may differ depending on the causative drug.[14,15] Although the involvement of antituberculosis drugs

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http://dx.doi.org/10.1016/j.tube.2012.10.010

(ATDs) in the etiology of HSS has not drawn much attention, ATDs are responsible for various types of hypersensitivity reactions and SCARs.[16,17] While some cases of ATD-induced HSS have been reported,[18,19] the clinical characteristics of ATD-induced HSS and its pathogenesis, including HLA associations, are not well known. In this study, we present the demographic and clinical characteristics of 14 subjects with ATD-induced HSS. In addition, we investigate whether specific HLA alleles are associated with ATD-induced HSS by comparing allele frequencies between cases and two control groups, ATD-tolerant controls and the general population in Korea.

2. Subjects and methods

2.1. Study population

Subjects with ATD-induced HSS and tolerant controls with no adverse reactions to ATD were recruited through inspection of the database of the Korean Pharmacogenetic Adverse Drug Reaction Research Network, which contains information on cases of adverse reactions induced by various drugs from seven university hospitals in Korea for the period 2002–2011. The schemes for pharmacological treatment of tuberculosis (TB) and evaluation of the development of adverse reactions were described previously.[20] Briefly, cases and control subjects were newly diagnosed with TB and treated daily with a combination regimen including isoniazid, rifampin, ethambutol, and pyrazinamide for two months and then without PZA for four or more following months according to treatment guideline by the American Thoracic Society, Centers for Disease Control and Prevention, and the Infectious Diseases Society of America.[21] Doses of each drug were adjusted based on body weight of the patient. According to the standardized phenotypic definitions of the Drug-Induced Skin Injury (DISI) Expert Working Group,[22] HSS was defined as major organ manifestations (skin and/or extracutaneous organs) in the presence of fever (body temperature $> 38\ ^{\circ}C$), eosinophilia (peripheral blood eosinophil count $> 500/mm^3$), and/or lymphadenopathy. We included cases with the presence of three or more features of HSS with skin and/or extracutaneous organ system involvement.[22] Causality was assessed for each case based on the World Health Organization–Uppsala Monitoring Centre (WHO–UMC) system.[23] Only cases with “certain” or “probable” causality were included in the study. The exclusion criteria were: (1) skin disease before treatment; (2) chronic renal failure or chronic liver disease affecting drug metabolism; (3) chronic alcoholism; (4) other chronic medical conditions requiring medication; and (5) non-adherence to the treatment. We selected age- and gender-matched control subjects from patients with TB who did not show any ATD-related adverse reactions during the 6- to 9-month treatment period. In addition to ATD-tolerant controls, previously reported HLA allele frequencies from a general population of adult Koreans were used for comparison.[24] This study was approved by the institutional review board of each participating hospital. Written informed consent was obtained from all enrolled subjects.

2.2. HLA typing

Genomic DNA was extracted from peripheral blood mononuclear cells of the study participants. Allele-level genotypes for HLA class I (A, B, and C) and II (DRB1 and DQB1) genes for each study sample were obtained by direct DNA sequence analysis performed using well-established protocols.[24] Of 166 ATD-tolerant controls, HLA class II genotyping could not be performed in 27 subjects due to a lack of DNA samples.

2.3. Statistical analysis

The demographic and clinical variables were compared between case and control subjects using the chi-squared test (for categorical variables) or Mann–Whitney *U* test (for continuous variables). Specific HLA allele frequencies for patients with ATD-induced HSS were compared with those for ATD-tolerant controls and the general population using a multivariate logistic regression model adjusted for age and gender. All statistical analyses were performed using SAS version 9.13 (SAS Institute, Cary, NC, USA). Values of $P < 0.05$ indicated statistical significance. To account for the observed alleles, we further evaluated statistical significance by correcting *P* values (*Pc*) for multiple comparisons using the Bonferroni method.

3. Results

3.1. Characteristics of ATD-induced HSS

Of the 14 enrolled subjects with ATD-induced HSS, all were ethnically Korean, and 9 (64.3%) were male (Table 1). Their ages ranged from 16 to 80 years. Duration of exposure to ATD before the development of HSS varied from 5 to 109 days (median, 27.5; IQR, 13.0–436.0). All patients showed both skin and liver manifestations; none had involvement of other organs such as lung, kidney, heart, or muscle. The most common skin manifestations were maculopapular eruptions, which were found in 13 patients (92.9%).

Table 1
Clinical and phenotypic manifestations in patients with antituberculosis drug-induced hypersensitivity syndrome.

Patient no	Sex	Age (years)	Drug exposure (days)	Skin manifestation	Liver manifestations			Eosinophils ($/mm^3$)	Fever (BT $> 38\ ^{\circ}C$)	Lymphadenopathy	Hospitalization
					AST (IU/L)	ALT (IU/L)	Total bilirubin (mg/dL)				
1	F	16	42	MPE	722	961	0.6	1403	+	–	+
2	M	28	34	MPE	464	817	4.5	NA	–	–	+
3	F	34	46	MPE	1149	1301	7.0	2950	+	–	+
4	M	35	25	MPE	1165	1552	1.2	1689	+	–	+
5	M	39	14	MPE	371	549	7.9	2648	+	+	+
6	M	40	16	MPE	315	479	0.6	635	–	–	+
7	M	44	7	MPE	429	421	0.9	1793	+	–	+
8	F	49	33	MPE	838	816	4.3	19	+	+	+
9	F	50	56	MPE	536	652	5.8	2090	–	–	+
10	M	68	18	MPE	96	38	2.5	1486	–	–	–
11	M	69	109	MPE	124	158	0.7	710	+	–	+
12	M	71	5	MPE	665	289	1.0	581	+	–	+
13	F	72	30	MPE	100	129	0.8	11,412	+	–	+
14	M	80	10	MPE	111	135	0.4	550	+	–	+

AST, aspartate aminotransferase; ALT, alanine aminotransferase; BT, body temperature; MPE, maculopapular eruption; NA, data not available.
In all subjects, baseline levels of liver function tests and peripheral blood eosinophil counts were within normal range before the administration of antituberculosis drugs.