Stevens-Johnson syndrome and toxic epidermal necrolysis: A cross-sectional analysis of patients in an integrated allergy repository of a large health care system

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Clinical Implications

- By examining patients' electronic allergy record in a large health care system, we identify a prevalence of 375 patients per million for Stevens-Johnson sydrome or toxic epidermal necrolysis. We identify new drugs reported to cause these severe cutaneous adverse reactions that may be emerging causative agents.

TO THE EDITOR:

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions, carrying an associated mortality ranging from 5% to 40%.[1,2] Known risk factors for SJS/TEN include HIV infection, female gender, and certain HLA genotypes.[1,3,4] Various medications have been described to cause SJS/TEN, with strongest associations with allopurinol, antiepileptics, nonsteroidal antiinflammatory drugs (NSAIDs), sulfa-containing antibiotics, β-lactam antibiotics, quinolones, and nevirapine.[3-6] SJS/TEN is rare, affecting about 2 persons per million per year, with SJS 3 times more common than TEN.[3,7] However, much of the epidemiologic data on SJS/TEN are limited to national and international reporting networks or cohorts after specialist referral or hospitalization.[2,5,6] The largest US epidemiologic data identified cases on the basis of *International Classification of Diseases, Ninth Revision, Clinical Modification* codes.[8,9] We aimed to determine the prevalence of SJS/TEN among patients in a large health system by searching an electronic allergy repository and to evaluate demographic, allergy, and allergen characteristics of this population.

METHODS

We conducted a cross-sectional analysis of patients who have reported allergies listed in the Partners Enterprise Allergy Repository (PEAR) at the Brigham and Women's Hospital or Massachusetts General Hospital between 1983 and 2013. PEAR maintains a record of all allergy information entered into electronic health records (EHRs) by a medical provider and communicates in all of Partners Healthcare in both inpatient and outpatient settings (see text in this article's Online Repository at www.jaci-inpractice.org). SJS/TEN cases were identified by using keyword search of the free-text reaction field (for entries similar to SJS, Steven, Johnson, toxic epidermal necrolysis, and TEN), followed by manual reaction review of all retrieved cases. Uncertainty of a SJS/TEN diagnosis was defined if the entry included the words "possible," "like," "question," or "?." Uncertainty of a causative agent was defined if the listed agent was an unknown or unrecognizable medication. Agents reported to cause SJS/TEN were manually categorized and frequencies calculated. We compared sex and ethnicity of patients with and without SJS/TEN by using the chi-square test, and $P < .05$ was considered statistically significant. SAS statistical software (version 9.3; SAS Institute, Inc Cary, NC) was used for statistical analysis. The Partners Human Research Committee approved the study.

RESULTS

Between 1983 and 2013, there were 1,877,075 PEAR patients. Of these, 745,813 (39.7%) had at least 1 allergy recorded in PEAR, with the remaining patients having "unknown" or "no known allergies." We identified 704 patients (0.0375% or 375 per million) with an active allergy reporting SJS or TEN.

Of the 704 patients, 66.5% were female (Table I). The overall PEAR population without SJS/TEN had significantly less women (57.4%; $P < .001$) though a similar female predominance was found in those with allergies (67.2%; $P > 0.69$). Patients with SJS/TEN were largely white (83.1%); this percentage of whites was greater than that in the overall PEAR population without SJS/TEN (74.3%; $P < .001$) but similar to that in those with allergies (83.2; $P > 0.9$). Of patients with SJS/TEN, 23 (3.5%) were Hispanic, which is fewer than in the PEAR population without SJS/TEN (155,868; 8.8%; $P < .001$) and those with allergies (36,481; 5.2%; $P = .04$). Thirty-five (5.3%) were Asian, which was a greater proportion than in the PEAR population without SJS/TEN (76,828; 4.3%; $P = .24$) and in those with allergies (20,076; 2.9%; $P < .001$).

Most patients (n = 652; 92.6%) had SJS. Only 24 (3.4%) had TEN. Fourteen (2%) had SJS/TEN overlap. Overlap syndromes with other immunologic reactions were rare (2%). Sixty-four (9.1%) reaction entries indicated diagnosis uncertainty. Only 3 (0.4%) allergen entries indicated causative agent uncertainty. Most of the patients (92.6%) had only 1 medication listed as the causative drug, 11.6% had 2 causative agents, and 5.3% had 3 or more. Patients with SJS/TEN reported an average of 3.1 ± 3.4 drug allergies, 0.1 ± 0.6 food allergies, and 0.1 ± 0.4 environmental allergies (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

Among the total of 901 drugs reported to cause SJS/TEN (Table II), antibiotics (n = 526, 58.4%) were most commonly implicated, including sulfonamides, β-lactams, macrolides, quinolones, vancomycin, tetracycline, and clindamycin. Antiepileptics were the causative agent for 175 (19.4%) patients. NSAIDs were the causative agent in 55 (6.1%) patients, with ibuprofen, naproxen, and aspirin the most commonly listed specific NSAID trigger. Allopurinol was the causative agent in 19 (2.1%) patients. Other causative drugs of note included hydroxychloroquine (0.7%) and nevirapine (0.7%). Notable drug classes include antidepressants (1.6%), beta blockers (0.6%), angiotensin-converting enzyme inhibitors (0.4%), and proton pump inhibitors (0.6%).

DISCUSSION

We assessed an integrated allergy repository of a large health system and found a prevalence of 375 patients per million for SJS/TEN. The demographic characteristics of our cohort showed a

TABLE I. Demographic characteristics and allergen information for patients reported to have had SJS or TEN (n = 704)

All patients in PEAR (N = 1,877,075)	With SJS/TEN (n = 704)	Without SJS/TEN (n = 1,876,371)	P*
Sex: female, n (%)	468 (66.5)	1,076,485 (57.4)	.001
Race, n (%)†			
White	549 (83.1)	1,315,209 (74.3)	.001
Black	43 (6.5)	133,612 (7.5)	.29
Hispanic	23 (3.5)	155,868 (8.8)	.001
Asian	35 (5.3)	76,828 (4.3)	.24
Other	11 (1.7)	68,105 (5.0)	.003
Patients in PEAR with allergies‡ (n = 745,813)	**With SJS/TEN (n = 704)**	**Without SJS/TEN (n = 745,109)**	**P**
Sex: female, n (%)	468 (66.5)	500,813 (67.2)	.69
Race, n (%)†			
White	549 (83.1)	581,641 (83.2)	.9
Black	43 (6.5)	38,844 (5.6)	.29
Hispanic	23 (3.5)	36,481 (5.2)	.04
Asian	35 (5.3)	20,076 (2.9)	.001
Other	11 (1.7)	22,072 (3.2)	.03
Allergy characteristic		**SJS/TEN (n = 704)**	
Hypersensitivity reaction, n (%)			
SJS		652 (92.6)	
TEN		24 (3.4)	
SJS/TEN		14 (2.0)	
Overlap syndromes		14 (2.0)	
SJS/Drug rash eosinophilia and systemic symptoms		3 (0.4)	
SJS/Erythema multiforme		2 (0.3)	
SJS/Other immune-mediated reactions		9 (1.3)	
Medications listed as causative agent, n (%)			
Mean ± SD		1.28 ± 0.96	
1		585 (83.1)	
2		82 (11.6)	
3		21 (3.0)	
4		9 (1.3)	
≥5		7 (1.0)	

*P value indicates the race category compared with the sum of the other categories (ie, white vs nonwhite, black vs nonblack, etc).
†Determined through patient self-report. Total n's do not match the sum of patients in race groups because of missing race entries including unknown, not given, or refused. All patients in PEAR without SJS/TEN has 106,271 total missing; patients in PEAR with allergies without SJS/TEN has 45,995 total missing; and 43 patients with SJS/TEN had missing race entries.
‡Excludes patients with "Allergy Unknown" and "No Known Drug Allergies".

female predominance, similar to published data.[1] Although patients with SJS/TEN were less likely to be Hispanic, there was a slight overrepresenation of persons from Asian backgrounds, potentially related to HLA associations.[3] Compared with SJS, TEN was rare, with SJS outnumbering TEN 27 cases to 1, which is greater than the 4 to 1 previously described.[7] Overlap syndromes were infrequent, similar to previous reports.[10] Although almost 93% of the patients had their SJS/TEN attributed to 1 medication only, there were 37 cases with 3 or more potential causative drugs listed. When a single causative medication cannot be identified, a patient's future treatment may be compromised.

TABLE II. Drugs reported to cause SJS or TEN among PEAR database entries in a large health care system (n = 901)

Drug type	No. (%)
Antibiotic	526 (58.4)
Sulfonamide	283 (31.4)
Penicillins*	91 (10.1)
Cephalosporin	42 (4.7)
Macrolides	23 (2.6)
Quinolone	20 (2.2)
Vancomycin	20 (2.2)
Tetracycline	18 (2.0)
Clindamycin	13 (1.4)
Metronidazole	4 (0.4)
Aminoglycosides	3 (0.3)
Trimethoprim	3 (0.3)
Nitrofurantoin	2 (0.2)
Carbapenem	1 (0.1)
Other antibiotic†	3 (0.3)
Antiepileptic	175 (19.4)
Lamotrigine	55 (6.1)
Phenytoin	40 (4.4)
Carbamezepine	30 (3.3)
Phenobarbital	20 (2.2)
Oxcarbazepine	8 (0.9)
Gabapentin	4 (0.4)
Topiramate	4 (0.4)
Divalproex	3 (0.3)
Other or unknown antiepileptic‡	11 (1.2)
NSAIDs	55 (6.1)
Ibuprofen	10 (1.1)
Naproxen	7 (0.8)
Aspirin	4 (0.4)
Sulindac	3 (0.3)
Meloxicam	2 (0.2)
Piroxicam	2 (0.2)
Indomethacin	2 (0.2)
Other§	25 (2.8)
Cardiovascular medications	22 (2.4)
Sulfa-containing diuretic‖	5 (0.6)
Beta blockers¶	5 (0.6)
ACE Inhibitors#	4 (0.4)
Calcium channel blockers**	3 (0.3)
Antiarrythmics††	2 (0.2)
Statins (atorvastatin)	2 (0.2)
Angiotensin-receptor blockers (valsartan)	1 (0.1)
Uricosuric	20 (2.2)
Allopurinol	19 (2.1)
Probenicid	1 (0.1)
Antiretrovirals	15 (1.7)
Nevirapine	6 (0.7)
Efavirenz	3 (0.3)
Other antiretrovirals‡‡	6 (0.7)
Antidepressants	14 (1.6)
Buproprion	6 (0.7)
Other antidepressants§§	8 (0.9)
Other neuro/psych medications‖‖	12 (1.3)

(continued)