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Characteristics of 1,544 Drug-induced Hypersensitivity Syndrome Cases Reported to Food and Drug Administration

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Characteristics of 1,544 Drug-induced Hypersensitivity Syndrome Cases Reported to Food and Drug Administration

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Abstract

Background: Drug-induced hypersensitivity syndrome (DIHS) is potentially life-threatening adverse drug reaction (ADR), characterized by clinical findings such as rash, fever, liver dysfunction, hematological abnormality and reactivation of human herpes virus 6. Most previous reports regarding the characteristics of patients with DIHS are limited to small case reports or drug-specific case series.

Objective: In this report, the reporting trend and characteristics of DIHS cases reported to Food and Drug Administration (FDA) are described.

Methods: A retrospective case series of DIHS cases between January 2004 and March 2010 reported to FDA were conducted. The analyses included the number of unique cases, age, gender and proportion of fatal outcome. Time to onset from beginning of the suspected drugs and frequently reported suspected drugs were also tabulated.

Result and Discussion: There were 1,544 DIHS case reports. Among them, 137 cases (8.9 %; 95%CI 7.5 - 10.4) were reported with fatal outcome. After the release of modern diagnostic systems of DIHS in 2005, number of the DIHS case report to FDA has been increasing. There was a mild inequality of reporting between genders. The male to female ratio was approximately 4 to 5. There were DIHS reports in wide age range. Most frequently reported age group was 60-69 yeas old. Individuals equal to or older than 70 years old appeared to associate with higher fatal outcome. Most cases (approximately 60%) developed DIHS within first 4 weeks of exposure to the suspected drugs. On the other hand, there were late-onset cases that developed after 6 months exposure.

Conclusion:

After release of diagnostic systems of DIHS in 2005, the ADR report of DIHS to FDA has been increasing. The characteristics of DIHS reports were described.

Introduction

Drug-induced hypersensitivity syndrome (DIHS) or drug rash with eosinophilia and systemic symptoms (DRESS) are potentially life-threatening adverse drug reaction (ADR), characterized by clinical findings such as rash, fever, lymphadenopathy, hepatitis and leukocytosis with eosinophilia and/or atypical lymphocytes (1-3). In many severe cases, these symptoms continue or exacerbate even for weeks after discontinuation of the suspected drugs. According to previous reports, the causes of DIHS are limited to carbamazepine, phenytoin, phenobarbital, mexiletine, dapsone, salazosulfapyridine, allopurinol and minocycline (1, 2). Reactivation of human herpes virus 6 (HHV-6) evidenced by the rise in HHV-6 IgG titers and the existence of HHV-6 DNA occurs usually 2 to 3 week after onset of rash (1, 2, 4, 5). Since I have felt recent increase of individual case safety report with DIHS through my daily Pharmacovigilance practice, I looked into safety database of food and drug administration (FDA). In this report, reporting trend of DIHS, characteristics of cases are described.

Methods

The FDA's safety database termed as Adverse Event Reporting System (AERS) was downloaded from FDA AERS web page (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/) Since FDA allows download data from their web page between 1st quarter of 2004 and 1st quarter of 2010 at the time of beginning of this study, and I analyzed FDA AERS database during this period.

Reports of DIHS associated with any drug use were obtained from FDA AERS database. Since reported ADR in FDA AERS database are coded according to Medical Dictionary for Regulatory Activities (MedDRA) (http://www.meddramsso.com/public_about_meddra.asp MedDRA MSSO3975 Virginia Mallory Drive chantilly, VA 20151 USA) , I identified DIHS case by preferred term (PT) coded as "Drug rash with eosinophilia and systemic symptoms", which is preferred term for ADR reporting for DIHS. There were 2,127 reports of DIHS between 2004 and 2010. Since the FDA AERS database has some duplicate reports, I removed older one from duplicate reports by sorting

case identification number. After the removal of the duplicate reports, there were 1,544 reports of DIHS. The 1,544 reports were placed on further analyses. Symptoms were adverse reactions other than DIHS reported in the identified DIHS cases.

Analyses were performed as previously reported. The identified reports were tabulated by reporting period, gender, age, and suspected drugs. Reporting period is calculated from reporting date (FDA_DT in the database) that is the date FDA received the report. Gender is calculated from gender code (GNDR_COD in the database). Age is calculated from age (AGE in the database) that is numeric value of patient's age at event. In this study, I converted all age in "years" unit if the reported age is not in "years". The suspected drugs are tabulated from DRUG data. It harbors not only suspected drugs but also concomitant drugs. In this study I tabulated only for suspected drugs. Since DRUG data contain not only general substance name but also brand name, DRUG data were converted into substance name. The duration between beginning of medication and event onset was also tabulated. Since some information is missing, number of reported case is diverse between tabulations. The SMQ (Standardized MedDRA Queries; http://www.meddramsso.com/public_about_meddra.asp MSSO3975 Virginia Mallory Drive Chantilly, VA 20151 USA) code 20000003 was used to identify decline in renal function. The PT terms corresponding SMQ code 20000003 within the REAC table of FDA AERS were searched. This procedure was supposed to search of a relatively rapid decline in renal function that lead to any of followings; the accumulation of water, crystalloid solutes, nitrogenous metabolites in the body, increase in serum creatinine and urea nitrogen levels (azotemia) greater than 0.5 and 10 mg per deciliter, respectively; oliguria; and changes in the rate of urine flow. Similarly SMQ code 20000004 and code 20000005 were used for searching of heart failure and liver dysfunction, respectively. SMQ code 20000004 is designed to search cases with a condition in which the heart is unable to pump an adequate amount of blood to meet metabolic and physiological needs of body. Classified (classes I - IV) on basis of severity according to criteria set by New York Heart Association (NYHA) starting from no limitation of physical activity to slight or marked limitation, up to the inability to carry out any physical activity without discomfort. Clinical findings vary but include: dependent edema, raised jugular venous pressure, hepatomegaly, pulmonary congestion/edema, tachycardia, cardiomegaly, and dyspnoea. Ejection fraction is less than 35%. Wheras SMQ code 20000005 was to search cases with disorders of the liver, including signs, symptoms, radiologic and laboratory findings.

Microsoft Access 2003 (Microsoft Corporation, Redmond WA, USA) was used for data management and analyses. For analyses of 95% confident interval of death proportion and logistic regression analysis were performed using CDC EpiInfo software is used (the Centers for Disease Control and Prevention (CDC), Atlanta GA, USA).

Results

There were 1,544 DIHS case reported to FDA. Among them, 137 cases (8.9 %; 95%CI 7.5 - 10.4) were reported with fatal outcome. This fatality shows that DIHS is potentially fatal ADR which requires appropriate diagnosis and effective treatment. The nine percent of fatality in DIHS case was compatible with past literatures reported approximately 10% (6-8).

Figure 1 shows reporting number of DIHS to FDA between first quarter of 2004 and first quarter of 2010. Number of DIHS case reports has been recently increasing. This may not directly mean increase of clinical occurrence of DIHS.

There were 625 male (40.5 %; 95%CI 38.0 - 43.0), 792 female (51.3 %; 95%CI 48.8 - 53.8) and 127 reports missing gender information (8.2 %) out of 1,544 DIHS cases. Previous literature mentioned no sex predilection for DIHS (1). On the other hand, male to female ratio was approximately 4 to 5 in the FDA AERS. Proportion of fatal outcome was 9.4 % (95%CI; 7.3 - 12.1) and 9.1% (95%CI; 7.2-11.3) for male and female cases, respectively. There was no significant difference in proportion of fatal outcome between genders.

Figure 2 indicate reporting of DIHS by age group. There were DIHS reports on cases in wide age range. Most frequently reported age group was 60-69 yeas. Since 70 years or older appeared to be with higher fatal proportion than other age groups, I performed additional tabulation to compare the proportions of fatal outcome between 70 years or older and younger than 70. Proportion for fatal outcome for younger group (younger than 70 years old) and older group (70 years old or older) were 6.7 % (95%CI; 5.3 – 8.6) and 16.4 % (95%CI; 11.7 – 22.2), respectively. The odds ratio was 2.43 (95%CI; 1.53 – 3.86). The p-value calculated by Fisher's exact test was less than 0.001. Thus, older age appeared to be associated with higher proportion of fatal outcome. However, the cases may be confounded by the potential risk of fatal outcome associated with underlying conditions in this age group; therefore, a clear causal relationship between older

age and fatal outcome could not be established based on this analysis.

There were 3,492 suspected drugs used in 1,544 cases. Out of 3,492 suspected drugs, 1,861 drugs were reported with relevant beginning of medication and DIHS occurrence date. Figure 3 shows frequency distribution of time to onset for 1,722 out of 1,861 drugs with onset within 30 weeks after beginning of medication. Median time to onset among 1,861 drugs was 3rd week. Approximately 60% and 92.5% of DIHS cases occurred first 4 and 30 weeks, respectively. On the other hand, approximately 8% of DIHS case occurred after 6 months of drug exposure. DIHS has been reported to occur in patients who took anticonvulsants for up to 40 years (9). Longest time to onset in FDA AERS database was approximately 15 years.

Table1 indicates 20 most frequently suspected substances out of 429 kinds of substances. Previous literatures limited the causes only to eight kinds of substances (1, 2), that included Carbamazepine, Phenytoin, Phenobarbital, Mexiletine, Dapsone, Salazosulfapyridine, Allopurinol, Minocycline. However, much more other kinds of suspected substances were reported to FDA.

Table 2 indicates 20 most frequently reported symptoms. As FDA does not require reporting symptoms associating with a major ADR, the absence of symptoms in a report does not always mean the absence of clinical symptoms. In some case, more than one related symptoms may be reported for a single case. Moreover, the reported symptoms were not wrapped up in related groups such as a liver dysfunction for an alanine aminotransferase increase, an aspartate aminotransferase increased and a gamma-glutamyltranferase increased or a hematological abnormality for an eosinophilia, an atypical lymphocyte increased. Thus the absolute number of reported symptoms may not allow us to discuss on the frequency or rate of clinical symptom. As shown in Table 2, frequently reported symptoms mostly included fever, dermatological abnormality, liver dysfunction, renal dysfunction and hematological abnormalities, which are listed in diagnostic criterias (6, 10).

Finally I checked whether demographical factors or organ damages were associated with fatal outcome among the DIHS cases. As shown in Table 3, age equal to or older than 70 years and existence of renal dysfunction appeared to be associated with increased proportion of fatal outcome.

Discussion

DIHS is potentially life-threatening adverse drug reaction, which usually begins with clinical symptoms such as fever, rash and spiky fever followed by eosinophilia, hepatic dysfunction and/or lymphocytosis with atypical lymphocytes (1-3). In many severe cases, these symptoms continue or exacerbate even for weeks after discontinuation of the suspected drugs. One outstanding character of DIHS is reactivation of HHV-6 evidenced by the rise in HHV-6 IgG titers and the existence of HHV-6 DNA that occurs usually 2 to 3 week after onset of rash (1, 2, 4, 5).

Historically, DIHS has been reported since 1950's, termed as "Dilantin sensitivity", "anti-convulsant hypersensitivity syndrome", "allopurinol hypersensitivity", "infectious mononucleosis caused by salazosulfapyridine"or others (6, 11). Bocquet regarded these syndromes as a single clinical entity and proposed to use the acronym of Drug Rash with Eosionophilia and Systemic Symptoms (DRESS) (6). Bocquet did not mention about HHV-6 as pathogenesis of the DRESS at the time of this proposal (6).

HHV-6 was first isolated as a novel human B-lymphotropic virus from the peripheral blood leukocytes of acquired immunodeficiency syndrome patients and human immunodeficiency virus seropositive individuals in 1986 (12). The pathogenic role of HHV-6 in exanthem subitum, that is a common disease of infancy characterized by high fever for a few days and appearance of a rash coinciding with subsidence of the fever, was reported in 1988 by Yamanishi (13). Akashi reported an adult case with a severe infectious mononucleosis-like syndrome caused by HHV-6 in 1993 (14).

Descamps first reported a causative role of HHV-6 infection in DIHS and associated hemophagocytic syndrome in 1997 (15). Following years, severe DIHS cases associated with HHV-6 infection were reported (4, 5). In spite of accumulation of DIHS cases associated with HHV-6 infection, until consensus group proposed set of criteria for diagnosis in 2005 (1, 2) there was no diagnostic criteria for DIHS that included a pathogenic role of HHV-6.. Since then reporting of DIHS case has been increasing as shown in Fig. 1.

In this tabulation, one of outstanding features is increasing reporting of DIHS cases. Reported drugs suspected as cause of DIHS are not newly approved and placed on marketed ones but most of suspected drugs have been well known as causes of DIHS. Since the suspected drugs are not limited to particular ones, the increasing reporting may not be a signal of

increasing risk on some particular drugs. Since FDA is a regulatory authority in United States, more than half of all ADR reports are 'domestic' that occurred within United States. However, only 12 % of DIHS cases were reported in the United States. Other countries reporting DIHS were France (527 cases, 34 %), Japan (286 cases, 19 %), Unknown (135 cases, 9 %), United Kingdom (79 cases, 5%) and so on. Thus French and Japanese physicians were more tend to report DIHS. This may be related to the fact that conventional diagnostic system were first released by French researchers (6) followed by Japanese researchers who released more modern diagnosis system (1, 10). Then diagnosis DIHS appears to be getting more and more widely used in these countries.

According to experts' reports, DIHS was reported typically occurs 3 weeks to 3 months after beginning of suspected drugs. The delayed onset is one of the important features of DIHS that can be distinguished from other types of drug eruptions, which typically occurs within 1 to 2 weeks after initiation of suspected drugs (1, 2). Different from the experts' reports, this analysis did not show the peak of 1-2 week delayed onset from beginning of the suspected drugs. A few weeks of delay may be needed to perform complicated and not clarified immune responses in DIHS. On the other hand, cross-reactivity among drugs has been frequently reported. In such cases, immune response to cross-reaction may occur much faster than first sensitization, which may at least in part explains earlier onset cases reported to FDA (Fig. 3). However the lack of the delayed reporting peak may possibly related to the lack of knowledge regarding the delayed onset rather than that most DIHS were occurred due to cross-reaction.

DIHS is reported to be caused by limited drugs including carbamazepine, phenytoin, phenobarbital, mexiletine, dapsone, salazosulfapyridine, allopurinol, and minocycline (1, 2). Accouding to Shiohara, atypical cases caused by other drugs were much less commonly reported (1, 2). As shown in Table 1, commonly reported drugs are seen in the table, and are compatible with previous reports. Other drugs were also reported to FDA, appeared to be less common but may not be rare (Table 1). Since the suspected drugs reported to FDA are not always confirmed as causes of reported ADRs, further investigations are needed to determine whether the suspected and frequently reported drugs are real cause of DIHS or not.

In this study, I described characteristics of DIHS cases reported to FDA. The FDA AERS is a computerized information database designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. ADR reports are entered into the AERS database since 1997 by drug and event. All market authorization-holding pharmaceutical companies are required to report ADR associated with their products to FDA. FDA also receives ADR reports directly from health care professionals such as physicians, pharmacists, and patients who were treated with the suspected drug(s). FDA allows downloading the various data extracted from AERS database. The data currently contains more than 2.0 million ADR cases. FDA received and entered approximately 490,000 reports into the AERS database in 2009.

The FDA ARES database does have some limitations. First of all, there is no certainty in that the reported event was actually due to the product. Even though the each provided individual case was reviewed by specialists, the causality assessment for each case is regarded as preliminary judgment and is only for regulatory purpose. Single ADR report does not directly mean the risk of the product for the reported ADR. More detailed causality assessment between reported ADR and the product will be done by reviewing aggregated reports later. Moreover, many potential confounding factors cannot be controlled such as underlying condition, use of concomitant medications and others. Therefore, clear causal relationship between reported medication and the ADR could not be established by single analysis on FDA AERS. Another limitation is that only a part of ADRs are reported to the FDA, which is called "underreporting". Since exact number of population who are exposed to the drugs is not known, the incidence of the ADR associated the drug cannot be calculated. The fraction of repots received by the FDA has been estimated to be 1% to 10%, but the absolute percentage is unknown (16). In some reports, instead of analyzing incidence, reporting rate is used. For the reporting rate denominator, patient treatment years estimated by sales or shipping of products, instead of really exposed population (17). In addition to the underreporting, since the report is highly dependent on the spontaneous reports, there are many potential factors which may affect reporting. If the errors occur randomly, the errors will reduce the potential signal and will be called as noise. Since spontaneous report is made in less strict condition compared to clinical study, there may be more chances of simple error. This kind of errors may usually result in noise. If the factor affects to mislead the result in a specific direction, the factor may be called bias. For example, if the ADR is serious, physicians may want to report the ADR. This could make the cases in database shift more serious events. In spite of underreporting, noise

and potential bias in the AERS database, since the AERS is the biggest source of ADR, many approach have been done to use the AERS in quantitative epidemiologic studies and hypotheses creation in drug safety studies (18-22). The data may allow me to describe the characteristics of DIHS based on the analysis of the AERS.

Conclusion

After release of a modern diagnostic systems of DIHS in 2005, the ADR reports of DIHS have been increasing. We further described about DIHS cases. Proportion of fatal outcome in DIHS was approximately 9.0 %. Individuals equal to or older than 70 years and renal dysfunction appeared to associate with higher proportion for fatal outcome. These factors could be a signal of potential fatal risk of the DIHS but no clear relationship could be established because the outcome of the older groups might be confounded by the other potential risk of higher fatal outcome and associated with underlying conditions that could lead fatal outcome. Most cases (approximately 60%) developed DIHS within first 4 weeks of exposure to the suspected drugs. However, 8% of reported cases developed after 6 months exposure.

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Illustrations

Illustration 1

Figure 1. Reporting of Drug-induced Hypersensitivity Syndrome case to FDA between 2004 Q1 and 2010 Q1. Upper panel indicates quarterly accumulated number of DIHS case reported to FDA between 2004 Q1 and 2010 Q1. Quarterly reporting appeared to be increasing. Lower panel indicates proportion of fatal outcome (%) of the reported DIHS case to FDA. Error bars indicate 95% confidence intervals. Proportion of fatal outcome are around 5.8~11.1 %.

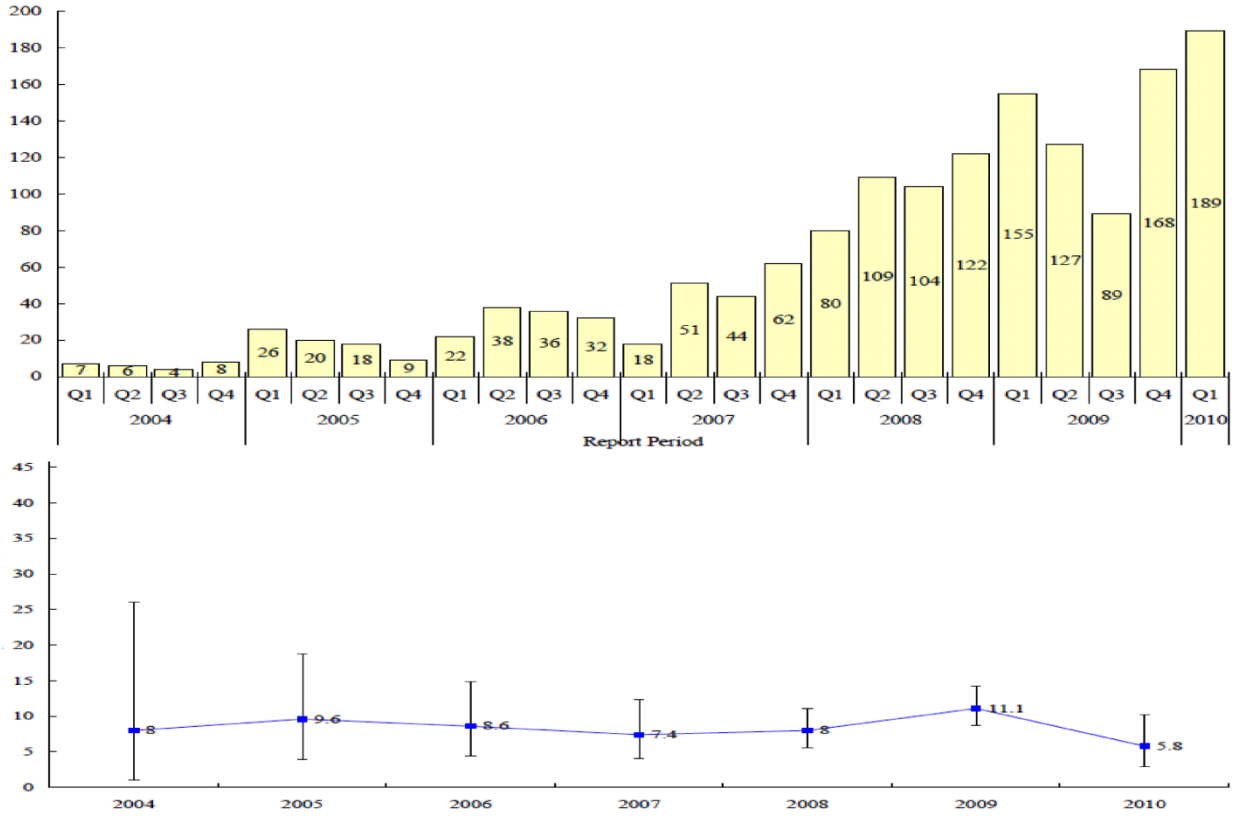

Illustration 2

Figure 2. Reporting of Drug-induced Hypersensitivity Syndrome case to FDA classified by age.

Upper panel indicates number of DIHS case by age group reported to FDA. Lower panel indicates proportion of fatal outcome (%) of the reported DIHS case. Error bars indicate 95% confidence intervals. Seventy years old or older population appeared to be associated with a little higher proportion of fatal outcome.

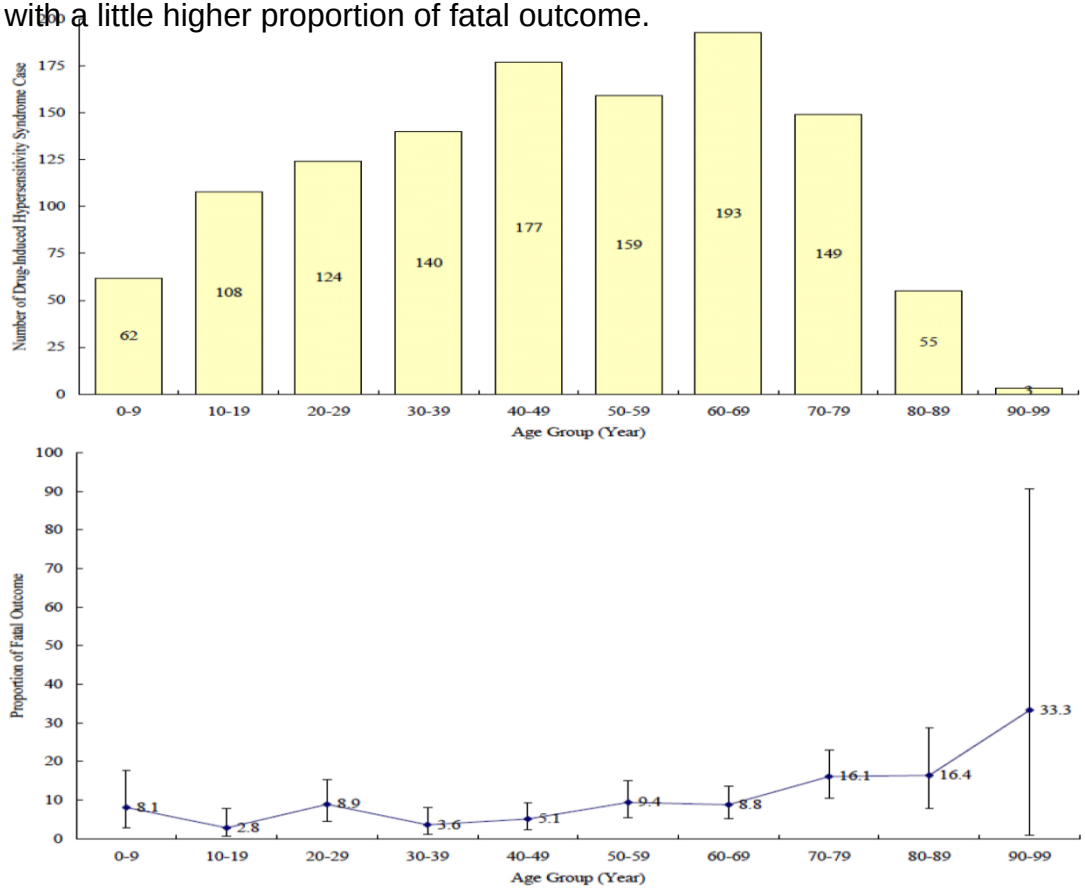

Illustration 3

Figure 3. Drug-induced Hypersensitivity Syndrome onset after beginning of suspected drug (n=1722).

Time to event onset of DIHS case reported to FDA is shown. 1,861 suspected drug have both the initiation date and event onset date. Indicated cases were 1722 out of 1861 suspected drug, which developed DIHS within their first 30 weeks. This mean approximately 92.5 % of reported case developed DIHS within 30 weeks after beginning of suspected drug

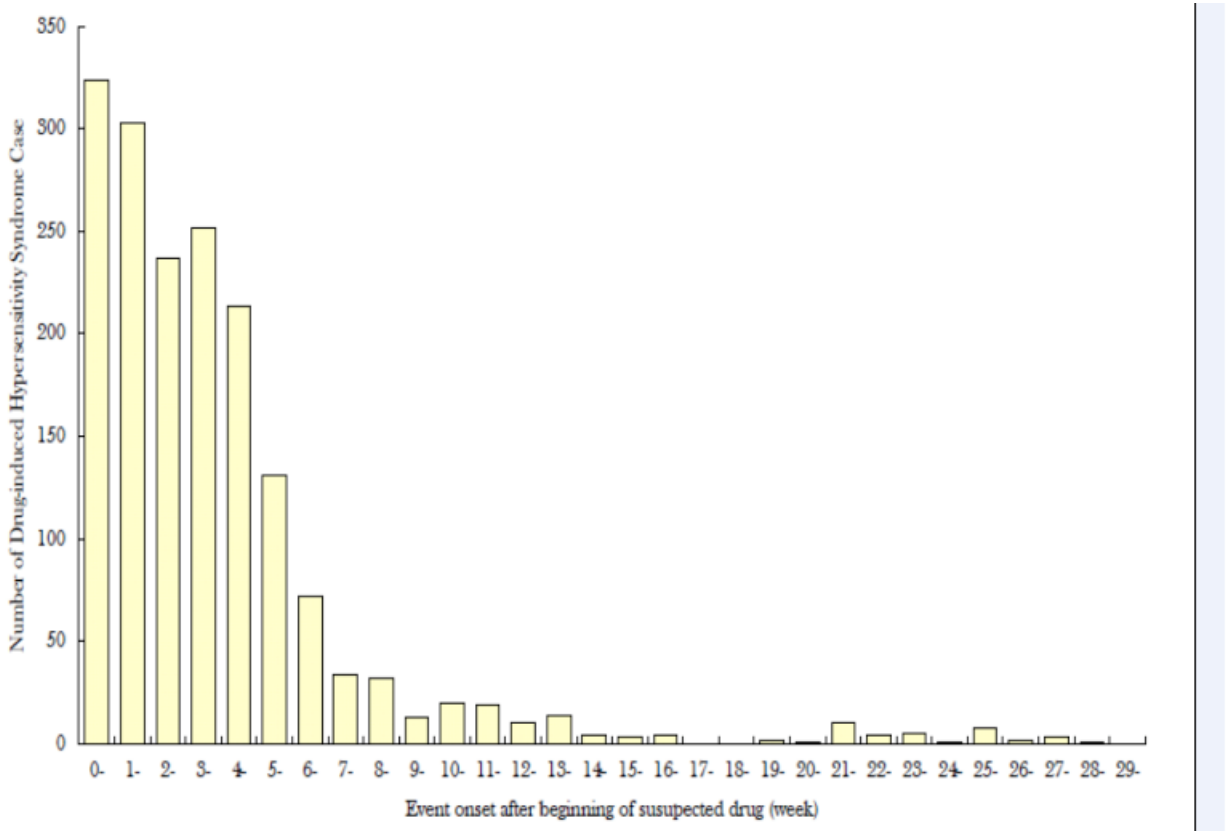

Illustration 4

Table 1. Frequently reported suspected drug in Drug-induced Hypersensitivity Syndrome case This table shows 20 most frequently reported substances. Since some cases were reported along with more than one suspected drug, there are 3,492 reported drugs for 1,555 cases.

Substance Name	Number of Report
carbamazepine	259
sulfasalazine	128
allopurinol	125
vancomycin	106
amoxicillin	103
lamotrigine	100
phenytoin	87
minocycline	70
zonisamide	67
abacavir	53
ciprofloxacin	51
piperacillin	47
rifampicin	46
ibuprofen	44
diclofenac	39
valproate	38
paracetamol	37
phenobarbital	36
lamivudine	35
omeprazole	34

Illustration 5

Table 2. Frequently reported symptoms in Drug-induced Hypersensitivity Syndrome case

This table shows 20 most frequently reported symptoms. Since some cases were reported along with more than one symptom, there are 9,291 symptoms for 1,555 cases. On the other hand, since the reporting of symptoms are not mandatory, report without symptoms does not always means the absence of clinical symptoms.

Reported Symptoms	Number of Report
PYREXIA	402
EOSINOPHILIA	245
LYMPHADENOPATHY	244
ALANINE AMINOTRANSFERASE INCREASED	173
RASH	159
FACE OEDEMA	148
ASPARTATE AMINOTRANSFERASE INCREASED	142
RASH MACULO-PAPULAR	122
DERMATITIS EXFOLIATIVE	107
CYTOLYTIC HEPATITIS	104
GAMMA-GLUTAMYLTRANSFERASE INCREASED	91
RENAL FAILURE	90
PRURITUS	87
LEUKOCYTOSIS	87
RENAL FAILURE ACUTE	84
SKIN EXFOLIATION	83
CHOLESTASIS	83
TOXIC SKIN ERUPTION	80
HEPATIC FUNCTION ABNORMAL	79
HEPATITIS	74

Illustration 6

Table 3. Logistic regression for fatal outcome in Drug-induced Hypersensitivity Syndrome case
Age, gender, heart failure, liver dysfunction and renal dysfunction were placed on logistic regression. The factors that may affect to fatal outcome were age equal to or older than 70 years old, and existence of renal dysfunction.

Variable	Odds Ratio	p-value
Age		
< 70		< 0.001
≥ 70	2.48 (1.54 - 3.99)	
Gender		
Female		0.581
Male	1.13 (0.73 - 1.73)	
Heart Failure		
No		0.142
Yes	1.62 (0.85 - 3.10)	
Liver Dysfunction		
No		0.140
Yes	1.40 (0.89 - 2.21)	
Renal Dysfunction		
No		< 0.001
Yes	3.08 (1.96 - 4.83)	

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