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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Incidence of Stevens-Johnson syndrome/toxic epidermal necrolysis among new users of different individual drugs in a European population: a case-population study

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Abstract

Purpose To estimate the specific incidences of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) among new users of drugs frequently reported to be associated with this serious event.

Methods We performed a case-population approach, which combined data from a registry of SJS/TEN cases from the Madrid region (numerator) during the study period 2005–2015 and a primary healthcare database from the same catchment population. The proportion of new users of drugs estimated in the primary healthcare database was stratified by calendar year, sex and age (5-year bands), and then applied to the same strata of Madrid's population census to compute the number of new users (denominator). Incidences were re-estimated using only cases in which the concerned drug had a probable or very probable causal relationship.

Results A total of 44 SJS/TEN cases aged > 14 years were registered during the study period. The highest SJS/TEN incidence was found for phenytoin with 68.9 per 100,000 new users (95% CI 27.7–141.9), followed by dexamethasone (5.48; 1.49–14.03), allopurinol (3.29; 1.07–7.67) and cotrimoxazole (3.19; 0.87–8.16). Considering only probable and very probable cases, the incidences hardly changed, except for dexamethasone, which was left without cases. Pantoprazole, levofloxacin and lorazepam showed incidences between 1 per 100,000 and 1 per 1,000,000 new users. Ibuprofen, amoxicillin-clavulanic acid, metamizole, amoxicillin, paracetamol and omeprazole showed incidences around 1 per one million new users.

Conclusions Phenytoin was the drug with the highest incidence of SJS/TEN, followed by allopurinol and cotrimoxazole. For the rest of the drugs, the estimated incidences were below 1 in 100,000 new users.

Keywords Toxic epidermal necrolysis · Stevens-Johnson syndrome · SCAR · Hypersensitivity · Case-population study

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Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous adverse reactions, characterised by a generalised detachment of the epidermis, often accompanied by mucosal erosions and systemic involvement [1, 2]. Both are considered severity variants for the same disease [1]. The mortality rate ranges from 12 to 46% at 6 weeks depending on the degree of skin detachment [3]. SJS/TEN is a hypersensitivity reaction mediated by cytotoxic T cells that can be caused by any foreign substance recognised by the cells of the immune system, drugs being the most common cause [4–6]. Among the most frequently reported drugs in association with this condition are the antigout drug allopurinol, the aromatic anticonvulsants, and the antimicrobials containing sulphonamides [6].

The incidence of SJS/TEN in the population has been estimated to be around 1–2 cases per million inhabitants per year [2]. Yet, specific incidences are largely unknown for most drugs. As an immuno-allergic reaction, SJS/TEN occurs at treatment onset, usually between 5 and 28 days after the causative drug intake [6]. Therefore, only people who initiate treatment (new users) are at risk of suffering SJS/TEN and, consequently, the number of new users should be the only valid denominator to estimate drug-specific incidences [7, 8]. However, the number of new users is difficult to quantify with traditional techniques, such as drug sales, a method of widespread use in pharmacovigilance [9]. A few years ago, Mockenhaupt et al. [8] developed a new approach to estimate the number of new users from the German national drug consumption, applying a correction factor ("the new-user fraction") based on the trends showed by the specific drug over the study period. With this method, they managed to estimate, for the first time, the incidence of SJS/TEN for several anticonvulsant drugs among new users. However, this approach has two limitations: (1) It is based on aggregate data and then no information at individual level can be obtained and (2) the estimation of new users is conditional to several assumptions and, thus, the result is only approximate.

Population-based electronic databases (including claims databases) are increasingly used in pharmacoepidemiology [10]. These databases can be used to estimate drug-specific incidences through ad hoc pharmacoepidemiologic studies [11–15]. Though databases provide an accurate estimate of the population at risk (the denominator), the correct identification and classification of potential cases (the numerator) may be a serious problem, as most rely on diagnostic codes which are not specific for SJS/TEN. For instance, ICD-9-CM code 695.1 includes erythema multiforme, in addition to SJS and TEN [14, 15]. Moreover, cases are not usually validated by physicians with experience in the diagnostic evaluation of these complex diseases with full access to the clinical manifestations, photographs, and histopathological findings, all of which may lead to an overt misclassification of cases [16, 17]. On the other hand, the index date, defined as the date in which the first symptoms appeared, crucial for the study of drug causality assessment of delayed hypersensitivity reactions, is often loosely defined in databases studies. For all these reasons, experts consider that, for these complex diseases, there is no alternative to the collection of detailed information at the bedside, as it is done in widely known registries, such as RegiSCAR [18]. Although, the ideal solution would have been to link at individual level the records from the disease registry with the corresponding records from other databases (prescriptions, primary healthcare etc.), such record linkage was not feasible in our country, and we decided to try a different strategy that combines the registry of cases from a geographically defined population (Madrid region) [19], with a primary healthcare database from the same region. Whereas such database is fully anonymised and linkage with the registry was not possible, it shares the same catchment population and, thus, we used it to obtain information on population drug exposure, mimicking the case-population approach but with the advantage of having information at the individual level [20]. This approach, conceived as a surveillance system, proved useful to estimate measures of association among new users [21] and in the present study, we tested its application to estimate incidences of SJS/TEN among new users of selected drugs.

Patients and methods

Data sources

The study has been carried out combining information from three different data sources (Fig. 1):

(1) The PIELenRed Registry is an interdisciplinary network for the study of severe cutaneous adverse reactions [19]. Eight main hospitals in Madrid region (population around 6 million inhabitants) participate in this network, including the two reference Burn Units that attend to SJS/TEN patients with a relevant percentage of total body surface area involved [22]. The project began in 2011, since then all SJS/TEN cases that arise in Madrid region are recorded prospectively; furthermore, all cases emerged between 2005 and 2010 were identified and registered retrospectively.

(2) BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria) [20] is a database of anonymised primary care electronic health records widely used and validated for pharmacoepidemiological research [11, 23–26]. BIFAP includes information on patient demographics, prescription details, clinical events, free text comments,

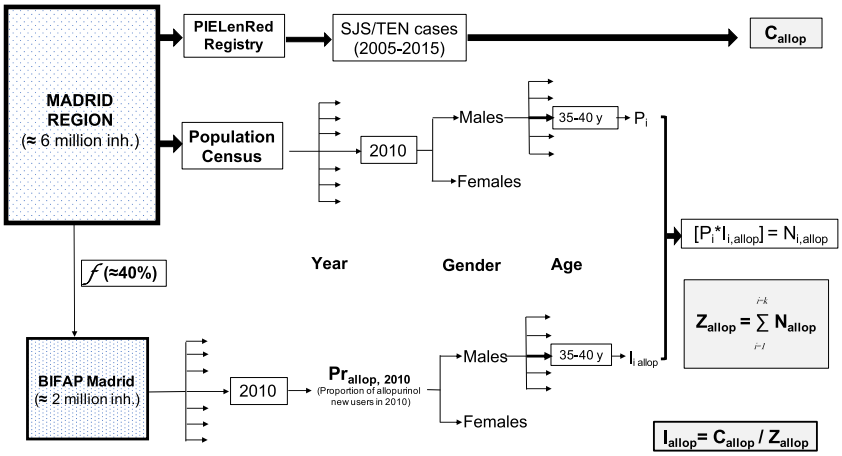

Fig. 1 Structure of the study. The study combines information from three sources: (1) The PIELenRed registry: provides information on (all) SJS/TEN cases (C) occurring in people who were living in Madrid region during the study period (2005–2015); (2) population census of Madrid region (P); and (3) BIFAP database: a primary healthcare database which can be considered a quasi-random sample from Madrid region; it provides information on the proportion (Pr) of new users per year (people who initiated the treatment with the drug of interest). Population from census and from BIFAP are distributed in *k* strata resulting from the combination of 3 variables: calendar year, gender (male, females) and age (5-year bands). The figure shows, as an example, how the incidence of SJS/TEN among new users of allopurinol is estimated. Notation: C_{allop} indicates cases who were new and current users of allopurinol in the PIELenRed registry. $N_{i,\ allop}$ indicates number of persons who initiated allopurinol in the i^{th} stratum. Z_{allop} indicates number of persons who initiated allopurinol during the period 2005–2015. This number results from the sum of all $N_{i,\ allop}$. I_{allop} indicates incidence of SJS/TEN among new users of allopurinol in Madrid region, period 2005–2015

referrals and laboratory test results from patients attended in Madrid and eight other Spanish regions (see a more detailed description of BIFAP in Online Resource 1). In the current project, only information from Madrid was utilised, which included around 2 million patients (13 million patient-years) covering around 40% of Madrid's total population. All patients had to be enrolled with their general practitioners for at least 1 year before being considered eligible for research purposes.

(3) Madrid Statistical Institute [27] which provides statistical information from the census population stratified by age groups, sex and calendar year.

Case definition and validation

All consecutive community cases of SJS/TEN living in Madrid and treated in any of the hospitals from the PIELenRed network during 2005–2015 (study period) were included in this study. We decided to restrict the analysis to patients older than 14 years of age because the number of cases occurring in children was very small ($n = 3$) and would not yield meaningful estimates. Clinical data, pictures, and histopathological examinations for each patient were collected by the study monitor (VL) and reviewed and validated by an expert committee (CGH, OG, TB, VL) in order to establish the final diagnosis according to the agreed international criteria [16]. The index date was considered the date of first signs and symptom(s) affecting the skin or mucous membranes and followed by blisters/erosions on same site(s). Fever or pain was used to set the index date if beginning no more than 1 day before the mucocutaneous signs and symptoms. For retrospective cases, we collected the data from hospital charts. For prospective cases, we retrieved the information from direct interviews to patients and/or relatives, as well as from hospital charts, using standardised forms developed by RegiSCAR and used previously in multiple studies [18] (the Spanish version is available in ref. 19). We collected information on demographic characteristics (i.e. age, sex and region), clinical, haematological and biochemical parameters at admission and during hospitalisation. Medication use was retrieved from patients (in prospective cases), as well as from linked primary care clinical records (prospective and retrospective cases). Patients included in this study who are also included in RegiSCAR are identified by their corresponding codes (Online Resource 2).

Exposure definition and population at risk

SJS/TEN cases were considered exposed when they were both new and current users of the drug of interest, according to the following definitions: (1) "New users": patients who started using the drug of interest within the last 56 days before the index date (with no reported or recorded exposure before that time) (this time window was selected, in accordance with previous studies [5, 6], taking into account that immunoallergic reactions like SJS/TEN are not plausible to occur beyond this time of exposure) and (2) "Current users": patients who continued taking the drug until the index date or within a

window of 8 days prior to the index date (assuming that after 8 days of discontinuation most drugs are totally eliminated from the body (more than 5 half-lives) and cannot be the causative agent).

To estimate new users of the drugs of interest older than 14 years from Madrid region (the denominator), we proceeded as follows: for each year within the study period, we identified all patients from BIFAP attended in Madrid primary care who received for the first time a new prescription for the drug of interest and checked that they did not have any previous prescription during the time available in the database before the index date (median of 7.0 years (interquartile range, 4.5–9.9) (new user). Then, we calculated the proportional incidence of new users of the study drug by sex, age (in five-year groups from 15 years) and calendar year from 2005 to 2015. Second, we applied such new-user incidences to the corresponding strata of the census population of Madrid in order to estimate the absolute number of new users expected for each study drug (population at risk) in Madrid per year. Finally, we added these figures to estimate the total population at risk in the entire study period, 2005–2015 (Fig. 1). Only drugs with at least two exposed cases were included in the analysis.

Statistical analysis

We calculated the proportional incidences of SJS/TEN for new users (the population at risk) dividing the number of cases registered in PIELenRed who were new and current users of the drug of interest by the number of new users of such drug in Madrid, estimated as described in the "Exposure definition and population at risk" section. We computed the 95% confidence interval (CI) for each incidence. For all analyses, we used STATA version 15.1 (StataCorp LP, College Station, TX, USA).

Individual causality assessment

The ALgorithm of Drug causality for Epidermal Necrolysis (ALDEN) [28] was applied to all drugs with exposure within the 56-day window before the index date of SJS/TEN cases. The ALDEN grades causality between drug exposure and SJS/TEN in five categories: very probable, probable, possible, unlikely or very unlikely. In addition, we estimated the incidences using in the numerator cases with either at least a possible causality category or at least a probable causality category, as specified. Also, we calculated two different parameters based on the ALDEN score: (a) IREC (Imputability Rate among Exposed Cases) defined as the proportion of cases with a probable or very probable ALDEN score for the drug of interest among the total number of cases exposed to such drug within the 56-day window period prior to the index date and (b) AltIREC (Alternative Imputability Rate among Exposed Cases) defined as the proportion of cases that, being exposed to the drug of interest, have a probable or very probable ALDEN score for at least another drug. The combination of a high IREC with a low AltIREC suggests that the drug of interest is the most probable cause for the majority of cases exposed to that drug within the registry, while a low IREC along with a high AltIREC means that for the majority of exposed cases, there are other drugs that are considered as probable or more probable.

Ethical approval

The PIELenRed registry received the approval of the Research Ethics Committee of the Príncipe de Asturias University Hospital (the coordinating centre of the PIELenRed Consortium). Prospective patients or their legal representatives gave the written informed consent. For retrospective patients, the committee granted a waiver to the informed consent under the commitment that the data were fully anonymised once extracted from clinical records. Access to anonymised data from BIFAP was granted by the BIFAP Scientific Committee (no. 05/2016).

Results

A total of 44 SJS/TEN cases aged > 14 years were attended in PIELenRed hospitals during the study period, resulting in a population incidence of 0.75 per million person-years. Twenty-five cases were collected retrospectively and 19 prospectively; 43.2% were men and the mean age was 54 years (SD 21.6). All but 1 case (2.3%) reported exposure to at least one drug in the 56-day window period; 6 reported exposure to one drug (13.6%); 6 to two drugs (13.6%); and 31 to three or more drugs (70.5%) (Table 1).

Overall, the highest incidence was found among new users of phenytoin with 68.9 per 100,000 new users (95% CI 27.7–141.9) followed by dexamethasone (5.48; 1.49–14.13), allopurinol (3.29; 1.07–7.67) and cotrimoxazole (3.19; 0.87–8.16). The other studied drugs showed incidences below 1 case per 100,000 new users (Table 2). The incidences by sex and age group (15–59 years and ≥ 60 years) are shown in Fig. 2. All confidence intervals largely overlapped, and no statistically significant differences were observed across sex or age strata.

We performed a causality assessment for 224 drugs with a reported exposure within the 56-day window period before the index date. According to ALDEN scores, 14 cases had at least 1 drug as a very probable cause (31.8%), 16 as probable (36.4%), 8 as possible (18.2%) and 5 as unlikely or very unlikely (11.4%). Drug-specific incidences corrected by the

Table 1 Characteristics of SJS/TEN cases

	Cases $n = 44$
Men	19 (43.2%)
Age (mean [± SD])	54.0 (21.6)
Age	
15–39	14 (31.8%)
40–59	13 (29.6%)
≥ 60	17 (38.6%)
Entity	
SJS	17 (38,6%)
SJS/TEN	12 (27.3%)
TEN	15 (34.1%)
History of	
Chronic kidney failure	8 (18.2%)
Rheumatoid arthritis	4 (9.1%)
Malignancy	10 (22.7%)
HIV infection	6 (13.6%)
Diabetes	6 (13.6%)
Epilepsy	5 (11.4%)
Recent acute infections[a]	
Respiratory	8 (18.2%)
Urinary	3 (6.8%)
Herpes	1 (2.27%)
Drug exposure (new and current users)	
Phenytoin	7 (15.9)
Allopurinol	5 (11.4)
Ibuprofen	5 (11.4)
Cotrimoxazole	4 (9.1)
Dexamethasone	4 (9.1)
Paracetamol	4 (9.1)
Amoxicillin-clavulanic acid	3 (6.8)
Lorazepam	3 (6.8)
Amoxicillin	2 (4.6)
Pantoprazole	2 (4.6)
Levofloxacin	2 (4.6)
Metamizole	2 (4.6)
Omeprazole	2 (4.6)

[a] Recent acute infections measured at the moment of the SJS/TEN episode

SD standard deviation

causality grades are shown in Table 2. Three drugs presented with the combination of high IREC with low AltIREC values: allopurinol (100%; 0%), cotrimoxazole (100%; 25%) and phenytoin (78%; 22%). At the other end, dexamethasone (0%; 100%), omeprazole (0%; 90%), lorazepam (0%; 80%), pantoprazole (0%; 75%), paracetamol (0%; 60%), amoxicillin-clavulanic acid (0%; 50%) and levofloxacin (0%; 50%) presented with the opposite combination (Table 3) (see alternative drugs in Online Resource 3).

Table 2 Specific-drug incidences of SJS/TEN in Madrid region during 2005–2015. Drugs are ordered from highest to lowest incidence per 100,000 new users

Drug of interest	Estimated number of new users	Cases exposed in PIELenRed	Incidence per 100,000 new users (95% CI)	Cases with an at least possible ALDEN score	Incidence per 100,000 new users corrected by ALDEN (95% CI)	Cases with an at least probable ALDEN score	Incidence per 100,000 new users corrected by ALDEN (95% CI)
Phenytoin	10,162	7	68.88 (27.70–141.90)	7	68.88 (27.70–141.90)	7	68.88 (27.70–141.90)
Dexamethasone	72,994	4	5.48 (1.49–14.03)	4	5.48 (1.49–14.03)	0	–
Allopurinol	152,089	5	3.29 (1.07–7.67)	5	3.29 (1.07–7.67)	5	3.29 (1.07–7.67)
Cotrimoxazole	125,516	4	3.19 (0.87–8.16)	4	3.19 (0.87–8.16)	4	3.19 (0.87–8.16)
Pantoprazole	293,436	2	0.68 (0.08–2.46)	2	0.68 (0.08–2.46)	0	–
Levofloxacin	540,627	2	0.37 (0.04–1.34)	2	0.37 (0.04–1.34)	0	–
Lorazepam	1,099,397	3	0.27 (0.06–0.80)	0	–	0	–
Ibuprofen	5,270,377	5	0.09 (0.03–0.22)	5	0.09 (0.03–0.22)	3	0.06 (0.01–0.17)
Amoxicillin-clavulanic acid	3,326,921	3	0.09 (0.02–0.26)	3	0.09 (0.02–0.26)	0	–
Metamizole	2,471,248	2	0.08 (0.01–0.29)	2	0.08 (0.01–0.29)	2	0.08 (0.01–0.29)
Amoxicillin	2,533,961	2	0.08 (0.01–0.29)	2	0.08 (0.01–0.29)	0	–
Paracetamol	5,858,917	4	0.07 (0.02–0.17)	3	0.05 (0.01–0.15)	0	–
Omeprazole	3,964,185	2	0.05 (0.01–0.18)	0	–	0	–

CI, confidence interval; *ALDEN*, ALgorithm of Drug causality for Epidermal Necrolysis

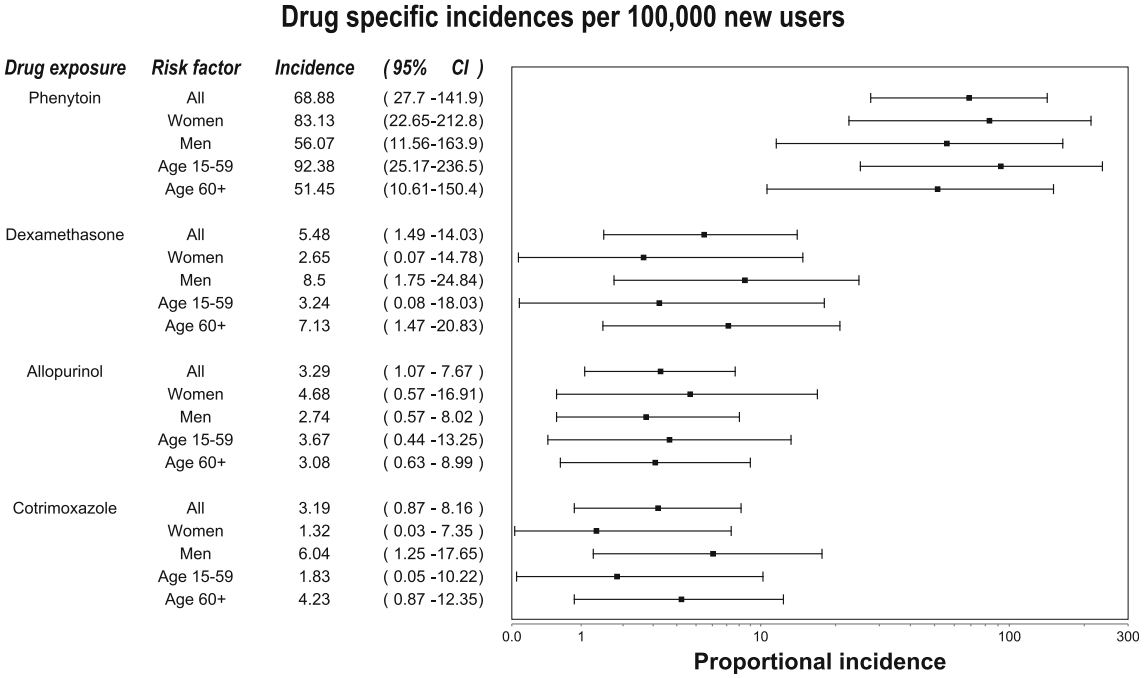

Fig. 2 Incidences of SJS/TEN by sex and age subgroups for selected drugs

Discussion

In the present study, we show the results of a method developed to estimate the incidence of SJS/TEN among new users of selected drugs (reported in at least two cases). For all drugs examined, the incidences can be categorised as rare (≥ 1/10.000 to < 1/1.000 exposed) or very rare (< 1/10,000 exposed), according to the widely used CIOMS classification [29].

Phenytoin showed the highest incidence of SJS/TEN in our study (6.9 per 10,000 new users), similar to the one reported by our group using a primary healthcare database (8.0 per 10,000 new users) [11] and by Mockenhaupt et al. [9] (8.1 per 10,000 new users). Diphoorn et al. [2] found an incidence of 3.23 cases per 10 million Defined Daily Doses per year, but this figure is difficult to compare because they only used aggregate data and were not able to exclude prevalent users. More recently, Frey et al. [12] using a UK-based primary healthcare database estimated a slightly lower incidence of 4.6 per 10,000 new users.

The second highest incidence was found for dexamethasone, although it dramatically lost its place when only cases with an at least probable score were considered. This is explained because all patients who were new users of dexamethasone were also new users of phenytoin, which was detrimental for dexamethasone ALDEN score assessment as phenytoin had a greater notoriety and the algorithm penalises drugs with a lower overall score. It is noteworthy, however, that the high notoriety of phenytoin was associated with its use as an antiepileptic drug and not for prevention of seizures associated with brain metastases. The high crude incidence associated with dexamethasone might also be explained by a protopathic bias (use of steroids to treat early symptoms of SJS/TEN), but in our series, the time since starting the drug to the onset of reaction was 24 days [21] which is not compatible with a protopathic bias. An interesting hypothesis raised by Lee et al. [30] and supported by our data [21] is that the prior or concomitant use of corticosteroids may have delayed the onset of reaction.

Cotrimoxazole presented the highest incidence among antimicrobials (five times higher than the one for levofloxacin, amoxicillin and amoxicillin-clavulanic acid). This result is consistent with previous studies [5, 6]. It is important to take into account that cotrimoxazole is frequently used in patients with HIV, who are reported to have a greater propensity to develop SJS/TEN [17]; however, none of our cases exposed to cotrimoxazole were HIV-infected patients. Recently, Frey et al. [13] in a study performed in a UK-based database found a risk of 1.32 per 100,000 new users of trimethoprim. For sulfamethoxazole or for cotrimoxazole, no cases were found which precluded the estimation of a proper incidence. We have not found other studies reporting SJS/TEN incidence for cotrimoxazole.

The results for allopurinol deserve a special comment. This drug has been reported as the "most common cause of SJS/TEN in Europe" [31]. Our study confirms that allopurinol ranks high among drugs causing SJS/TEN, but it is not the riskiest drug, as the above statement might suggest. Thus, the top position of allopurinol in the registries of cases should be partly attributed to the wide use of the

Table 3 ALDEN-based imputability parameters among cases the SJS/TEN cases. Drugs are ordered from highest to lowest IREC value and, in case of equal IREC, from lowest to highest AltIREC

D Drug of interest	N All cases reporting an intake of drug D within the 56-day window period[a]	A Cases exposed to D with an ALDEN score of probable or very probable	IREC for D Imputability rate among exposed cases (IREC = A/N)	C Cases exposed to D with alternative drugs presenting with an ALDEN score of probable or very probable	AltIREC for D Alternative imputability rate among exposed cases (AltIREC = C/N)
Allopurinol	5	5	100%	0	0%
Cotrimoxazole	4	4	100%	1	25%
Phenytoin	9	7	78%	2	22%
Metamizole	4	2	50%	3	75%
Ibuprofen	13	3	23%	6	46%
Dexamethasone	6	0	0%	6	100%
Amoxicillin	3	0	0%	0	0%
Levofloxacin	2	0	0%	1	50%
Amoxicillin-clavulanic acid	4	0	0%	2	50%
Paracetamol	10	0	0%	6	60%
Pantoprazole	4	0	0%	3	75%
Lorazepam	5	0	0%	4	80%
Omeprazole	10	0	0%	9	90%

[a] The number of exposed cases is slightly different from the one given in Table 2 because in this analysis, new and current use criteria (see the "Exposure definition and population at risk" section) are not a pre-condition for inclusion as exposed cases. This is because ALDEN specifically assesses both elements and assigns a high score to them ("delay from initial drug component intake to onset of reaction" and "drug present in the body on index day")

ALDEN, ALgorithm of Drug causality for Epidermal Necrolysis; *IREC*, imputability rate among exposed cases; *AltIREC*, alternative imputability rate among exposed cases (see the "Patients and methods" section)

drug, probably in questionable indications such as asymptomatic hyperuricaemia. We have identified three other epidemiological studies [14, 32, 33] which provide data on incidence of hospitalised cases with hypersensitivity reactions associated with allopurinol, but none of them provides specific data for SJS/TEN, as all of them used ICD-9-CM codes which do not distinguish between SJS/TEN and erythema multiforme, which nowadays are considered different diseases. As far as we know, our study is the first to estimate the incidence of SJS/TEN among allopurinol new users in a European population.

For the rest of the drugs examined, the incidences were below 1 case per 100,000 new users, or even lower when the incidence was corrected using the causality algorithm. The baseline incidence of SJS/TEN among non-users of drugs is unknown. However, bearing in mind that the population incidence is 1–2 per million persons per year and that the fraction of cases non-attributed to drugs is around 10–20% [34], we could estimate this baseline incidence among non-users of drugs in 0.1–0.4 per million person-years. It is likely that for some drugs included in our study, the incidence estimated is mostly reflecting this baseline incidence. Along these lines, it is interesting that omeprazole, lorazepam, pantoprazole, paracetamol, amoxicillin-clavulanic acid and levofloxacin showed a combination of low IREC and high AltIREC which suggests that other drugs were more probable, and they could rather be innocent bystanders. These parameters revealed a useful complement to the epidemiological estimation of risk.

The most important strength of our approach is that cases were validated using detailed clinical information, clinical photographs and histopathological images and reports, assessed by an expert committee with extensive experience in SJS/TEN [17]. Among the limitations, we should mention that the number of new users in Madrid region was not directly calculated but estimated through BIFAP database which is a large but not a purely random sample of the population of Madrid. However, the incidences of new users were estimated by age and sex strata and applied to the respective strata in Madrid region, a strategy that should improve the validity of the estimation. Some hospitals did not participate in the registry, and the possibility exists that some SJS/TEN cases were not captured in our study (in particular for the retrospective part), but this is probably not applicable to the most severe cases, as all of them are usually transferred to the reference Burn Units available in the region, and both participated in PIELenRed. This potential under-recording of less severe cases could explain that our population incidence is slightly lower than the one reported in other studies. New user definition requires no exposure to the drug of interest before the 56-day window prior to the index date, which is highly dependent on patient's recall (for cases), and its accuracy cannot be assured. It is also important to note that BIFAP, as many other primary healthcare databases, only records prescriptions filled by general practitioners; thus, drugs dispensed over the counter are not systematically recorded and the possibility of a misclassification exists for these drugs (e.g. paracetamol or ibuprofen). The impact of this misclassification would be to overestimate the incidence of SJS/TEN associated with these drugs [21]. Finally, the number of exposed cases for most drugs was rather low which yielded imprecise estimates (wide confidence intervals).

In conclusion, we developed a method that enabled us to estimate the incidence of SJS/TEN in a European population among new users of 13 drugs identified in a case registry as potential causative agents. According to our data, controlled by age and sex, the riskiest drugs were phenytoin, allopurinol and cotrimoxazole. For dexamethasone, we also estimated a high incidence, but it decreased considerably when we adjusted the individual causality score.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all prospective individual participants or legal representatives. For retrospective cases, the Ethics Research Committee granted us an exemption. BIFAP is a fully anonymised database, and according to the Spanish law, an informed consent is not required when no personal data is collected.

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