Table 1. Backgrounds of Japanese patients with antiepileptic drug-induced Stevens–Johnson syndrome/toxic epidermal necrolysis and their four-digit HLA types (cont.).

Patient ID	ADR phenotype	Aromatic antiepileptics administered	Sex/age (years)	Primary disease	Period of latency (days)	Potential other causative drugs[†]	*HLA-A*	*HLA-B*	*HLA-C*	*HLA-DRB1*
P105	TEN	ZNS	M/52	Symptomatic epilepsy after brain bleeding	32	Valsartan Lansoprazole	*02:07/24:02*	*35:01/46:01*	*01:02/03:03*	*08:03/14:05*
P106	TEN	ZNS	M/78	Symptomatic epilepsy after brain bleeding	22	None	*02:01/24:02*	*39:01/67:01*	*07:02/07:02*	*09:01/12:01*
P107	SJS	ZNS	M/6	Epilepsy	24	None	*24:02/26:03*	*15:11/40:06*	*03:03/08:01*	*09:01/14:02*
P7	SJS	PHT/ZNS	F/31	Symptomatic epilepsy	40	Sodium valproate	*02:01/02:01*	*15:18/38:02*	*07:02/08:01*	*11:01/13:02*
P108	SJS	ZNS	M/63	Symptomatic epilepsy because of glioblastoma	18	None	*02:07/24:02*	*46:01/52:01*	*01:02/12:02***	*08:03/15:02*
P109	SJS	ZNS	F/30	Symptomatic epilepsy after surgery	18	Sodium valproate	*24:02/24:02*	*51:01/54:01*	*01:02/14:02*	*04:05/12:01*
P110	SJS	ZNS	M/56	Symptomatic epilepsy because of brain cancer	30	None	*02:06/24:02*	*07:02/52:01*	*07:02/12:02*	*01:01/15:02*
P111	SJS	ZNS	M/59	Symptomatic epilepsy after head injury	28	None	*24:02/26:01*	*40:02/52:01*	*03:04/12:02*	*08:02/15:02*
P201	SJS	PB	M/6	Epilepsy	14	None	*24:02/24:02*	*15:01/51:01*	*03:04/04:01*	*04:06/09:01*
P202	SJS	PB	M/69	Epilepsy	11	None	*24:20/26:03*	*15:01/51:01*	*03:03/14:02*	*04:03/04:10*
P203	TEN	PB	F/42	Symptomatic epilepsy because of glioblastoma	29	Temozolomide	*24:02/24:02*	*51:01/54:01*	*01:02/14:02*	*09:01/13:01*
P204	TEN	PB	F/26	Epilepsy	10	None	*26:01/26:01*	*40:02/40:06*	*03:04/08:01*	*04:10/09:01*
P205	SJS	PB	F/67	Symptomatic epilepsy after head injury	20	Candesartan cilexetil Famotidine	*02:01/26:01*	*15:01/51:01*	*08:01/15:02*	*12:02/14:01*

[†]Drugs other than aromatic antiepileptics that were coadministered no more than 2 months prior to the onset of SJS/TEN.
ADR: Adverse drug reaction; CBZ: Carbamazepine; F: Female; M: Male; P: Patient; PB: Phenobarbital; PHT: Phenytoin; SJS: Stevens–Johnson syndrome; TEN: Toxic epidermal necrolysis; ZNS: Zonisamide.

Table 1. Backgrounds of Japanese patients with antiepileptic drug-induced Stevens–Johnson syndrome/toxic epidermal necrolysis and their four-digit HLA types (cont.).

Patient ID	ADR phenotype	Aromatic antiepileptics administered	Sex/age (years)	Primary disease	Period of latency (days)	Potential other causative drugs†	*HLA-A*	*HLA-B*	*HLA-C*	*HLA-DRB1*
P5	TEN	PHT/PB	F/41	Unavailable	9	None	*11:01/24:20*	*51:01/55:02*	*01:02/15:02*	*04:05/15:01*
P206	TEN	PB	F/28	Unavailable	Unavailable	None	*02:06/24:02*	*51:01/51:01*	*14:02/14:02*	*04:05/04:05*
P207	SJS	PB	M/3	Localization-related epilepsy	13	None	02:01/33:03	39:04/44:03	*07:02/14:03*	*04:03/13:02*

†Drugs other than aromatic antiepileptics that were coadministered no more than 2 months prior to the onset of SJS/TEN.
ADR: Adverse drug reaction; CBZ: Carbamazepine; F: Female; M: Male; P: Patient; PB: Phenobarbital; PHT: Phenytoin; SJS: Stevens–Johnson syndrome; TEN: Toxic epidermal necrolysis; ZNS: Zonisamide.

patients/million/year) [30], and the control subjects were therefore highly unlikely to develop SJS/TEN throughout their entire lives. The use of healthy controls provides more conservative results than the use of tolerant patient controls. Fisher's exact test was conducted using JMP version 7.0.1 (SAS Institute Japan Ltd), and odds ratios and 95% CIs were calculated using the same software.

Results

SJS/TEN patients with *HLA* class I and *HLA-DRB1* recruited in this study are shown in Table 1. Nine patients developed SJS/TEN within 60 days after the start of phenytoin treatment, and the average latency after the first exposure to phenytoin was 13.6 ± 8.1 days. Seventeen *HLA* types were detected in multiple patients and carrier frequencies were compared with those of healthy Japanese controls for these alleles. Five of nine patients with phenytoin-induced SJS/TEN carried *HLA-B*51:01*, and the carrier and allelic frequencies in these cases (55.6 and 27.8%, respectively) were considerably higher than those in the controls (15.2 and 7.87%, respectively; Table 2). However, the association between *HLA-B*51:01* and phenytoin-induced SJS/TEN was not significant after adjustment for multiplicity of testing (corrected P by Bonferroni's method [Pc] = 0.1037 in a dominant mode). No other alleles showed a remarkable association with phenytoin-induced SJS/TEN.

Twelve patients had SJS/TEN for which zonisamide was a causative drug. The average latency after the first exposure to zonisamide was 23.8 ± 8.5 days. *HLA-A*02:07*, *HLA-B*46:01* and *HLA-DRB1*08:03* were associated with zonisamide-induced SJS/TEN in a dominant mode ($p = 0.0008$, odds ratio: 9.77 [95% CI: 3.07–31.1]; $p = 0.0037$; odds ratio: 6.73 [95% CI: 2.12–21.36]; and $p = 0.0306$, odds ratio: 3.78 [95% CI: 1.20–11.97], respectively), although only *HLA-A*02:07* was significantly associated with the disease after Bonferroni's correction (Pc = 0.0176). These alleles, that is, *HLA-A*02:07*, *HLA-B*46:01* and *HLA-DRB1*08:03*, appeared to be linked to each other, as shown in Table 1. Indeed, the haplotype *HLA-A*02:07_HLA-B*46:01_HLA-C*01:02_HLA-DRB1*08:03* has been previously reported by Saito *et al.* [31]. Among the alleles constituting this haplotype, only *HLA-C*01:02* did not show a statistically significant association with zonisamide-induced SJS/TEN, even before Bonferroni's correction, because of its high allelic frequency in the controls (17.1%; data not shown).

The haplotype frequency in SJS/TEN patients (5/24; 20.8%) was significantly higher than that in controls (2.9%; p = 0.0001; odds ratio: 12.36 [95% CI: 4.54–33.65]; Pc = 0.0021). No other *HLA* genotypes or haplotypes showed a remarkable association with zonisamide-induced SJS/TEN.

Phenobarbital was a causative drug for eight patients with SJS/TEN. The average latency after the initiation of treatment with phenobarbital was 15.1 ± 7.1 days, which was slightly longer and approximately 1 week shorter than those for phenytoin- and zonisamide-induced SJS/TEN, respectively. The results of association studies between phenobarbital-induced SJS/TEN and the HLA types are summarized in Table 2. Six of eight SJS/TEN patients carried *HLA-B*51:01* and an association between phenobarbital-induced SJS/TEN and *HLA-B*51:01* was observed (p = 0.0003; odds ratio: 16.71 [95% CI: 3.66–83.06]). This association was still significant after Bonferroni's correction (Pc = 0.0042). Carrier frequencies of other *HLA* types, that is, *HLA-A*24:20*, and *HLA-DRB1*04:10*, were also higher in the SJS/TEN patient group than in the healthy volunteers, although the associations were not significant after the correction. Despite the very low allelic frequency of *HLA-A*24:20* in the Japanese population (0.834%), we found two patients carrying this *HLA* type, and both patients also carried *HLA-B*51:01*.

Discussion

Researchers have been discovering an increasing number of genomic biomarkers associated with CARs. For carbamazepine-induced CARs, *HLA-B75* (which includes *HLA-B*15:11*, *HLA-B*15:08* and *HLA-B*15:21* as well as *HLA-B*15:02*) and *HLA-A*31:01* have been reported as biomarkers [6–14,16–20]. In this study, we investigated genetic biomarkers for phenytoin-, zonisamide- and phenobarbital-induced SJS/TEN and, despite small sample sizes, found two completely different risk factors to those for carbamazepine-induced CARs; *HLA-A*02:07* and *HLA-B*51:01* were found to be significantly associated with SJS/TEN induced by other aromatic antiepileptic drugs, that is, zonisamide and phenobarbital, in Japanese patients.

In this study, the haplotype *HLA-A*02:07_HLA-B*46:01_HLA-C*01:02_HLA-DRB1*08:03* and the single allele *HLA-A*02:07* were found to be significantly associated with zonisamide-induced SJS/TEN. A borderline p-value was also obtained for the association with *HLA-B*46:01*, based on a dominant mode analysis, although the association was not

Table 2. Major associations between HLA types and antiepileptic drug-induced Stevens–Johnson syndrome/toxic epidermal necrolysis observed in this study.

Allele	Healthy Japanese volunteers		SJS/TEN		Dominant genotypic model	
	Allele frequency (%)	*Carriers, n (%)*	*Allele frequency (%)*	*Carriers, n (%)*	*p-value Pc-value*	*Odds ratio (95% CI)*
Phenytoin-induced SJS/TEN						
*HLA-B*51:01*	438/5756 (7.87)	438/2878 (15.22)	5/18 (27.78)	5/9 (55.56)	p = 0.0061 Pc = 0.1037	6.96 (1.86–26.03)
Zonisamide-induced SJS/TEN						
*HLA-A*02:07*	201/5756 (3.49)	196/2878 (6.81)	5/24 (20.83)	5/12 (41.67)	p = 0.0008 Pc = 0.0176	9.77 (3.07–31.1)
*HLA-B*46:01*	286/5756 (4.97)	276/2878 (9.59)	5/24 (20.83)	5/12 (41.67)	p = 0.0037 Pc = 0.0814	6.73 (2.12–21.36)
*HLA-DRB1*08:03*	475/5756 (8.25)	457/2878 (15.88)	5/24 (20.83)	5/12 (41.67)	p = 0.0306 Pc = 0.6732	3.78 (1.20–11.97)
Phenobarbital-induced SJS/TEN						
*HLA-A*24:20*	48/5756 (0.83)	47/2878 (1.46)	2/16 (12.50)	2/8 (25.00)	p = 0.0074 Pc = 0.1036	20.08 (3.95–102.07)
*HLA-B*51:01*	453/5756 (7.87)	438/2878 (15.22)	7/16 (43.75)	6/8 (75.00)	p = 0.0003 Pc = 0.0042	16.71 (3.66–83.06)
*HLA-DRB1*04:10*	115/5756 (2.00)	114/2878 (3.96)	2/16 (12.50)	2/8 (25.00)	p = 0.0383 Pc = 0.5362	8.08 (1.61–40.48)

Pc: Corrected p-value by Bonferroni's method; SJS: Stevens–Johnson syndrome; TEN: Toxic epidermal necrolysis.

significant after Bonferroni's correction. Therefore, *HLA-A*02:07* or *HLA-B*46:01* rather than *HLA-C*01:02* and *HLA-DRB1*08:03* may be responsible for the development of zonisamide-induced SJS/TEN in Japanese patients. The allelic frequencies of *HLA-A*02:07* in Japanese, Korean and Chinese individuals are 0.07–2.2, 3.0 and 0–22.7%, respectively, and the frequencies are very low in Caucasian and African individuals (0.0–1.0%) [32]. The allelic frequencies of *HLA-B*46:01* in Japanese, Korean, Chinese, Caucasian and African individuals are 1.0–6.1, 4.4, 0.0–25.4, 0.0–0.7 and 0.0–3.1%, respectively [32]. Strong associations between *HLA-B*59:01* and SJS/TEN caused by methazolamide and acetazolamide, which are sulfonamide derivatives used as carbonic anhydrase inhibitors for lowering intraocular pressure in glaucoma, have been reported in Japanese [33] and Korean patients [34,35]. Although zonisamide has a sulfonamide structure, as shown in Supplementary Figure 1 (see www.futuremedicine.com/doi/suppl/10.2217/PGS.13.180), no patients with SJS/TEN caused by zonisamide carried *HLA-B*59:01* in this study.

We found an association between phenobarbital-induced SJS/TEN and *HLA-B*51:01*, even after the correction for multiple testing. This allele was also marginally associated with phenytoin-induced SJS/TEN in analyses based on a dominant model ($p = 0.0061$; $Pc = 0.1037$; Table 2). The allelic frequency of *HLA-B*51:01* has also been reported to be higher in Han Chinese patients in Taiwan with phenytoin-induced SJS/TEN than in a tolerant control group, although the association was not statistically significant [15]. As shown in Supplementary Figure 1, phenobarbital and phenytoin have a very similar chemical structure that are very different from the structures of carbamazepine and zonisamide. Phenobarbital and phenytoin are heterocyclic compounds with two nitrogen atoms embedded in their rings that are substituted with at least two carbonyl groups and with at least one phenyl group. Therefore, it is not surprising that the same HLA molecule type is potentially involved in the onset of SJS/TEN caused by phenobarbital and phenytoin. The same mechanism, such as direct interactions with *HLA-B*51:01* molecules, may be involved in the pathogenesis of SJS/TEN for these two drugs, as previously shown for carbamazepine-induced SJS/TEN [36]. Thus, *HLA-B*51:01* may be a risk factor for SJS/TEN caused by phenytoin and phenobarbital in Asian individuals.

Three HLA types, that is, *HLA-A*02:07*, *HLA-B*46:01* and *HLA-B*51:01*, which were associated with zonisamide- or phenobarbital-induced SJS/TEN, were also detected in patients with SJS/TEN caused by the other drugs collected by the JSAR research group, but their allelic frequencies were similar to those in healthy volunteers (data not shown). Since three of the five carriers of *HLA-A*02:07* and three of the nine carriers of *HLA-B*51:01* were patients with secondary epilepsy caused by various conditions, such as brain bleeding, brain surgery, brain injury or brain tumors (Table 1), these alleles have been suggested to be risk factors for SJS/TEN rather than biomarkers for epilepsy.

As shown in Table 2, the allele frequencies of *HLA-B*51:01*, *HLA-A*02:07* and *HLA-B*46:01* in our Japanese population were 7.87, 3.49 and 4.97%, respectively, and they were therefore relatively common alleles in Japanese individuals. As the incidence of SJS/TEN caused by these three drugs is very low, as assumed from the patient numbers reported to the regulatory agency according to the pharmaceutical affairs law, most patients carrying these alleles will not develop SJS/TEN when they receive these drugs. This discrepancy between the incidence of adverse reactions and biomarker allele frequencies is also seen in the case of carbamazepine-induced SJS/TEN in Taiwan, where the allele frequency of *HLA-B*15:02* is relatively high (8.6%) [6] and the incidence of carbamazepine-induced SJS/TEN among patients to whom the drug was newly given was very low (0.22–0.24%) [37]. For the case of carbamazepine-induced SJS/TEN, biased usage of a specific repertoire of the third complementarity-determining region of the T-cell receptor, VB-11-ISGSY, is associated with the development of SJS/TEN in addition to carrying *HLA-B*15:02* [38]. In the development of SJS/TEN induced by zonisamide, phenobarbital or phenytoin, other risk factors, which could be specific to culprit drugs and phenotypes of adverse reactions, may also be required. To elucidate these factors, *in vitro* or clinical studies using blister fluid or T-cells obtained from patients are necessary.

Sensitivities of *HLA-A*02:07* (41.7%) in zonisamide-induced SJS/TEN and *HLA-B*51:01* (55.6%) in phenytoin-induced SJS/TEN were not as high as those observed in carbamazepine-induced SJS/TEN and allopurinol-induced CARs observed in Taiwanese

patients (98–100%) [6,21]; the reasons for this are unclear. However, the sensitivities of the biomarkers observed in this study are nearly comparable with those of *HLA-B*58:01* in patients with allopurinol-induced SJS/TEN in Japan (55.6%) [24] and in Europe (55.6%) [13], and with those of *HLA-A*31:01* in Japanese and European patients with carbamazepine-induced CARs (58.4 and 27.3%, respectively) [19,20]. The clinical usefulness of biomarkers that show such moderate associations with adverse reactions remains inconclusive.

The results obtained in this study may have limited impact due to the very small sample size. Performance characteristics of *HLA-A*02:07* and *HLA-B*51:01*, such as positive predictive value, negative predictive value or number of patients needed to test, could not be calculated or estimated since this was a retrospective case–control study and the prevalence of SJS/TEN caused by these aromatic antiepileptic drugs in Japan is not known. Furthermore, we could not rule out the effects of population stratification on our results. Independent replication studies are necessary to confirm the roles of these *HLA* types detected in our study in the development of SJS/TEN induced by zonisamide, phenobarbital or phenytoin.

Conclusion

Our exploratory study suggested associations of the haplotype *HLA-A*02:07_HLA-B*46:01_HLA-C*01:02_HLA-DRB1*08:03* and the allele *HLA-A*02:07* with zonisamide-induced SJS/TEN, and an association of the allele *HLA-B*51:01* with phenobarbital-induced SJS/TEN in Japanese patients. The involvement of these alleles in the development of SJS/TEN should be confirmed by independent replication studies with larger sample sizes as well as *in vitro* studies, such as binding studies with HLA molecules expressed in cells.

Future perspective

Genomic biomarkers showing an association with the onset of CARs have been identified, and personalized medicine has started identifying patients at high risk of severe CARs based on pharmacogenomics by using biomarkers, such as *HLA-B*15:02* and *HLA-B*57:01*. However, among more than 100 causative drugs, including aromatic antiepileptic drugs, biomarkers have only been identified for a select few, such as carbamazepine, allopurinol and abacavir. Therefore, more intensive, nationwide or even international case–control studies are necessary to identify corresponding biomarkers that can predict patients at high risk on the basis of ethnicity and the causative drug. The accumulation of such data may help to uncover the pathogenic mechanisms of SJS/TEN, which will be useful for determining the safety of new molecules at early stages of the drug-development process and, thus, contribute to the development of new treatments for, or prevention of, severe CARs.

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Executive summary

Background

- Recently, the serotype HLA-B75 has been reported to be a risk factor for carbamazepine-induced SJS/TEN in Asians, and *HLA-A*31:01* has been reported to be a risk factor for carbamazepine-induced severe cutaneous adverse reactions, including SJS/TEN, in both Asians and Europeans.
- *HLA-B*15:02* is associated with phenytoin-induced SJS/TEN in Han Chinese patients in Taiwan.
- We conducted a case–control study investigating genetic biomarkers related to antiepileptic drug-induced SJS/TEN in Japanese patients.

Methods

- *HLA* class I and *HLA-DRB1* loci were genotyped in Japanese patients with zonisamide-, phenobarbital- or phenytoin-induced SJS/TEN and in healthy Japanese volunteers.

Results

- In dominant genetic models, *HLA-A*02:07* and *HLA-B*51:01* were associated with zonisamide- and phenobarbital-induced SJS/TEN, respectively, in Japanese patients.

Conclusion

- *HLA-A*02:07* and *HLA-B*51:01* are potential risk factors for zonisamide- and phenobarbital-induced SJS/TEN in Japanese patients.
- Independent replication studies are necessary to confirm the roles of these HLA types in the development of SJS/TEN induced by these aromatic antiepileptic drugs.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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Affiliations

- **Nahoko Kaniwa**
Division of Medicinal Safety Science, National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan
and
The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
- **Emiko Sugiyama**
Division of Medicinal Safety Science, National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan
and
The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
- **Yoshiro Saito**
Division of Medicinal Safety Science, National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan
and
The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
- **Kouichi Kurose**
Division of Medicinal Safety Science, National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan
and
The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
- **Keiko Maekawa**
Division of Medicinal Safety Science, National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan
and
The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
- **Ryuichi Hasegawa**
Division of Medicinal Safety Science, National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya-ku, Tokyo 158-8501, Japan
and
The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
- **Hirokazu Furuya**
The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
and
Department of Neurology, Neuro-Muscular Center, National Omuta Hospital, Omuta, Japan
- **Hiroko Ikeda**
The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
and
Shizuoka Institute of Epilepsy & Neurological Disorders, National Epilepsy Center, Shizuoka, Japan
- **Yukitoshi Takahashi**
The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
and
Shizuoka Institute of Epilepsy & Neurological Disorders, National Epilepsy Center, Shizuoka, Japan
- **Masaaki Muramatsu**
The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
and
Molecular Epidemiology, Medical Research Institute, Tokyo Medical & Dental University, Tokyo, Japan
- **Masahiro Tohkin**
The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
and
Division of Medicinal Safety Science, Graduate School of Pharmaceutical Sciences, Nagoya City University, Nagoya, Japan
- **Takeshi Ozeki**
Center for Genomic Medicine, RIKEN, Yokohama, Japan
- **Taisei Mushiroda**
Center for Genomic Medicine, RIKEN, Yokohama, Japan
- **Michiaki Kubo**
Center for Genomic Medicine, RIKEN, Yokohama, Japan
- **Naoyuki Kamatani**
Center for Genomic Medicine, RIKEN, Yokohama, Japan
- **Masamichi Abe**
The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
and
Department of Dermatology, Fujita Health University School of Medicine, Toyoake, Japan

- **Akiko Yagami**
  The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
  and
  Department of Dermatology, Fujita Health University School of Medicine, Toyoake, Japan
- **Mayumi Ueta**
  The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
  and
  Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan
- **Chie Sotozono**
  The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
  and
  Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan
- **Shigeru Kinoshita**
  The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
  and
  Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan
- **Zenro Ikezawa**
  The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
  and
  Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan
- **Kayoko Matsunaga**
  The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
  and
  Department of Dermatology, Fujita Health University School of Medicine, Toyoake, Japan
- **Michiko Aihara**
  The Japan Severe Adverse Reactions (JSAR) Research Group, Tokyo, Japan
  and
  Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan
- **Japan Pharmacogenomics Data Science Consortium**
  The Japan Pharmacogenomics Data Science Consortium (JPDSC) is composed of Astellas Pharma Inc., Otsuka Pharmaceutical Co., Ltd, Daiichi Sankyo Co., Ltd, Taisho Pharmaceutical Co., Ltd, Takeda Pharmaceutical Co., Ltd and Mitsubishi Tanabe Pharma, and is chaired by Ichiro Nakaoka (Takeda Pharmaceutical Co., Ltd)

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REVIEW ARTICLE

Long-term outcome of patients with severe cutaneous adverse reactions

Yoko Kano*, Tetsuo Shiohara

Department of Dermatology, Kyorin University School of Medicine, Mitaka, Tokyo, Japan

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ABSTRACT

Visceral involvement associated with Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) is well documented. However, little is known about the long-term outcomes of severe drug eruptions due to a lack of long-term follow-up. Long-term sequelae may arise in patients who survive the acute complications of severe drug reactions. In SJS/TEN, extensive scarring that result from the healing of mucocutaneous ulcerative lesions may interfere with organ function. Severe sequelae include visual impairment and pulmonary obliterative disease that impair patients' quality of life. In DIHS/DRESS, recent observations suggest that fulminant type 1 diabetes mellitus (FT1D) and autoimmune diseases such as autoimmune thyroiditis and lupus erythematosus can occur after a disease-free period of several months to years. Thus, DIHS/DRESS may lead to the development of autoimmune diseases, which may be overlooked. Dermatologists need to be aware of the sequelae that may arise following resolution of severe cutaneous adverse reactions and should be vigilant for manifestations of autoimmune disease during follow-up.

Introduction

Severe cutaneous adverse eruptions include Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS). Visceral involvement can occur during the course of these diseases, including sepsis and pneumonitis in SJS/TEN, and hepatitis and renal failure in DIHS/DRESS. However, the long-term sequelae after resolution of severe drug eruptions is not well known, due to the lack of long-term follow-up and the potential development of sequelae after a disease-free period of several months to years. As there is limited information on the long-term outcomes of severe drug eruptions,[1–3] we present a review on the long-term outcomes of SJS/TEN and DIHS/DRESS.

Sequelae in SJS/TEN

SJS/TEN are rare, potentially life-threatening conditions triggered by drug administration and infections.[4,5] SJS and TEN are now recognized as variants of the same condition with differing severities. Although the pathomechanism of epidermal necrosis in SJS/TEN remains unknown, various factors have been implicated, including drug-specific T cells and/or monocytes/macrophages,[6] regulatory T cell function,[7,8] Fas/Fas ligand and perforin/granzyme B,[9] pro-inflammatory cytokines,[10,11] and granulysin produced by natural killer cells.[12] The skin and mucous membrane are affected in SJS/TEN, and mucosal involvement can be more severe than cutaneous involvement. Healing of ulcerative mucosal lesions may result in extensive scarring that interferes with organ function. Ocular and dermatologic long-term sequelae may occur and affect patients' quality of life, emphasizing the need for long-term follow-up of patients after resolution of SJS/TEN.

Ocular sequelae in SJS/TEN

Ocular sequelae in patients with SJS/TEN are well documented. The involvement of the ocular surface is very common and can result in long-term complications. In the acute disease, many patients experience mild to severe ocular involvement,[1] which include conjunctivitis and epithelial sloughing in mild cases, and pseudomembranous and membranous conjunctivitis and corneal and/or conjunctival epithelial defects with severe pain and photophobia in severe cases.[13] Inflammation of the ocular surface frequently persist

* Corresponding author. Department of Dermatology, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan. Tel.: +81 422 47 5511; fax: +81 422 47 9632.
E-mail address: kano@ks.kyorin-u.ac.jp (Y. Kano).

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after complete resolution of cutaneous lesions, leading to ocular sequelae in chronic stage, at least 1 year from the onset of SJS/TEN. Even minor involvement of the ocular surface in the acute disease may lead to chronic ocular discomfort that requires long-term therapy.

The ocular sequelae are broadly classified into three categories depending on the involving area. Corneal sequelae include superficial punctate keratinopathy, epithelial defect, loss of the palisades of Vogt, conjunctivalization, neovascularization, opacification, and keratinization. Conjunctival sequelae include conjunctival hyperemia and symblepharon formation. Eyelid sequelae include trichiasis, mucocutaneous junction involvement, meibomian gland involvement, lacrimal gland and duct involvements, and punctal damage (Figure 1).[1] These lesions can cause prolonged ocular discomfort and visual impairment, and may require long-term therapy. Among ophthalmic problems, severe dry eye is the most common long-term ocular sequela and is present in approximately 50% of patients with SJS/TEN. Trichiasis is also a common ocular sequela. In particular, corneal involvement such as neovascularization, opacification, and keratinization correlates with visual acuity (Table 1).

With respect to possible causes, *Mycoplasma pneumoniae*-associated SJS induced more ocular involvement during the acute stage than drug-induced SJS. *Mycoplasma pneumoniae*-associated SJS seldom caused long-term ocular sequelae in children, while adult patients remained at risk for long-term sequelae.[14,15] Recent genotype analyses revealed that multiplicative interactions of human leukocyte antigen (HLA)-A and Toll-like receptor 3 (TLR3) genes might be required for the development of ocular complications in SJS/TEN.[16]

Mucocutaneous sequelae in SJS/TEN

Despite documented involvement of the genitals in female patients with SJS/TEN, little information exists regarding long-term genital complications. Genital involvement during SJS/TEN includes erosive and ulcerative vaginitis, vulvar bullae, and vaginal synechiae.[17] Extensive scarring that affects genital function may occur with the healing of mucosal ulcerations.

Vaginal or vulvar areas of necrosis may form adhesions. Very few cases of symptomatic vaginal obstruction after SJS/TEN have been documented. Pathologic changes in the vulvovaginal area have been observed in women with SJS/TEN. Vulvovaginal adenosis/endometriosis—defined by the presence of metaplastic cervical or endometrial glandular epithelium within the vaginal wall—has been reported, causing dyspareunia and postcoital bleeding.[17] The cause remains unknown; it has been proposed that tubal or uterine epithelium implant over the raw areas during SJS/TEN.[18] The malignant potential of adenosis is unknown, but transformation to adenosis with cellular atypia of the vagina has been reported.[17] In a pediatric case, extensive labial synechiae and hydrocolpos occurred several years after an episode of SJS/TEN. Amenorrhea, cyclical abdominal pain, or a hypogastric mass in girls after an episode of SJS/TEN may indicate acquired vaginal obstruction. Thus, after a diagnosis of SJS/TEN in girls, it is prudent to schedule a prepubertal genital examination to avoid obstructed menstruation and future sexual problems.[18]

Table 1 Sequelae in SJS/TEN.

Ocular lesion
Cornea: superficial punctate keratinopathy, epithelial defect, loss of palisades of Vogt, conjunctivalization, neovascularization, opacification, keratinization
Conjunctiva: conjunctival hyperemia, symblepharon formation
Eyelid: trichiasis, mucocutaneous junction involvement, meibomian gland involvement, lacrimal gland and duct involvements, punctal damage
Mucocutaneous lesion
Urogenital system: vaginal obstruction/vaginal stenosis, vulvovaginal adenosis/endometriosis, urinary stream egress obstruction
Skin: pigmentary change, dry skin (xeroderma), appearance of melanocytic nevi or ectopic sebaceous gland, nail deformity
Pulmonary lesion
Obliterative bronchitis/bronchiolitis
Esophageal lesion
Stricture formation

SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis.

Several strategies to prevent vulvovaginal sequelae have been described. The application of intravaginal glucocorticoids, use of vaginal molds, and menstrual suppression during SJS/TEN have been proposed to reduce the formation of adhesions and limit metaplastic changes in affected areas.[17]

Other mucosal sequelae resulting from an obstructed urinary system include urinary retention and recurrent cystitis. Persistent lingual ulcerations and recurrent oral aphthae can be observed months after the resolution of SJS/TEN.[19]

Unlike mucous membranes, the skin usually heals within weeks without scarring if wounds are treated adequately. The development of hypertrophic scars in SJS/TEN has rarely been described in the literature.[20] Other cutaneous sequelae include dyspigmentation, nail deformity and fingernail loss, and xeroderma. It is likely that nail involvement is associated with ophthalmic involvement (Figure 2).[21] It is well known that Sjögren-like syndrome frequently

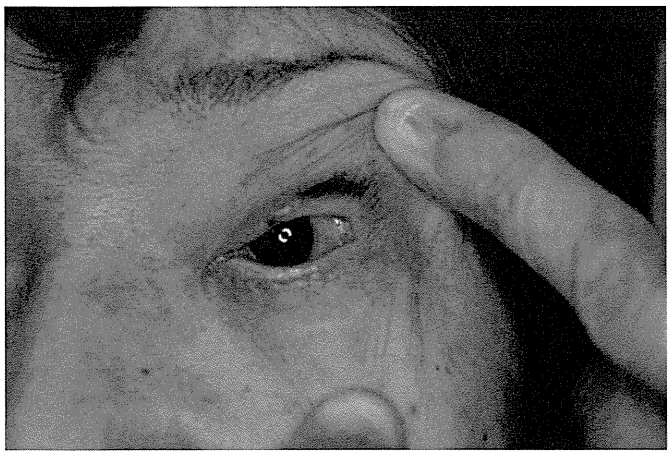

Figure 1 Blepharosynechia after resolution of toxic epidermal necrolysis (TEN).

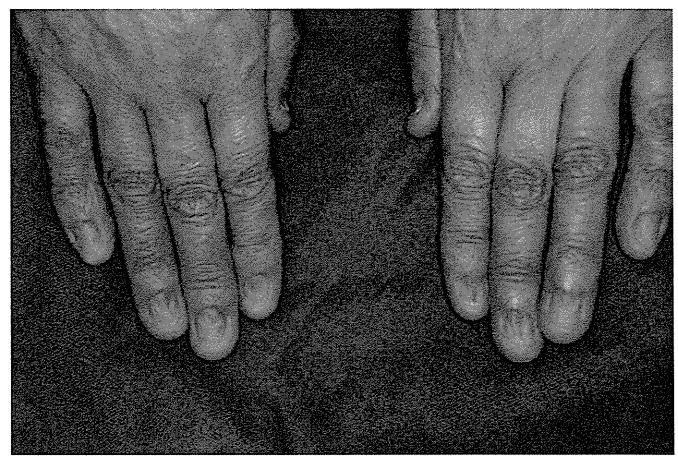

Figure 2 Nail loss after resolution of toxic epidermal necrolysis (TEN).

occurs after resolution of TEN.[22] Dry skin and heat intolerance are common complaints among survivors of SJS/TEN with involvement of the eccrine duct, although the secretory gland is usually normal.[23]

The sudden appearance of numerous melanocytic nevi following severe bullous lesions in a patient with SJS had been reported; it was speculated that the production of cytokines and growth factors during epidermal regeneration may have led to the proliferation of melanocytes.[24] In a separate case, widespread eruption of ectopic sebaceous glands occurred 4 months after an episode of SJS.[25] Similar to the aforementioned case, cytokines and growth factors were thought to be responsible for the proliferation of residual sebaceous gland cells.[25]

Pulmonary sequelae in SJS/TEN

The incidence of pulmonary involvement in SJS/TEN has not been examined. Pulmonary involvement in SJS/TEN is divided into two types: interstitial pneumonia during the course of SJS/TEN, and obliterative bronchitis/bronchiolitis after the resolution of SJS/TEN.[26] According to one report, pulmonary sequelae tend to occur in relatively young patients.[27] A few cases of obliterative bronchitis/bronchiolitis after SJS/TEN have been documented, as well as respiratory tract obstruction and bronchiectasis. The interval from the onset of SJS/TEN to development of pulmonary sequela is unclear because some reported cases show persistent respiratory symptoms from the onset of SJS/TEN.[27]

Obliterative bronchitis/bronchiolitis is diagnosed using imaging and respiratory function tests, with findings of bronchiectasis on high resolution computed tomography (CT) of the chest, occlusion of the bronchus on bronchoscopy, and a severe obstructive pattern in the flow–volume curve. Although the pathomechanism remains unknown, immunological pathways, infection, and remodeling of the bronchial mucosa are implicated in the pulmonary sequelae of SJS/TEN.

If patients suffer from recurrent respiratory symptoms after the resolution of SJS/TEN, they should be closely monitored using respiratory function tests and CT. No effective treatment is available for permanent obstructive pulmonary changes in obliterative bronchitis/bronchiolitis. In severe cases, mechanical ventilation is required, and living-donor lung transplantation may be necessary. Patients with pulmonary sequela after resolution of SJS/TEN tend to have a poor prognosis.

Esophageal sequelae in SJS/TEN

Long-term sequelae involving the gastrointestinal tract have rarely been reported. Esophageal stricture as a consequence of SJS has been reported in children but is rare in adults.[28,29] Two patients had foreign bodies lodged in esophageal strictures, occurring at 7 months after the episode of SJS in one case and at 18 months after the episode of SJS in the other case. The delay in the onset of dysphagia suggests that stricture formation may be subclinical. SJS/TEN-related esophageal stricture is thought to occur because of irritation caused by orally administrated medications, ingestion of coarse food, or nasogastric feeding during SJS/TEN. Esophageal strictures after SJS/TEN are easily dilated, suggesting that the condition is caused by injury to the esophageal mucosa without involvement of the muscularis.[29]

Sequelae in DIHS/DRESS

DIHS/DRESS is a severe adverse drug reaction caused by specific drugs such as anticonvulsants and allopurinol, and is characterized by visceral involvement and reactivation of human herpesviruses (HHV).[30–32] Various internal organs can be affected during the course of disease.[33–39] Furthermore, the development of autoimmune diseases several months to years after clinical resolution of DIHS/DRESS have been reported.[2,3] Several autoimmune diseases can develop sequentially in a single patient.[40] The emergence of autoimmune disease might be overlooked unless dermatologists perform long-term follow-up of patients after their recovery from DIHS/DRESS (Figure 3).[41]

Internal organ failure

Previous reports reveal that severe renal insufficiency increases the risk of mortality, and mortality depends in part on the degree of renal involvement rather than hepatic involvement.[41] Renal insufficiency following after acute interstitial nephritis at the acute stage of DIHS/DRESS could require a lifetime hemodialysis.[2] It is more likely to occur in elderly patients with pre-existing renal disease or those receiving diuretic therapy. Because renal function declines steadily with age, elderly patients are vulnerable to renal complications and sequelae.

Appearance of autoantibody after onset of DIHS/DRESS

Autoantibodies have been detected in patients with DIHS/DRESS after resolution of the disease. According to an analysis of 34 cases of DIHS/DRESS at our institution, autoantibodies such as antinuclear antibody (ANA), anti-thyroperoxidase (TPO), and anti-thyroglobulin antibodies were observed without any clinical manifestations.[3] The proportion of DIHS/DRESS patients with autoantibodies is higher than that seen in SJS/TEN patients.[42] The percentage of DIHS/DRESS patients with autoantibodies was higher in the group that received supportive treatment alone than those who received systemic corticosteroids.[3] The autoantibody titers fluctuated but remained elevated during the observation period. Our study showed that autoantibodies are present in some patients after clinical resolution of DIHS/DRESS without causing clinically overt diseases.

Autoimmune thyroid disease as a sequela in DIHS/DRESS

Thyroid disease is the most frequently detected sequela following the resolution of DIHS/DRESS, with a cumulative incidence of 3.8%. This incidence is more than 10-fold higher than the expected incidence of this disease in the Chinese population.[2] Endocrinologic evaluation of patients with DIHS/DRESS revealed thyroid gland abnormalities, such as increased free thyroxine (FT4), low thyroid-stimulating hormone (TSH), and elevated TSH levels, and production of autoantibodies, including anti-TSH receptor, anti-TPO, and anti-thyroglobulin antibodies. As symptoms are not usually observed, these abnormal findings may be missed if evaluation of thyroid function and antibodies are not performed.

Graves' disease may develop after the resolution of DIHS/DRESS. Recently, it has been reported that the interval between discontinuation of the causative drug and the onset of Graves' disease is approximately 2 months to 1 year. A recent case report described the appearance of a diffuse large thyroid goiter followed by hyperthyroidism 2 months after the onset of sulfasalazine-induced DIHS/DRESS.[43] Thyrotoxicosis can be the initial presenting symptom of thyroid disease.[44] Two patients diagnosed with Graves' disease with symptoms of hyperthyroidism and elevation in FT4 plus suppression of TSH have been documented—one case had symptoms 1 month after the onset of DIHS/DRESS while the other had symptoms 9 months after the onset of DIHS/DRESS.[2] Brown et al described a patient with Graves' disease confirmed by thyroid tests that developed 5 months after withdrawal of the causative

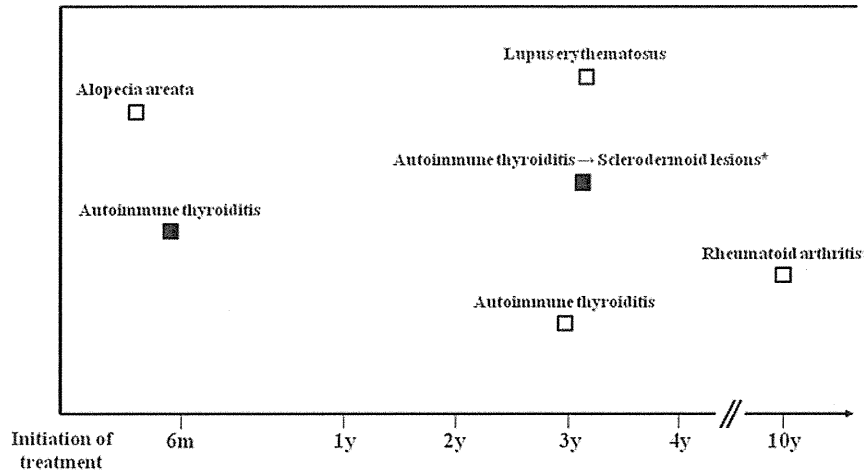

Figure 3 Autoimmune diseases developed after resolution of drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS). Six out of the 37 patients with DIHS/DRESS developed autoimmune diseases in our institution. The period of follow-up was more than 6 months after the initiation of treatment. (■), treated with systemic corticosteroid; (□), treated with supportive therapy alone; *, sclerodermoid graft-versus-host disease (GVHD)-like lesions.

drug.[45] The patient had low TSH and elevation of FT4 without symptoms of hyperthyroidism, and tests for anti-TSH receptor antibody and thyroid-stimulating immunoglobulin were negative at that time. Autoimmune thyroiditis can develop following the relapse of DIHS/DRESS.[46]

The emergence of Hashimoto's disease, characterized by the presence of anti-TPO antibody and anti-thyroglobulin antibodies, has also been observed after the resolution of DIHS/DRESS. The authors have encountered a patient with DIHS/DRESS who developed Hashimoto's disease 3 years after resolution of the clinical symptoms of DIHS/DRESS, characterized by elevated levels of anti-TPO and anti-thyroglobulin antibodies.[3] Alopecia has been noted in patients with autoimmune thyroid disease.[2,3,40] The presence of HHV-6 in the thyroid was significantly higher in Hashimoto's thyroiditis than in controls, highlighting a possible association between HHV-6 reactivation and autoimmune thyroid disease.[47,48]

Type 1 diabetes mellitus as a sequela in DIHS/DRESS

Some cases of fulminant type 1 diabetes mellitus (FT1D) have been associated with DIHS/DRESS.[49–52] FT1D is a subtype of type 1 diabetes mellitus (T1D) characterized by an abrupt onset, absence of islet-related autoantibodies, and nearly complete destruction of pancreatic β-cells. The initial symptoms of T1D are vomiting and dull epigastric pain; laboratory examinations reveal hyperglycemia, hyperosmolarity and metabolic acidosis, and a relatively normal glycosylated hemoglobin level; these features are compatible with diabetic ketoacidosis. The onset of FT1D is characterized by elevated levels of pancreatic exocrine enzymes such as lipase and amylase, which is consistent with acute pancreatitis.

According to a nationwide survey in Japan, there were 15 cases of FT1D associated with DIHS/DRESS between 1985 and 2010. The mean age at onset of FT1D associated with DIHS/DRESS was 53.4 years; the interval between the onset of DIHS/DRESS to the development of FT1D was 39.9 days (range, 13–199 days). The incidence of FT1D in patients with DIHS/DRESS (0.54%) is much higher than that in the general Japanese population (0.010%).[53] The clinical manifestations of FT1D associated with DIHS/DRESS are similar to those not associated with DIHS/DRESS. It is possible that genetic susceptibility contributes to the development of FT1D. Notably, the incidence of HLA-B62 is significantly increased in this type of diabetes mellitus in Japanese patients with DIHS/DRESS. Viral reactivation may contribute to the development of FT1D in patients with DIHS/DRESS, based on the observation that FT1D is associated with viral infections such as influenza B, HHV-6, herpes simplex virus, and Coxsackie B3 virus.[54,55] In this setting, the rapid and severe damage to pancreatic β-cells may be caused by viral infections, an immune response, or an interplay between viruses and the immune response.[56]

By contrast, autoimmune T1D is rare in patients with DIHS/DRESS. In autoimmune T1D, various autoantibodies including anti-glutamic acid decarboxylase (GAD) and islet cell antibodies are detected. The coexistence of autoimmune T1D and autoimmune thyroiditis has been associated with DIHS/DRESS.[45] In this case, various autoantibodies including insulinoma antigen 2 (IA2), anti-GAD, anti-TPO, anti-thyroglobulin, and anti-SSA antibodies and ANA were detected over a period of several months. A case of T1D following methimazole-induced hypersensitivity syndrome has been reported,[51] in which high glucose levels with a low serum C-peptide were detected 5 months after the onset of DIHS/DRESS in a patient with Graves' disease. Interestingly, anti-GAD antibodies were detected but at a relatively low level. A case of FT1D and Hashimoto's disease that developed concurrently after the onset of DIHS/DRESS has been reported, characterized by the presence of anti-thyroglobulin antibodies, ANA, and anti-SSA antibodies with an absence of GAD and islet cell antibodies.[57]

The consequences of missing the diagnosis of T1D can be fatal. It is essential to recognize the initial symptoms of T1D in patients with DIHS/DRESS in order to initiate appropriate treatment.

Other sequelae in DIHS/DRESS

Besides autoimmune thyroiditis and T1D, other autoimmune sequelae—heralded by autoimmune manifestations and/or presence of autoantibodies—can arise after resolution of DIHS/DRESS following a symptom-free interval of several months to years. These autoimmune diseases include sclerodermoid graft-versus-host disease (GVHD)-like lesions,[40] lupus erythematosus,[58] autoimmune hemolytic anemia (AIHA),[2] and rheumatoid arthritis (Table 2).

The authors have encountered three interesting cases of DIHS/DRESS with autoimmune sequelae of sclerodermoid GVHD-like lesions and autoimmune thyroiditis, atypical SLE, and rheumatoid arthritis, which appeared 3.5 years, 4 years, and 10 years after resolution of DIHS/DRESS, respectively. The first patient had a history of zonisamide-induced DIHS/DRESS and presented with fatigue and symptoms of thyroid dysfunction; diffuse alopecia on the scalp and multiple ill-defined brownish, indurated plaques with xerosis on the

Table 2 Autoimmune diseases as sequelae in DIHS/DRESS.

Alopecia
AIHA
Graves' disease
Hashimoto's disease
Lupus erythematosus
Rheumatoid arthritis
Sclerodermoid GVHD-like lesion
T1D (fulminant and autoimmune)

AIHA = autoimmune hemolytic anemia; DIHS/DRESS = drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms; GVHD = graft-versus-host disease; T1D = type 1 diabetes mellitus.

extremities were observed on examination.[40] Interestingly, ANA was negative during the course of DIHS/DRESS, but was detectable at the time of presentation to our hospital.[40] The second patient had a history of carbamazepine-induced DIHS/DRESS with reactivation of HHV-6 and EBV, and presented with a high-grade fever, general fatigue, cervical lymphadenopathy, and erythematous lesions on his face and ears.[58] After resolution of DIHS/DRESS, he developed prominent cervical lymphadenopathy. Histological findings of a lymph node biopsy specimen were compatible with those of Kikuchi-Fujimoto disease, and expression of EBV-encoded RNA (EBER) was detected in the lymph node by *in situ* hybridization, but not in the blood. Clinical manifestations of SLE including fever, general fatigue, discoid lesions, leucopenia, and proteinuria appeared 2 weeks after the onset of Kikuchi-Fujimoto disease. The third patient had a history of carbamazepine-induced DIHS/DRESS with the appearance of autoantibodies such as ANA, anti-TPO, and anti-thyroglobulin antibodies after the resolution of DIHS/DRESS. The autoantibody levels fluctuated without overt clinical symptoms. Ten years after the onset of DIHS/DRESS, the patient developed rheumatoid arthritis with characteristic joint deformities of the hands. It was noted that the second and third cases of DIHS/DRESS had been treated with supportive therapy alone. Chen et al described a case of AIHA and suspected SLE after the resolution of dapsone-induced DIHS/DRESS.[2] In that case, the patient had a high lactate dehydrogenase level, elevated percentage of reticulocytes, decreased haptoglobin concentration, and a positive Coombs test.

Pathomechanism of autoimmune disease in DIHS/DRESS

The pathomechanism underlying the emergence of autoimmune disease in DIHS/DRESS is poorly understood. A genetic susceptibility may contribute to their development.[53] Based on long-term follow-up of patients with DIHS/DRESS, several observations regarding the development of autoimmune sequelae were noted: young patients[2] and those treated with non-corticosteroid therapy were more susceptible,[3] and that herpesvirus reactivation—in particular, Epstein-Barr virus reactivation—is implicated in its development.[3,56]

From an immunological perspective, our previous study showed that the number of fully functional $CD4^+CD25^+FoxP3^+$ regulatory T (Treg) cells is markedly increased during the course of DIHS/DRESS compared with other drug reactions, which contributed to viral reactivation. These $FoxP3^+$ T cells lost their ability to inhibit the cytokine production and proliferation of effector T cells, which coincided with their contraction upon clinical resolution of DIHS/DRESS. The functional defect of Treg cells might be responsible for the development of autoimmune disease.[8,56,59]

Conclusion

In summary, the development of long-term sequelae after resolution of severe cutaneous adverse drug reactions may be overlooked because of an asymptomatic interval after resolution of the acute disease. The emergence of sequelae should be closely monitored following the resolution of SJS/TEN and DIHS/DRESS, especially autoimmune disease in DIHS/DRESS. The reactivation of herpesviruses and development of autoimmune disease in DIHS/DRESS may indicate a possible link between viral infections and autoimmune disease.

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LETTER

RESEARCH LETTER

Methylprednisolone pulse therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis: Clinical evaluation and analysis of biomarkers

To the Editor: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe, potentially life-threatening, cutaneous reactions.[1] Progress has been made in determining the pathophysiologic mechanisms of SJS/TEN; however, there has been little progress in the treatment of these conditions.[2,3] Thus, the efficacy of steroid pulse therapy and alterations of biomarkers were assessed retrospectively.

The medical records of 8 patients treated with methylprednisolone pulse therapy (MPT) for SJS/TEN were reviewed, documenting clinical findings and specific biomarkers. The diagnosis of SJS/TEN was based on Bastuji-Garin criteria.[4] High-grade fever was present on admission in 6 of 8 patients and all had mucosal lesions. Causative agents were identified in 7 of 8 patients. These agents were nonsteroidal anti-inflammatory drug (diclofenac and loxoprofen), antimicrobial agent (garenoxacin and penicillin), anticonvulsant (lamotrigine and zonisamide), and bromhexine. Notable coexisting conditions included malignancy (lung and colon) in two patients, cerebral hematoma complicated by tachycardia and diabetes mellitus in 1 patient, and increased serum creatinine in 1 patient. In the calculation of SCORTEN (a severity-of-illness score for TEN that predicts mortality),[5] the mean SCORTEN on admission was 2.1 (range, 0-4) (Table I). [T1]

An infusion of methylprednisolone at 1000 mg/d for 3 consecutive days was administered. Oral prednisolone at 0.8-1 mg/kg/d was initiated if no new mucocutaneous lesions were observed on the day following the last dose of MPT, and prednisolone was subsequently tapered every week. If the high-grade fever persisted or a reduction in body surface area (BSA) involvement was not observed after the last dose of MPT, a course of half-dose methylprednisolone pulse therapy (500 mg/d for 2 consecutive days) was administered.

No patients died during the follow-up period of 3 months, whereas predicted mortality was 1.6 deaths according to SCORTEN. In 7 of 8 patients after initiation of MPT, the mean BSA of epidermal detachment was reduced at day 4, and complete re-epithelialization was observed in a mean interval of 12.7 ± 7.5 days (range, 7-28 days). Plasma exchange was given to 1 patient in whom the BSA had increased from 70% to 80% and was accompanied by a high-grade fever. Severe bacterial infection, such as sepsis, pneumonia, and pyelitis, was not observed during or after MPT. Cytomegalovirus antigenemia was detected in 2 patients at 10 and 25 days after the last dose of MPT. A 7-day course of ganciclovir was given to both patients. Increase in hepatitis B virus load was detected in 1 patient who was an asymptomatic carrier.

Table I. Patient characteristics and clinical evaluation

No. Age, y / Sex	Diagnosis	Previous treatment (day)	Interval day*	SCOR-TEN†	Treatment	BSA of detachment lesion (%) Day 0	Day 4	Day 7 or 8	Re-epitheliali-zation day§
1/31/F	SJS	PSL 50 mg/d (3)	10	0	MPT	5	4	2	13
2/66/M	SJS	Hydrocortisone 100 mg/d (1)	5	2	MPT	8	6	1	8
3/74/M	SJS	IVIg 20 g/d (3)	3	4	MPT + HD-MPT	8	6	5	28
4/32/F	Overlap	PSL 30 mg/d (4)	6	2	MPT	15	12	1	8
5/40/F	Overlap	PSL 60 mg/d (3)	8	2	MPT	15	10	0	7
6/48/M	TEN	PSL 20 mg/d (4)	5	2	MPT	80	72	10	9
7/48/F	TEN	PSL 60 mg/d (3)	6	2	MPT + HD-MPT	35	20	5	16
8/70/F	TEN	PSL 60 mg/d (2)	3	3	MPT➡PE	70	80	NA	NA

BSA, Body surface area; *HD-MPT,* half-dose MPT; *IVIg,* intravenous immunoglobulin; *MPT,* methylprednisolone pulse therapy; *NA,* not applicable; *Overlap,* overlap of Stevens-Johnson syndrome and toxic epidermal necrolysis; *PE,* plasma exchange; *PLS,* prednisolone; *SCORTEN,* severity-of-illness score for toxic epidermal necrolysis; *SJS,* Stevens-Johnson syndrome; *TEN,* toxic epidermal necrolysis; *y,* year; ➡, switched to.
*Between onset of disease and initiation of MPT.
†Level of serum bicarbonate was not measured.
§Interval between initiation of MPT and complete re-epithelialization.

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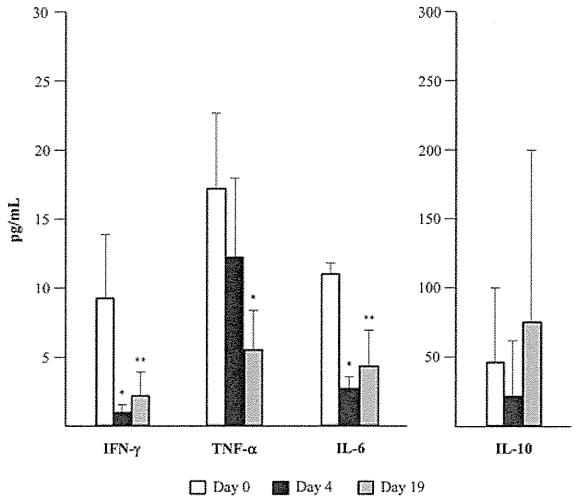

Fig 1. Alterations in cytokine levels. *Day 0,* Before methylprednisolone pulse therapy (MPT); *Day 4,* the day after the third dose of MPT or last administration of half-dose MPT, *Day 19,* mean 19 days (range, 13-28 days) from day 0; *IFN,* Interferon; *IL,* interleukin; *TNF,* tumor necrosis factor. Cytokine levels were measured using bead-based multiplexing assays (Luminex xMAP® technology). $^{*}P < .05$, $^{**}P < .005$; compared with day 0.

Biomarkers (serum interferon [IFN]-γ, tumor necrosis factor [TNF]-α, interleukin [IL]-6 and IL-10) were available for 5 of 8 patients. At day 4 after MPT administration, mean levels of IFN-γ, TNF-α, IL-6, and IL-10 were decreased compared with preadministration levels (day 0), but only changes in IFN-γ and IL-6 reached statistical significance. At day 19, a significant reduction in the mean levels of IFN-γ, TNF-α, and IL-6 was observed compared with levels before administration-of MPT, while the mean level of IL-10 was higher than that on day 0, although the difference was not statistically [F1] significant (Fig 1).

The decrease in proinflammatory cytokine levels suggests that MPT may have contributed to the survival of these patients with drug-induced SJS/TEN. Large-scale, prospective, blinded trials will be required to prove that MPT is effective in the treatment of SJS/TEN.

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Kazuhisa Hirahara, MD,[a] Yoko Kano, MD, PhD,[a] Q2 *Yohei Sato, MD,[a] Chiho Horie, MD,[a] Aki Okazaki, MD,[a] Tadashi Ishida, MD,[a] Yumi Aoyama, MD, PhD,[b] and Tetsuo Shiohara, MD, PhD[a]*

Department of Dermatology, Kyorin University School of Medicine,[a] and Department of Dermatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences,[b] Tokyo, Okayama, Japan

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Correspondence to: Yoko Kano, MD, PhD, Department of Dermatology, Kyorin University School of Medicine, 6-20-2 Shinkawa Mitaka, Tokyo 181-8611, Japan

E-mail: kano@ks.kyorin-u.ac.jp

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