

ALDEN, an Algorithm for Assessment of Drug Causality in Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis: Comparison With Case–Control Analysis

B Sassolas^{1,2}, C Haddad^{2,3}, M Mockenhaupt⁴, A Dunant^{2,5}, Y Liss⁴, K Bork⁶, UF Hausteiner⁷, D Vieluf⁸, JC Roujeau^{2,3} and H Le Louet⁹ for the RegiSCAR Study Group⁴

Epidermal necrolysis (EN)—either Stevens–Johnson syndrome (SJS) or toxic EN (TEN)—is a severe drug reaction. We constructed and evaluated a specific algorithm, algorithm of drug causality for EN (ALDEN), in order to improve the individual assessment of drug causality in EN. ALDEN causality scores were compared with those from the French pharmacovigilance method in 100 cases and the case–control results of the EuroSCAR study. Scores attributed by ALDEN segregated widely. ALDEN pointed to a “probable” or “very probable” causality in 69/100 cases as compared to 23/100 with the French method ($P < 0.001$). It scored “very unlikely” causality for 64% of medications vs. none with the French method. Results of ALDEN scores were strongly correlated with those of the EuroSCAR case–control analysis for drugs associated with EN ($r = 0.90$, $P < 0.0001$), with probable causality being reported in 218/329 exposures. ALDEN excluded causality in 321 drugs that the case–control analysis had described as “probably not associated” and in 22/233 drugs that had been described as inconclusive exposures. Being more sensitive than a general method, ALDEN, which correlates well with case–control analysis results, can be considered a reference tool in SJS/TEN.

Assessment of the causality of adverse events is important not only in the management of patients who have experienced such events but also in drug monitoring for better evaluation of the benefit/risk profiles of drugs.¹ Since the initial work of Irey in 1976,² many methods have been proposed to assess the causal relationship between an adverse event and a medication taken by a patient. Most of these methods belong to one of three categories: expert clinical judgment,³ probabilistic approaches,⁴ and algorithms.⁵ Clinical judgment is the first mandatory step, largely used in daily practice. However, universal expert judgment presents pitfalls, such as subjectivity and lack of standardization, which lead to poor reproducibility. Furthermore, the decision-making process is often not explicit, so that it is neither transparent nor replicable. The main limitation of probabilistic approaches is the need to model

probability distributions, which is difficult to accomplish in routine practice. The algorithm methods seem easier in routine practice. They are mainly based on decision trees or successive evaluation of criteria resulting in a sum of scores. Many algorithms for assessing the causality of drug reactions have been published in the literature.⁶ Most combine five criteria: challenge, dechallenge, rechallenge, previous bibliographic description, and other etiologic alternatives. With algorithms, the intra- and interevaluator agreements are usually high, but the results depend critically on the weight given to each criterion, which is rather empirical. These methods are either general (i.e., intended for all reactions and all drugs) or specific (i.e., adapted to the reaction or medication concerned). None of the methods proposed or used has yet been validated⁷ or compared with a reference method.

¹Department of Dermatology, CHU Morvan, Brest, France; ²Reference Center for Toxic and Autoimmune Blistering Diseases, University of Paris XII, Henri Mondor Hospital, Créteil, France; ³Department of Dermatology, University of Paris XII, Henri Mondor Hospital, Créteil, France; ⁴Dokumentationszentrum schwerer Hautreaktionen (dZh), Department of Dermatology, University Medical Center, Freiburg, Germany; ⁵Biostatistics and Epidemiology Unit, Institut Gustave–Roussy, Villejuif, France; ⁶Department of Dermatology, Johannes Gutenberg University, Mainz, Germany; ⁷Department of Dermatology, Universitätsklinikum Leipzig, Leipzig, Germany; ⁸Facklinikum Borkum, Borkum, Germany; ⁹Department of Pharmacovigilance, University of Créteil Paris XII, Henri Mondor Hospital, Créteil, France. Correspondence: B Sassolas (bruno.sassolas@chu-brest.fr)

Received 27 July 2009; accepted 29 October 2009; advance online publication 7 April 2010. doi:10.1038/clpt.2009.252

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are usually drug related and are characterized by a high death rate. The process of epidermal necrolysis (EN) results in extensive blisters and detachment of skin and mucous membranes.⁸ SJS and TEN are two forms of EN, differing only with respect to the amount of skin detachment relative to the body surface area involved.^{8–10} Although rare, these diseases remain of high interest in the field of drug safety and risk/benefit ratio evaluation of medicines because of their severity: the death rate from EN averages 23%.¹¹ Therefore, a proper identification of the drug responsible for the disease is essential, not only for sponsoring and regulatory agencies but also for the purposes of adequate *in vitro* investigations into the mechanisms involved. The identification of the causative drug is even more important for the patients and their physicians. In the acute phase, withdrawal of the suspected medication(s) is an urgent requirement for improving the immediate prognosis,¹² while other treatments often need to be continued. After the patient has recovered, it is of the utmost importance to prevent re-exposure to the culprit drug while also permitting the use of other medicines. Causality assessment for EN should therefore rely on validated methods. For rare outcomes, the case–control design is considered most appropriate for valid assessment of global medication risks.¹³ However, it does not provide the individual causality assessment needed for the patient’s immediate and future care and for the purpose of research.

To assess the medication risks in EN, we were involved in two successive case–control studies (SCAR and EuroSCAR)^{14,15} and, more recently, in a registry of cases (RegiSCAR).¹⁶ This prompted us to design a specific causality assessment method tailored to EN. Our aim was to create an algorithm that can be used by clinicians who are not necessarily experts in pharmacovigilance and not capable of discriminating between the effects of the many drugs to which patients with EN may be exposed (six drugs was the mean in the SCAR study).¹⁴

As a first step, an algorithm—algorithm of drug causality for EN (ALDEN)—was elaborated by a group of experts who had participated in the assessment of hundreds of cases, based on their knowledge of the results of the SCAR study.¹⁴ In the second step, the algorithm assessment of drug causality was carried out on all the cases enrolled in the EuroSCAR study.¹⁵ The results were compared with those provided by case–control analysis of the same cases.

RESULTS

Reproducibility of the algorithm

The comparison of scores assigned for 101 drugs by two investigators provided κ concordance values of 0.73, 0.71, and 0.71 for the individual score of each medication, classification of medications in causality groups, and determination of the drug with the highest score for each patient, respectively. Because the discrepancies consisted of differences in evaluation in only two parameters—“drug notoriety” and “pharmacokinetics”—we created a database of “notoriety” and “pharmacokinetics” for all drugs to which the patients had been exposed. (The data are not

shown but are available from the corresponding author as a Web table; the data will be posted at a future date on the RegiSCAR website.)

Comparison of ALDEN with the French pharmacovigilance method

In the study sample of 100 French cases of EN in patients who together were taking a total of 697 drugs, the algorithm scores for causality defined only one drug in the categories “very probable” or “probable” for 69 patients and two drugs in these categories for 3 patients, leaving 28 patients with no drug assessed as “probable” or “very probable” to have caused the adverse reaction. For this same set of 100 patients, the French pharmacovigilance method of causality assessment showed one drug in the category “possible” or “probable” for only 23 patients and two drugs for 17 patients, and no conclusion was possible with regard to drug causality in 60 patients. Therefore, the outcomes from causality assessment differ greatly between the two methods ($P < 10^{-3}$, χ^2 -test). The two methods had similar potential to confirm the causality of drugs with prior “notoriety” and to assess causality in drugs with unknown specific risk. However, the French pharmacovigilance method never classified a drug as “very probable.” On the other hand, the specific algorithm scored 64% of the whole set of drugs in the category “very unlikely.” No drug was in this category with the French pharmacovigilance method, which classified 77% of the drugs as “possible” or “unlikely” (Figure 1).

Drug risk as assessed by ALDEN in the EuroSCAR cases

Among the 379 validated cases of SJS/TEN in the EuroSCAR study, 7 patients (2%) had not received any systemic drug in the 4 weeks before the onset of the reaction. For the other patients, the distribution of individual drug scores (total number: 2,279) is shown in Figure 2a. The distribution of causality assessment for each patient is shown in Figure 2b.

In a total of 237 cases (63%), drug causality was assessed as “probable” or “very probable.” In 224 cases, a single drug was implicated as probable (104) or very probable (110). In the other 23 cases, 2 or 3 (in only 1 case) drugs had a probable/very

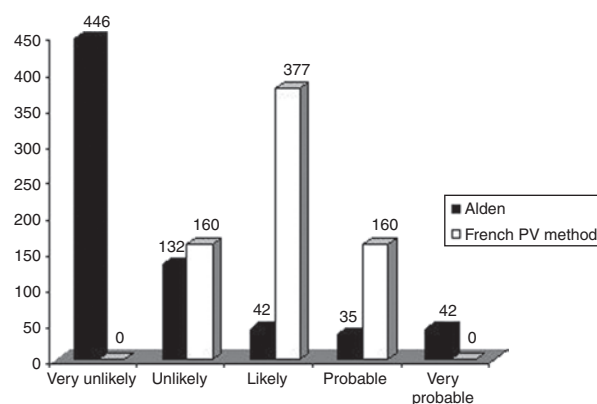


Figure 1 Distribution within classes of causality for the 697 drugs taken by 100 French patients, using the algorithm of drug causality for epidermal necrolysis (ALDEN) and the French pharmacovigilance (PV) method.

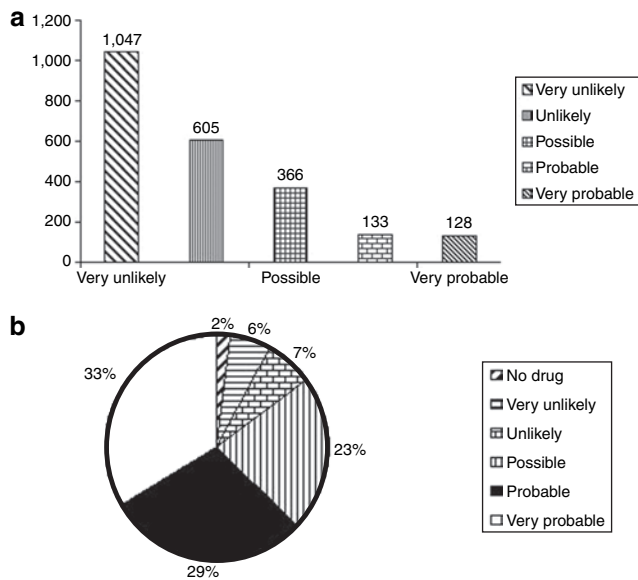


Figure 2 Results of causality assessments using the algorithm of drug causality for epidermal necrolysis (ALDEN) on data related to EuroSCAR patients. **(a)** Distribution of classes of causality provided by ALDEN for all 2,279 drugs taken by the 372 patients in the EuroSCAR study (7 patients did not take any drugs). **(b)** Distribution of drug causality per patient. Repartition of maximum score for at least one medication for the 379 cases of Stevens–Johnson syndrome/toxic epidermal necrolysis.

probable causality. In 1 of these cases, 2 drugs had a similar “very probable” score; in 6 cases, 2 drugs had a similar “probable” score; in 15 cases, 2 drugs were ranked as “very probable” or “probable”; and 1 case had 3 drugs ranked with a “very probable” (1 drug) or “probable” scores (2 drugs). In addition to the 2% of patients who had not used any medications, 13% had been exposed only to drug(s) for which causality was determined as “very unlikely” (6%) or “unlikely” (7%). In 23% of the cases, the highest drug score assigned for causality was “possible.”

Most drugs assigned a probable or very probable causality belonged to the “strongly associated” notoriety list established in the previous SCAR study. For drugs marketed after or toward the end of that study, a “suspected risk” designation was considered appropriate in the notoriety list, on the basis of alerts from reports in the literature (e.g., lamotrigine, nevirapine, and sertraline).

Comparison with case–control analysis

Drugs definitely associated with EN. **Table 1** lists all the drugs that are associated with EN according to the EuroSCAR study. For each drug, it provides the “attributable risk” (proportion of cases attributed by the algorithm) and the “etiologic fraction” calculated from case–control analysis in the same population. There was a very strong correlation between the two values ($r = 0.90$, $P < 10^{-4}$) (95% confidence interval, 0.74–0.97). The two values differed by more than 2 units (see boldface in **Table 1**)

Table 1 Comparison between etiologic fraction and causality assessment for medications with a definite association with EN according to the EuroSCAR study

Drug (generic name) or coalition	Probable/very probable causality ^a	Exposed patients ^b	Attributable ratio (algorithm)%	Etiologic fraction (case–control analysis) ^c
Allopurinol	54	66	14.2	14.4
Carbamazepine	27	31	7.1	7.4
Sulfamethoxazole	18	24	4.7	4.8
Other anti-infectious sulfonamides	15	15	4.0	2.9
Nevirapine	15	21	4.0	5.0
Phenobarbital	16	20	4.2	4.0
Phenytoin	17	19	4.5	4.2
Lamotrigine	9	14	2.4	3.4
Acetic acid NSAIDs	14	27	3.7	5.8
Oxicam NSAIDs	11	11	2.9	2.8
Quinolones	6	13	1.6	2.9
Cephalosporins	3	19	0.8	4.3
Cyclines	6	7	1.3	1.6
Aminopenicillins	3	18	0.8	2.8
Sertraline	4	6	1.1	0.5
Macrolides	0	18	0	4.1

The etiologic fraction was calculated from case–control analysis, and causality was ascertained by the algorithm of drug causality for epidermal necrolysis (ALDEN) for all medications with a definite association with EN according to the EuroSCAR study.¹⁵ Boldface indicates the drugs or coalitions whose difference between attributable ratio and etiologic fraction differed by more than 2 units.

EN, epidermal necrolysis; NSAIDs, nonsteroidal anti-inflammatory drugs.

^aCounting each drug when two (eight cases) or three (one case) had equal causality, except when these were drugs that belong to the same coalition line (e.g., one patient had taken two other anti-infectious sulfonamides having very probable causality). ^bIn the 7-day period (or longer for drugs with long elimination half-life) before the index day as defined in the EuroSCAR study.¹⁵ ^cRestricted to drug exposure started in the first 8 weeks for drugs used as long-term therapy.

in 4 of 16 coalitions or medications: cephalosporins, macrolide antibiotics, aminopenicillins, and acetic acid nonsteroidal anti-inflammatory drugs. For drugs associated with significantly elevated relative risk (RR) for EN, the plot of results of attributable risk vs. etiologic fraction shows that 12 coalitions had etiologic fractions that were above the 95% limits of the correlation slope (data not shown).

Table 2 Causality assessment for drugs in common use classified by case–control methods as having “no evidence of association” with SJS or TEN

Drug or coalition	Probable causality using ALDEN (no. of patients)	Number of exposed patients ^a	Multivariate RR (95% CI) ^b
Nitrates and vasodilators	0	47	1.6 (1.0–2.8)
Benzodiazepines	0	45	0.8 (0.4–1.3)
β-Blockers	0	37	0.9 (0.5–1.5)
ACE inhibitors	0	44	0.9 (0.5–1.5)
Calcium channel blockers	0	45	1.4 (0.8–2.4)
H1 anti-histamine	0	30	1.2 (0.6–2.4)
Thiazide diuretics	0	26	0.7 (0.4–1.4)
Levothyroxine	0	15	0.8 (0.3–1.8)
HMG-CoA reductases, statins	0	12	0.4 (0.1–1.1)
Sulfonylurea antidiabetics	0	11	1.3 (0.6–2.5)
Spironolactone	0	9	1.0 (0.4–2.7)

Results of algorithm of drug causality for epidermal necrolysis (ALDEN) for drugs of common use classified by case–control methods as “no evidence of association” with SJS or TEN (nonsignificant association and upper limit of confidence interval <3).

ACE, angiotensin-converting enzyme; CI, confidence interval; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; RR, relative risk; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

^aIn the 7-day period before the index day as defined in the EuroSCAR study.¹⁵ Multiple exposures within a coalition were counted only as a single exposure. ^bFrom the EuroSCAR study, restricted to drug exposure in the first 8 weeks after starting the drug, for drugs used as long-term therapy.¹⁵

“Probably not associated” drugs. Table 2 lists the 11 medications in common use (>1.5% exposure in controls) that have no significant association with EN (the upper limit of the confidence interval <3). For these 11 drugs, in a study of a total of 321 exposures, ALDEN did not categorize the causality in any of these exposures as “probable” or “very probable.”

Among the drugs for which association with EN was considered doubtful because of a high potential for confounding by indication (Table 3), four were judged to be probably causal by use of the algorithm. These were pyrazolone analgesics (six exposures), corticosteroids (seven exposures), acetaminophen (paracetamol) (eight exposures), and nimesulide (one exposure), for a total of 22 of 233 exposures. Interestingly, no exposure to acetylsalicylic acid or ibuprofen was deemed causal.

Table 4 presents all the other medications¹³ that were considered probable or very probable causes of EN in a total of 20 cases. In 10 cases, they were associated with drugs of equal causality. In none of these 13 different drugs did the case–control analyses suggest “no association,” and the upper limit of the 95% confidence interval of the RRs was always >3.

DISCUSSION

In our experience, most patients who survive SJS or TEN are instructed to stop taking—and never again use—the medications they had taken before the onset of the reaction. This overly prudent attitude contributes to patients’ belief that they are allergic to all medications, with the risk of inadequate management of future diseases. It also results in the confused opinion that virtually every drug can induce SJS or TEN, an opinion that has not been supported by a previous study.¹⁷

In constructing an algorithm aimed at evaluating the causality of medications in SJS and TEN, our main goal was to clearly identify in each patient not only the drug that had most probably induced the reaction but also the drugs that were mere innocent bystanders and could safely be administered to the patient again.

Parameters were chosen on the basis of clinicians’ expertise of 1 experts, and previous scoring systems, including the Naranjo

Table 3 Causality assessment using ALDEN for drug unclassified by case–control method

Drug or coalition	Probable causality using algorithm (no. of patients)	Other drug with probable/very probable causality (no. of patients)	Exposed patients ^a	Multivariate RR (95% CI) ^b
Acetaminophen (paracetamol)	8	0	88	1.9 (1.2–2.8)
Pyrazolone analgesics ^c	6	Allopurinol (1) Phenylbutazone (1) Phenytoin (1)	18	3.1 (1.2–7.7)
Acetylsalicylic acid	0	0	46	1.6 (0.9–2.7)
Tramadol	0	0	10	28 (3.5–230) ^d
Nimesulide	1	0	5	6.0 (1.0–38)
Ibuprofen	0	0	10	0.9 (0.3–2.6)
Corticosteroids	7	0	56	4.5 (2.4–8.7)

Drugs designated unclassified because of “high potential for confounding by indication.”

ALDEN, algorithm of drug causality for epidermal necrolysis; CI, confidence interval; RR, relative risk.

^aIn the 7-day period before the index day as defined in the EuroSCAR study.¹⁵ Multiple exposures within a coalition counted once. ^bFrom EuroSCAR study, restricted to drug exposure in the first 8 weeks after starting the drug, for drugs used as long-term therapy. ^cInclude metamizole (five cases) and phenazone (one case). ^dUnivariate RR because of insufficient number of controls.

Table 4 Other medications with probable causality assessed by ALDEN

Drug	Probable causality (ALDEN)	Other drug with probable/very probable causality (no. of patients)	Case-control analysis		
			Exposed ^a	Relative risk	
			Cases	Univariate	Multivariate ^b
Ketoprofen	3	Sulfamethoxazole (1)	3	6.0 (1.0–36)	
Valproic acid	3	Lamotrigine (1) Allopurinol (1)	16	9.4 (3.9–23)	2.0 (0.6–7.4)
Phenylbutazone and kebutzone	3	Metamizole (1) Allopurinol (1)	4	16 (1.8–144)	
Fluoxetine	2	Metamizole (1)	5	2.0 (0.7–5.9)	0.8 (0.1–5.4)
Fluconazole	1	Thiabendazole (1)	1	0.10-Infinite	
Thiabendazole	1	Fluconazole (1)	1	0.10-Infinite	
Metronidazole	1	Phenytoin (1)	3	1.6-Infinite	
Citalopram	1	0	1	1 (0.1–8.9)	
Paroxetine	1	0	3	0.92 (0.26–3.2)	0.61 (0.09–4.0)
Leflunomide	1	0	2	0.75-Infinite	
Thioacetazone	1	0	1	0.10-Infinite	
Naproxen	1	Allopurinol (1)	2	2.7 (0.44–16)	

ALDEN, algorithm of drug causality for epidermal necrolysis.

^aIn the 7-day period (or more for drugs with long elimination half-life) before the index day as defined in the EuroSCAR study.¹⁵ Multiple exposures within a coalition were counted as only one exposure. ^bAs in the EuroSCAR study, estimated when there were more than three cases of exposure and three controls.¹⁵

scale,¹⁸ and weighted on the results of a previous international case-control study.¹⁴ To each parameter, we attributed a rather large range of negative to positive values, in order to better discriminate the score of each drug taken by a patient. Most of the parameters we included were the same as those used in previous methods.

Among the original features, one must take into account the likelihood that the drug under investigation was present in the patient's body at the onset of the disease. This is obviously considered to be of high importance, given the drug-specific mechanisms of the disease.^{19,20} In this study, for 30% of the drugs that were evaluated, the drug had been withdrawn from the patient's medication regimen before the index day. Instead of blood or tissue drug levels¹⁸ (which are rarely available, in our experience), we used the known elimination half-life value as an approximate estimate of the potential persistence of the drug in the body. In order to be more conservative in our approach, we considered the presence of kidney or liver disease and the simultaneous administration of more than five other medications as markers of probable interaction, and these were given due weight in the score as a part of uncertainty.²¹

Another important original feature of ALDEN is the concept of a “negative prechallenge.” Because the “high-risk period” was restricted to the first weeks of a new treatment in the SCAR study,¹⁴ we considered a patient's previous intake of a specific drug without any adverse reaction (“negative prechallenge”) to decrease the probability that the drug could be the cause of SJS/TEN.

The last innovative step was the final “confrontation” that was arranged among the “intermediate” scores of all the medications taken by each patient. In a given patient, if at least one of the drugs had a score >3, all the other co-medication drugs with

lower scores had 1 point subtracted from their scores because of “likelihood of another cause.”

The algorithm was validated on a database of well-ascertained cases in which standardized collection of information on drug intake had been completed before the reaction commenced. The database included information on drug intake collected up to the day of admission to hospital for EN, but we did not track information about the continuation of the drugs after the day of hospitalization. Therefore, the item on “dechallenge” could not be used, and this score was 0 for all drugs. In theory, this could overestimate by only 2 points the final score of drugs that had been continued during the course of the disease. Such a continuation is infrequent in our experience and would occur only for drugs that the physicians considered as being unlikely to be responsible for the disease. We assume that the missing information in this regard resulted in possible misclassification of medications mainly in the “lower” causality classes. Obviously, that assumption needs validation with prospectively enrolled patients.

This algorithm proved complex and time consuming. Decisions regarding the impact of kidney or liver alterations and of drug interactions should be made by experts. The intergrader reproducibility was good but far from perfect. Discrepancies were related to interpretations of two items: “notoriety” and “pharmacokinetics.” Therefore, we created and used a database listing the appropriate values under these heads for each drug, and three authors checked all these items for all the drugs. To simplify the process, we are now working on a computerized version of ALDEN with direct links to databases.

Having been built for this purpose, it is not surprising that our specific SJS/TEN algorithm has proved to have a better ability to discriminate both “culprit” and “innocent” drugs than the

general algorithm that is used by French pharmacovigilance for evaluating all types of drug reactions. However, the rather low sensitivity of the French pharmacovigilance method was surprising because it was expected to be a sensitive tool for detecting new alerts. The integration of drug “notoriety” in our algorithm did not prevent it from detecting causality for several drugs that had a “suspected” notoriety and would have been missed by the French pharmacovigilance method.

The very good overall agreement of the results provided by the algorithm with those of the case–control analysis of the EuroSCAR study is important but should not be overstated. To our knowledge, this is the first time that a drug causality algorithm can be compared to what is considered the gold-standard method for assessing very rare drug-induced diseases.¹³ However, we are aware of several limitations with regard to ALDEN. First, ALDEN was constructed by experts who were aware of the results of case–control analyses and were looking for a good correlation. Second, given that more than half of the cases of SJS and TEN are related to a limited number of “high-risk” drugs, there was a rather high *a priori* probability of observing an agreement. The strength of the observed correlation is nevertheless encouraging.

Discrepancies are also noteworthy. They occurred in relation to drugs that had been deemed in the EuroSCAR results as having “low risk” or a “high potential for confounding by indication.”¹⁵ Macrolides, cephalosporins, and aminopenicillins are widely prescribed antibiotics that may be used to treat early and not-yet-specific symptoms of what could turn out to be SJS/TEN. The same is true for acetaminophen and systemic corticosteroids. Interestingly, in all the instances, ALDEN ascribed much lower “attributable risks” than the case–control analysis did, but it also found cases that were attributable to drugs such as acetaminophen (eight probable) or corticosteroids (seven probable), for which causality is controversial. To a certain degree, the algorithm addresses the problem of confounding by indication, because a short delay between starting intake of the drug and the index day is judged to be only likely. Nevertheless, we emphasize the need to rely on the most precise possible determination of the index day of the disease, based on clinical information, as was done in this study. This helps to rule out attributing causality to drugs that are taken for the very early symptoms of the disease, thereby avoiding a situation with high potential for confounding by indication. This effort is needed both when using the specific causality algorithm and when dealing with case–control data.

Some years ago, the accepted hypothesis was that TEN is nearly always drug related, whereas SJS could be induced by drugs, infections, or both.²² Epidemiologic studies challenged that hypothesis by demonstrating that the etiologic fraction for drugs was exactly the same (~65%) in both SJS and TEN.²³ At that time, some of us believed that the missing fraction (to explain 100% causality) could be accounted for by a few dozens of drugs that were too rarely used to allow for multivariate analysis, in other words, that epidemiologic studies did not have enough power to detect a RR <3. Interestingly, when applying ALDEN, we observed a few cases that were attributable to these types of drugs and that these were not assessable with case–control analysis. But

their numbers remained low, and 15% of the patients either had taken no drug at all or had taken only drugs for which causality was “unlikely” or “very unlikely.” Information bias may explain a small percentage of these 15% but certainly not all. We have to accept the existence of “idiopathic,” probably not drug-related, cases of SJS and TEN.

The results of this work have several important practical implications. For decision makers, whether in pharmaceutical companies or regulatory agencies, an overall evaluation of risk is of tremendous importance. For research purposes, immunologic mechanisms as well as genetic predisposition factors appear to be drug specific.^{19,20,24–25} Investigations need individual causality assessments that are not provided by epidemiology alone. The fact that this algorithm provides fairly good individual assessments of drug causality in SJS/TEN, comparable to risk estimates with case–control analysis, can be a source of appreciable savings in costs. In the context of EN, the limits of case–control analyses are linked to the rarity of both the disease and the exposure to certain drugs. Collecting cases through a registry is far less expensive than conducting case–control studies.

However, the use of ALDEN requires good data. A precise clinical history of the patient is needed to determine the index day and to document alterations in liver and kidney function because these are taken into account in determining the presence of the drug in the body at the time of onset of the adverse reaction. A comprehensive collection of exposures to all drugs taken by the patient must be ensured, with precise dates and details of previous exposures and reactions. Infections as possible causes of SJS/TEN are currently not integrated into the scoring system because there is still a lack of good evidence in this regard, despite some persuasive case reports. However, the category “other possible etiological alternatives” will allow for this to be factored into the score when needed.

ALDEN will permit more accurate, patient-specific information about the (usually single) medication that is contraindicated and about the many drugs that can be used again with safety. It should also help to clarify the legal issues raised by the persons who have found themselves on the wrong side of the risk/benefit ratio with respect to medications.

This algorithm is specific to SJS and TEN because it includes some characteristics that are specific to these diseases. This specificity precludes its application in other adverse events, even those related to the skin, without specific changes in the algorithm and proper evaluation.

The data generated by ALDEN and presented in this article relate to a large series of patients and are compared with case–control data from the same set of patients. The outcome of this comparison suggests that ALDEN can be a useful tool for assessing drug causality in SJS and TEN.

METHODS

Throughout the article, the term “drug” refers to the international denomination of each active component of a medication.

Construction of an algorithm specific to EN. With an algorithm that had been used for many years and that was based mainly on certain time

windows of exposure and the notoriety of drugs, the expert committee on severe skin reaction of the German Registry was able to identify highly suspect drugs but failed to clearly separate drugs with a lower likelihood of causing SJS/TEN from those that were not associated with the condition at all.²⁶ Therefore, a combined effort was made to elaborate a new specific algorithm for causality assessment in SJS/TEN on the basis of six parameters, as detailed in **Table 5**:

1. Time lag from initiation of drug intake to onset of reaction

Timing was categorized as suggestive, compatible, likely, unlikely, or excluded based on data from previous publications regarding the effects of the drug.^{14,17}

2. Probability that the drug was present in the body at the onset of the reaction

This was estimated as definite, doubtful, or excluded in cases in which the drug had been discontinued before the onset of the reaction; the estimation was carried out on the basis of known pharmacokinetic parameters and after taking into account renal or hepatic dysfunction and possible drug interactions.

For evaluating parameters 1 and 2, the date of onset of the reaction had to be specified. We used the probable “index day” as defined in the SCAR study.¹⁴

3. Prechallenge/rechallenge

Rechallenge is very rare. We defined “prechallenge” as administration of the same drug to the same patient in the past. Such an occurrence, which is more frequent than rechallenge, was given a similar weight. To classify drugs as the same or similar with respect to prechallenge, we used the World Health Organization’s anatomical therapeutic chemical (ATC) codes (<http://www.whocc.no/atcddd>). Drugs were considered to be similar if they shared an ATC code up to the fourth level (chemical subgroup). Drugs were considered to be the same if they shared an ATC code up to the fifth level (chemical substance).

4. Dechallenge

Dechallenge was taken into account in only one way, i.e., to decrease the causality score for drugs that had been continued beyond the progression phase of the disease. All other situations were considered to be uninformative.

5. Drug notoriety

This was derived from previous results of the SCAR study.¹⁴ An estimation of the RRs (determined by multivariate analysis when possible, univariate otherwise, restricted to drug exposure in the first 8 weeks after starting the drug in the case of drugs used for long-term treatments) allowed us to define the following categories of drugs in relation to EN:

- “Strongly associated drugs” are those significantly associated with a lower limit of the confidence interval >5.
- “Associated drugs” are those that are significantly associated with lower limits of RRs.
- “Suspected drugs” include drugs about which several previous reports in this regard have been published (drugs “under surveillance”) and drugs with ambiguous epidemiologic results.
- “Not suspected drugs” are those with both a nonsignificant RR and an upper limit of the confidence interval <3. All other drugs, including those newly released to the market, were considered to have an “unknown” notoriety.

6. Other possible etiological alternatives

There is growing suspicion that some infectious agents, such as *Mycoplasma pneumoniae*, may cause SJS or TEN. While awaiting better evidence, we considered only medications as plausible causes of these diseases. Evaluation of the sixth category was carried out only after the first five had been completed for each drug taken by a patient, by comparing all the “intermediate scores” and downgrading the scores of all drugs except the most probable one, provided its score was >3.

In practice, each parameter was scored as shown in **Table 5**. A total score, varying from –12 to +10, was assigned to each drug taken by each patient. The scores attributed to each drug were pooled in categories aimed at reflecting causality: “very probable”: score ≥6; “probable”: score

4–5; “possible”: score 2–3; “unlikely”: score 0–1; and “very unlikely”: score <0. The boundaries between categories were arbitrarily set by experts based on the overall distribution of score values; these experts were blinded to the relationship between score values and specific medications.

Origin of the SJS/TEN cases used in algorithm evaluation. The algorithm was applied to the 379 cases enrolled in EuroSCAR, a case–control study of SJS and TEN, conducted in six countries (Austria, France, Germany, Israel, Italy, and the Netherlands) between April 1997 and December 2001.¹⁵ The cases and controls were validated by an expert committee (that was blinded to details of drug exposures) on the basis of the medical histories, medical records, clinical photographs, and biopsies. Detailed medication information was collected by trained interviewers using a standardized questionnaire. Global drug risks had been quantified, with multivariate RRs restricted to recent initiation of the drug (within 8 weeks).¹⁵

Application of the algorithm. The algorithm was first applied by a single investigator, a pharmacist with training in pharmacovigilance but without any experience in SJS/TEN, to every drug present in the patient at any time in the 2-week period before the index day (4 weeks for drugs with long elimination half-life values).

Validation of the algorithm

Interobserver reproducibility: The medications (101 drug components) that were being taken by 14 EuroSCAR patients (a random sample) were re-scored for EN causality by another investigator, and the scores generated by the two investigators were compared.

Comparison with the French pharmacovigilance method: All medications (697 drug components) taken by 100 French patients (a random sample of those included into the EuroSCAR study) were also evaluated using the causality assessment method used by French pharmacovigilance.²⁷ This allowed a comparison of the outcomes of the two methods.

Comparison with the results of EuroSCAR case–control analysis: These comparisons were conducted for three categories of drugs.

1. For drugs found to be associated with a significantly elevated RR in case–control analyses, an etiologic fraction (or attributable risk) was estimated using the following formula:²⁸

$$EF = \frac{RR - 1}{RR} \times \% \text{ exposed cases}$$

The RR values were those obtained from multivariate analysis, taking into account risk assessment for <8 weeks of exposure to drugs; the 8-week cutoff was applied for the analysis because it has been demonstrated that no significant risk persists after 8 weeks of use when appropriate (drugs for long-term use).¹⁵ If multivariate analysis was not feasible, we used the lower figure of the 95% confidence interval provided by univariate analysis. For each of these drugs, an algorithm-derived attributable risk was calculated as the proportion of patients for whom the drug score was ≥4 (i.e., probable or very probable causality).

2. Drugs of common use (exposure rate of at least 1.5% of controls) considered in the EuroSCAR study as “probably not associated” on the basis of two criteria: multivariate RR not significantly different from 1 and upper limit of the 95% confidence interval <3. For these medications, an etiologic fraction was not calculable (or would be zero).
3. Drugs for which the case–control results had been considered inconclusive in two situations: (i) insufficient numbers of exposed cases or controls to allow a multivariate analysis to be carried out or (ii) a significant or borderline RR in multivariate analysis but a high potential for confounding by indication (e.g., analgesics and corticosteroids).

Table 5 Details of the algorithm of drug causality for epidermal necrolysis (ALDEN)

Criterion	Values	Rules to apply	
Delay from initial drug component intake to onset of reaction (index day)	Suggestive +3	From 5 to 28 days	-3 to 3
	Compatible +2	From 29 to 56 days	
	Likely +1	From 1 to 4 days	
	Unlikely -1	>56 Days	
	Excluded -3	Drug started on or after the index day	
		In case of previous reaction to the same drug, only changes for: Suggestive: +3: from 1 to 4 days Likely: +1: from 5 to 56 days	
Drug present in the body on index day	Definite 0	Drug continued up to index day or stopped at a time point less than five times the elimination half-life ^a before the index day	-3 to 0
	Doubtful -1	Drug stopped at a time point prior to the index day by more than five times the elimination half-life ^a but liver or kidney function alterations or suspected drug interactions ^b are present	
	Excluded -3	Drug stopped at a time point prior to the index day by more than five times the elimination half-life ^a , without liver or kidney function alterations or suspected drug interactions ^b	
Prechallenge/rechallenge	Positive specific for disease and drug: 4	SJS/TEN after use of same drug	-2 to 4
	Positive specific for disease or drug: 2	SJS/TEN after use of similar ^c drug or other reaction with same drug	
	Positive unspecific: 1	Other reaction after use of similar ^c drug	
	Not done/unknown: 0	No known previous exposure to this drug	
	Negative -2	Exposure to this drug without any reaction (before or after reaction)	
Dechallenge	Neutral 0	Drug stopped (or unknown)	-2 or 0
	Negative -2	Drug continued without harm	
Type of drug (notoriety)	Strongly associated 3	Drug of the "high-risk" list according to previous case-control studies ^d	-1 to 3
	Associated 2	Drug with definite but lower risk according to previous case-control studies ^d	
	Suspected 1	Several previous reports, ambiguous epidemiology results (drug "under surveillance")	
	Unknown 0	All other drugs including newly released ones	
	Not suspected -1	No evidence of association from previous epidemiology study ^d with sufficient number of exposed controls ^c	
		Intermediate score = total of all previous criteria	-11 to 10
Other cause	Possible -1	Rank all drugs from highest to lowest intermediate score	-1
		If at least one has an intermediate score >3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely)	

Final score -12 to 10

<0, Very unlikely; 0-1, unlikely; 2-3, possible; 4-5, probable; ≥6, very probable.

ATC, anatomical therapeutic chemical; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

^aDrug (or active metabolite) elimination half-life from serum and/or tissues (according to pharmacology textbooks, tentative list available in complementary table), taking into account kidney function for drugs predominantly cleared by kidney and liver function for those with high hepatic clearance. ^bSuspected interaction was considered when more than five drugs were present in a patient's body at the same time. ^cSimilar drug = same ATC code up to the fourth level (chemical subgroups), see Methods. ^dSee definitions for "high risk," "lower risk," and "no evidence of association" in Methods, ref. 15 (detailed list available in complementary table).

ACKNOWLEDGMENTS

We are indebted to all the patients whose participation made this study possible. In addition, we thank all collaborating colleagues for their support and H. Chutter for her help in the correction of the manuscript. Participants:

Austria: Elisabeth Kowald, Dennis Linder, Gudrun Ratzinger, Alexis Sidoroff.

France: Fabienne Bazin, H el ene Bocquet, Laure Dangoumaud, Yves Dorleans, Alain Dupuy, Jean-Paul Fagot, A Flahault, Catherine Paoletti, Annie-Claude Paty, Sylvie Rodriguez, Patricia Thion, Loic Vaillant, C Viboud. Germany: Olaf Hering, Klaus Kitta, Brigitte Loleit, Oliver Pfeiffer, Thekla Renker, Birgit Schneck, J urgen Schneck, Werner Schr oder, Esra Tas. Israel: Arnon D. Cohen, Sima Halevy, Sara Weltfreund.

Italy: Laura Atzori, Grazia Manfredi, Davide Melandri, Luigi Naldi, Annalisa Pinna.

The Netherlands: Christianne Bearda Bakker-Wensveen, Jan Nico Bouwes Bavinck, Joost Govaert, Viña Williams-Snijders.

Funding:

The EuroSCAR study was funded by the followings institutions/companies: ADIR & Cie, Bayer Pharma/AG/Vital, Boehringer Ingelheim, Cassenne, Ciba-Geigy/Novartis, Cilag GmbH, Willmar Schwabe, Goedecke Parke Davis, Glaxo Wellcome/GlaxoSmithKline, Hoechst AG/Hoechst Marion Roussel/Aventis, Hoffmann-La Roche, IRIS Servier, Jouveinal Lab, LEO, Lilly, MSD Sharp & Dohme, Pfizer, Rhône-Poulenc Rorer, Sanofi Winthrop/Sanofi Synthelabo GmbH, Schering AG. The funds from Pharmaceutical Companies in France were managed through a contract with INSERM (Institut National de la Santé et de la Recherche Médicale), French Ministry of Health (PHRC AOM 98027 and AOM 05092). The German Registry (the basis for EuroSCAR in Germany) was funded in part by the Federal Institute for Drugs and Medical Devices (BfArM).

CONFLICT OF INTEREST

The authors declared no conflict of interest.

© 2010 American Society for Clinical Pharmacology and Therapeutics

- Macedo, A.F., Marques, F.B., Ribeiro, C.F. & Teixeira, F. Causality assessment of adverse drug reactions: comparison of the results obtained from published decisional algorithms and from the evaluations of an expert panel. *Pharmacoepidemiol. Drug Saf.* **14**, 885–890 (2005).
- Irey, N.S. Diagnostic problems in drug-induced diseases. *Ann. Clin. Lab. Sci.* **6**, 272–277 (1976).
- Edwards, I.R., Lindquist, M., Wiholm, B.E. & Napke, E. Quality criteria for early signals of possible adverse drug reactions. *Lancet* **336**, 156–158 (1990).
- Clark, J.A., Klinecicz, S.L. & Stang, P.E. Spontaneous adverse event signaling methods: classification and use with health care treatment products. *Epidemiol. Rev.* **23**, 191–210 (2001).
- Arimone, Y. *et al.* A new method for assessing drug causation provided agreement with experts' judgment. *J. Clin. Epidemiol.* **59**, 308–314 (2006).
- Macedo, A.F., Marques, F.B. & Ribeiro, C.F. Can decisional algorithms replace global introspection in the individual causality assessment of spontaneously reported ADRs? *Drug Saf.* **29**, 697–702 (2006).
- Meyboom, R.H., Hekster, Y.A., Egberts, A.C., Gribnau, F.W. & Edwards, I.R. Causal or casual? The role of causality assessment in pharmacovigilance. *Drug Saf.* **17**, 374–389 (1997).
- Roujeau, J.C. & Stern, R.S. Severe adverse cutaneous reactions to drugs. *N. Engl. J. Med.* **331**, 1272–1285 (1994).
- Bastuji-Garin, S., Rzany, B., Stern, R.S., Shear, N.H., Naldi, L. & Roujeau, J.C. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch. Dermatol.* **129**, 92–96 (1993).
- Paquet, P. & Piérard, G.E. Erythema multiforme and toxic epidermal necrolysis: a comparative study. *Am. J. Dermatopathol.* **19**, 127–132 (1997).
- Schneck, J., Fagot, J.P., Sekula, P., Sassolas, B., Roujeau, J.C. & Mockenhaupt, M. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic epidermal necrolysis: a retrospective study on patients included in the prospective EuroSCAR Study. *J. Am. Acad. Dermatol.* **58**, 33–40 (2008).
- García-Doval, I., LeCleach, L., Bocquet, H., Otero, X.L. & Roujeau, J.C. Toxic epidermal necrolysis and Stevens-Johnson syndrome: does early withdrawal of causative drugs decrease the risk of death? *Arch. Dermatol.* **136**, 323–327 (2000).
- Kaufman, D.W. & Shapiro, S. Epidemiological assessment of drug-induced disease. *Lancet* **356**, 1339–1343 (2000).
- Roujeau, J.C. *et al.* Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N. Engl. J. Med.* **333**, 1600–1607 (1995).
- Mockenhaupt, M. *et al.* Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. *J. Invest. Dermatol.* **128**, 35–44 (2008).
- EU project focus. RegiSCAR project: the newsletter of the rare disease task force <<http://www.orpha.net/actor/EuropaNews/2006/060124.html>> (2006).
- Guillaume, J.C., Roujeau, J.C., Revuz, J., Penso, D. & Touraine, R. The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell's syndrome). *Arch. Dermatol.* **123**, 1166–1170 (1987).
- Naranjo, C.A. *et al.* A method for estimating the probability of adverse drug reactions. *Clin. Pharmacol. Ther.* **30**, 239–245 (1981).
- Nassif, A. *et al.* Drug specific cytotoxic T-cells in the skin lesions of a patient with toxic epidermal necrolysis. *J. Invest. Dermatol.* **118**, 728–733 (2002).
- Paquet, P., Paquet, F., Al Saleh, W., Reper, P., Vanderkelen, A. & Piérard, G.E. Immunoregulatory effector cells in drug-induced toxic epidermal necrolysis. *Am. J. Dermatopathol.* **22**, 413–417 (2000).
- Ajayi, F.O., Sun, H. & Perry, J. Adverse drug reactions: a review of relevant factors. *J. Clin. Pharmacol.* **40**, 1093–1101 (2000).
- Roujeau, J.C., Chosidow, O., Saiag, P. & Guillaume, J.C. Toxic epidermal necrolysis (Lyell syndrome). *J. Am. Acad. Dermatol.* **23**, 1039–1058 (1990).
- Auquier-Dunant, A., Mockenhaupt, M., Naldi, L., Correia, O., Schröder, W. & Roujeau, J.C.; SCAR Study Group. Severe Cutaneous Adverse Reactions. Correlations between clinical patterns and causes of erythema multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis: results of an international prospective study. *Arch. Dermatol.* **138**, 1019–1024 (2002).
- Hung, S.I. *et al.* Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet. Genomics* **16**, 297–306 (2006).
- Lonjou, C. *et al.*; RegiSCAR study group. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet. Genomics* **18**, 99–107 (2008).
- Rzany, B. *et al.* Epidemiology of erythema exsudativum multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis in Germany (1990–1992): structure and results of a population-based registry. *J. Clin. Epidemiol.* **49**, 769–773 (1996).
- Bégaud, B., Evreux, J.C., Jouglard, J. & Lagier, G. [Imputation of the unexpected or toxic effects of drugs. Actualization of the method used in France]. *Thérapie* **40**, 111–118 (1985).
- Benichou, J. Attributable risk. In *Encyclopedia of Epidemiologic Methods* (eds. Gail, M.H. & Benichou, J.) 50–63 (John Wiley & Sons, New York, 2000).