Clinical, Viral and Genetic Characteristics of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) in Shanghai, China

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DRESS is one of the most severe drug reactions. The aim of this retrospective study was to summarize the clinical presentation, genetic predisposition and prognostic factors of DRESS. A total of 52 patients with DRESS, who were inpatients at a medical referral centre in Shanghai, China, from January 2011 to December 2016, were analysed retrospectively. All the patients had skin eruption, 83% had liver involvement, and ≤10% had other organ involvement. Mean cost of hospitalization was US$5,511±3,050. The 3 most common causative agents were allopurinol (18/52; 35%), salazosulphapyridine (11/52; 21%) and carbamazepine (5/52; 10%). HLA-B*5801 and HLA-B*1302 were associated with allopurinol-induced DRESS. HLA-B*1301 was related to salazosulphapyridine-induced DRESS. The mortality rate was 6% (3/52). Epstein-Barr virus DNA was found in 10 patients (19%) and indicated a poor prognosis. Human herpes virus 6 DNA was detected in 17 patients (33%) and was associated with autoimmune sequelae. Due to its high medical cost and sometimes poor prognosis, prevention of DRESS should be a high priority.

Key words: drug reaction with eosinophilia and systemic symptoms; drug hypersensitivity; adverse drug reaction; human herpes virus; human leukocyte antigen.

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Drug reaction with eosinophilia and systemic symptoms (DRESS), or drug-induced hypersensitivity syndrome (DIHS), ranks among the most severe cutaneous drug reactions and may be life-threatening. Apart from extreme eosinophilia and organ dysfunction, its characteristics include a long latent period, fever, skin rash and lymphadenopathy. Because of its complex natural course and various clinical manifestations, it is difficult to make a diagnosis of DRESS. In 2007, the European registry of severe cutaneous adverse reactions (RegiSCAR) established the diagnostic criteria for DRESS (1) and thus clarified the definition.

During the past decade, numerous studies have reported genetic predispositions of severe cutaneous adverse reactions (SCARs). Correlations between multiple human leukocyte antigen (HLA) alleles with specific drug-induced SCARs have been identified (2). For example, HLA-B*5801 has a strong correlation with allopurinol (ALP)-induced SCARs in Thai and Han Chinese populations (3, 4). The negative predictive value of HLA-B*5801 was high, although its positive predictive value was comparatively low (3, 5). This means that many ALP-tolerant patients also carry this allele. Moreover, very few studies have analysed the associations between HLA alleles and each subtype of SCARs. Due to its low incidence, a large population analysis concerning the association between the HLA allele and DRESS is currently lacking.

Apart from genetic predisposition, reactivation of the human herpes virus (HHV) family also plays a key part in the pathogenesis of DRESS. However, the role of the HHV family is controversial. Some authors report that DRESS is the consequence of viral reactivation (6), while others regard these infections as complications of immunosuppressive therapy (7). Previous studies have observed an association between HHV6 reactivation and the severity of DRESS (8, 9). However, the role of virus reactivation in the natural chronic course of DRESS and in relapses remains hypothetical (10). Large-scale retrospective studies analysing the relationship between HHV reactivation and the prognosis of DRESS are limited.

The aim of the current study was to analyse the most common culprit drugs, latent period and medical cost of Chinese patients with DRESS. Particular attention was paid to the genetic predisposition and prognostic factors of DRESS.

METHODS

Subject enrollment and sample collection

Medical records of all patients hospitalized in the Department of Dermatology at Huashan Hospital affiliated to Fudan University in Shanghai, China between January 2011 and December 2016 were retrospectively reviewed. Patients diagnosed with "drug eruption" and "drug hypersensitivity syndrome" were listed as suspected DRESS patients. These patients' whole-blood samples were prospectively collected within 2 days after admission unless otherwise indicated. Follow-up was accomplished via a phone interview. All patients were followed up for at least 6 month after discharge.

According to RegiSCAR diagnostic criteria, patients with suspected DRESS were classified as definite, probable, possible, or no case. Those whose final points failed to reach 2 (defined as no case by RegiSCAR diagnostic criteria) were excluded from the study.

Two control groups were recruited in this study. The first control group was chosen from the human MHC database (dbMHC) (11). It consisted of 283 unrelated healthy Chinese people. The other control group consisted of patients who did not develop any

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cutaneous eruptions after being treated with ALP or salazosulphapyridine (SASP) for more than 3 months (i.e. ALP-tolerant and SASP-tolerant group). The second control group was recruited from the Department of Rheumatology of Huashan Hospital. The ethics committee of Fudan University approved the study. Informed consent was provided by each participant. Patients in the control groups were all Han Chinese.

Laboratory examinations and culprit drug determination

Eosinophilia was diagnosed when absolute eosinophil counts exceeded 700/μl. If the total leukocyte count was less than 4,000/μl, it was considered when the percentage of eosinophils surpassed 10%. A high level of serum IgE (sIgE) was defined as sIgE exceeding 240 ng/ml. Hepatic damage was considered when the level of serum alanine aminotransferase (ALT) exceeded twice the normal limit, or 2 times the patients' baseline levels. Renal damage was defined as the level of serum creatinine exceeding twice the normal values or when the patient developed recent onset of haematuria or proteinuria. Cardio-muscular and pancreatic involvement were considered when the patient's cardiac or muscular enzymes or amylase levels exceeded the normal range. Culprit drugs were identified by the criteria proposed by Naranjo et al. (12).

HLA genotyping and detection of Epstein-Barr virus and HHV6 DNAs

QIAamp DNA Blood mini kit (Qiagen Inc., Valencia, CA, USA) was used to extract genomic DNA from peripheral blood samples. LABT® SSO Kit (One Lambda, CA, USA) was used to detect HLA-A, -B and -C alleles by PCR sequencing of specific oligonucleotides. All genotypings were reanalysed by HLA Fusion™ software, version 3.0 (One Lambda, CA, USA). Mentality Bio-Tech Co. Ltd (China) helped with the genotyping.

Taqman real-time PCR procedure was used to amplify and quantify respectively the EBV and HHV6 gene region from the DNA sample. EBV and HHV6 reactivations were defined as quantity of DNA copies above the detection threshold (1×10^3 copies/ml).

Statistical analysis

Descriptive variables were listed as number (percentage) or mean ± standard deviation (SD) or median (range). Comparisons of the parametric data were performed using Student's 2-tailed *t*-test. Non-parametric data were compared by χ^2 square or Fisher's exact test, if appropriate. A multivariate logistic regression was performed to eliminate the effects of confounding factors. Differences were regarded as significant when $p<0.05$. Data were analysed with SPSS17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Of all inpatients of the Dermatology Department at Huashan Hospital affiliated to Fudan University between January 2011 and December 2016, 52 were classified as DRESS patients and were enrolled in this study. Among them, 15 (29%) patients were classified as definite cases, 33 (63%) as probable cases, and 4 (8%) as possible cases by the RegiSCAR scoring system.

Demographic and baseline characteristics

A total of 34 male patients and 18 female patients were enrolled. The male:female ratio was 1.88:1, and the median age was 47.5 years (range 20–81 years). Median latency time was 30 days (range 4–100 days). The mean length of stay was 13 ± 6 days. The mean cost of medicine to treat DRESS was US$4,091 ± 2,618 (¥26,749 ± 17,120). The mean hospitalization cost was US$5,511 ± 3,050 (¥35,938 ± 19,890). The 3 most common causative agents were ALP (18/52; 35%), SASP (11/52; 21%) and carbamazepine (CBZ, 5/52; 10%).

HLA genotyping

HLA alleles correlated strongly with ALP, SASP, and CBZ-induced DRESS by Fisher's exact tests are listed in **Table I**. HLA genotypes of all 52 patients with DRESS, along with their general clinical characteristics, are available from the authors on request.

Four alleles were significantly associated with the ALP-induced DRESS group: HLA-B*5801, HLA-A*3303, HLA-C*0302 and HLA-B*1302. Because of the high co-appearance rate with HLA-B*5801: 76% (16/21) for HLA-A*3303 and 100% (21/21) for HLA-C*0302, these 2 alleles were regarded as haplotype alleles of HLA-B*5801 (13). Therefore, only HLA-B*5801 and HLA-B*1302 remained relevant. HLA-B*5801 was most closely related to ALP-induced DRESS ($p<0.001$, odds ratio (OR) 175.3, 95% confidence interval (95% CI) 10.4–2,960.0).

In SASP-induced DRESS group, 3 alleles were found to be strongly correlated: HLA-B*1301, HLA-A*2402 and HLA-C*0304. The HLA-C*0304 allele is recognized as a haplotype allele of HLA-B*1301 (13), emerging along with HLA-B*1301 in 17 (89%) of 19 cases. Therefore, HLA-B*1301 was most closely related to SASP-induced DRESS ($p<0.001$, OR 9.8, 95% CI 2.7–34.8).

In the CBZ-induced DRESS group, both HLA-A*3101($p=0.033$, OR 11.1, 95% CI 1.7–71.4) and

Table I. Genetic risk factors for allopurinol (ALP)-, salazosulphapyridine (SASP)-, and carbamazepine (CBZ)-induced drug reaction with eosinophilia and systemic symptoms (DRESS)

	HLA genotypes/total n/N (%)		Cases vs. controls	
Drug/Allele	DRESS	Controls	*p*-value	OR (95% CI)
ALP				
*B*5801*	18/18 (100)	49/283 (17)	<0.001*	175.3 (10.4–2,960)
*A*3303*[a]	14/18 (78)	64/283 (23)	<0.001*	12.0 (3.8–37.7)
*C*0302*[a]	18/18 (100)	48/283 (21)	<0.001*	180.0 (10.6–3,034)
*B*1302*	3/18 (17)	10/283 (4)	0.035*	5.5 (1.36–22.0)
SASP				
*B*1301*	7/11 (64)	43/283 (15)	<0.001*	9.8 (2.7–34.8)
*C*0304*[b]	6/11 (55)	65/283 (23)	0.027*	4.0 (1.2–13.6)
*A*2402*	7/11 (64)	89/283 (31)	0.044*	3.8 (1.1–13.4)
CBZ				
*A*3101*	2/5 (40)	16/283 (6)	0.033*	11.1 (1.7–71.4)
*B*1301*	3/5 (60)	43/283 (15)	0.030*	8.4 (1.4–51.6)
Pooled				
*B*1301*	19/52 (37)	43/283 (15)	0.001*	3.2 (1.7–6.2)
*B*1302*	7/52 (13)	10/283 (4)	0.008*	4.3 (1.5–11.7)
*B*5801*	21/52 (40)	49/283 (17)	0.001*	3.2 (1.7–6.1)

[a]Haplotype allele of HLA-B*5801. [b]Haplotype allele of HLA-B*1301.
*Significant difference, χ^2.
CI: confidence interval; HLA: human leukocyte antigen; OR: odds ratio.

HLA-B*1301(p=0.030, OR 8.4, 95% CI 1.4–51.6) were associated.

Pooled analysis identified HLA-B*1301, HLA-B*1302 and HLA-B*5801 as independent risk factors to induce DRESS (Table I). The correlations remained significant after multivariate logistic regression to eliminate interactions between the alleles (**Table II**).

Clinical features and laboratory findings

All patients (n=52) had skin eruption. Fever and lymphadenopathy were the other most common clinical manifestations, present in 39 (75%) and 36 (69%) patients, respectively. At least one internal organ involvement was observed in 48 (92%) patients. Liver damage was the most frequently observed (43/52; 83%). Other impaired organs included heart (3/52; 6%), pancreas (2/52; 4%) and kidney (2/52; 4%). Eosinophilia was present in 42 (81%) patients, 29 (56%) patients had high sIgE level. More than half of the patients with high sIgE level (52%) had values higher than 2,000 ng/ml. EBV reactivation was found in 10 (19%) patients, and HHV6 reactivation in 17 (33%) patients.

Treatments

The culprit drug was discontinued in every patient. The longest duration until discontinuation was 4 months (in this case CBZ was the culprit drug, with a cumulative dose of 5,500 mg). All patients received systemic corticosteroid therapy. Additional intravenous immunoglobulin (IVIG) therapy for 3–5 days was given to patients with aggravating signs (exacerbation of skin eruptions, worsening of laboratory findings, or other complications) after the treatment by 1.5 mg/kg/day of methylprednisolone for 3–5 days. IVIG was given by continuous infusion to patients without severe renal or heart failure. Twenty (38%) patients received corticosteroid therapy alone and 32 (62%) patients received additional IVIG therapy.

Prognosis

In this study, 3 patients died of infection within 3 months post-discharge. The clinical features of deceased cases are available from the authors on request. One patient developed fulminant type 1 diabetes mellitus (FT1D) during her stay in hospital. She was still on insulin therapy despite cessation of systemic corticosteroids 4 months post-discharge. HLA-A*0203, HLA-A*2402, HLA-B*5801, HLA-B*4003, HLA-C*0302, HLA-C*0304 alleles were carried by this patient. Three patients (6%) developed hyper/hypothyroidism during follow-up (within 1 year post-discharge). Prior HHV-6 reactivations were detected in all 3 patients.

Table II. Comparison of human leukocyte antigen (HLA)-B*5801, HLA-B*1302, HLA-B*1301 in predicting drug reaction with eosinophilia and systemic symptoms (DRESS) (multivariate logistic regression)

	HLA genotypes/total, n/N (%)		Cases vs. controls	
Allele	DRESS	Controls	p-value	OR (95% CI)
*B*1301*	19/52 (37)	43/283 (15)	<0.001[a]	7.0 (3.2–15.4)
*B*1302*	7/52 (13)	10/283 (4)	<0.001[a]	8.1(2.6–25.6)
*B*5801*	21/52 (40)	49/283 (17)	<0.001[a]	6.4 (3.0–13.8)

[a]Significant difference, χ^2.
Hosmer–Lemeshow test p-value = 0.845; correlation matrix < 0.8.
CI: 95% confidence interval; OR: odds ratio.

DISCUSSION

The reported incidence of DRESS varied from 1 in 10,000 to 1 in 1,000 drug exposures (14, 15). Despite the low incidence, DRESS is associated with high mortality, very high healthcare costs and chronic autoimmune sequelae (10). In this study, the mean hospitalization cost of DRESS is 164% of per capita disposable annual income in China (US$3,067 or ¥ 20,167) (16).

In accordance with previous pharmacogenetics research, HLA-B*5801 was strongly associated with ALP-induced DRESS in Han Chinese patients (4, 5). However, pretreatment screening of HLA-B*5801 alone might overestimate the risk as the ALP-tolerant population also carried HLA-B*5801, (7/63; 11%) in this study and 20/153 (15%) in other published data (5). As described in Table I, HLA-B*1302 was also related to ALP-induced DRESS. Moreover, none of the ALP-tolerant control carried HLA-B*1302 allele (**Table III**). Therefore, we speculate that HLA-B*1302 plays a complementary role in the pathogenesis of DRESS. Additional pretreatment screening of HLA-B*1302 could help physicians to choose ALP-tolerant patients from a HLA-B*5801-positive population.

SASP is frequently used to treat inflammatory colitis and ankylosing spondylitis. As previously reported by our research group (17), HLA-B*1301 was most closely associated with SASP-induced DRESS. In the SASP-tolerant group, the carrier frequency was 13%

Table III. Comparison of human leukocyte antigen (HLA)-B*5801 and HLA-B*1302 in predicting allopurinol-induced DRESS

	HLA genotypes/total, n/N (%)		Cases vs. controls		Predicting power			
Allele	ALP-DRESS	ALP-Tolerant	p-value	OR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
*B*5801*	18/18 (100)	7/64 (11)	<0.001*	283.7 (15.4–5,212)	1.00 (0.81–1.00)	0.89 (0.79–0.95)	0.72 (0.51–0.88)	1.00 (0.94–1.00)
*B*1302*	3/18 (17)	0/64 (0)	0.013*	24.4 (1.2–494.5)	0.14 (0.03–0.36)	1.00 (0.94–1.00)	1.00 (0.29–1.00)	0.78 (0.68–0.86)

*Significant difference, χ^2.
95% CI: 95% confidence interval; OR: odds ratio.

(4/30). The negative and positive predictive values were 0.87 (95% CI 0.69–0.96) and 0.64 (95% CI 0.31–0.89), respectively. HLA-B*1301 was also reported to be related to the dapsone hypersensitivity syndrome among patients with leprosy (18). The structural and metabolic similarity between dapsone and SASP might explain this overlap (19, 20).

In addition to genetic predisposition, reactivation of the HHV family also plays a role in the development of DRESS. HHV6 reactivation was found to be exclusive to DRESS, while reactivation of other HHV family members was observed in other SCARs (7, 21). In our series, interestingly, HHV6 was positive in all 3 patients who developed hyper/hypothyroidism during follow-up. The infection rate was significantly higher than those without autoimmune sequelae ($p = 0.03$, OR 17.14, 95% CI 0.83–353.40). In agreement with previous studies (22, 23), the high incidence suggested that chronic virus reactivation might have triggered excessive autoimmune responses and induced autoimmune diseases after DRESS remission. Another proof is the low incidence of autoimmune sequelae in SJS/TEN (24), during which viral reactivations were less frequently observed.

In this study, the mortality rate was 6% (3/52), consistent with reported mortality rate of DRESS (3–10%) (15, 25, 26). Multiple organ failure and sepsis were the main reported causes of death. No significant difference was found between patients receiving additional IVIG therapy and those without IVIG in terms of mortality (**Table IV**). IVIG has been widely used in SJS/TEN as it could block the Fas-Fas ligand interaction and thus prevent death of keratinocytes (27). Its use in patients with DRESS was suggested mainly because of its antiviral and immunomodulatory effects. In effect, experts have not yet reached consensus concerning the use of IVIG in patients with DRESS. One study found that the use of IVIG alone to treat patients with DRESS rendered poor benefit/risk balance (28). On the other hand, another consensus group suggested use of 2 g/kg/day IVIG for 5 days in association with corticosteroid to treat patients with life-threatening signs (29). Nevertheless, controlled clinical trials investigating the effectiveness and potential long-term complications of IVIG plus corticosteroid therapy for DRESS are currently lacking.

Table IV. Risk factors of death in patients with drug reaction with eosinophilia and systemic symptoms (DRESS)

Risk factors	Deceased patients	Surviving patients	*p*-value	OR	95% CI
Eosinophilia, yes/no[a]	3/0	39/10	> 0.99	1.8	0.1–38.9
High sIgE, yes/no[b]	2/1	27/22	> 0.99	1.6	0.1–19.2
Liver involvement, yes/no	2/1	41/8	0.44	0.4	0.03–4.8
Renal involvement, yes/no	1/2	1/48	0.11	24.0	1.1–539.5
HHV6 reactivation, yes/no	1/2	16/33	> 0.99	1.0	0.9–12.2
EBV reactivation, yes/no	3/0	7/42	< 0.001*	39.7	1.9–8,949.3
IVIG therapy, yes/no	2/1	30/19	> 0.99	1.3	0.1–15.0

[a]Eosinophilia was diagnosed when absolute eosinophil counts exceeded 700/µl. If total leukocyte count was lower than 4,000/µl, it was considered when the percentage of eosinophils surpassed 10%. [b]High IgE serum level (sIgE) was defined as sIgE exceeding 240 ng/ml. *Significant difference, Fisher's exact test. HHV6: human herpes virus 6; EBV: Epstein-Barr virus; IVIG: intravenous immunoglobulin; 95% CI: 95% confidence interval; OR: odds ratio.

EBV reactivation, detected in all 3 deceased patients, was associated with poor prognosis (Table IV). However, we could not perform multivariate logistic regression due to the limited number of deceased cases.

Due to the scarcity of DRESS, the number of patients included in our study was still limited. Furthermore, we only examined viral DNA on admission. A large-scale retrospective study concerning viral reactivation at different time-points of DRESS might be of greater interest.

In conclusion, we analysed the clinical features, HLA-genotypes and viral reactivation of 52 DRESS patients hospitalized in China during a 6-year period. Despite the heterogeneous clinical manifestations, DRESS represents a specific disease entity. High priority in public health and drug control agency should be given to the prevention of DRESS. HLA allele pretreatment screening, especially HLA-B*1301, HLA-B*1302 and HLA-B*5801 pretreatment screening, may help to prevent SASP and ALP-induced DRESS. EBV and HHV6 detections may predict the prognosis of patients with DRESS.

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The authors have no conflict of interest to declare.

REFERENCES

1. Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol 2007; 156: 609–611.
2. Cheng CY, Su SC, Chen CH, Chen WL, Deng ST, Chung WH. HLA associations and clinical implications in T-cell mediated drug hypersensitivity reactions: an updated review. J Immunol Res 2014; 2014: 565320.
3. Tassaneeyakul W, Jantararoungtong T, Chen P, Lin PY, Tiamkao S, Khunarkornsiri U, et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. Pharmacogenet Genomics 2009; 19: 704–709.
4. Cao ZH, Wei ZY, Zhu QY, Zhang JY, Yang L, Qin SY, et al. HLA-B*58: 01 allele is associated with augmented risk for both mild and severe cutaneous adverse reactions induced by allopurinol in Han Chinese. Pharmacogenomics 2012; 13: 1193–1201.
5. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. Proc Natl Acad Sci U S A 2005; 102: 4134–4139.
6. Picard D, Janela B, Descamps V, D'Incan M, Courville P, Jacquot S, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response. Sci Transl Med 2010; 46: 46–62.
7. Ishida T, Kano Y, Mizukawa Y, Shiohara T. The dynamics of herpesvirus reactivations during and after severe drug eruptions: their relation to the clinical phenotype and therapeutic outcome. Allergy 2014; 69: 798–805.
8. Kano Y, Hiraharas K, Sakuma K, Shiohara T. Several herpesviruses can reactivate in a severe drug-induced multiorgan

reaction in the same sequential order as in graft-versus-host disease. Br J Dermatol 2006; 155: 301–306.
9. Tohyama M, Hashimoto K, Yasukawa M, Kimura H, Horikawa T, Nakajima K, et al. Association of human herpesvirus 6 reactivation with the flaring and severity of drug-induced hypersensitivity syndrome. Br J Dermatol 2007; 157: 934–940.
10. Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. Lancet 2017.
11. US National Library of Medicine National Institutes of Health (2016). dbMHC Home http://www.ncbi.nlm.nih.gov/projects/gv/mhc.
12. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239–245.
13. Trachtenberg E, Vinson M, Hayes E, Hsu YM, Houtchens K, Erlich H, et al. HLA class I (A, B, C) and class II (DRB1, DQA1, DQB1, DPB1) alleles and haplotypes in the Han from southern China. Tissue Antigens 2007; 70: 455–463.
14. Fiszenson-Albala F, Auzerie V, Mahe E, Farinotti R, Durand-Stocco C, Crickx B, et al. A 6-month prospective survey of cutaneous drug reactions in a hospital setting. Br J Dermatol 2003; 149: 1018–1022.
15. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol 2013; 169: 1071–1080.
16. National Bureau of Statistics of China. Statistical Communiqué of the People's Republic of China on the 2014 National Economic and Social Development. China Population Today 2015; 32: 20-36.
17. Yang F, Gu B, Zhang L, Xuan J, Luo H, Zhou P, et al. HLA–B*13: 01 is associated with salazosulfapyridine-induced drug rash with eosinophilia and systemic symptoms in Chinese Han population. Pharmacogenomics 2014; 15: 1461–1469.
18. Zhang FR, Liu H, Irwanto A, Fu XA, Li Y, Yu GQ, et al. HLA-B*13: 01 and the dapsone hypersensitivity syndrome. N Engl J Med 2013; 369: 1620–1628.
19. Paniker U, Levine N. Dapsone and sulfapyridine. Dermatol Clin 2001; 19: 79–86.
20. Sjöquist B, Ahnfelt N-O, Andersson S, d'Argy R, Hatsuoka M, Ljungstedt-Påhlman I. Pharmacokinetics of Salazosulfapyridine (Sulfasalazine, SASP). (III). Metabolism and biliary excretion of SASP in the rat after a single intravenous or oral administration. Drug Metab Pharmacokinet 1991; 6: 457–473.
21. Chen YC, Chiang HH, Cho YT, Chang CY, Chen KL, Yang CW, et al. Human herpes virus reactivations and dynamic cytokine profiles in patients with cutaneous adverse drug reactions – a prospective comparative study. Allergy 2015; 70: 568–575.
22. Kano Y, Ishida T, Hirahara K, Shiohara T. Visceral involvements and long-term sequelae in drug-induced hypersensitivity syndrome. Med Clin North Am 2010; 94: 743–759.
23. Ushigome Y, Kano Y, Ishida T, Hirahara K, Shiohara T. Short- and long-term outcomes of 34 patients with drug-induced hypersensitivity syndrome in a single institution. J Am Acad Dermatol 2013; 68: 721–728.
24. Yang C, Cho Y, Chen K, Chen Y, Song H, Chu C. Long-term Sequelae of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis. Acta Derm Venereol 2016; 96: 525–529.
25. Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol 2010; 146: 1373–1379.
26. Vachiramon V, Wongkitisophon P, Chanprapaph K, Rattanakaemakorn P. Six-year Retrospective Review of Drug Reaction with Eosinophilia and Systemic Symptoms. Acta Derm Venereol 2012; 92: 200–205.
27. Zhu QY, Ma L, Luo XQ, Huang HY. Toxic epidermal necrolysis: performance of SCORTEN and the score–based comparison of the efficacy of corticosteroid therapy and intravenous immunoglobulin combined therapy in China. J Burn Care Res 2012; 33: 295–308.
28. Joly P, Janela B, Tetart F, Rogez S, Picard D, D'Incan M, et al. Poor benefit/risk balance of intravenous immunoglobulins in DRESS. Arch Dermatol 2012; 148: 543–544.
29. Descamps V, Ben Said B, Sassolas B, Truchetet F, Avenel-Audran M, Girardin P, et al. Prise en charge du drug reaction with eosinophilia and systemic symptoms (DRESS). Ann Derm Venereol 2010; 137: 703–708.