



Cutaneous drug hypersensitivity: developments and controversies

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Purpose of review

Cutaneous drug hypersensitivity reactions (CDHRs) are a complicated area with multiple clinical manifestations and differential diagnoses, requiring differentiated diagnostic measurements and optimized therapeutic management.

Recent findings

Disseminated CDHRs to classical drugs can be classified by a simple algorithm, whereas chemotherapeutics or biopharmaceuticals may show drug-specific and atypical clinical presentations. Controversies in drug hypersensitivity diagnosis exist about the benefit and accuracy of in-vitro tests. Although skin tests are the best means of detecting sensitization to drugs, methods have not been sufficiently standardized. The necessity for skin tests before performing drug provocation test (DPT) and of prolonged DPTs is discussed in selected patients. If a suspicion has been documented, β -lactam allergy should be excluded. The standard allergy diagnosis is done by an allergist. In case of urgent need because of an infection and low risk according to history, faster delabeling pathways have been developed. There is weak evidence that patients with mastocytosis may have a slightly increased risk of developing immediate-type drug hypersensitivity; however, if considerations are taken, drugs do not have to be withheld for this patient group. There is particular need for improved diagnostic measurements in patients with drug-induced severe cutaneous adverse reactions (SCARs), both identifying the offending drug and detecting individuals at risk. Further challenges encompass appropriate treatments during the acute as well as chronic phase of SCARs.

Summary

Recent literature has contributed to our understanding of clinical manifestations and existing controversies and future needs in this area.

Keywords

allergy diagnosis, β -lactam allergy, clinical manifestations, controversies, cutaneous drug hypersensitivity reaction, severe cutaneous adverse reaction

INTRODUCTION

There have been several developments on different clinical manifestations with attempts to classify typical entities and to describe cutaneous adverse reactions of chemotherapeutics and biopharmaceuticals as well as controversies on the accuracy of different methods diagnosing cutaneous drug hypersensitivity during the last years. These developments and controversies will be described in this article.

CLASSIFICATION OF CLINICAL MANIFESTATIONS OF CUTANEOUS DRUG HYPERSENSITIVITY

Maculopapular exanthems and urticaria are the most frequent manifestations of cutaneous drug

hypersensitivity reactions (CDHRs) [1]. The diagnosis of CDHRs has been regarded as difficult, because of a broad spectrum of manifestations [1]. To enable the adequate planning of allergy tests, comparing of test results and patients in multicenter studies, it is

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KEY POINTS

- Manifestations of CDHRs have been described and categorized to conventional as well as to chemotherapeutic and biopharmaceutical drugs.
- Still multiple controversies in drug hypersensitivity diagnosis do exist, which have recently been addressed by experts.
- The benefit of in-vitro tests, skin test methods, necessity for skin tests before DPTs, prolonged DPTs, how to exclude BLA, faster BLA delabeling pathways, risk for drug hypersensitivity in patients with mastocytosis and appropriate treatment for severe cutaneous drug reactions like SJS or TEN still have not been finally clarified.

crucial to identify different entities of CDHRs. Recently, cutaneous manifestations of drug hypersensitivity have been described [2[¶]]. A simple algorithm enables classification of more than 95% of all CDHRs. Disseminated or generalized CDHRs are classified by the presence of either wheals +/- angioedema into a diagnosis of drug-induced urticaria/angioedema/anaphylaxis (depending on further noncutaneous organ involvement), or into the clinical picture of an exanthem with various subentities. An exanthem is a widespread, rapidly erupting rash that has diagnostic features of an infectious disease. The presence of blisters, pustules or purpura, severe noncutaneous organ involvement and the distribution of lesions define specific exanthematous subentities. If no specific features do exist, the diagnosis is maculopapular exanthema (MPE). Although some reports subclassify maculopapular exanthems descriptively (e.g. morbilliform, lichenoid, acneiform or granulomatous), this does not carry any evidence of pathologic or prognostic implications. Recently, pityriasis lichenoides-like drug reactions have been described, which should also be considered as variants of an MPE [3].

HYPERSENSITIVITY REACTIONS TO NEW TREATMENTS FOR MELANOMA

The clinical spectrum of drug hypersensitivity reactions (DHRs) to chemotherapeutic drugs and biopharmaceutical drugs has additional specific features as well as own chronologies. The majorities of these reactions are because of immune deviations rather than allergic reactions. Targeted therapy and immunotherapy against advanced melanoma have emerged during the last decade, and have tremendously improved chances for survival of patients with this disease. For many of these DHRs, the skin

is the target organ. For BRAF inhibitors, the main cutaneous side-effects are either inflammatory, such as rashes, photosensitivity reactions and hand-foot skin reactions, or tumorous, such as cutaneous squamous cell carcinoma, keratoacanthoma and verrucal keratosis [4[¶]]. Special attention has to be paid to the development of new primary melanomas or changes on nevi during BRAF inhibitor therapy [5]. Combination therapy with mitogen-activated protein kinase-inhibitors significantly reduces CDHRs, although acneiform exanthems may develop [5].

Checkpoint inhibitors (CPIs) target immune inhibitory receptors, either cytotoxic T-lymphocyte-associated Protein 4 reducing antigen presentation, or programmed death 1 (PD-1) or PDL-1 reducing tumor cell recognition by T cells. CPIs induce immune reactivation with possible loss of self-tolerance and development of autoimmunity. The most common CDHRs are rashes, pruritus and vitiligo. However, the overall spectrum of CDHRs is wide and includes eczematous, psoriasiform and lichenoid reactions, acneiform rashes and alopecia as well as autoimmune skin disorders, such as bullous pemphigoid, vasculitis and dermatomyositis [5]. MPEs can occur, and severe cutaneous adverse reactions (SCARs) have been described [6]. Skin reactions often occur at least 3 months after beginning therapy with PD-1 inhibitors (median 4.2 months, range 0.5–38 months) and may even develop after the drug therapy was terminated [7]. Most CDHRs show a histologic pattern of a lichenoid or spongiotic dermatitis [8]. Further features may develop, such as bullous pemphigoid-like reaction and sarcoid-like reaction, suprabasal acantholytic vesicle formations with paraneoplastic pemphigus-like features or transient acantholytic dermatosis resembling Morbus Grover [8]. Therapeutic strategies are directed by the clinical dermatological disease the CDHR is resembling. Most CDHRs to CPI are nonsevere and require symptomatic treatment only. Because of the importance of this therapy, a treat-through approach is warranted in most cases. There are promising preliminary studies showing a potential role of CDHRs as surrogate biomarkers of efficacy of CPI treatment; however, larger prospective studies are needed to confirm this association [9,10].

CONTROVERSIES IN DRUG HYPERSENSITIVITY

A series of international expert consensus documents was developed [11,12[¶],13[¶],14^{¶¶},15[¶],16[¶]]. Questions concerned β -lactam testing, delabeling of penicillin allergy, radiocontrast media (RCM)

hypersensitivity, in-vitro testing as well as skin testing in delayed hypersensitivity. In addition, adverse reactions to drugs and biopharmaceuticals in patients with clonal mast cell disorders have been clarified [17^{••}].

IN-VITRO TESTING FOR THE DIAGNOSIS OF DRUG HYPERSENSITIVITY

There is no consensus about the role of in-vitro tests being discussed either as an important routine tool in the routine diagnostic process or as a research tool [12[•]]. Regarding immediate DHRs, sIgE immunoassays are recommended for DHRs to β -lactams, neuromuscular blocking agents and chlorhexidine in some European countries, whereas their use is critically regarded in the United States because of suboptimal sensitivity and specificity [12[•],18]. Likewise, the basophil activation test is frequently used in European expert centers in immediate DHRs, but only exceptionally in the United States [19,20].

For nonimmediate DHRs, lymphocyte transformation test (LTT), cytokine determination test or combined cytokine and cytotoxicity assays are quite complicated and labor-extensive; the results dependent on the expertise of the respective center [21]. They are used more for experimental and basic research than for routine analysis [12[•]]. It might be that we are missing the best reactive agents, for example drug metabolites or drug-carrier conjugates for in-vitro tests. Before we implement in-vitro tests into our routine diagnosis of DHRs worldwide, several unmet needs still have to be solved.

In one nested case-control retrospective study in 170 patients, the diagnostic value of tissue eosinophilia in skin biopsies has been evaluated as a diagnostic criterion for the diagnosis of CDHRs [22]. CDHRs did not have a higher eosinophil count per high power field in comparison to skin reactions, where DHRs were excluded by in-vitro assays and telephone interview. Thus, tissue eosinophilia is not a reliable indicator of CDHRs. Markers of systemic involvement and death may be helpful in hospitalized cancer patients with SCARs. In a retrospective review of 49 hospitalized cancer patients, the markers interleukin-6 and interleukin-10 were significantly higher in serum of patients with SCARs in comparison to those with uncomplicated morbilliform rash, and the markers Elafin, interleukin-6 and tumor necrosis factor α (TNF α) were significantly higher in patients who died compared with patients who were still alive at 6 months [23]. These markers might be potential targets for the treatment of SCARs.

ROLE OF SKIN TESTING

Skin tests are the best available and evaluated tests to detect sensitization in DHRs [24]. However, the standard of the methodology and interpretation as well as of skin test concentrations in skin tests has not been sufficiently standardized [13[•],25]. In particular, for some drugs, the highest nonirritating concentrations of the drugs to be used in skin tests are still controversial and have not been properly defined with regard to nonimmediate reactions [25]. Recommendations for performing intradermal tests concerning methodology differ between international guidelines and across geographic regions [24]. There is a lack of consensus about the meaning of a positive or negative skin test for the prognosis of a drug hypersensitivity versus tolerance [26]. For nonimmediate DHRs, some groups propose to go straight to oral challenge without previous skin testing, as has been recommended for children with 'benign maculopapular' exanthems [26–28]. The sensitivity of skin tests in Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) is considered to be very low [13[•]].

In radiographic contrast media hypersensitivity, there is increasing evidence that skin tests may potentially identify safe alternatives for reexposure [16[•],29]. Although positive skin tests to RCM are common in patients with exanthems, they are only positive in a minority of patients with immediate DHRs to RCM [16[•],30]. For a reliable conclusion concerning the tolerability of RCM, an increasing number of centers have begun to do drug provocation tests (DPTs) with different time intervals and doses [16[•]]. Available data indicate that in the hands of experienced centers, DPTs with RCM appear to be safe and sensitive [31,32].

Skin prick tests and intradermal tests are considered dangerous in patients with drug reaction with eosinophilia and systemic symptoms and severe bullous cutaneous adversary actions. A French study assessed the value and tolerance of intradermal tests with drugs in patients with drug rash with eosinophilia and systemic symptoms (DRESSs) with negative patch test with the same drug [33]. Skin tests were tolerated in all 14 included patients tested more than 6 months after the resolution of DRESS. In six patients, delayed readings of intradermal tests were positive, identifying culprit drugs or sensitization to additional drugs. Thus, in patients with DRESS after negative patch tests tested more than 6 months after DRESS recovery, intradermal tests may be helpful to identify culprit or nontolerated drugs.

DURATION OF PROVOCATION TESTS IN PATIENTS WITH EXANTHEMS

There is no consensus on the duration of DPT in patients with a history of maculopapular exanthems [13[■]]. Although some centers recommend prolonged challenges, others consider a 1-day protocol sufficient. Most guidelines do recommend DPTs with drugs with a duration of 1 or 2 days in patients with nonimmediate DHRs [34]. However, recent studies reported a higher rate of reactivity, if the duration of the DPT was extended. In 550 children with DHRs to β -lactams, the diagnostic value of late-reading skin tests and prolonged DPTs was assessed [35]. In this population, skin tests were only positive in 3.1% of children with the majority of positive skin test responses (82.3%) after the sixth day reading. In the DPT performed with an extended duration of 1 to 2 days longer than from begin of intake to symptoms at the index reaction, DPT was positive in 43 of 527 children (8.2%). The mean time interval between onset of the DPT and the reactions was 72 h (range 3 h–11 days). The authors concluded that late readings of skin tests and prolonged DPT are safe and might improve the performance of DPTs in the diagnosis of nonimmediate DHRs. In contrast, a study of 97 children with nonimmediate DHRs to beta lactams studied a 1-day hospital provocation test followed by DPT at home for a duration of a time interval between the first dose and development of symptoms at the index reaction [36]. The majority of patients (11/14) reacted to the 1-day provocation test, only three reactions occurred during the extended DPT at home. It was concluded that severe immediate hypersensitivity reactions of concern were identified on the first day of a DPT, whereas the prolonged DPTs only identified mild exanthems or mild urticarial rashes. Thus, the evidence does not support the necessity for prolonged DPTs for avoidance of severe reactions. An additional study by Tonson [37] showed that in β -lactam allergic children with a previous positive DPT result, 89% had no reactions at rechallenge 3 years later, and that 68% of those tolerated subsequent treatments, suggesting the natural acquisition of tolerance. Thus, the benefit of prolonged DPT is questionable for their contribution to improved outcomes.

β -LACTAM HYPERSENSITIVITY TESTING IN THE ALLERGY DEPARTMENT

β -Lactams are the most widely used antibiotics and the first choice drug to control several bacterial infections. Penicillins are the β -lactams most frequently implicated in DHRs, with anaphylaxis occurring after 0.004–0.015% of exposures [15[■]].

In Europe, the broad-spectrum penicillins, such as amoxicillin, account for the majority of DHRs [38]. Regional differences exist among different countries with small-spectrum penicillins more often used in Northern Europe and the United States, also influencing the DHR prevalence [38]. A major problem with the clinical use of β -lactams is that only a small minority of reported β -lactam allergy (BLA) can be confirmed by allergy testing. Penicillin allergy labeling negatively impacts patient outcomes, antibiotic appropriateness and costs [39]. β -Lactam-mislabeled patients typically do not receive narrow-spectrum penicillins and cephalosporins when clinically indicated, the alternative antibiotics giving results in poorer clinical outcomes, increased incidence of antibiotic-resistant infections, prolonged hospitalizations and greater healthcare utilization [15[■],40,41]. On the contrary, penicillins and cephalosporins are the most common causes of fatal drug-related anaphylaxis in the United States [42]. There is a consensus that β -lactam delabeling is needed; however, they are still controversies on how to do so safely.

Individuals with a history of DHRs to β -lactams should be evaluated and tested, if possible [43]. Allergy testing should be performed when patients are clinically stable and not during an acute infection [15[■]]. However, delabeling pathways have also been developed in case of urgent need of β -lactams in low-risk patients [44]. Carbapenems and monobactams are considered to be safe alternatives for most patients with BLA in case of urgent need, because of their very low rate of immunologic cross-reactivity (<1%) [15[■]]. However, even here skin tests, if available, or DPTs have been recommended [15[■]]. Direct DPT without skin test may be recommended in children with a history of benign β -lactam-associated exanthems [45]. Desensitization is an option in patients with skin test-confirmed IgE-mediated penicillin allergy, when a penicillin is the drug of choice [46]. Also, 'treating-through' benign maculopapular exanthems is warranted in certain clinical situations under clinical monitoring [47]. Even after β -lactam delabeling, up to half of patients carried a BLA label in their electronic file despite of an uneventful DPT [48]. Thus, proper allergy documentation must follow BLA evaluation. A drug allergy passport has been constructed [49].

There is no agreement on the additional value of the major determinant and benzylpenicillin and the number of necessary penicillin reagents to be tested in a patient with BLA [15[■]]. There is increasing evidence that cross-reactivity among β -lactams can be predicted by the side chain similarity of the β -lactams [15[■]]. Although cross-reactivity

between penicillins and cephalosporins generally appears to be between 2 and 5%, the risk is much higher for high-risk allergic reactions when β -lactams with a similar or identical side chain were tested, resulting in 40% cross-reactivity [50]. Even in patients with severe reactions, such as allergic myocardial infarction, alternative β -lactams could be identified for future use [51]. However, further confirmative studies are needed for the role of skin tests to safely predict cross-reactivity.

FAST TEST PATHWAYS FOR DELABELING LACTAM ALLERGY IN LOW-RISK PATIENTS

BLAs have been recorded in up to 15% of hospitalized populations [14¹¹]. A vague suspicion of BLA often leads to labeling and subsequent β -lactam avoidance. Most patients reporting a BLA are not allergic [14¹¹]. A recent meta-analysis reported only 5% of patients with a penicillin allergy label in acute care settings to be allergic (i.e. against penicillins/specific IgE antibodies) [52]. Normal allergy evaluation of drug allergy is labor-intensive, time-consuming, resource-dependent and complex. Allergy specialist consultation with a meticulous history, skin tests +/- in-vitro test followed by DPT is the safest and most time-consuming and resource-consuming approach [40]. Skin testing before giving β -lactam under suspicion carries low to minimal risk, but requires trained personnel, and patient has to be eligible for skin testing [52]. In one study of 179 skin test-eligible patients, only 43 were finally skin-tested [44]. Reasons for skin testing failures included coordination issues, patient test refusal and team test refusal. Additional computerized or systematic assessment tools are required for further pathways for low-risk patients [40]. Without such pathways, allergy evaluations are vastly underutilized. A widely discussed computerized guideline for the management of patients with suspicion of BLA, but acute need for anti-infectious therapy, was developed at the Massachusetts General Hospital [44]. Decisions are based on the clinical reaction in the patient's history with faster diagnostic tracks for those with lower risk. Similar approaches have recently been adopted in other US institutions and in the United Kingdom [53]. An even simpler BLA assessment tool has been proposed in Australia [54]. Typical clinical manifestations of BLA were classified into four color-coded risk groups according to severity as well as to the time interval elapsed after the last reaction and was connected to four different management recommendations. Correct sorting into risk groups and management options depended on the operator, for example nurses compared to

doctors. Implementation of BLA pathways should take into account that the performance of risk stratification varies by operator, who may not have sufficient drug allergy education and knowledge. Professional liability concerns have to be regarded [14¹¹].

The critical step of these pathways is patient risk stratification. The allergy history is used for identifying high-risk severe phenotypes. In patients with positive BL challenge, there was a 10- to 30-fold risk increase observed in patients with the index clinical reaction of anaphylaxis [53,55]. Other predictors for true Penicillin allergy were hospitalization and an interval of at least 5 years since the index reaction [53]. History has to identify patients with severe DHRs including those with SCAR, organ-specific reactions and type II or type III DHRs. Patient risk stratification, however, implies that patients can make a judgment about the presence of blisters, pustules, involvement of mucous membranes, which still has to be proven [14¹¹]. Patients who cannot recall their index reaction mostly had only a benign cutaneous exanthem [55]. However, a risk of erogenous patient history remains with significant consequences. Risk categories and pathways have to be adapted to the local environment, consider the experience of the interviewer, the reliability of the BLA interview instrument, the epidemiology, cross-reactivity as well as the resources.

ADVERSE DRUG REACTIONS IN PATIENTS WITH CLONAL MAST CELL DISORDERS

Providers caring for patients with mastocytosis are confronted with the allegation that many drugs would not be tolerated in patients with mastocytosis because of histamine-releasing properties in primates, rodents and mast cell lines [56]. A workgroup report of the American Academy of Allergy, Asthma and Immunology clarified therapeutic options in the management of patients with clonal mast cell disease. Patients with mastocytosis have a greater risk of anaphylaxis, predominantly to hymenoptera venoms [57]. They do react to the same drugs as those without mastocytosis, such as β -lactam antibiotics, nonsteroidal antiinflammatory drugs (NSAIDs) and RCM [56]. In children with mastocytosis, DHRs are uncommon [17¹¹]. Perioperative anaphylaxis might be more common in patients with mastocytosis and the management of these patients requires a thorough understanding of mastocytosis, a detailed patient history, avoidance of previously nontolerated drugs and a meticulous preparation to treat possible adverse events. Venom immunotherapy is recommended in all patients with hymenoptera venom anaphylaxis suffering

from mastocytosis. There is yet no evidence of a greater risk of anaphylaxis to RCM in patients with mastocytosis as compared to the general population. Mastocytosis is no contraindication for vaccination. A higher reaction rate in children with mastocytosis might exist, especially in patients with diffuse cutaneous mastocytosis being vaccinated with hexavalent preparations and receiving their first injection [58]. Patients who tolerate specific NSAIDs have no need to avoid these substances after the diagnosis of mastocytosis. In a recent study, the frequency of hypersensitivity to acetylsalicylic acid was assessed in a double-blind, placebo-controlled provocation test [59]. Fifty patients with mastocytosis underwent DPT. A DPT was positive only in one patient who developed urticaria (2%). In addition, in a retrospective chart review, eight of 191 mastocytosis patients with history of NSAID-related hypersensitivity reactions (4.1%) were identified. The authors proposed that no NSAID avoidance would be necessary in those patients who have not had a history of prior NSAID hypersensitivity reactions or in patients with previous hypersensitivity reactions to other drugs. An important limitation of the study, however, is that the highest given single dose of acetylsalicylic acid was 400 mg only; thus, further confirmatory studies are needed.

SEVERE CUTANEOUS ADVERSE DRUG REACTIONS

A particular set of CDHRs is the subgroup of drug-induced SCARs, which are characterized by marked systemic impairment including fever, chills, reduced general condition and involvement of internal organs and/or severe cutaneous damage with widespread blisters, extended erosions and detachment of skin and mucous membranes. Drug-triggered SCARs encompass acute generalized exanthematous pustulosis, DRESS, also referred to as drug hypersensitivity syndrome, generalized bullous fixed drug eruption (GBFDE) and the entity of SJS/TEN [60]. As they pose serious risks of secondary complications, long-term sequelae or even mortality, special efforts focus on improved diagnostic measurements on the one hand (e.g. detecting the culprit drug or determining individuals at risks) and on optimized treatment on the other hand.

DIAGNOSTIC MEASUREMENTS

Particular challenges are the need for immediate and reliable assays substantiating the diagnosis of drug-triggered SCAR, especially when SJS/TEN is suspected, sensitive as well as specific tests identifying the offending drug and appropriate methods

revealing people predisposed to develop SCARs. For example, in case of SJS/TEN, the diagnosis relies on clinical features and histologic evaluation of a skin biopsy showing the typical picture of 'full-thickness' epidermal necrosis [61]. As this procedure is laborious and time-consuming and its diagnostic significance dependent on both appropriate tissue material and dermatohistological experience, simpler and faster available assays are warranted. Different in-vitro approaches focus on the detection of cytotoxic markers as essential effector molecules mainly released from drug-specific T cells. Recently, a case report of a 1-year-old boy with vancomycin-induced SCAR acknowledged the value of determining serum granulysin in diagnosing SJS/TEN [62]. The rapid granulysin test is a 15-min immunochromatographic assay with a sensitivity of 80% and a specificity of 96% in detecting granulysin [63]. However, although granulysin levels have not been found elevated in GBFDE, suggesting its value in discriminating SJS/TEN from other SCARs [64], significantly increased concentrations recently have also been reported both in serum and lymphocytes' supernatants of patients with DRESS because of dapsone hypersensitivity [65].

Early recognition of internal organ involvement is essential for proper and organ-specific treatment and to prevent secondary complications. Although this is mainly performed by laboratory screening, a recent study asked about the appropriate diagnostic measures for detecting cardiac involvement in patients with DRESS, also evaluating its frequency and impact on patient outcome. Interestingly, in a cohort of 41 individuals with DRESS, 19.5% demonstrated cardiac involvement as detected by elevated cardiac enzymes or abnormal echocardiography, with hypoalbuminemia and anemia being independent risk factors for its occurrence [66]. Although none of the patients showed signs of hemodynamic instability and only one experienced chest pain at the time of diagnosis, their mortality rate was significantly higher than in the other DRESS individuals (50 vs. 6.1%), indicating that this subgroup carries an increased risk for poorer outcome.

An important parameter in the diagnosis of SCARs is the estimated prognosis, which has an impact on the therapeutic management. For evaluation of the mortality risk in SJS/TEN, the SCORTEN scale is recommended, which encompasses seven independent risk factors, namely age, associated malignancy, heart rate, involved body surface area, blood urea nitrogen level, serum bicarbonate and glucose [67]. As previous evaluations assessing its accuracy showed mixed results, two recent studies further investigated this issue. In a retrospective analysis of 128 patients with SJS/TEN, including

both adults and children, SCORTEN allowed good discrimination of differently affected patients but exhibited a low, nonsignificant mortality ratio [68]. Another retrospective, multicenter study of 370 patients proposed a modified score of only five parameters, namely age, affected body surface area, serum bicarbonate, active cancer and dialysis prior to admission, which accurately predicted mortality, whereas discrimination was not significantly different from SCORTEN [69]. Ultimately, a serum biomarker mirroring the prognosis of SJS/TEN patients would be the diagnostic parameter of choice. Here, the cytokine interleukin-15, which among others is produced by cytotoxic T as well as natural killer cells, recently has gained attention. In both Asian and European individuals suffering from SJS/TEN, of several elevated serological factors (interleukin-6, interleukin-8, interleukin-15, TNF- α , granulysin), only granulysin and interleukin-15 correlated with disease severity, with only elevated interleukin-15 values being significantly associated with increased mortality risk [70]. Interestingly, interleukin-15 augmented the cytotoxicity of patients blister cells and stimulated the release of granulysin and granzyme B, whereas its neutralization reduced drug-specific T-cell activation *in vitro*, suggesting an important role in the pathogenesis of SJS/TEN [71]. Thus, the significance of interleukin-15 in SJS/TEN deserves further attention, also regarding as a potential therapeutic target [72].

Apart from looking for diagnostic biomarkers, an important focus are measures to identify the culprit drug [73]. The ELISPOT-assay has been reported as a very sensitive measurement allowing the detection of one antigen-specific T cell among 300 000 peripheral blood mononuclear cells [74]. A recent review on in-vitro testing in drug allergy has emphasized the distinct value of this assay showing increased sensitivity compared to the LTT in patients with SJS/TEN and still being able to give conclusive results in individuals on immunosuppression [21]. This was also demonstrated in a study last year, comparing these two assays in 23 SCAR patients of whom 74% were positive for IFN- γ -secreting T cells in the ELISPOT-assay (with more than 50% taking systemic steroids), but only 52% by LTT [75[¶]]. Notably, in contrast to LTT, which was performed during the recovery phase, the ELISPOT-assay was undertaken during active disease, thus allowing very early identification of the responsible drug. Another lately report even found its sensitivity to be distinctly higher during the acute phase (79%; weeks 1–6 after onset) compared to thereafter (53%) [76].

As they carry a significant risk of mortality and long-term sequelae, prevention of CDHRs is of

utmost importance. Recently, relevant progress has been made in detecting genetic markers indicating an increased risk of developing particular types of SCARs to certain drugs. These markers mainly belong to the group of human leukocyte antigens (HLAs). Activation of cytotoxic T lymphocytes (CTLs) by keratinocytes displaying drug molecules in the context of HLAs on their surface is pivotal for the development of SCARs [77]. Several pathophysiologic mechanisms have been proposed, how CTLs become stimulated through an aberrant interplay of their T-cell receptor with HLA and drug molecules [78]. They include the hapten/prohapten model, in which a drug or its metabolite as a hapten or prohapten, respectively, becomes an antigen by binding to an endogenous protein; the p-i (pharmacological interaction with immune receptors) model postulating that the drug promotes an interplay with the T-cell receptor and its HLA-ligand by direct bond to either one; and the altered peptide model, in which the drug modifies the antigen-binding groove of an HLA in a way, that T-cell activating neo-epitopes can be displayed to the T-cell receptor. As the HLA composition is of particular significance in these models, structural modifications because of genetic variance have an essential effect on the potential interactions with drugs. Of note, the genes encoding HLAs are extremely polymorphic showing more than 8000 possible variants of HLA I molecules [79].

Examples of HLA-restricted drug reactions detected during the last years entail DRESS to carbamazepine in HLA-A*15:02, both DRESS and SJS/TEN to carbamazepine in HLA-B*31:01, DRESS to abacavir in HLA-B*57:01, SJS/TEN to allopurinol in HLA-B*58:01 and most recently DRESS to dapsone in HLA-B*13:01 patients [80[¶],81]. For the later, HLA*13:01-dependent activation of granulysin-secreting CTLs exposed to dapsone has just convincingly shown in a well-designed study with lymphocytes of patients who suffered from dapsone-induced DRESS [80[¶]]. Recent investigations documented that genetic testing has significantly increased in people with an ethnic background at risk, whereas cases of drug-induced SCARs have dropped, confirming the efficiency of these measures [82,83].

However, although there are significant associations between specific HLA alleles and drug-induced SCARs in certain ethnic groups, nowhere near all of individuals who come into question developing DRESS or SJS/TEN when exposed to the distinct drug become diseased, strongly arguing for additional needed factors. These could be environmental effects like danger signals provided by infections and/or additional genetic variables. For example, lately, it has been found in a retrospective

study that in individuals carrying certain HLA alleles in addition to HLA-B*58:01, namely HLA-B75 or DR14, or who were homozygous for DR13, the percentage of allopurinol-triggered SCARs rose from 3 to 22.2, 10.7 or 20%, increasing their odds ratio to experience DRESS to 19.568, 19.355 or even 38.458, respectively [84]. Furthermore, polymorphisms of other genes might also be of importance. Two recent independent genome-wide association studies among Korean patients point to genetic variants in the Fas signaling pathway as risk enhancing factors for developing SCARs [85], confirming a previous report of increased Fas gene polymorphisms in Japanese SJS/TEN patients [86]. As Fas signaling is discussed to be involved in the pathophysiology of SJS/TEN, these results suggest its dysregulation serving as a genetic predisposition for individuals at risk.

THERAPEUTIC MANAGEMENT

Therapeutic management of SCAR patients includes swift withdrawal of the offending drug, optimal supportive care and local treatment of skin lesions. For systemic therapy, corticosteroids are in general the mainstay. However, the appropriate treatment of SJS/TEN is a matter of intense discussion, because of variable outcomes of different therapies including corticosteroids, other immunosuppressants, intravenous immunoglobulins and plasmapheresis, the potential side-effects, especially of the former two, and the lack of data from well-designed, randomized prospective studies [87]. Recently, interesting results from several clinical trials have placed two agents as very promising options into focus, namely cyclosporine and the TNF- α inhibitor etanercept.

In 2017, four reports demonstrated a substantial reduction of the mortality rate in SJS/TEN patients treated with cyclosporine, with one study presenting results of a virtually randomized patient distribution among chosen therapies, comparing data of two burn units specialized in SJS/TEN treatment in Madrid, one utilizing cyclosporine, the other mainly supportive care [88]. These results and concurrent data from a systematic review [87] provided new evidence for the value of cyclosporine in the treatment of SJS/TEN patients [89]. A lately meta-analysis and a comprehensive literature review strongly support this perception. The former included nine studies performed between 2010 and 2017, which consisted of eight retrospective case series and one open phase II trial, encompassing a total of 255 patients [90]. Most patients were treated with a dosage of 3–5 mg/day for about 7–20 days, sometimes gradually tapered. The pooled standardized mortality ratio amounted to 0.32, strongly indicating that cyclosporine was able

to decrease mortality in SJS/TEN patients, although a publication bias was noticed. The literature review summarized 56 articles, including reviews, case series, guidelines and a meta-analysis [91[¶]]. Altogether, a significant survival benefit was seen for patients treated with cyclosporine, in comparison either to other therapies or to the expected death ratio. Frequent adverse events encompassed hypertension and nephrotoxicity, the latter of which led to the termination of cyclosporine treatment in 25% of patients in one study. In conclusion, treatment with 3 mg/kg/day as a starting dose was recommended, considering dose adjustments or discontinuation in patients with elevated serum creatinine (≥ 120 or $\geq 150\%$ baseline, respectively) or hypertension (diastolic blood pressure ≥ 100 or ≥ 110 mmHg/systolic blood pressure ≥ 160 mmHg, respectively).

TNF- α inhibitors have been proposed as a therapeutic option for SJS/TEN, as TNF- α promotes the release of granulysin and can induce Fas-mediated keratinocyte apoptosis [92]. Since 2002, several case reports, a few case series and two randomized controlled trials of a total of 91 SJS/TEN patients treated either with infliximab or etanercept have been published, as summarized in a very recent systematic review [93]. However, while most reports suggest treatment with TNF- α inhibitors an effective and safe therapy for SJS/TEN, their significance is largely hampered by the generally small numbers of patients, frequently given additional (immunosuppressive) therapies and missing controls. However, one study published last year clearly stands out as a well-designed prospective, open-label randomized controlled trial comparing two different drugs as monotherapies, here a corticosteroid (prednisolone i.v. 1–1.5 mg/kg/day) and a TNF- α inhibitor (etanercept s.c. 25 or 50 mg, depending on the body weight, twice a week), in a reasonably high number of SJS/TEN patients (33 and 38, respectively) [94[¶]]. Individuals (median age 56.09 $\pm$ 20.81 years) were relatively evenly distributed among both groups with 39.5% of the steroid-treated cohort and 37.5% of the etanercept cohort showing $\geq 10\%$ of their body surface skin detached. Compared to systemic corticosteroids, etanercept treatment demonstrated a shorter skin healing time (14 vs. 19 days for complete reepithelialization; $P=0.01$), an equal safety profile but lower incidence of gastrointestinal hemorrhages (2.6 vs. 18.2%, $P=0.03$) and a – although not significant – reduced mortality rate (8.3 vs 16.3%). Notably, levels of granulysin and TNF- α decreased in both plasma and blister fluid, whereas the frequency of plasma regulatory T cells increased during anti-TNF therapy, all in all arguing for TNF- α blocker as a treatment option for SJS/TEN.

A different aspect of proper care for SCARs patients which has only little attention paid to until recently is treatment in the chronic phase, after patients have been dismissed from the hospital. A study following SJS/TEN survivors for up to 10 years listed frequent cutaneous and ophthalmologic sequelae like scarring, post-inflammatory skin changes, dry eyes, chronic ocular surface inflammation and symblepharon [95]. However, other internal organs, such as the respiratory or gastrointestinal tract, may also be affected. For example, bronchiolitis obliterans has been reported lately both in an adult and children as a delayed complication [96,97]. Furthermore, psychological consequences have to be considered, which even could be aggravated by often experienced chronic fatigue and pruritus. A prospective study revealed that almost one quarter (23%) of the investigated SJS/TEN patients suffered from posttraumatic stress disorder 6 months after the acute phase [89]. Thus, long-term and interdisciplinary follow-up of SCARs patients including a systematic psychiatric evaluation for at least 1 year has been recommended [98*,99].

CONCLUSION

Although CDHRs are common, they are still not fully understood and several aspects of their management remain unstandardized. Disseminated CDHRs to classical drugs can be classified by a simple algorithm, but chemotherapeutics and biopharmaceuticals can present individual clinical pictures. Many controversies in drug hypersensitivity diagnosis exist, such as about the benefit of in-vitro tests, value and standardization of skin tests, necessity for skin tests before performing DPT, need of prolonged DPTs, how to diagnose BLA in an outpatient or in an inpatient with urgent need for β -lactams and how much risk patients with mastocytosis have of drug hypersensitivity. Furthermore, the value of in-vitro assays in the diagnosis of drug-induced SCARs, identification of culprit drugs and for genetic screening of individuals at risk are debated. Also, new therapeutic options for better treatment of SCAR patients are controversially discussed. Recent literature has contributed to our understanding of clinical manifestations, existing controversies, novel opportunities and future needs in this area.

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There are no conflicts of interest.

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