Management of Nonimmediate Hypersensitivity Reactions to Drugs

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KEYWORDS

- Drug-allergic liver injury (DALI) • Drug-induced nephritis (DIN)
- Drug-induced vasculitis
- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Stevens-Johnson syndrome (SJS) • Toxic epidermal necrolysis (TEN)

KEY POINTS

- Early diagnosis, early identification, and early withdrawal of suspect drug or drugs are essential.
- Severe reactions need an immediate referral to specialized centers.
- Patients should be provided with clear recommendations for follow-up, when needed, and for future use of medicines.

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J.C. Roujeau: For the past 5 years, *Punctual expertise of cases of SCAR* for: AB-Science, Negma, Johnson & Johnson, Hoffman La Roche, Boehringer-Ingelheim; *Safety boards*: Vertex (2008–2011), OM-Pharma (2008–2012), Servier (2009–2011), Janssen (2010–2012), Boehringer-Ingelheim (2010–2013), Menarini (2012), Pfizer (2013); *Expert witness* in 5 cases of litigation in the United States concerning McNeil Consumers/Johnson & Johnson; *Research:* member of the RegiSCAR International study group funded in France by GSK, Novartis, Boehringer Ingelheim, OM-Pharma, Science & Technologie, Astellas Pharma.
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INTRODUCTION

The denomination "nonimmediate hypersensitivity" explicitly refers to idiosyncratic, type B, reactions mediated by a drug-specific immune response belonging to types II, III, and IV of the classification proposed by Coombs and Gell.[1]

Type II reactions, antibody-mediated reactions, are considered responsible for a variety of drug-induced blood dyscrasias (eg, thrombocytopenia).[2] Type III reactions, involving depositions of immune complexes, are definitely the cause of serum-sickness, a reaction that is quite rare nowadays. For "serum-sickness-like syndromes" and drug-induced vasculitis, often quoted as other examples of type III hypersensitivity, the pathomechanisms are actually more complex, with T cells playing a role and drug-specific antibodies being rarely detected. Most nonimmediate reactions to drugs are actually type IV, delayed, T-cell-mediated reactions.

The present review focuses on these "type IV," T-cell-mediated reactions that are not only by far the most frequent but also diverse enough to justify the subclassification proposed by Pichler[3] in subtypes IVa to IVd. Nonimmediate drug hypersensitivity may affect a single organ, most often the skin, or present as a complex multisystem disease (eg, DRESS, abacavir hypersensitivity, systemic vasculitis).

Table 1 presents the incidence of the reactions discussed in the present review.[4–13]

Management includes the following steps: accurate diagnosis of the type of the reaction, evaluation of severity, identification of the most suspect drug or drugs, decision on drug discontinuation, treatment, confirmation of drug causality, reporting to regulatory agencies, and counseling patients on future use of medications.

CLINICAL DIAGNOSIS

Skin

As demonstrated by a large prospective study, 90% of reactions affecting the skin manifest as benign "maculopapular eruptions."[4] Such eruptions most often occur 4 to 20 days after the first intake of the inducing drug with a peak around 7 days. They are difficult to distinguish from viral eruptions, which are more common in childhood. A skin biopsy would be useless, because histologic changes are very mild and nonspecific.

Many other phenotypes may occur, including delayed urticaria, eczematous eruptions, lichenoid reactions, fixed drug eruptions (round, well-demarcated patches of erythema usually leaving pigmented areas). Whatever the clinical presentation, pruritus is almost constantly observed.

Table 1
Incidence of reactions included in this review

	Phenotype	Population	Exposed to "High-Risk Drugs"
Single organ			
Skin	Maculopapular eruption	2%–4%[a,4]	5%–10%
	AGEP	<10/million/y	Unknown
	SJS/TEN	2/million/y[5]	1/100,000 to 1/1,000[6]
Liver	Drug-induced liver injury	10–20/million/y[7,b]	1/100,000 to 1/10,000[8]
Kidney	Acute interstitial nephritis	NA	1/100,000 to 1/5,000[9]
Multisystem	DRESS	9/million/y[10,c]	1/10,000 to 1/1,000[11]
	Vasculitis	NA	Up to 3/100[12]

[a] Overestimated since obtained among hospitalized patients (higher rate of exposure to medications than general population).
[b] Overestimated since including "toxic" and "allergic" cases.
[c] Probably overestimated since obtained from West Indies in a population likely at increased risk.

Severe cutaneous adverse reactions (SCARs) are defined as life-threatening effects that most often lead to hospitalization. They are very rare but may initially resemble a trivial eruption (see evaluation of severity later in discussion). They include the following:

- Epidermal necrolysis (from less severe Stevens-Johnson syndrome [SJS] to toxic epidermal necrolysis [TEN]) characterized by high fever, skin pain, erosions of mucous membranes, targetlike lesions, blisters, positive Nikolsky sign, and large erosions resulting from detachment of dead epidermis (**Fig. 1**).[14]
- Acute generalized exanthematous pustulosis (AGEP) with fever and rapid progression of large patches of burning erythema covered by dozens of small pustules.[15]
- Drug reaction with eosinophilia and systemic symptoms (DRESS), also sometimes called drug-induced hypersensitivity syndrome (DIHS).[16]

If not useful in mild eruptions, a skin biopsy is mandatory for all cases of severe reactions. It will allow a retrospective validation of the diagnosis and in some cases may help to exclude nondrug causes of a reaction pattern.

Taking photographs of the lesions is also of tremendous importance, because it may help in making an earlier diagnosis, if transmitted to an expert center, and also allowing for better retrospective evaluation.

Liver

Drug-induced liver diseases are often reported under the denomination of DILI (drug-induced liver injury),[7] with the limitation of not only immune-mediated reactions but also toxic injuries (such as "type A" acetaminophen-related liver failure). Calling the former DALI (for drug-allergic liver injury[8]) would be more appropriate. Usually, definition and classification are based on liver test alterations. Cases are classified

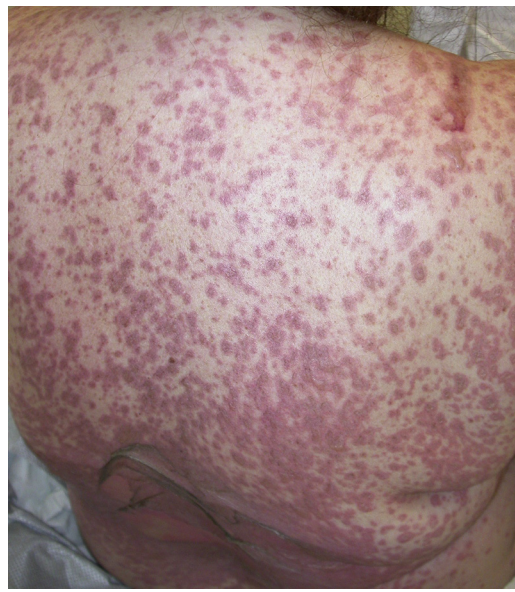

Fig. 1. SJS/TEN overlap with atypical targets and macules as well as large areas of skin detachment.

depending on dominant biologic alterations as "hepatocellular" (ALT greater than twice the upper limit of normal range), "cholestatic" (AP greater than twice the upper limit of normal or ALT/AP ratio <2), or "mixed."[7]

Kidney

Immune-mediated reactions affecting the kidney most often present as acute interstitial nephritis. It is generally considered that 70% of cases of acute interstitial nephritis are caused by drugs.[17] Hence, the denomination of "drug-induced interstitial nephritis" (DIN) was coined.[9] Clinical signs appear 2 to 3 weeks, or even later, after initiation of the inducing medication. Patients with DIN typically present with nonspecific symptoms of acute renal failure, including oliguria, malaise, anorexia, nausea, and vomiting. Alteration of renal function may also be totally asymptomatic, but detected because of other symptoms of hypersensitivity (fever, rash, arthralgia, etc). The latter symptoms, even if mild and transient, should not be missed because they are good markers for suggesting that the mechanism is more likely hypersensitivity than toxicity. A definitive diagnosis of DIN can be established only by kidney biopsy. Eosinophiluria is frequently used as a surrogate marker, but its sensitivity is probably low.[18]

Multisystem

DRESS

DRESS (formerly known as "hypersensitivity syndrome" and also called DIHS in Japan) is a multisystem drug reaction beginning typically 3 to 6 weeks after the use of a new drug and characterized by the varying association of fever, skin eruption of variable severity (**Fig. 2**), enlarged lymph nodes, and visceral lesions (liver, kidney, and lung being the most frequent, whereas gut, pancreas, and the peripheral and central nervous systems are rarely involved). Blood counts show leukocytosis with marked eosinophilia, lymphocytosis, activated "atypical" lymphocytes, and strong elevation of inflammation markers. A frequent characteristic of DRESS is the reactivation of latent viral infections (human herpesvirus 6 [HHV6], Epstein-Barr virus (EBV), cytomegalovirus [CMV]) that can be detected by elevation of serology at 2-week intervals and/or viremia (evidenced by quantitative polymerase chain reaction on serum or plasma). The course of DRESS is often prolonged with partial remissions and relapses, which are often associated with viral activation and also occasionally with the introduction of a new medication. A scoring system was proposed for retrospective validation of suspected cases of DRESS.[19]

Abacavir hypersensitivity, occasionally reported as DRESS, is actually different by a shorter time latency between the beginning of drug use and the reaction onset,

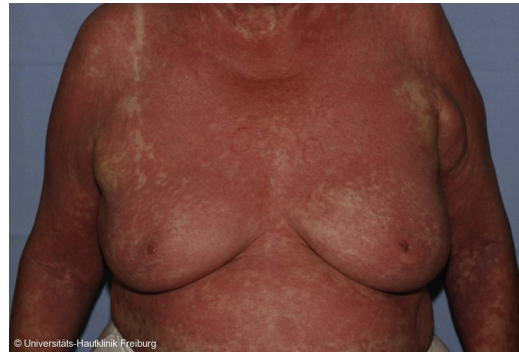

Fig. 2. Infiltrated and edematous inflammation of the skin in DRESS.

infrequent eosinophilia, lymphadenopathy, visceral involvement, and shock in the case of rechallenge.[20,21]

On the other hand, DALI and DIN have a rather long latency. DALI often displays eosinophilia, rash, and fever[7]; lymphadenopathy and atypical lymphocytes are also reported.[8] DIN is associated with rash (42%), fever (46%), and eosinophilia (40%).[9] Further evaluation of the degree of overlap between DRESS, DALI, and DIN is obviously needed.

Drug-induced vasculitis

This reaction usually manifests with skin purpura, arthralgia, and myalgia with possible involvement of kidney and lung combined with features of a lupuslike condition, especially in patients on long-term treatment with antithyroid drugs. Patients affected by drug-induced vasculitis are very often positive for myeloperoxidase–antineutrophil cytoplasma antibodies (MPO-ANCAs). They may also have antinuclear antibodies (ANAs), antihistone antibodies, high levels of immunoglobulin M anticardiolipin antibodies, and low C4 values. This pattern of autoantibodies contrasts with the usual absence of ANAs, antihistone and anticardiolipin antibodies, and normal C4 levels in patients with idiopathic systemic vasculitis.[22]

EVALUATION OF SEVERITY

Skin

The severity of a skin reaction is evaluated on the following:

1. Type of lesions: pustules (suspicion of AGEP or DRESS), vesicles, blisters, erosions (suspicion of epidermal necrolysis), infiltration, facial edema, scaling (suspicion of AGEP or DRESS), purpura (suspicion of vasculitis or DRESS).
2. Associated symptoms and signs: high fever (suspicion of SCAR), intense skin pain (suspicion of epidermal necrolysis), and presence of erosions affecting the mucous membranes (suspicion of SCAR). On this point, it is important to distinguish between peri-orificial skin and true mucous membranes (eg, lips vs mouth, eyelids vs conjunctiva). Only erosive mucous membrane lesions indicate a severe reaction.
3. Extent: evaluated as the proportion of body surface area (BSA) involved. This criterion is prone to errors by excess, resulting from confusion between "dissemination" and surface. An eruption made of small nonconfluent "spots" disseminated to most parts of the body, as seen in measles, is very unlikely to affect more than 10% of the total BSA.[23] The name of exfoliative dermatitis is used when redness and scaling are confluent on more than 90% of the BSA. Exfoliative dermatitis can be caused by several skin diseases, including a drug reaction that most often fulfills the criteria for DRESS. Whatever its cause, exfoliative dermatitis is associated with high morbidity and requires specialized treatment.
4. Rapid progression is a characteristic of SCAR. In case of doubt, severity should be re-evaluated within a few hours.

Any skin lesion is associated with alteration of the "skin barrier," leading to exaggerated water and electrolyte losses and to facilitated systemic penetrations of bacteria colonizing the skin. Such alterations are extreme when erosions (epidermal necrolysis) or scaling (DRESS) affect a high percentage of the BSAs. Sepsis is a frequent cause of death in severe skin reactions, especially SJS/TEN.[24]

Liver

As for hepatitis of any cause, the severity of drug-induced liver disease is most often appreciated on the existence of jaundice and strong elevation of ALT (>10 times ULN) or of AP (>2 times ULN).[8] Any of these alterations requires rapid advice from a liver

specialist because of the risk of progression to liver failure (usually defined as international normalized ratio $\geq$1.5, ascites, or encephalopathy) with possible need for emergency transplantation.[25]

Kidney

The absence of a decrease of creatinine level 1 week after discontinuation of the responsible drug suggests severe nephritis and often leads to using systemic corticosteroids with or without prior renal biopsy.[17,18]

Multisystem

Severity of multisystem reactions is logically proportional to that of the most severely involved organ or organs, but multisystem reactions may also be complicated by nonspecific syndromes resulting from inflammation and organ failure, such as systemic inflammatory response syndrome, disseminated intravascular coagulation, or hemophagocytic syndrome.[26]

IS REFERRAL TO SPECIALIZED WARDS NEEDED?

Referral to a specialized center should be considered based on severity at admission and on quickness of progression of signs and symptoms. Acute failure of any organ including the skin needs specialized measures for surveillance and/or management.[26]

As an example, an algorithm evaluating the need for referral to an expert center of cases of SJS or TEN has been proposed. It is based on the main prognosis factors, as evaluated by a disease-specific score (SCORTEN) reliably predicting the risk of death.[27] Recommendations issued by the French health authorities state that SCORTEN of 2 or more indicates the need for immediate transfer to an expert center.[28]

Box 1 presents SCORTEN values.

IDENTIFICATION OF SUSPECT DRUGS

To identify the most likely causing drug is not always easy in the frequent situation of patients exposed to several drugs, not even with the help of diagnostic tests after the patient's recovery. Results of tests, discussed elsewhere, are obviously not available

Box 1
SCORTEN

One point for each of the following 7 items:

A score greater than or equal to 2 indicates a risk of death greater than or equal to 10% and the need for referral to a specialized center[28]

1. Age greater than or equal to 40 years
2. Current malignancy
3. Detached/detachable epidermis on greater than 10% of BSA
4. Heart rate greater than 120
5. Serum urea greater than 10 mmol/L
6. Serum glucose greater than 14 mmol/L
7. Serum bicarbonate less than 20 mmol/L

Adapted from Guégan S, Bastuji-Garin S, Poszepczynska-Guigné E, et al. Performance of the SCORTEN during the first five days of hospitalization to predict the prognosis of epidermal necrolysis. J Invest Dermatol 2006;126(2):273; with permission.

to physicians who have to face the early management of a patient with drug hypersensitivity. At this stage there are 4 main criteria helping to consider a drug as a likely suspect. These criteria were integrated in many algorithms, especially a recent one that proved useful for SJS/TEN.[29]

Delay Between Initiation of the Medication and Onset of the Reaction

Studies addressing the time relationship of the risk were done for SJS/TEN and have shown that the odds ratios for "high-risk" drugs were no more significant with long-term treatments (more than 8 weeks).[30] That cannot be extrapolated to all types of drug reactions, but it is patent that most types of reaction have a suggestive "time-window" or delay that is helpful in the evaluation of causality.

Table 2 presents the suggestive time-window by type of reaction.

Is the Medication Still Present in the Patient's Body?

The pertinence of this question is based on the demonstration that most types of nonimmediate hypersensitivity reactions (HSR) are directed by drug-specific T cells. In vitro, these cells react only in the presence of the drug (or a metabolite) at concentrations in the range of the serum level of efficacy. Much lower concentrations do not elicit any response from drug-specific T-cell clones.[31] This strongly suggests that a drug stopped before the onset of reaction for more than 5 times the duration of "elimination half-life" (10 times in the case of alteration in the kinetics of drug elimination) is very unlikely the culprit.[29]

Did the Patient Use the Same Drug in the Past?

The authors' experience with SCAR has been that "associated" drugs were nearly always administered for the first time, with very rare exceptions of recurrent cases with a precipitated onset. The authors, therefore, consider not only that a prior reaction to the same medication increases the probability that it is responsible, but also that prior usage without a problem decreases the probability.

What Is the Notoriety of the Drug for Inducing This Type of Reaction?

Whatever the phenotype of the reaction, a limited number of medications are responsible for most cases (**Table 3**).

Table 3 presents drugs most often responsible for a certain type of reaction.

If initiated within a suggestive "time-window," such drugs are definitely first-rank suspects to be withdrawn in priority.

Table 2
Suggestive "time-windows" (days between beginning of drug use and onset of the reaction) by type of reaction

Nature of Reaction	Suggestive Delay (from First Intake of Medication to Onset of Reaction)
Maculopapular eruption	4–12 d[4]
AGEP	Hours to 2 d (antibiotics), 4–12 d (other drugs)[15]
SJS/TEN	4–28 d[29]
DALI	5–90 d (peak >4 wk)[8]
DIN	2–3 wk or later[9]
DRESS	2–5 wk[16]
Vasculitis	Months with propylthiouracil[22]

Table 3
Drugs most often responsible by type of reaction

MPE[4]	AGEP[a,15]	SJS/TEN[a,30]	DALI[8]	DIN[9,32]	DRESS[b,16]	Vasculitis[22]
Aminopenicillins	Aminopenicillins	Allopurinol	Allopurinol	Penicillins	Carbamazepine	Propylthiouracile
Cephalosporins	Pristinamycine	Lamotrigine	Sulfamethoxazole[c]	Cephalosporins	Allopurinol	Other antithyroid
Other antibiotics	Diltiazem	Sulfamethoxazole[c]	Amoxi/clavulanate	NSAIDs	Lamotrigine	AntiTNF-α
AEDs	(Hydoxy)chloroquine	Phenytoin	Macrolides	Proton pump inhibitors	Salazopyrine	Cefotaxim
	Quinolones	Carbamazepine	AEDs		Phenytoin	Minocycline
	Sulfamethoxazole[a]	Nevirapine	Vitamin K antagonists		Vancomycin	Hydralazine
	Terbinafine	Phenobarbital				
		Oxicam NSAIDs				

Abbreviations: AED, antiepileptic drugs; MPE, Maculopapular eruptions; NSAIDs, nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor.
[a] Listed drugs account for 50% of cases.
[b] Listed drugs account for 60% of cases.
[c] And other anti-infectious sulfonamides.

DECISION ON WITHDRAWAL

The Rule

The rule is to withdraw as soon as possible any suspected drug. This attitude was supported in SJS/TEN by a study showing that an early withdrawal of the "culprit drug" was associated with a significantly lower mortality, provided the drug had a rather short elimination half-life.[33]

On the other hand, the authors recommend that drugs that are both *nonsuspected AND important* for future treatment should rather be continued. In the authors' experience, most patients are indeed reluctant to take again any of the medications that were stopped because of the hypersensitivity reaction, even when further tests identify a single one as the most likely culprit. Conversely, they consider easily as "innocent" medications that were not withdrawn during the course of the disease.

A Few Exceptions

It is important to keep in mind that in the context of a mild to moderate drug eruption, not accompanied by systemic symptoms, and attributed to an important medication (eg, for treating HIV infection), patients were sometimes "treated through" the rash.[34] That was usually not followed by progression of the reaction, and resolution of the "rash" occurred in about the same time as expected if the drug had been withdrawn.

A decision of "treating through" depends obviously on a thorough evaluation of the balance between the severity of the adverse reaction, the severity of disease to be treated, and the existence of alternative medications. The decision to treating through needs information of the patient and very close surveillance, preferably in hospital.

TREATMENT

Skin Reactions

Maculopapular eruptions

There is no treatment of proven efficacy for common drug eruptions. Mild to moderate eruptions vanish in a few days without any treatment. Oral antihistamines and topical emollients are often prescribed. There is no evidence that they shorten the evolution, but they may help to alleviate pruritus (as demonstrated for many other skin diseases where pruritus is an important symptom). In the case of severe pruritus, topical corticosteroids of mild or moderate potency are probably useful.

Severe reactions—SCAR

AGEP Most patients with AGEP are hospitalized because the combination of widespread pustules, fever, and high neutrophil count often raises the suspicion of severe sepsis. Investigations for infection are negative; there is no need for antibacterial treatment, and the eruption disappears within 7 to 15 days with or without treatment using oral antihistamines.[15]

SJS/TEN Because these conditions are the most severe forms of drug hypersensitivity with 30% mortality,[35] most physicians are obligated to give "some specific treatment" even though available evidence is that none has demonstrated any benefit and none is free of potentially severe side effects.

Systemic corticosteroids (high oral dosage or intravenous "pulse") and intravenous human immunoglobulins (IVIg) are the immune-modulating treatments most often prescribed. For IVIg, the rationale was based on expected inhibition of Fas-Ligand, a cytokine considered responsible for the widespread death of cells in the epidermis. This rationale has been refuted by recent studies demonstrating that Fas-Ligand

had no role or a very minor role in the mechanisms of TEN.[36] Furthermore, one large cohort study[35] and 2 meta-analyses[37,38] observed no benefit from IVIg on mortality. The same cohort[35] and one meta-analysis[37] also evaluated systemic corticosteroids and found no benefit.

Waiting for further results of ongoing studies testing a possible benefit of cyclosporine[39] or etanercept, physicians should focus their efforts on providing the best supportive care as the only treatment that can save the patient's life in such severe diseases. That is best done in specialized hospital settings (intensive care unit or burn units in cases with large amounts of skin detachment, dermatology units in cases not requiring intensive care) with skilled nurses and a multidisciplinary team of physicians capable of managing the multiple complications of "acute skin failure," especially severe sepsis.[24] It is not within of the scope of this review to detail the complex symptomatic measures that resemble in many parts (but not all) what is needed for the management of severe burns.

Liver

Systemic corticosteroids are often used in drug-induced hepatitis, especially with evident markers of hypersensitivity (rash, eosinophilia), but their benefits are still not proven.[8] Management is centered on the prompt withdrawal of the suspected drug. That usually results in a 50% decrease in serum ALT within 8 days of discontinuation in the hepatocellular type. Improvement may require a longer period in the cholestatic type.

In cases with acute liver failure, a randomized controlled trial (RCT) has suggested a significant increase in spontaneous survival of a subgroup of patients (ie, without liver transplantation) with intravenous *N*-acetylcysteine.[40] However, this trial suffered from some methodological bias and was not confirmed by a further randomized trial that instead suggested worsening with *N*-acetylcysteine.[41] Based on these RCTs, routine use of *N*-acetylcysteine cannot be recommended for the treatment of DALI.[42]

Kidney

There is no consensus on the treatment of DIN. On one hand, most cases improve after drug withdrawal without any "specific" treatment. On the other hand, 2 retrospective analyses found that treatments with corticosteroids were followed by more frequent recovery of normal renal function. In the first study, the benefit was restricted to cases with treatment initiated less than 2 weeks after diagnosis.[43] In the second study, a benefit from steroids was observed whatever the delay in initiating treatment.[44] Taking the results of both studies into account, data support the recommendation of (1) withdrawing suspected drugs and (2) initiating steroid treatment if creatinine level is not substantially decreased after 1 week. The typical corticosteroid regimen is "pulse" methylprednisolone (250–500 mg intravenous injection) for 2 to 4 days followed by oral prednisolone 1 mg/kg/d tapered over 8 to 12 weeks.

DRESS

Prompt withdrawal of the offending drug is the mainstay of treatment. The authors also suggest avoiding the introduction of new medications during the course of DRESS because of the risk of a flare-up that may be considered "multiple drug allergy."[45] Patients with severe cutaneous manifestations are usually hospitalized for treatment. Those with exfoliative dermatitis require fluid and electrolyte replacement as well as nutritional support. Additional measures include a warm and humid environment and gentle skin care with warm baths/wet dressings and emollients.

An expert consensus in France proposed that in the absence of clinical, laboratory, or imaging evidence of renal or pulmonary involvement and with only modest elevation of liver enzymes, patients with DRESS can be treated symptomatically.[46]

Relief of pruritus and skin inflammation is obtained with high-potency topical corticosteroids applied 2 to 3 times per day for 1 to 2 weeks. That is enough for obtaining complete recovery in patients without severe organ involvement. For more severe cases, there is consensus among experts on the use of systemic corticosteroids, particularly in patients with renal and/or pulmonary involvement. The optimal dose and duration of corticosteroid therapy are not known. After a usual initial dose of 1 to 2 mg/kg/d of prednisone or equivalent maintained up to the beginning of remission, the daily dose is tapered progressively. Waiting for a better evaluation of treating DRESS with systemic corticosteroids, the authors recommend using them only for the most severe cases.

There are no studies evaluating the treatment of DRESS with antiviral agents active against HHV6 or CMV (eg, ganciclovir, foscarnet, or cidofovir). Given the substantial toxicity of antiviral agents and the natural course of spontaneous resolution, antiviral agents are rarely used in the treatment of DRESS. However, they may be warranted for cases in which virus reactivation is both demonstrated and strongly suspected of contributing to severe complications (eg, severe erosive colitis).[47]

Systemic Vasculitis

In the absence of involvement of kidney or lung, discontinuation of the causal agent is usually enough. A course of systemic corticosteroids is justified in the case of organ involvement. Prednisone or equivalent is used at a daily dose of 1 mg/kg for 4 to 8 weeks. In cases with severe nephritis, the treatment may begin with intravenous "pulse." Corticosteroid therapy is then tapered off over 6 to 12 months. Periodic checking of MPO-ANCA levels may help to accelerate or stop decreasing steroid dosage. In contrast to idiopathic systemic vasculitis, the addition of immune-suppressive agents is rarely necessary.[22]

CONFIRMATION OF CAUSALITY

Before embarking a patient in long and expensive investigations, the authors suggest to clearly define the objectives. What level of evidence is needed and for what aim?

Is it for better understanding the immune mechanisms of an adverse drug reaction? That is a research objective to be explored following the rules of good clinical practice.

Is it for helping the patient and the general practitioner in future use of medicines? In more than 50% of cases, a single medication or a couple of medications is highly suspected on clinical judgment. In such cases, prescribing an alternative treatment without any further investigation is costless and effective.

What will be the interpretation of a negative in vivo or in vitro test? No allergy expert will conclude that the reaction was not allergy.

The authors' experience with SJS/TEN is that the skin biopsies *always* exhibit a pattern of cytotoxic T cells invading the epidermis. When extracted and tested, these T cells revealed drug-specific cytotoxicity. Clinically, one or occasionally 2 medications are strongly suspected in 65% to 70% of cases of SJS/TEN.[29] Patch tests with these drugs are positive in 20% to 25%[48] and lymphocyte transformation test (LTT) in no more than 30% of patients. Rather than concluding that the reaction was not immune-mediated in the case of negative results, the authors consider more plausible that the sensitivity of tests available nowadays is too low to be useful to assess causality. The authors do not doubt that new tests will be developed that will prove more helpful.

REPORTING

After the marketing of a new drug, pharmaceutical companies and regulatory agencies have to reassess its benefit/risk balance in real life, because (1) the most severe reactions are too rare to be detected in premarketing clinical trials and (2) patients with comorbidities that may increase the risk are often not enrolled in clinical trials.

It is, therefore, an essential duty of all physicians interested in drug hypersensitivity to report cases to pharmacovigilance systems.

FOLLOW-UP

There is growing evidence that many nonimmediate HSR may induce some sequelae, which may be long-lasting. Sequelae occur very frequently after SJS/TEN, impairing daily life in most patients. Not only may the eyes be severely affected but also other mucosal sites, skin, appendages, bronchial tract, and others. A follow-up examination is recommended 3 months and 1 year after discharge for the evaluation of sequelae and referral to organ specialists for optimal management.

Many recent case reports have also insisted on the possible development of autoimmune diseases following DRESS. In a retrospective study of 43 patients with DRESS followed up for at least 1 year, 4 patients developed autoimmune diseases (Grave disease, diabetes mellitus type 1, and autoimmune hemolytic anemia) and 2 patients developed chronic renal failure.[49]

FUTURE USE OF MEDICATIONS

Patients who experienced a hypersensitivity reaction to a medication must be educated about future avoidance of that specific medication. In the case of prior severe reaction, re-exposure to the culprit drug may be fatal. Relevant information should be inscribed on an "allergy passport" that patients must carry with them at all times. Patients should be able to report the precise type of hypersensitivity they suffered and the generic name for the causative medication, but this might be a challenge in elderly patients needing assistance.

Whatever the mechanisms (true "cross-reactivity", common genetic susceptibility, or other), the risk of "multiple drug hypersensitivity" exists and should be addressed.[48] Patients with hypersensitivity to one of the following anticonvulsants, such as phenytoin, carbamazepine, phenobarbital, or lamotrigine, should be informed that they have also a risk of similar reaction to the others in the list for themselves certainly and possibly their family members. However, numerous patients have been seen with SJS/TEN after one of these drugs that were treated with another one subsequently without any problems.

The risk of recurrence with structurally distinct agents (within the same therapeutic class of drugs) is unknown but low enough for being acceptable. As an example, the authors recommend patients with past severe reaction to cotrimoxazole avoid other anti-infectious sulfonamides but authorize the use of thiazide diuretics or sulfonylurea-derived antidiabetics.

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