



Identifying the Culprit Drug in Severe Cutaneous Adverse Reactions (SCARs)

Rosario Cabañas^{1,2,3,4,*} 

Elena Ramírez^{2,3,5}

Teresa Bellón^{2,3,6}

Address

¹Allergy Unit, Hospital Universitario La Paz, Madrid, Spain

²La Paz Hospital Institute for Health Research (IdiPAZ), Madrid, Spain

³PIElenRed Consortium, Madrid, Spain

⁴Centro de Investigación en Red de Enfermedades Raras (CIBERER, U754), Madrid, Spain

Email: mrosario.cabanas@salud.madrid.org

⁵Pharmacology Department, La Paz University Hospital, Madrid, Spain

⁶Drug Hypersensitivity Laboratory, La Paz University Hospital, Madrid, Spain

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Abstract

Purpose of review Identifying the culprit drug or drugs in SCARs (Severe Cutaneous Adverse Reactions) is a complex and challenging task. However, it is necessary for the patient to know which drugs to avoid in the future, alternatives for treatment and not to have forbidden for all his life drugs that were not responsible for the reaction. When to use causality algorithms? To which extent are valid in vitro tests? Are they useful in clinical practice or just research techniques? Are skin tests sensitive and safe in all SCARs? When performing them? What about the re-exposure tests? Is there any indication for them? This review gives answers to these questions.

Recent findings Causality algorithms and the calculation of the index day is the first approach. In vitro tests, LTT (lymphocyte transformation test) is a sensitive and specific test for SJS/TEN (Stevens-Johnson syndrome/toxic epidermal necrolysis) and DRESS (drug reaction with eosinophilia and systemic symptoms) in the recovery phase. ELISpot is useful during the acute phase. Skin tests have different sensitivity according to every particular SCAR and are safe if performing according to guidelines recommendations.

Summary An approach combining causality algorithms, LTT, and skin tests allow us to identify the culprit drugs or at least limiting the forbidden drugs for the future in a safe way.

Introduction

Severe cutaneous adverse reactions (SCARs) are those adverse skin reactions, which pose a significant morbidity or mortality and are caused by an immunologically mediated inflammatory reaction with a prominent phenotype in the skin [1•]. They include acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) [2].

Identification of the culprit drug or drugs is critical to avert future reactions and to identify safe alternatives. However, making the diagnosis can be complex and challenging. As far as we know, there is not any published consensus of experts' guidelines on identification of the culprit drug on SCARs except for DRESS [3••].

The aim of this review is to provide reference guidelines on this field based on scientific evidence and thus optimize the quality of care and the quality of life of patients who experience such reactions.

Clinical history

For a correct identification of the culprit drug, we have to make first an accurate diagnosis of the clinical entity as the time window from first drug intake to disease onset, and the putative involvement of infectious agents (or additional alternative causes) may vary largely depending on the clinical entity, having thus a great impact in causality assessment of the reaction. We suggest different articles to perform the correct phenotypic characterization of the acute event [1•, 4•, 5].

A detailed clinical history is an essential step toward a correct diagnosis [6]. It must be carefully obtained. Medical background of the patient and family history of SCARs (due to the genetic susceptibility to suffer them) must be recorded. Whenever possible, we must interview the patient and/or their relatives to obtain more detail of all drugs including over-the-counter drugs and the consumption of herbal or homeopathic products and dechallenge or rechallenge information (if available). For each drug taken by the patient, document any previous exposures and any previous adverse reactions. All drugs taken during exposure windows must be recorded (including formulation, dose, route, timing of administration, and clinical course after drug withdrawal). A timeline chart should be constructed to bring together signs and symptoms (e.g., fever, malaise, eosinophilia, ocular inflammation, skin signs, cutaneous pain, and increase in transaminases), time of onset and resolution, and all of the drugs taken with a latency period that is compatible with that specific SCAR [3••, 7•].

Assessment of causality using algorithms

Many methods have been proposed to assess the causal relationship between an adverse event and a medication taken by a patient. The algorithm methods are mainly based on decision trees or successive evaluation of criteria resulting in a sum of scores. Algorithms give structured and standardized methods of assessment in a systematic approach to identify adverse drug reactions (ADRs) based on parameters such as time to onset of the adverse event or temporal sequence, previous drug/adverse reaction history and dechallenge and rechallenge.

Causality algorithms present high (nearby to 100%) sensitivity and positive predictive value, but low (no more than 37.5%) specificity and negative predictive values [8]. The algorithms show the highest levels of interobserver agreement, also the highest agreement beyond chance. The algorithm of Naranjo is most used in Anglo-Saxon speaking countries [9]; in the French-speaking world, it is the Bégaud, while Spanish speaking countries use the algorithm of the Spanish pharmacovigilance system (ASPS). All of them are general algorithms based on the Karch and Lasagne one, and they differ on the sets of questions associated with scores for calculating the likelihood of a cause-effect relationship. The ASPS score has been detailed elsewhere [10•]. The final case evaluation of each drug is listed as not related (if unrelated or conditional) or related (if possible, probable, or definitive) [11•]. The RegiSCAR group used two case-control studies and their own registry to construct an algorithm for assessment of drug causality for SJS-TEN, being more sensitive than a general method [12••]. The ALDEN (algorithm of drug causality in epidermal necrolysis) score is recognized as one of the most reliable tools for identifying culprit drugs for SJS and TEN [13]. Detailed information on ALDEN has been provided previously [12••]. ALDEN is generally used as a tool for retrospective assessment of drug causality [7•]; however, it can also be helpful in the acute phase of illness when the rentability of the allergy work-up is rather low. This has been the experience of our group Piel $\acute{e}$ nRED consortium [14•].

In short, six criteria were scored for each drug, and drug causality was determined by the sum of the scores: (1) time latency, (2) drug present in the body on the day of onset of the reaction (index day), (3) prechallenge/rechallenge, (4) dechallenge, (5) type of drug (notoriety), and (6) other cause. The final score (–12 to 10) (<0, very unlikely; 0–1, unlikely; 2–3 possible; 4–5, probable; >6, very probable) [12••]. The final case evaluation of each drug is listed as not related (including the categories of very unlikely, unlikely, and possible) or related (probable and very probable).

The calculation of the index day (IxD), which is necessary to establish a temporal relationship with the drugs, was deemed to be the day on which prodromal symptoms/signs first occurred. It is necessary to perform an exhaustive clinical history as detailed above to record all the essential data.

The authors of this review strongly recommend to calculate the index day and perform the causality assessment according to a causality algorithm (a general one in cases of DRESS or AGEP and ALDEN for SJS/TEN) as soon as diagnosis of an specific SCAR is made and stop and forbid provisionally every drug in the category of possible to very probable or definitive.

Time latency, named the delay from initial drug component intake to IxD, depends on the entity, and it is an important criteria on the algorithms.

SJS/TEN has a typical latency of 5–28 days and cases rarely occurring after 8 weeks of continuous use, being also possible but infrequent from 1 to 4 days. In addition, the drug is considered “present in the body on the IxD” (data needed to calculate ALDEN score) if the drug continued until the IxD or stopped at a time less than five times the elimination half-life before the IxD [12••].

DRESS is characterized by a long latency (2–8 weeks). All drugs used less than 6 months and stopped no more than 14 days before IxD are suspicious mainly those known to have a high risk of inducing DRESS [15]. The latency period in antibiotic-induced DRESS could be significantly shorter than in anticonvulsant-induced DRESS [16]. In a series of Piperacillin-induced DRESS,

the latency period was from 8 to 28 days [17]. A detailed assessment of causality in DRESS by the ASPS has been previously described [3••].

AGEP manifests 1–2 days following exposure to antibiotics (i.e., aminopenicillins, sulfonamides, and macrolides) [18, 19] being 11 days median of exposure time for other associated drugs such as terbinafine, diltiazem, and antimalarials [19].

When a patient is diagnosed with any SCAR related to a drug a complete adverse reaction report must be submitted to the local pharmacovigilance center, in order to be included in the Pharmacovigilance System Registry.

Causality assessment by the allergist

The information obtained with clinical history and the causality algorithms enables us to identify the suspect drugs with which performing our allergy work-up.

SCARs induced by drugs are T-cell orchestrated hypersensitivity reactions (DRESS subtype IVb, SJS/TEN subtype IVc, and AGEP subtype IVd) [20]. Patch tests (PTs), delayed-reading intradermal tests (IDT), and lymphocyte transformation tests (LTT) are useful tools for evaluating non-immediate hypersensitivity drug reactions. For safety reasons, it is advisable to start the allergy work-up by performing *in vitro* tests in SCARs [21•].

Assessment of causality using “*in vitro*” allergy tests

In vitro tests have the advantage over *in vivo* diagnostic tests of being safe. Generation of drug-specific T cell lines and clones confirms their central role in the pathogenesis of SCARs [22–25]. Hence, *in vitro* tests are aimed to the identification of drug-specific T cells by measuring well-known antigen-specific T cell responses (such as proliferation, production of cytokines and soluble mediators, or identification of cell membrane activation markers), in patient's peripheral blood lymphocytes after *in vitro* stimulation with the suspected culprit drug or its metabolites [26•].

Cell proliferation assays (LTT, CFSE dilution assay)

The lymphocyte proliferation assay, also known as lymphocyte stimulation test or lymphocyte transformation test (LTT), relies in the ability of drug-specific memory cells to proliferate upon stimulation with the nominal antigen and has been the most widely used for identification of culprit drugs in type IV hypersensitivity reactions [27••]. LTT requires specialized laboratory and skilled personnel. Detailed technical aspects have been described elsewhere [27••]. A stimulation index (SI) is calculated as the ratio of ³H incorporated by drug-stimulated cultures and by unstimulated cells. The recommended timing for LTT performance is 4–8 weeks after the reaction [22, 27••] and at least 4 weeks after stopping treatment with systemic corticosteroids and other immunosuppressants. Analysis in the first 6 months to 1 year is recommended, although later tests may be positive [28]. High variability in LTT sensitivity (S) and specificity (Sp) has been reported which may arise from the heterogeneity in readout systems, clinical entities, and drugs tested [29•]. The lack of a gold-standard diagnostic test, along with the paucity of large-scale studies, precludes

accurate determination of sensitivity and specificity specifically in SCARs, although a tentative calculation was performed in a thorough revision of LTT assays performed in SCARs and reported up to 2017 [29•]. A study involving 8 cases suggested higher sensitivity of LTT specifically in SJS/TEN when performed during the acute phase [30]. However, a more recent study by our group including 26 SJS/TEN validated cases, 56 drugs to which the patients were exposed, and using ALDEN as reference for culprit drugs, found 86% sensitivity and 73.5% specificity when the test was performed after resolution of the clinical symptoms, while sensitivity and specificity for 18 drugs studied during the acute phase were lower [14•]. Similarly, sensitivity and specificity were 74% and 82% respectively in the recovery phase of DRESS, while values in the acute phase dropped to 40% sensitivity and 30% specificity in another study performed by our group including 41 cases of DRESS. LTT showed high sensitivity and specificity for anticonvulsants (S 100%, Sp 100%), anti-tuberculosis drugs (S 87.5%, Sp 100%), and β -lactam (S 73%, Sp 100%) [11•]. LTT has recently proved useful to diagnose multiple drug hypersensitivity in DRESS cases [31] and to evaluate drug causality in children with SCARs [32•].

The fluorescent dye 5,6-carboxylfluorescein diacetate succinimidyl ester (CFSE) dilution assay may be used to evaluate cell proliferation in LTT. In this assay, the radioactive label is substituted by a flow cytometry analysis. Data using this technique are scarce in SCARs. Drug-specific T cells were detected in SJS/TEN, AGEP, and DRESS cases [33, 34].

Production of cytokines and soluble mediators (ELISA, ELISpot)

Standard proliferation assays have been supplemented by a panel of tests which analyze the secretory or cytotoxic potential of effector cells [35]. Analysis of a wide variety of cytokines or cytotoxic proteins by flow cytometry, ELISA, or ELISpot has been used to evaluate drug causality in SCARs [34, 36–39]. An exhaustive review was published by Porebski [29•]. Detection of the cytotoxic protein granzyme by ELISA has been reported in cell culture supernatants of culprit drug-stimulated PBMCs from SJS/TEN and DRESS patients [40, 41].

The enzyme-linked immune absorbent spot (ELISpot) assay is considered as one of the most sensitive cellular assays available and is the second more widely used after LTT [29•]. Several reports indicate good sensitivity and specificity of IFN- γ ELISpot when performed in the acute phase of SCARs [42, 43]. A recent report suggests the use of ELISpot during the acute disease and LTT after recovery in SCARs [44••]. While IFN- γ is the cytokine most widely evaluated in SJS/TEN and DRESS [42, 43, 45, 46], other cytokines such as IL-17 [47] or IL-36 [48] might be useful for drug causality in AGEP.

Flow cytometry identification of lymphocyte activation

After activation, lymphocytes express several molecules on their surface. CD69 upregulation in response to the culprit drugs was detected in several patients with SJS, DRESS, and AGEP in which positive LTT to the same drugs were also observed [34, 49]. Upregulation of CD137 by drug-specific CD8⁺T cells has been proposed for identification of culprit drugs in TEN cases [50].

Because no in vitro test has high enough sensitivity, an ENDA/EAACI Drug Allergy Interest Group position paper on in vitro tests for hypersensitivity

reactions recommends the combination of results from different assays (LTT, ELISpot, cell markers, and cytokine release) in evaluating non-immediate reactions (Level of Evidence 3) (Grade of Recommendation D) [21•].

Assessment of causality using “in vivo” allergy tests

Patch tests

Patch tests have proved helpful in the identification of the culprit drug in SCARs [51••] and to examine for cross-reactivity to similar drugs considered as therapeutic alternatives [52–54]. Positivity on PTs depends on the drug [51••, 55] and the type of SCAR [51••, 56•].

In AGEF patients, positivities from 50% (7/14) [56•] to 58% (26/45) [51••] have been reported in controlled studies. Eighteen percent of positivity was found if induced by antibiotic and higher with dicloxacillin and ciprofloxacin [57]. There is a long list of case reports showing positive PTs with a wide variety of agents (more than 40) such as diltiazem [58–60], clindamycin (a series of 5 patients) [61], hydroxychloroquine [62], ceftriaxone [63], terbinafine [64], corticosteroids [65], pseudoephedrine [66], dalteparin [67], and radiocontrast-media [68], among others.

As for DRESS, positivities reported in the largest series range from 32% (18/56) [55] to 64% (46/72) [51••]. Studies on anticonvulsants have reported a 51.5% positive rate [55] and specifically for carbamazepine more than 70% [51••, 52, 55]. PTs have also been found highly positive for antibiotics (β -lactam and quinolones) [57], pump proton inhibitors, and pristnamycin [51••]. By contrast, PTs always yielded negative with allopurinol [51••, 55] and sulfasalazine [51••].

The sensitivity of PTs in SJS/TEN is lower than that found in DRESS and AGEF. In 1996, Wolkenstein et al. found a positivity of 2/22 patients, and they concluded that patch testing had a weak sensitivity, and it was not appropriate in these diseases [56•]. More recently, a positivity of 24% (4/17) was reported [51••]. Positive PTs were also found in children [32•]. Positivity is also very dependent on the drug; 62.5% (10/16) was reported in cases induced by carbamazepine [52] and 20% in those by antibiotic [57]. Case reports with positive PTs with aminopenicillins [69, 70], fexofenadine [71], tetrazepam [72], chlorambucil [73], diclofenac [74], and sulfamethoxazole have been published, and in this last case, the positivity was only detected in an area previously affected [75].

Since drug PTs entail a moderate re-exposure of patients to offending drugs, safety concerns are involved. Are PTs safe?

Systemic features have been published when patch-testing patients with DRESS [76–80]. Identified risk factors for these reactions were patch-testing 4 different cross-reactive drugs at the same time [77] and performing PTs in duplicate and with different vehicles in HIV-infected patients [78, 79]. The systemic features observed in HIV patients included rash, transaminitis, fever, and eosinophilia [79, 80] and a severe recurrence of DRESS [78].

Mild systemic and local reactions have also been reported when patch-testing AGEF patients. That is the case when testing diltiazem [58, 59]. Assier et al. suggested to patch test diltiazem at 1% instead of 10% of pure diltiazem [59]. Other cases with acetaminophen [81], hydroxychloroquine [62], and

ceftriaxone [63] had been reported. In this last case, simultaneous PTs with 3 different concentrations of ceftriaxone had been done [63].

Nevertheless, results from a multicentre study including 72 patch-tested patients with DRESS, 45 with AGEP, and 17 with SJS/TEN showed that it was a safe procedure, with only one mild relapse of AGEP [51••]. Same results of safety were found in the study by Santiago et al. with 56 DRESS patch-tested patients [55]. Lin et al. reported that PTs with carbamazepine at 10% and 30% in petrolatum were safe in SJS/TEN (16 patients) and in DRESS (10 patients) [52].

PTs should be performed according to the European guidelines for skin tests previously described [6, 82–85]. In AGEP and DRESS cases, it is recommended to use a 10% concentration in petrolatum with the active ingredient and a 30% concentration of the final product when the commercialized form of the drug is used [3••, 51••]. A list of references of DRESS cases studied with PTs together with the vehicles and drug concentrations used is available in the repository material of Cabañas et al. [3••]. In cases of SJS/TEN, it is recommended to perform PTs starting to 1% dilution and if negative to repeat with 30% dilution in petrolatum of the final product [6, 51••, 82]. Concentrations and vehicles previously considered as most adequate for certain drugs should also be chosen.

The authors of this review recommend to test all suspect drugs according to the clinical history and the results of algorithms for assessment of causality (see above). They do not recommend to patch-test different concentrations nor the drug in different vehicles at the same time for safety reasons [3••]. Special precaution is recommended in immunocompromised patients [78–80]. The ENDA/EAACI (European Academy of Allergy and Clinical Immunology) Drug Allergy Interest Group position paper on in vitro tests for drug allergy hypersensitivity recommends in cases of severe reactions to perform LTT to identify the culprit drugs before performing skin tests [21•]. PTs are recommended as the first step in allergy work-up if in vitro tests are not available.

Prick and intradermal tests

Patch tests are less sensitive than IDT in antibiotic delayed reactions [57, 86]. IDT specificity is similar to that of PT [86]. If a negative result with PT is obtained and suitable injectable form is available, then intraepidermal (prick) and posterior IDT with delayed reading can be helpful [3••, 6, 17, 51••, 87]. IDT have revealed useful in β -lactam, heparin, glycopeptides, corticosteroid, and radiocontrast media-induced SCARs' work-up [17, 51••, 69, 70, 87•].

European guidelines specify how to perform prick and IDT and how the reading should be done [84]. Although better tolerated than presumed [87•], there is a theoretical risk of eliciting a relapse of the initial cutaneous adverse drug reaction especially when performing IDT [82]. For IDT in SCARs, the drug should be initially tested with the highest dilution (usually 1/100 of the skin prick test concentration and then increased in logarithmic steps 1/10, 1/1) and only if prick test has resulted negative [84, 85]. In severe non-immediate reactions, it has to be considered to extend the time interval between tests [84]. We suggest a 5–7 day interval between tests to be sure that the late reading is negative. More precise guidelines have been drafted for non-immediate β -lactam reactions including SCARs [85, 86].

IDT with delayed reading were shown to be useful for determining the responsible drug in patients with AGEP and negative PTs [51••, 88]. They were also helpful in the diagnosis of 3 cases of TEN caused by delayed hypersensitivity to β -lactam antibiotics [69, 70].

Data about utility of intraepidermal and/or IDT in DRESS have also been reported [17, 51••, 79, 87•, 89] including children [32•]. They are useful to identify the culprit drug and to study cross-reactivity and co-sensitization to some drugs [87•].

Safety of IDT in AGEP and DRESS patients has been shown in the multicenter study of Barbaud; only one DRESS patient had a relapse of maculopapular exanthema in his arms with delayed positive IDT with glycopeptides [51••]. Other studies confirm its safety [17, 87•, 89]. However, Lehloenya et al. reported 3 DRESS patients with systemic reactions after prick testing with isoniazid in HIV patients [79].

As for SJS/TEN, the literature is really scarce. No reactions were reported with IDT positive to ampicillin and amoxicillin in the investigation of 3 cases of TEN caused by these drugs [69, 70].

Guidelines for performing skin tests in patients with DRESS syndrome have been previously published [3••]. No specific guidelines have been published for allergy work-up in AGEP and SJS-TEN patients. The ESCD (The European Society of Contact Dermatitis) considers as contraindications for intradermal testing severe cutaneous reactions such as erythema multiforme, TEN, and SJS, whereas in such cases, the ENDA (European Network on Drug Allergy) advises performing first PTs and then, in case of negative results, IDT using the highest dilution [86, 90].

The diagnostic work-up approach of PIELenRed Consortium Researching group is detailed as follows (see Fig. 1). After drug causality assessment by algorithms (ASPS for DRESS and AGEP and ALDEN for SJS/TEN) and exhaustive clinical history, LTT with the suspect drugs are performed. If the culprit drug has been clearly identified, no skin tests are performed. In doubtful cases or unidentified culprit drug, PTs are performed according to the European guidelines, and we do not test the same drug at different concentrations neither different vehicles at the same time. If negative PTs, prick and IDT (if available) are performed. Personal risk and benefit of the allergy work-up in every patient are taken into account and discussed with the patient. Special caution is taken in immunocompromised patients. In SJS/TEN patients, IDT are only performed if the benefit for the patient clearly outweighs the risk of its performance. This approach has revealed safe in our experience in the last 10 years [11•, 14, 91, 92].

Controlled re-exposure tests

Since SCARs are severe and life-threatening conditions, challenge testing with the suspect culprit drug and cross-reactive drugs are fully contraindicated [1•, 6, 93•]. Accidental re-exposures to the full dose of the culprit drug can produce severe reactions or even fatal as reported [94–96].

However, a search of the literature reveals cases of AGEP [32•, 62, 67, 68, 97], DRESS [76, 79, 80, 98–100], and SJS/TEN [72, 79, 101, 102] in which re-exposure tests were done under special circumstances.

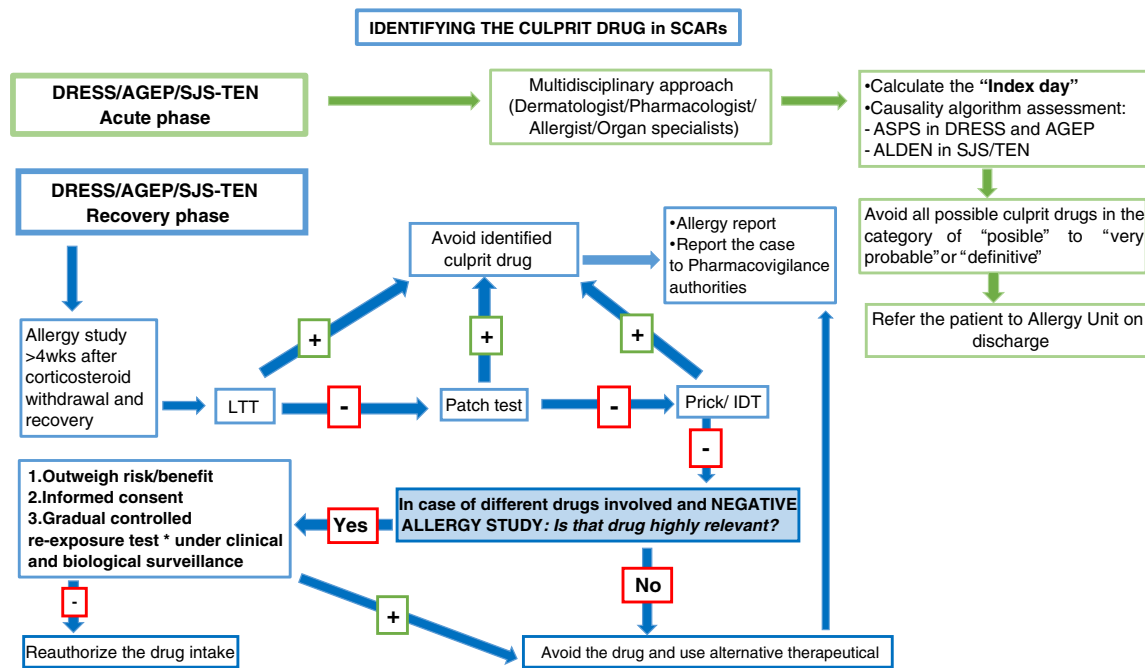


Fig 1.. Causality assessment of culprit drug in acute and recovery phase in SCARs. AGEP (Acute Generalised Exantematous Pustulosis); ASPS (Algorithm of the Spanish Pharmacovigilance System); DRESS (drug reaction with eosinophilia and systemic symptoms); IDT (intradermal test); LTT (lymphocyte transformation test); SJS/TEN (Stevens-Johnson syndrome/toxic epidermal necrolysis) *Under exceptional circumstances in SJS/TEN

In reported re-exposed patients with AGEP, in some cases, the challenge was to confirm the culprit drug in doubtful diagnosis [32•], sometimes accidental [97], or to find alternative required treatments for the patients as the case of low molecular weight heparin [67] and radiocontrast media [68].

DRESS cases in which controlled exposure tests were performed were induced by β -lactam, and the challenge was done with an alternative one guided by the allergy study [17, 98–100], gentamycin in an amikacin-induced DRESS [76] and anti-tuberculosis (anti-TB) drugs [79, 103].

In 1996, Pasricha reported a series of 5 patients with SJS/TEN that had been controlled challenged with anti-TB drugs, anti-convulsants, or with an antidepressant [101]. After detecting tetrazepam as the culprit drug by a positive PT, the other involved drugs with negative allergy tests were controlled and administered in another study [72]. Lehloenya et al. reported a series of 5 patients with SJS/TEN challenged with anti-TB drugs [79].

Anti-TB drugs are a special group of drugs with deserves special consideration because challenge testing may be indicated for adequate management of tuberculosis. A series of DRESS [103] and another with DRESS and SJS/NET [79] with rechallenge tests with anti-TB drugs have been published. In this second publication after performing allergy tests [79], these authors do not recommend routine rechallenge with first-line anti-TB drugs following severe SCARs unless serious consideration is given to associated risks compared with benefits [79].

In reference to rechallenge with drugs in patients with SCARs induced by anti-HIV and anti-TB drugs in low- and middle-income countries, a recent

international consensus document stated that if the risk of morbidity and mortality from the disease outweighs or at least equals the risks from the drug reaction, the risk-benefit ratio sways toward sequential rechallenge with potentially implicated drugs. Allergy testing to guide rechallenge choices would be extremely helpful [93•].

Specific consensus of experts' guidelines of how to perform the controlled re-exposure, if necessary, in cases of DRESS, has been recently published [3••]. Specific recommendations for β -lactam and anti-TB drugs are detailed [3••]. Careful risk-benefit assessment in discussion with the patient and informed consent is strongly recommended (level of evidence 4, expert opinion consensus, grade of recommendation D) [3••].

There are no specific guidelines published for AGEP nor for SJS/TEN so far. There is an urgent need of developing expert consensus guidelines to help clinicians to perform these risky procedures (guided by the allergy work-up) in cases under extraordinary circumstances in which the benefits for the patient outweigh or at least equal the risk.

Conclusions

Causality assessment algorithms and allergy work-up (in vitro and in vivo) are complementary and extremely useful to identify the culprit drug or drugs in SCARs.

In vitro diagnosis provides valuable information, and it should be promoted due to its absolute safety. LTT and ELISpot should be available in routine diagnosis at least in reference centers of management of SCARs. Multidisciplinary and intercenter networks are necessary to drive science and translation to develop new in vitro tests for diagnosis and to improve the knowledge of SCARs.

Declarations

Conflict of Interest

Rosario Cabañas, Elena Ramirez, and Teresa Bellon declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Interesting article where the algorithm of assessment of causality of the Spanish pharmacovigilance system is described. In short, the following seven criteria were scored for each drug, and drug causality was determined by the sum of the scores: (1) the chronology referred to as the interval between drug administration and effect, (2) the literature, defining the degree of knowledge of the relationship between the drug and the effect, (3) the evaluation of drug withdrawal, (4) the rechallenge effect, (5) other cause, (6) risk factor, (7) complementary explorations.
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