

Drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: Proportion and determinants of underreporting to pharmacovigilance

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Clinical Implications

- More than two-thirds of French Stevens-Johnson syndrome/toxic epidermal necrolysis cases are not reported to the French national pharmacovigilance. This high underreporting rate is alarming because it may lead to failure to detect early an unacceptable risk associated with a drug.

TO THE EDITOR:

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are immunologically mediated severe cutaneous adverse reactions (SCARs) secondary in most cases to the administration of a drug.¹ Reporting to national pharmacovigilance databases is an important source of information on adverse drug reactions (ADRs). In France, health care professionals, including physicians and pharmacists, are *legally* required to report to pharmacovigilance *all* suspected ADRs. However, it has been estimated that only 5% to 15% of serious ADRs are reported to pharmacovigilance, even though very little accurate data are available.^{2,3} No data are available regarding SJS/TEN cases.

The aims of this study were to estimate the underreporting (ie, any not reported cases) rate of SJS/TEN to pharmacovigilance and to assess determinants of underreporting.

This was a retrospective study of all observations of SJS/TEN reported to the French pharmacovigilance network from 3 national sources: RegiSCAR France (2003-2012, 2015-2016), Programme de Médicalisation des Systèmes d'Information (PMSI; 2008-2016), and French Epidemiological Center for the Medical Causes of Death (CépiDC; 2003-2015). The French pharmacovigilance consists of a network of 31 regional pharmacovigilance centers mandated to collect reports of ADRs that health care professionals are legally required to declare in France since 1995.⁴ ADRs are collected, documented, reviewed, and stored using a standardized file. For this study, the preferred terms SJS/PT (10042033) and TEN/PT (10044223) were used to identify SJS/TEN cases. RegiSCAR France is a network of dermatology departments spread over France involved in care of patients with SCARs. An employee of the registry helps physicians to include patients in the registry and reminds them to

declare cases to the pharmacovigilance. All cases of drug-induced SJS/TEN collected in the registry were included. CépiDC is an administrative database collecting the medical causes of death from the anonymized death certificates. The PMSI database contains administrative and medical data on hospital stays in France. Both for CépiDC and for PMSI, the diagnoses are encoded using the *International Classification of Diseases, Tenth Revision* classification used in France since 1998. We extracted cases of SJS/TEN using L511 and L512 codes and excluded PMSI patients with hospital stay duration of 7 days or less and who did not die or did not stay in an intensive care unit. We cross-checked 4 variables (ie, age, sex, date of SJS/TEN, and localization of hospital stay) to identify in pharmacovigilance patients from the other databases.

Groups were compared by the Wilcoxon or Student *t* test for continuous variables and the chi-square or Fisher exact test for categorical variables. Multivariate logistic regression models were used to identify independent variables associated with underreporting. Variables associated with the outcome with a *P* value of less than .20 in univariate analyses were included in the multivariate models. Statistical analyses were performed using Stata version 14.0. The Commission Nationale de l'Informatique et des Libertés approved extraction and analyses of data from each databases.

Characteristics of patients and proportions of underreporting are detailed in Table I. Underreporting rates were 30.7% for RegiSCAR, 69.0% for CépiDC, and 71.2% for PMSI, respectively (*P* < .001 for the comparison of the 3 databases). Few variables were associated with underreporting (Table II). Compared with reported cases from the PMSI database, the underreported cases were younger and more often male. Among the patients who died (CépiDC database), SJS/TEN overlap and TEN cases were more underreported than SJS cases. The rate of underreporting in patients recorded in RegiSCAR database significantly increased with time. Interestingly, evolution to death was not associated with reporting to pharmacovigilance.

At the national level, more than two-thirds of suspected SJS/TEN cases were not reported to the pharmacovigilance system, whether or not the patients died. This high underreporting rate is alarming because SJS/TEN is probably one of the most severe and most iconic ADR. This confirms previous data evidencing that underreporting of ADRs does not concern only outpatients seen by general practitioners but also inpatients cared for by hospital-based physicians.³

However, underreporting was much lower for patients included in RegiSCAR. This may be explained both because someone actively reminded the physician to declare the case and/or because dermatologists with experience with SJS/TEN may be more aligned with the responsibility to report the cases.

Our study included a very large number of SJS/TEN cases, with sources of information extracted from 3 different national databases, each one with its own characteristics. Therefore, our findings are probably a good description of the magnitude of underreporting of severe ADRs. There are, however, some limitations, most of them being inherent to the use of administrative databases. First, there may have been some misclassifications in PMSI and CépiDC databases in which diagnoses are based on

TABLE I. Patients' characteristics

Characteristic	FPV	PMSI	RegiSCAR	CépiDC
Identified cases, n	1273	1516	352	348
Number of cases not notified to the FPV, n (%)	—	1080 (71.2)	108 (30.7)	240 (69.0)
Age (y), mean $\pm$ SD	49.4 $\pm$ 24.4	46.4 $\pm$ 28.5	48.1 $\pm$ 22.5	69.5 $\pm$ 19.4
Women, n (%)	694 (54.5)	763 (50.3)	194 (55.1)	188 (54.0)
Diagnosis, n (%)				
SJS	730 (57.3)	824 (54.4)	142 (40.3)	38 (10.9)
SJS/TEN overlap and TEN	543 (42.7)	692 (45.6)	210 (59.7)	310 (89.1)
Evolution to death, n (%)	191 (15.0)	190 (12.5)	48 (13.6)	348 (100)

FPV, French Pharmacovigilance.

TABLE II. Factors associated with underreporting to pharmacovigilance

Factor	Univariate analyses			Multivariate analyses	
	Reported cases	Not reported cases	P value	OR (95% CI)	P value
PMSI, n (%)	436 (28.8)	1080 (71.2)			
Age (y), mean $\pm$ SD	50.2 $\pm$ 25.9	44.9 $\pm$ 29.4	.001	0.95 (0.91-0.99)*	.02
Women, n (%)	242 (55.5)	521 (48.2)	.01	0.78 (0.62-0.97)	.03
Diagnosis, n (%)			.21	—	—
SJS	226 (51.8)	598 (55.4)			
SJS/TEN overlap and TEN	210 (48.2)	482 (44.6)			
Evolution to death, n (%)	67 (15.4)	123 (11.4)	.03	0.79 (0.57-1.11)	.17
Year of notification, median (IQR)	2012 (2010-2014)	2012 (2010-2014)	.99	—	—
RegiSCAR, n (%)	244 (69.3)	108 (30.7)			
Age (y), mean $\pm$ SD	47.0 $\pm$ 22.7	50.5 $\pm$ 21.9	.17	1.07 (0.97-1.19)*	.20
Women, n (%)	132 (54.1)	62 (57.4)	.56	—	—
Diagnosis, n (%)			.91	—	—
SJS	98 (40.1)	44 (40.7)			
SJS/TEN overlap and TEN	146 (59.8)	64 (59.2)			
Evolution to death, n (%)	34 (13.9)	14 (12.9)	.80	—	—
Year of notification, median (IQR)	2007 (2004-2010)	2009 (2006-2011)	.0001	1.12 (1.06-1.20)†	<.0001
CépiDC, n (%)	108 (31.0)	240 (69.0)			
Age (y), mean $\pm$ SD	68.1 $\pm$ 18.0	70.1 $\pm$ 20.0	.38	—	—
Women, n (%)	55 (50.9)	133 (55.4)	.44	—	—
Diagnosis, n (%)			.007	2.48 (1.26-4.91)	.009
SJS	19 (17.6)	19 (7.9)			
SJS/TEN overlap and TEN	89 (82.4)	221 (92.1)			
Year of notification, median (IQR)	2008 (2005-2012)	2009 (2006-2012)	.59	—	—

IQR, Interquartile range; OR, odd ratio (cases adequately reported compared with not reported cases).

*Per 10-y increase.

†Per 1-y increase.

codes. Because SJS and erythema multiform may be difficult to distinguish clinically and to code using *International Classification of Diseases, Tenth Revision* codes (code L510 “nonbullous erythema multiform” and code L511 “bullous erythema multiform”), SJS is often overdiagnosed when searched for by coding in electronic health care databases.⁵ To limit this bias, we excluded from the PMSI database all patients with short hospital stay if they did not die or did not stay in an intensive care unit. Furthermore, it may be hypothesized that reporting was associated with the culprit drug and/or the avoidability of SJS/TEN. These were likely to be different between men and women and between younger and older patients.⁶ If this unavailable information would have been included in the analyses, results regarding predictors may have been different. Second, some cases

of SJS/TEN not associated with a specific drug exposure could have been included among PMSI and CépiDC cases, which may have introduced an overestimation of underreporting. However, non—drug-induced SJS/TEN accounts for only 10% of all SJS/TEN cases (G. Chaby, S. Ingen-Housz-Oro, N. De Prost, P. Wolkenstein, O. Chosidow, L. Fardet, unpublished data, 2018).⁷ Finally, these results reflect French practices and we are unsure whether they reflect practices in other countries.

Reporting ADRs to national pharmacovigilance databases plays a critical role in enhancing drug safety in the postmarketing setting and, at the national level, may help improve treatment decision making. Underreporting may be minimized by different methods such as passive (ie, facilitating the process) or active (eg, collaboration between pharmacovigilance and medical staffs,

teaching session) promotion of ADR reporting or automation of the process (ie, computer programs).⁸ Projects encouraging patients to proactively report ADR should also be favored.⁸

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