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Letter to the Editor

Drugs causing severe ocular surface involvements in Japanese patients with Stevens–Johnson syndrome/toxic epidermal necrolysis

Dear Editor,

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse drug reactions often affecting mucosal tissues such as ocular surface, oral cavity, and genitals.[1,2] The severe ocular surface disorders include pseudomembrane formation and epithelial erosion in the acute phase, often leading to permanent impairment or loss of vision.[3]

We recruited Japanese patients with SJS/TEN through participating universities and hospitals and via the nationwide case collection network from June 2006 to June 2013.[4,5] The study was approved by the institutional review boards of all participating institutions, and written informed consent was obtained from all the patients (patient anonymity was preserved using the approved methods). Clinical information such as patients' background, primary (underlying) disease, symptoms, and administered drugs before the onset of SJS/TEN was also collected. Two experts diagnosed the disease using a standardized case report form, containing the criteria proposed by Bastuji-Garin *et al.*[6] except that the SJS–TEN overlap was categorized as TEN according to the severity criteria currently used in Japan.[7] Drugs that were administered continuously to the patients from 1 day to 2 months before the onset of SJS/TEN were assumed to be the causative agents.

According to the clinical information, the ocular surface involvements were graded as follows: 0, no symptoms; 1, only hyperemia of the bulbar and palpebral conjunctiva; 2, either pseudomembrane formation or a defect/erosion of the conjunctiva/corneal epithelia; and 3, both pseudomembrane formation and a defect/erosion of the conjunctiva/corneal epithelia. Grades 0/1 and 2/3 were grouped as mild and severe ocular surface involvements, respectively.

A total of 197 patients with SJS/TEN (97 females, mean age 56.6 ± 22.3 years) were enrolled. The number of probable SJS, SJS, and TEN cases was 23, 115, and 59, respectively. The frequency of severe ocular surface involvement tended to be higher among female and patients younger than 60 years but was not statistically significant (Table 1).

The frequencies of mild and severe ocular surface involvements caused by the drug or the drug group, the number of which was more than 14, were statistically evaluated by Fisher's exact probability test using JMP ver. 7.0.1 (SAS Institute Japan, Tokyo, Japan). As shown in Table 2, patients with SJS/TEN who were treated with cephalosporins or loxoprofen exhibited relatively higher tendencies of experiencing severe ocular surface involvements, but the difference was marginal ($0.05 < p < 0.07$). No differences were observed in the rates of experiencing severe ocular surface involvements in patients with SJS/TEN that is associated with other drugs such as carbamazepine, allopurinol, and quinolones.

On the other hand, we found that patients with SJS/TEN associated with acetaminophen showed a significantly higher rate (55.6%) of experiencing severe ocular surface involvements than those not treated with acetaminophen (27.6%) ($p < 0.01$). Among 27 acetaminophen-administered patients, 16 patients had been diagnosed by DLST, and 10 (62.5%) of them were positive. In the SJS group, the rate of acetaminophen-associated severe ocular involvements (7/36 patients, 19.4%) was significantly higher than those with mild involvements (4/79, 5.1%) ($p = 0.034$, data not shown) while there was no significant association in the case of TEN group, although the skin reaction of TEN is more severe than SJS. These results suggest that the ocular surface would be severely damaged by acetaminophen more frequently than by the other drugs in SJS patients. When acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) were combined as an antipyretic–analgesic (AA) group, the significance was lost ($p = 0.26$).

We divided these AA-associated patients with SJS/TEN into two groups: one group comprised patients taking drugs for common cold and the other comprised patients taking such drugs for conditions other than common cold, before the onset of SJS/TEN. We found that the patients taking these drugs for common cold experienced severe ocular surface involvements at a significantly higher rate (65.4%) than those taking these drugs for conditions other than common cold, such as rheumatoid arthritis (19.5%) ($p < 0.001$). The same was true in the case of acetaminophen ($p < 0.01$). Drugs other than AAs did not show such a tendency ($p > 0.05$, data not shown).

In a previous study by the EuroSCAR group, despite the high relative risk, acetaminophen was regarded as a confounding factor for the assessment of the risk of SJS/TEN because it was often administered concomitantly with other "highly suspected" drugs such as allopurinol and carbamazepine.[8] In the present study,

Table 1
Results of association analysis for patient's background and SJS/TEN with severe ocular involvements.

Category	Factors	Mild	Severe	Severe/Total (%)	Fisher's exact test (p value)
Sex	Male	73	27	27.0	0.22
	Female	62	35	36.1	
Age	≥60	79	28	26.2	0.09
	<60	56	34	37.8	

Number of Japanese SJS/TEN patients with mild/severe ocular involvements and the frequencies of severe cases are shown.

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Table 2
Drugs/drug groups and frequencies of ocular surface involvements in Japanese SJS/TEN patients.

	Patients receiving the drug(s)			Patients not receiving the drug(s)			Fisher's exact test (p value)	Odds ratio (95% CI)
	Mild	Severe	Severe/Total (%)	Mild	Severe	Severe/Total (%)		
All patients	135	62	31.5					
Aromatic anti-epileptics (AAE)								
All of AAE	35	17	32.7	100	45	31.0	0.86	
Carbamazepine	11	5	31.3	124	57	31.5	1.00	
Lamotrigine	9	7	43.8	126	55	30.4	0.27	
Anti-hyperuricemia								
Allopurinol	16	10	38.5	119	52	30.4	0.50	
Antibacterial drug								
Quinolones	15	7	31.8	120	55	31.4	1.00	
Proton pump inhibitors	12	3	20.0	123	59	32.4	0.40	
Antibiotics								
All of antibiotics	30	18	37.5	105	44	29.5	0.26	
Cephalosporins	11	11	50.0	124	51	29.1	0.05	2.43 (0.99/5.97)
Antipyretic analgesics (AAs)								
All of AAs	42	25	37.3	93	37	28.5	0.26	
Aspirin	8	7	46.7	127	55	30.2	0.25	
Loxoprofen	13	12	48.0	122	50	29.1	0.07	2.25 (0.96/5.28)
Acetaminophen	12	15	55.6	123	47	27.6	0.0065	3.27 (1.43/7.50)
Patients receiving AAs for treatment of cold[†]	9	17	65.4				0.0002	7.79 (2.55/23.8)
Patients receiving AAs for treatment of other diseases	33	8	19.5					
Acetaminophen for treatment of cold[†]	4	13	76.5				0.0069	13.0 (1.92/88.0)
Acetaminophen for treatment of other diseases	8	2	20.0					

Japanese SJS/TEN patients were categorized by culprit drugs/drug groups.
[†] Judged according to primary (underlying) disease in the filled case report forms (e.g. common cold, acute upper respiratory inflammation, and acute adenoiditis) and/or drug name (e.g. multi-ingredient cold remedy). Mycoplasma pneumoniae or influenza were excluded from this category.

however, 14 of 15 patients with acetaminophen-associated SJS/TEN and severe ocular surface involvement had not taken such drugs together. Therefore, at least among Japanese patients with SJS/TEN with severe ocular surface involvements, acetaminophen is strongly suspected to be a causative drug, particularly when this drug was taken for the treatment of common cold.

In conclusion, we found that 1) patients with SJS/TEN taking acetaminophen showed a significantly higher rate of experiencing severe ocular surface involvements than those taking other SJS/TEN frequently causative drugs such as carbamazepine, allopurinol, and quinolones; 2) the patients taking AAs, including acetaminophen and/or NSAIDs, for the treatment of common cold showed a high frequency of patients with SJS/TEN experiencing severe ocular surface involvements compared with those taking AAs for the treatment of other diseases. These results suggest that not only AAs including cold medicine but also viral infections causing cold-like symptoms play some important roles in the development of severe ocular surface involvements. Note that our recent study showed that cold medicine-associated patients with SJS/TEN with severe ocular complications are associated with certain types of HLA (*HLA-A*02:06* and *HLA-A*44:03*)[9] and/or *IKZF1*.[10] Taken together, these results suggest the existence of unknown unique mechanisms underlying the development of ocular disorders in SJS/TEN caused by AAs. The patients with SJS/TEN taking these drugs for common cold should be taken special care of their eyes and the skin to prevent severe ocular sequelae.

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Conflict of interest
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