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Idiopathic Stevens-Johnson syndrome and toxic epidermal necrolysis: Prevalence and patients' characteristics



To the Editor: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered severe cutaneous adverse reactions to drugs. However, in some cases, no causative drug is identified. Cases of "nontoxic" SJS/TEN have been associated with *Mycoplasma pneumoniae* infection or connective tissue diseases or considered idiopathic.¹ Very few data about idiopathic cases of SJS/TEN are available.

Our retrospective study included 193 patients who were hospitalized in our center (ie, the French Referral Center for Epidermal Necrolysis) for SJS/TEN during the period from 2005 to 2016. Four patients were excluded from the analyses (Fig 1). For 2 patients (1.1%) of the 189 studied, *M pneumoniae* infection was identified as the most probable cause of SJS/TEN (Fig 1). The diagnosis of SJS/TEN-like connective tissue was made for 3 other patients (1.6%) (Fig 1). The disease of 2 of them was diagnosed as lupus erythematosus. For the other, a

history of Sjogren syndrome, progressive cutaneous involvement over a 13-day period, concomitant arthralgia, positive antinuclear antibody test result (titer, 1/320), and positive anti-double-stranded DNA test result (titer, 20 IU/mL) made the diagnosis of SJS/TEN-like connective tissue disease possible. Lastly, 12 patients without underlying connective tissue disease or *Mycoplasma pneumoniae* infection (6.3%) were considered to have idiopathic SJS/TEN. For these patients, no initiation of systemic drug was found within the month preceding the start of skin and/or mucous symptoms despite a thorough drug investigation (that included the patient, relatives, general practitioner, and/or pharmacy). One of these patients was 2 months pregnant, and another had concomitant streptococcal abscessed tonsillitis. Compared with patients with drug-induced SJS/TEN, those with idiopathic SJS/TEN were younger and tended to have less severe skin involvement (Table 1). No biologic parameters measured routinely on admission were clearly discriminative.

Few data are available regarding SJS/TEN cases that are not related to drug exposure. Review articles often report that no causative drug is identified in 20% of 30% of SJS/TEN cases,^{2,3} even though lower proportions (ie, ≤15%) have been found in cohort studies.^{3,4} However, these proportions include both patients with no drug exposure and patients exposed to drugs for whom the causality assessment for each drug is considered very unlikely or unlikely when an algorithm for assessment of drug causality is used.⁵

In a previous study of 379 patients included in the EuroSCAR study between 1997 and 2001, 7 patients (1.8%) had not received any systemic drug in the 4 weeks before the onset of the skin/mucous symptoms.⁴ More recently, in the United States, the Society of Dermatology Hospitalists SJS/TEN Study Group found that 8.7% of SJS/TEN cases (n = 405) occurred in patients not exposed to a culprit drug.³

In conclusion, even though systematic screening for *M pneumoniae* infection or lupus erythematosus could be considered in all patients with SJS/TEN for whom no culprit drug is identified, these etiologies are unlikely to account for the majority of SJS/TEN cases not induced by drugs, as suggested by our study. Inadvertent intake of drugs, for instance by consuming meat or milk containing occult veterinary drugs such as nonsteroidal anti-inflammatory drugs, has been hypothesized as a possible cause of idiopathic SJS/TEN.⁵ However, this hypothesis has not been confirmed so far.⁵

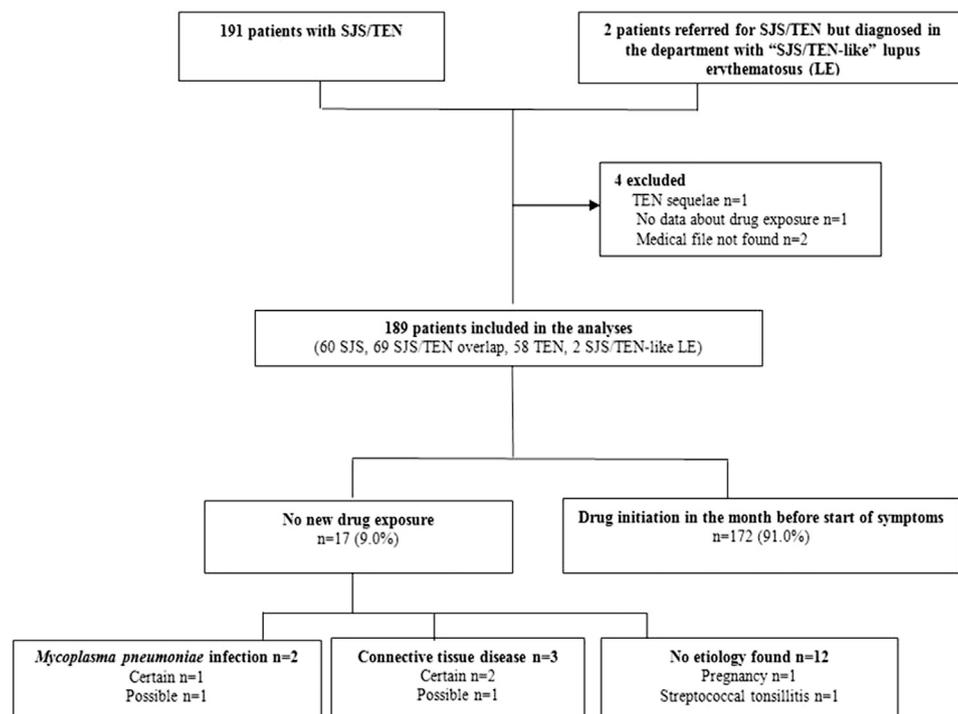


Fig 1. Study flowchart. *SJS/TEN*, Stevens-Johnson syndrome/toxic epidermal necrolysis.

Table I. Patients' characteristics

Characteristic	Idiopathic SJS/TEN (n = 12)	Drug-induced SJS/TEN (n = 172)	P value
Median age, y (IQR)	31 (23-43)	47 (35-61)	.004
Female, n (%)	9 (75.0)	89 (51.7)	.10
Median Scorten score at admission (IQR)*	0.5 (0-2)	1 (1-2)	.04
Median temperature at admission, °C (IQR)	39.1 (37.6-40.1)	38.3 (37.4-39.2)	.21
Median skin detachment, % (IQR)			
At admission	6 (2-13)	10 (2-20)	.39
At day 1	6 (2-12)	13 (4-25)	.09
At day 5	3 (1-9)	16 (4-35)	.02
Median biologic parameters at admission (IQR)			
Urea level (mmol/L)	3.7 (3.4-4.7)	5.3 (3.5-8.0)	.05
Creatinine level (μmol/L)	57 (49-75)	82 (64-99)	.008
Glucose level (mmol/L)	7.3 (5.7-7.7)	6.1 (5.1-7.9)	.50
AP level (IU/L)	51 (38-63)	64 (49-85)	.04
ALT level (IU/L)	35 (22-51)	38 (24-79)	.30
AST level (IU/L)	36 (27-57)	40 (25-68)	.50
GGT level (IU/L)	29 (19-46)	52 (26-108)	.05
LDH level (IU/L)	250 (129-355)	291 (184-415)	.35
Leukocyte count (10 ⁶ /L)	5800 (3600-8400)	5850 (4450-7950)	.59
Hemoglobin level (gm/dL)	11.7 (10.5-12.4)	11.9 (10.7-13.1)	.82
Platelet count (10 ⁹ /L)	184 (131-253)	210 (168-291)	.25
ICU admission, n (%)	4 (33.3)	54 (31.4)	1.0
In-hospital mortality, n (%)	0 (0)	17 (9.9)	.61

The Fischer exact test and Wilcoxon rank-sum test were used to compare categoric and quantitative data, respectively.

ALT, Alanine transaminase; AP, alkaline phosphatase; AST, aspartate transaminase; GGT, gamma glutamyl transferase; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

*According to Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau J, Wolkenstein P. Scorten. A severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol.* 2000;115:149-145.

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Interruption of oral clindamycin plus rifampicin therapy in patients with hidradenitis suppurativa: An observational study to assess prevalence and causes



To the Editor: Combination therapy with oral clindamycin, 300 mg twice daily, plus rifampicin, 300 mg twice daily or 600 mg once daily, for 10 weeks is among the keystone treatments for moderate-to-severe hidradenitis suppurativa (HS).¹ Since 2006, 6 small studies involving a total of 178 patients have investigated the efficacy of this antibiotic combination.²⁻⁴ Most of the studies had a retrospective design, and only 1 reported safety outcomes.⁴ The prevalence of treatment interruption ranged from 9.1% to 28.6% (mean, 16.3%), and the rate of appearance of adverse events ranged from 9.1% to 38.3% (mean, 21.9%).²⁻⁴ The most common adverse events were gastrointestinal (GI) disturbances (diarrhea, vomiting, abdominal pain, and dyspepsia), followed by cutaneous rash, vaginitis, nonspecific pain, and arthralgia.

A better understanding of the reasons for poor adherence and adverse events associated with treatment may help dermatologists to better advise patients, potentially allowing prevention of some side effects.

We designed a descriptive, observational, retrospective multicentric study to determine the prevalence of interruption of clindamycin plus rifampicin before 10 weeks in patients with HS. A retrospective chart review was performed; included were patients who were at least 18 years old, had Hurley stage II or III HS, and were receiving clindamycin plus rifampicin for the first time. Patients simultaneously receiving other systemic therapies for HS were excluded.

We enrolled 509 patients from 14 Spanish hospitals (Table 1); 135 of them (26.5%) interrupted antibiotic treatment. We did not observe differences between the proportions of men (26.6%) and women (26.5%) who interrupted their treatment. After dividing the study population into quartiles by age (≤ 30 years, $n = 133$; 31-38 years, $n = 127$; 39-49 years, $n = 125$; and ≥ 50 years, $n = 124$), we observed that older age was associated with interruption of treatment. The odds ratio (OR) for treatment interruption in patients aged 50 or older versus patients in the youngest age group was 1.9 (95% confidence interval [CI], 1.1-3.3; $P = .03$). Ever-smokers had 1.5 times the odds of interrupting their treatment as compared with never-smokers (95% CI, 1.1-2.1; $P = .02$). In multivariable