ORIGINAL REPORT

Incidence, causative factors and mortality rates of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in northern Italy: data from the REACT registry

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ABSTRACT

Purpose Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but severe cutaneous adverse drug reactions. We assessed incidence, drug exposure and mortality, analysing data obtained from the Lombardy Registry of Severe Cutaneous Reactions (REACT).

Methods Data were collected from hospitals in the Italian Lombardy region (9 502 272 people). A trained monitor was sent to the reporting hospital to collect data on drug exposure and clinical features. The algorithm for drug causality for epidermal necrolysis algorithm was applied to assess drug causality. Defined Daily Dose (DDD) was used to express drug consumption.

Results From April 2009 to November 2014, 17 cases of TEN and 59 cases of SJS were collected. The overall incidence rate was 1.40 cases (95%CI, 1.12–1.76) per million people per year. A total of 15 cases died during hospitalization with a mortality rate of 16.9% for SJS and 29.4% for TEN. Overall, 55.4% of cases had a probable or very probable relation with drug exposure. In a total of five patients (6.6%), no causative drug for the reaction was identifiable. Allopurinol contributed to the highest number of cases (23 cases), while the highest incidence based on more than one case reported was observed for cotrimoxazole and lamotrigine, with 5.37 cases (95%CI, 2.09–13.80) and 3.54 (95%CI, 1.21–10.42) per 10million DDD/year, respectively.

Conclusions We confirmed that SJS and TEN are rare adverse cutaneous reactions. As expected, mortality was influenced by the degree of skin detachment. The profile of drugs associated with the reactions was in agreement with data from other surveillance systems.

key words—Stevens–Johnson syndrome (SJS); toxic epidermal necrolysis (TEN); pharmacovigilance; causal factors/aetiology; incidence; mortality; pharmacoepidemiology

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INTRODUCTION

The skin represents the organ most commonly affected by adverse drug reactions. Some of these reactions are

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severe and may result in a significant mortality and morbidity. These include, in particular, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) or Lyell's syndrome. Such reactions are characterized by confluent erythema and areas of skin detachment reflecting epidermal necrosis because of keratinocyte apoptosis. There is usually erosive mucosal involvement of the oral, nasal, ocular, genital or anal area.[1–3] A few days before the skin manifestations appear, there might be flu-like symptoms with fever, sore throat and ocular pain.[4] The main difference between SJS and TEN is represented by the extent of dermo-epidermal detachment.

When the detachment is less than 10%, the reaction is classified as SJS; if the detachment is equal to or greater than 30%, it is classified as TEN. The intermediate stages are classified as SJS-TEN overlap.[5–8] The reaction usually appears within 4–28days after starting a new drug.[4] Drugs that have been described in previous studies as having a stronger association with SJS/TEN are mainly anti-epileptics, allopurinol, anti-infective sulphonamides and oxicams.[9] SJS and TEN are, in most instances, induced by drugs, but in some cases, no drug is found in association with the reaction.[3,5,9] Continuous active monitoring of severe reactions such as SJS and TEN is needed to estimate risks, identify new signals and assess outcome. The Lombardy Registry of Severe Cutaneous Reactions (REACT) was established in 2009 to collect all the cases of severe cutaneous reactions occurring in Lombardy, a region in northern Italy, with more than 9million people, to harmonize clinical management of the reactions, favouring a multidisciplinary approach, and to educate physicians on clinical patterns. The present analysis in the context of the REACT registry was conducted to assess incidence rates of SJS and TEN, to evaluate etiological factors with particular emphasis on recently marketed drugs and to estimate mortality rates associated with the reactions.

MATERIALS AND METHODS

Surveillance network and data collection

The REACT network includes a total of 22 hospitals, covering 94% of the Lombardy population. Detailed characteristics of the network were described elsewhere.[10] Every new case of suspected SJS and TEN observed in the participating hospitals was to be reported to the coordinating centre by fax or mail by the treating clinician or hospital pharmacist. A trained monitor was then sent to the reporting hospital in order to collect all the data necessary for case validation. Data that were collected included standardized information on symptoms prior to the reaction, diagnosis at admission, morphology of skin lesions and their location, patients' medical history and exposure to any drug during the 4 weeks before admission. Data were collected through direct contact with the physician and/or patient when possible and by inspecting the patients' clinical file. Photographic documentation of clinical manifestations and histological features from skin biopsy was collected as well.

Inclusion criteria for the evaluation of a patient as a potential case of SJS/TEN were hospitalization, skin detachment over 1% of body surface area and erosive mucosal involvement. Cases of SJS/TEN were first classified by hospital doctors. The documentation collected was, then, regularly submitted for discussion and case validation to an expert review panel including dermatologists, plastic surgeons and clinical immunologists. Based on clinical history and blind to drug exposure, a disease onset was identified for each patient (index date).

Imputability criteria

To evaluate the likelihood of a causal relation between a drug and SJS or TEN, the Algorithm of Drug causality for Epidermal Necrolysis (ALDEN) was applied.[11] All the drugs taken by the patient within the previous 4weeks were evaluated and scored with points according to the algorithm. Based on this algorithm, the relation between the drugs a patient took and the reaction could be classified as very unlikely (total score<0), unlikely (total score 0–1), possible (total score 2–3), probable (total score 4–5) or very probable (total score ≥6).[8,11] The drug with the highest score was used as a proxy for causality of the reactions in each patient. In case of multiple drugs with an equal score, all those drugs were taken into account for causality. History of previous adverse reactions and presence of other risk factors such as infections, cancer and immune-related diseases were also considered in the assessment of drugs causality.

Drug exposure and incidence

Regional data on drug prescription (IMS Health, Danbury, CT, USA) during the study period were used to estimate exposure rates to drugs of interest in the underlying population expressed as defined daily doses (DDD). For incidence rates computation according to

drug use, only probable and very probable cases after application of the ALDEN algorithm were considered.

Statistical analysis

For descriptive analysis, data were presented as number with percentages or as medians with ranges for nominal and continuous variables, respectively. For analytical purpose, continuous variables were categorized by using clinical relevant cut-off points or quartiles of their distributions as thresholds.

In the incidence rate computation, analyses were performed taking into account the number of collected cases as numerator and the 2011 population of Lombardy (ISTAT data) as the average denominator, excluding the Mantua province, which did not participate in the study. The total annual incidence as well as the gender and age group-specific rates were reported along with their 95% confidence intervals (CI), by using standard methods for rare events. Incidence rate ratio (IRR) with 95%CI were also calculated when required. Linear trend across different age categories was computed by Cochran–Armitage test for trend. Mortality rate within the cohort of patients of the study was calculated as cumulative incidence with its 95% CI. Proportion differences between groups, which were tested by using Pearson's chi-squared test or Fisher exact test, where required. For statistical purpose, overlap SJS/TEN cases were grouped with TEN cases. Analysis was carried out using MATLAB (MathWorks, Natick, MA, USA). All tests were considered significant at $p\text{-value}<0.05$.

RESULTS

From April 2009 to November 2014, 17 cases of TEN or overlap SJS/TEN and 59 cases of SJS were collected through the REACT network. General characteristics of these patients are reported in Table 1. There were 25 men (32.9%) and 51 women (67.1%). The median age of reported cases was 64 years, ranging from 3 to 92years. In a total of 31 cases (40.8%), a history of an infectious condition was reported prior to the onset of the reaction. In a total of 22 cases (28.9%), there was a history of renal disease and in 13 cases (17.1%), a history of current cancer. A case of association with HIV was also registered. Oral, ocular and/or genital mucosa involvement was present in 86.8%, 77.6% and 47.1% of patients, respectively. In one of the patients, there was a history of a previous reaction classified as SJS or TEN. One patient reported a previous exanthema related to the use of paracetamol.

Out of the 76 cases of SJS/TEN, 34 (44.7%) were treated at the Burn Unit of the Niguarda Ca' Granda Hospital in Milan (the referral centre for severe reactions within the REACT network), being referred from other hospitals (91.2%) or having direct access to

Table 1. General characteristics of 76 patients with a diagnosis of SJS/TEN syndrome during the surveillance period

(April 2009–November 2014)
N %
Gender
Men 25 32.9
Women 51 67.1
Age (median, range) (years) 64 (3–92)
<25 16 21.1
25–49 11 14.5
50–74 31 40.8
≥75 18 23.7
Classification
SJS 59 77.6
Overlap SJS-TEN 8 10.5
TEN 9 11.8
Mucosal involvement*
Oral 59 86.8
Ocular 52 77.6
Genital 32 47.1
Other 10 14.7
Recent pathological history
Cancer 13 17.1
Renal disease 22 28.9
Liver disease 11 14.5
Prior infections† 31 40.8
Autoimmune diseases‡ 4 5.2
Diabetes 10 13.2
HIV 1 1.3
SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.
*Nine patients with missing data were excluded.
†Any reported infection; ranging from respiratory airway infections, to gastrointestinal infections, to urinary tract infections and to sepsis.
‡Two cases of systemic lupus erythematosus, one Crohn's disease and one case of autoimmune hepatic cirrhosis.

the emergency department of Niguarda Ca' Granda Hospital (8.8%).

Incidence and mortality

Based on a total population of 9 502 272 inhabitants, the incidence rate was 0.31 cases (95%CI, 0.20–0.50) per 1 million persons/year for TEN and 1.09 (95%CI, 0.84–1.40) for SJS, with an overall incidence of 1.40 cases (95%CI, 1.12–1.76) per 1 million persons/year. Age-specific and gender-specific incidence rates are shown in Figure 1.

The incidence rates per 1 million persons/year ranged from 1.27 in people aged 0–24 years (0.77 men and 1.80 women), to 0.54 in people aged 25–49 years (0.48 men and 0.60 women), to 1.93 cases in people aged 50–74 years (1.68 men and 2.16 women) and to 3.47 cases in people over 75 years (1.06 men and 4.83 women). There was a significant trend towards increasing incidence with age ($p<0.001$), although significant only in women after stratifying by gender (men $p=0.10$, women $p=0.0008$). The overall women/men IRR was 1.95 (95%CI, 1.25–3.07), reaching the highest value of 4.54 (95%CI, 1.51–15.29) in the age group above 75 years.

The overall mortality rate during hospitalization was 19.7% (95%CI, 12.3–30.0). It was 16.9% (95%CI, 9.5–28.5) for SJS (10 cases) and 29.4% (95%CI, 13.3–53.1) for SJS/TEN overlap or TEN (5 cases). The mortality rate at the referral centre of Niguarda

Ca' Granda Hospital was 11.8% (95%CI, 4.7–26.6); thus lower, although not significantly different (p=0.12), from mortality rates in other hospitals of the network (26.2%; 95%CI, 15.3–41.1).

Suspected drugs

After applying the ALDEN algorithm, 92 drugs in 76 patients were evaluated for causality. As described before, in case of multiple drugs with an equal score in one patient, all those drugs were taken into account for causality. In total, there were 22 (23.9%) drugs in 22 patients classified as very probable, 29 (31.5%) drugs in 26 patients as probable, 34 (37.0%) drugs in 23 patients as possible, 5 (5.4%) drugs in 3 patients as unlikely and 2 (2.2%) drugs in 2 patients as very unlikely.

Altogether, 51 (55.4%) of the drugs in 48 (63.2%) of patients were classified as either probable or very probable. For calculations of incidence rates by DDD, only probable and very probable associations were used.

The incidence of reactions for each specific drug is shown in Table 2. Overall, 23 cases were associated with allopurinol use, with an incidence adjusted by drug consumption of 1.76 (95%CI, 1.17–2.64) cases of reaction per 10 million DDD/year. Drugs with the highest incidence rates adjusted for consumption, and more than one case reported, were cotrimoxazole and lamotrigine with 5.37 (95%CI, 2.09–13.80) and 3.54 (95%CI,1.21–10.42) cases per 10 million DDD/year, respectively. High rates were also observed for phenytoin (3.23 cases per 10million DDD/year, 95%CI 0.89–11.77), carbamazepine (1.01 cases per 10million DDD/year, 95%CI 0.34–2.97), ceftriaxone (7.41 cases per 10million DDD/year, 95%CI 1.31–41.99) and ketorolac (3.26 cases per 10million DDD/year, 95%CI 0.58–18.47). But estimates for the last two drugs were based on only one case with wide CI.

In a total of 23 cases (30.3%), the relationship between drugs and reactions was evaluated as possible. These drugs included paracetamol (three cases), amoxicillin (three cases), ceftriaxone (two cases) and several other medications with only one case reported.

In a total of five cases (6.6%), no causative drug was identifiable (this category included drug exposures

Figure 1. Age and gender specific incidence rates of Stevens–Johnson syndrome/toxic epidermal necrolysis syndrome

classified as unlikely and very unlikely by the ALDEN algorithm). In Table 3, the presence of other possible triggering factors is shown according to the degree of association of the reaction with drug exposure based on the ALDEN algorithm.

DISCUSSION

Our study confirms the rarity of the conditions we considered;

our estimates of the incidence of SJS/TEN syndrome were consistent with data from previous studies, although slightly lower.[3,5,12–15] Interestingly, the risk of reactions was higher in women than in men, with a value four times higher in women than in men after age 75 years. The risk tended to increase after age 50 years in both sexes; however, the trend was significant only in women. The gender differences are confirmed by findings in previous studies, where a higher risk for women is described, especially for TEN.[9,14,16,17] In the study of Weinand et al., the gender ratio of woman to man for SJS and TEN were 3:2 and 11:9, respectively.[16] While the gender differences are difficult to explain, the increased incidence with age, which is also supported by previous literature,[12,16,17] may at least partly be related to an increased exposure to drugs in older people and/or presence of co-morbidities and variations in pharmacokinetics and/or pharmacodynamics.[16] In our study, the group with age <25years had a higher incidence than the group of 25–49years; this might be related with a higher prevalence of infections in younger children.[14] The profile of drugs carrying a higher risk for SJS/TEN, based on consumption data, was consistent

Table 2. Incidence of SJS-TEN reactions for each specific drug per 10 million defined daily doses (DDD)/year

Drug	DDD*	Cases	Incidence rate (95%CI)
Allopurinol	130590064.9	23	1.76 (1.17–2.64)
Cotrimoxazole (sulfamethoxazole-trimethoprim)	7452862.9	4	5.37 (2.09–13.80)
Lamotrigine	8464969.1	3	3.54 (1.21–10.42)
Carbamazepine	29739520.3	3	1.01 (0.34–2.97)
Levofloxacin	29996619.9	3	1.00 (0.34–2.94)
Paracetamol	102445844.1	3	0.29 (0.10–0.86)
Phenytoin	6197223.5	2	3.23 (0.89–11.77)
Amoxicillin	275772850.3	2	0.07 (0.02–0.26)
Ceftriaxone	1349182.6	1	7.41 (1.31–41.99)
Ketorolac	3067276.6	1	3.26 (0.58–18.47)
Ciprofloxacin	16326198.2	1	0.61 (0.11–3.47)
Phenobarbital	43320019.4	1	0.23 (0.04–1.31)
Paracetamol codeine	47334267.2	1	0.21 (0.04–1.20)
Clarytromycin	48149024.0	1	0.21 (0.04–1.18)
Naproxen	58733448.7	1	0.17 (0.03–0.96)
Pantoprazol	236078066.2	1	0.04 (0.01–0.24)

CI, confidence interval.
*DDD sold in Lombardy (with the exclusion of Mantua province) during the 5.7 years study period.

Table 3. Presence of other factors that might have contributed to the development of SJS/TEN, separated for highest ALDEN category

	Probable & very probable (n = 48 patients)	Possible (n = 23 patients)	Unlikely & very unlikely (n = 5 patients)	p-value*
Infection				
Yes	16 (33.3%)	12 (52.2%)	3 (60.0%)	0.26
No	32 (66.7%)	11 (47.8%)	2 (40.0%)	
Cancer				
Yes	8 (16.7%)	5 (21.7%)	0 (0%)	0.70
No	40 (83.3%)	18 (78.3%)	5 (100%)	
Auto-immune disease				

with data obtained from other studies employing different methodologic approaches (e.g. case-control studies).[6,11,18–22] They included, among the others, cotrimoxazole (trimethoprim-sulfamethoxazole), anticonvulsants especially lamotrigine and phenytoin, and allopurinol. For a long list of drugs, only one probable or very probable case of reaction was

reported, making risk estimates for these drugs very unstable. Among drugs with only one case reported, ceftriaxone and ketorolac had a high incidence. Ketorolac was the only drug for which we were unable to find any previous case reported in the literature. However, a higher risk is described for other molecules in the same non-steroidal anti-inflammatory drugs class of ketorolac, namely, acetic acid derivatives.[6]

In absolute terms, the highest number of cases of SJS/TEN was attributed to allopurinol, with 23 cases. This is consistent with previous data describing allopurinol as a leading cause of SJS/TEN in the general population.[5,21,23] The large number of cases reflects the intrinsic risk connected with the drug and the widespread use of the drug for the indication of hyperuricemia, which more frequently occurs in elderly people who represent per se a high-risk population.[24] It is expected that a better, more careful use of allopurinol, especially in the elderly, could reduce the overall number of cases of SJS/TEN.

A total of three probable and very probable cases of SJS/TEN were attributed to paracetamol and one case to paracetamol/codeine. The association of paracetamol with SJS/TEN has been debated since many years. Multiple case reports and larger studies have been published linking paracetamol to these reactions.[5,25,26] In the case-control study of Roujeau et al., a higher risk for paracetamol was found in Germany, Italy and Portugal, although not in France.[5] It was suggested that the association with paracetamol could be confounded by drug indication, especially fever, which may represent an early clinical manifestation of the reaction.[26] In our opinion, people should be aware of the possible association between paracetamol exposure and SJS/TEN and should use the drug carefully.[25]

Only probable and very probable associations were used for the calculation of the incidence rates of drugs. In a total of five (6.6%) patients, no causative drug was identifiable. The presence of a proportion of patients without any recognizable drug exposure is a common finding in many surveillance systems of these severe reactions and it is intriguing, pointing to the existence of other triggering factors besides drug exposure.[3,9,17] Factors identified as triggers and/or risk modifiers include infections, vaccination, recent cancer, immune-related diseases[3,18] and genetic predisposition (HLA-B alleles).[17,19]

In our study, an infection was reported prior to the onset of the reaction in more than 40% of cases. Interestingly, the rate of infections preceding the

reaction was higher, although not significantly, in the group where no drug related with the reaction was identifiable. This suggests that infections might contribute alone or in combination with drugs to the development of the reaction.[5] Mycoplasma pneumonia infection has been described in multiple cases of SJS, especially in children associated or not with drug exposure.[27–29]

Mortality in our study was about 20%, comparable with figures reported in other surveillance systems.[2,30,31] Death occurred in five cases (33.3%) aged 90 years or older and in six cases (40.0%) with a recent history of cancer. Both age and cancer have been described to be associated with a poor prognosis.[2,32]

A remarkable difference, even if not statistically significant, was documented for mortality between the specialized Burn Unit and peripheral hospitals, suggesting that optimized wound care may help improve survival.

All in all, our study indicates the utility of a registry to collect cases of rare and severe cutaneous adverse reactions, using homogeneous clinical criteria and standardized collection of data on exposure. Harmonization of management criteria and educational activities could also be promoted within the registry.

CONCLUSION

The REACT registry proved to be a useful tool to estimate the incidence and to assess the pharmacological risk of severe adverse skin reactions. It is important to maintain the network also to optimize the clinical management of severe drug reactions, possibly by extending it to other Italian regions.

Our incidence data were similar to those obtained in other studies, and mortality rates were also comparable.

Allopurinol was responsible for most cases in absolute terms, reflecting the widespread use of the drug in the population. Cotrimoxazole and lamotrigine showed the highest incidence rates adjusted for drug consumption. The risk increased with age and was particularly high in women.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- In line with previously published data, the combined incidence of Steven–Johnson syndrome and toxic epidermal necrolysis in the Lombardy population was in the order of one case per million people per year, with an overall mortality of about 20%. The elderly population and especially

women were at higher risk.

- Allopurinol was responsible for the largest number of cases reflecting its widespread use in the population. As for drugs with more than one case reported, cotrimoxazole and lamotrigine had the highest incidence rates adjusted for drug consumption.
- No causative drug was identifiable in five cases (6.6%). Infections, malignancies and immunerelated diseases were frequently associated with the reactions and might have played a role in their development.
- This study confirms the utility of an active surveillance system to monitor incidence rates and to identify drugs with highest risks in the population.

ETHICS STATEMENT

The study was approved by the Ethics Committee of each participating hospital, and all patients were to sign written informed consent before data collection. If patients were unable to provide written informed consent, this was performed by one of their family members.

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