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REVIEW ARTICLE

Drug-Induced liver Injury Associated with Severe Cutaneous Hypersensitivity Reactions. A Complex Entity in Need of a Multidisciplinary Approach

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Abstract: Idiosyncratic drug-induced liver injury (DILI) occasionally occurs in the setting of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). This strengthens the proposed immunologic mechanism associated with this adverse reaction. DRESS exhibits the most common association with DILI. SCARs have a wide spectrum of heterogeneous clinical presentations and severity, and genetic predisposition has been identified. In the context of SCARs, DILI present a different clinical picture, ranging from mild injury to acute liver failure. Elucidating the role of DILI in the clinical presentation and outcome of SCARs represents a challenge due to limited information from published studies and the lack of consensus on definitions. The cholestatic and mixed pattern of liver damage typically predominates in the case of DILI associated with SCARs, which is different from DILI without SCARs where hepatocellular is the most common injury pattern. Only a few drugs have been associated with both DILI and SCARs. Is this article, the criteria used for DILI recognition among SCARS have been revised and discussed, along with the drugs most commonly involved in these syndromes as well as the outcome, prognostic factors and the need for a multidisciplinary approach to improve the management of DILI in the context of SCARs.

Keywords: Drug-induced liver injury, severe cutaneous adverse reactions, toxic epidermal necrolysis, liver injury, hypersensitivity reactions, hepatocellular.

1. INTRODUCTION

Idiosyncratic (unpredictable, specific to an individual) drug reactions are often life-threating. They can targ*et al*most any organ, however, the skin, blood cells and liver are the most commonly affected, being a major concern among clinicians and health authorities. Idiosyncratic drug-induced liver injury (DILI) is a rare adverse reaction to drugs and other xenobiotics and a challenging liver disorder due to the presence of a wide range of clinical and pathological phenotypes and the absence of specific diagnostic biomarkers. While an immune mechanism of liver damage has long been considered to occur in a fraction of DILI cases as a downstream event, genome-wide association (GWA) studies in the recent years have identified class I and II human leukocyte antigen (HLA) alleles that influence the susceptibility to DILI due to a variety of drugs [1]. This underscores the important role of the adaptive immune system at the early stages of the damage occuring in the cellular cascade, even in instances where clinical manifestations, suggesting an immune-mediated damage, are absent [2]. Indeed, DILI usually occurs without typical hypersensitivity features (rash, fever or peripheral eosinophilia, which occur with a frequency ranging from 15% to 23% [3, 4]. However, these features are important because they highlight the immune-allergic reaction to drugs during the DILI causality assessment [5]. In addition, DILI is more commonly related to the anti-infective pharmacological group across large prospective DILI cohorts in Western countries and India [3, 4, 6].

Moreover, DILI can occur in the setting of systemic symptoms of a more generalized immune-allergic syndrome in which liver damage may not be the most prominent manifestation, instead skin reactions typically dominate the clinical picture. Severe cutaneous adverse reactions (SCARs) can manifest in a spectrum of heterogeneous clinical presentations with severity ranging from exanthema to Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN), including drug reactions with eosinophilia and systemic symptoms (DRESS). These syndromes display some common characteristics, such as the delayed onset of symptoms after drug initiation and a strong genetic association involving the HLA region, which underscores the relevance of immune pathogenesis [7-9]. An intriguing peculiarity of these types of reactions is that drugs do not have a common signature. Instead, some patients develop a liver injury, skin reactions, or both. So far, the HLA-A*31:01 allele been identified as a risk allele only for carbamazepine, shared by both SCARs and DILI clinical phenotypes [10]. Clearly, the number of causative drugs associated with SCARs and DILI is limited, with the most commonly involved therapeutic groups being anti-infective, anti-epileptics drugs and allopurinol [11-13].

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In the existing literature on serious cutaneous adverse reactions related to drugs, the associated liver injury has often been overlooked and/or inconsistently defined. In this review, idiosyncratic DILI is discussed in the setting of drug-induced hypersensitivity syndrome, its phenotypic presentation, culprit drugs and the outcome and analysis of the pathogenesis and genetic risk factors.

2. DEFINITIONS AND DIAGNOSTIC CRITERIA

2.1. Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

SJS and TEN are considered a type of delayed-hypersensitivity-T-cell-mediated reaction and are the most serious conditions among SCARs [14]. They occur with a similar spectrum of adverse cutaneous reactions and are distinguished by the affected body surface area (BSA). The current classification proposed by French in 2006 is more clear : SJS is defined as an area of skin detachment below 10% of the BSA, TEN is detachment above 30% of the BSA and SJS/TEN overlap is when detachment affects 10% - 30% of the BSA [15]. The Phenotype Standardization Project provided a consensus definition of these phenotypes [16]. Clinical presentation includes a prodromal phase (fever, malaise), followed by painful cutaneous and mucous membrane lesions (ocular, oral and genital) with severe, often hemorrhagic, erosions of the mucous membrane. Mucocutaneous involvement and complete epidermal necrosis are typical pathological features of SJS/TEN. Other systemic manifestations can also occur, such as secondary internal organ involvement (mainly renal, but also pulmonary and hepatic involvement is frequent) [16,17].

2.2. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

This immune-mediated reaction occurs with variable clinical phenotypes and severity. The multinational Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) [18] states that DRESS cases must have at least three of the following systemic features: acute skin rash, fever above 38ºC, enlarged lymph nodes, internal organ involvement, or hematological abnormalities, including lymphocytosis, lymphocytopenia, eosinophilia or thrombocytopenia. The terminology of this hypersensitivity-drug reaction is controversial, and the acronym DRESS is still questioned, as eosinophilia is not a mandatory criterion in this syndrome. DRESS is a diagnosis of exclusion that presents different skin features, predominantly urticaria and exanthema, among others. The extent of skin detachment is variable [16, 19]. Other terms used to describe the hypersensitive cutaneous adverse reactions include hypersensitivity syndrome (HSS), drug-induced hypersensitivity syndrome (DIHS) or drug-induced delayed multiorgan hypersensitivity syndrome (DIDMOHS) [16].

2.3. Liver Injury Associated with SCARs

The liver is the organ most frequently involved in SCARs. The criteria for the definition of DILI used among the different studies on SCARs are quite variable. Although every liver injury associated with SCARs is assumed to be DILI, other potential liver diseases were not excluded in the majority of retrospective studies, which focused on skin toxicities (Table **1**).

The most widely recognized and accepted definition of DILI was proposed by an international expert group consensus, which recommended specific serum aminotransferase cut-off points for case qualification, which take into account the current high prevalence of nonalcoholic fatty liver disease (NAFLD) or mild increases in transaminases that usually resolve during treatment and exhibit an adaptive response, in order to avoid false-positive cases [20,21]. However, even DILI definitions adopted in prospective DILI registries and DRESS/SJS/TEN studies show significant variations ranging from very strict criteria [3, 11, 22] to a wide range of liver biochemical alterations [12, 23, 24], unspecific information, such as transaminitis [25, 26] or undefined [27] (Tables **1** and **2**).

According to the criteria used in the RegiSCAR study, the associated liver dysfunction in DRESS is defined as alanine aminotransferase (ALT) >2 × ULN (upper limit of normal) or conjugated bilirubin >2 x ULN on at least 2 successive dates or aspartate aminotransferase (AST), total bilirubin and alkaline phosphatase levels all >2 × ULN [18]. In the prospective DRESS study by Walsh *et al*. [28], liver injury definition was very similar to the RegiSCAR study except for the presence of increases in gamma-glutamyl transpeptidase (GGT) values in the diagnostic criteria. Thus, the lack of harmonization of the DILI criteria makes it difficult to compare the studies with regard to severity and outcome as some may consider patients with only mild elevations in liver biochemistries.

On the contrary, in different DILI registries, the definitions of liver injury have more stringent pre-established thresholds [20,21]. The US DILIN study reported jaundice (serum bilirubin 2.5 mg/dL) or coagulopathy (international normalized ratio >1.5) with elevations in ALT, AST or ALP levels; or, in the absence of jaundice or coagulopathy, elevations of ALT or AST >5 x ULN or ALP >2 x ULN were observed [3]. In the Indian registry [29], SJS/TEN associated liver dysfunction was considered when patients fulfilled any of the following criteria, AST or ALT >3 x ULN with symptoms; AST or ALT >5 x ULN; ALP >2 x ULN; TB >2 mg/dL with AST/ALT or ALP elevated.

2.4. Causality Assessment

The Algorithm for Drug Causality for Epidermal Necrolysis (ALDEN) is used for SJS/TEN causality assessment. ALDEN is a widely used clinical diagnostic tool that categorizes drugs into different grades of probability: very probable, probable, possible, unlikely, and very unlikely [30]. However, the need for refinement of this scale to improve its validity and objectivity has recently been suggested [31]. For the characterization of DRESS cases, the RegiSCAR study group has established the precise criteria for its evaluation and assessment [18]. The standard liver-specific diagnostic tool for DILI causality assessment is the CIOMS (the Council for International Organizations of Medical Sciences) / RUCAM (Roussel Uclaf Causality Assessment Method) scale that does not take into account the presence of immunoallergic manifestations and efforts are ongoing to improve its performance [32]. Interestingly, the general Naranjo Adverse Drug Reactions Probability Scale lacks validity and should not be recommended in DILI ascertainment [33].

3. OVERVIEW OF DILI IN THE SETTING OF SEVERE CUTANEOUS ADVERSE REACTIONS

Most of the available information of DILI associated with SCARs comes from retrospective studies on limited cohorts of SCARs patients [11-13, 23, 24, 26, 27, 34, 35] (Table **1**). These studies were mainly from Asia (Singapore, Korea Taiwan and Thailand) and scarcely from Europe and Oceania (France and Australia), indicating that this type of cutaneous adverse reaction is more frequent in Asians. To our knowledge, no study from Africa has been published so far, but there are studies that include African patients [35, 36]. The number and characteristics of the included patients varied among studies. Only one study included pediatric patients (n =10) [26]. The largest study on SJS/TEN including 76 cases was conducted using cross-linkage of multiple databases [11].

In prospective studies (Table **2**), most of the information came from DILI registries and two other prospective DRESS cohorts. Prospective DILI registries include the Spanish DILI Registry [22] , Latin-American DILI Registry [22], the US DILIN study [3] and the Indian Registry [29]. The number of DILI patients with SCARS was small, except for the RegiSCAR study, which is the largest international registry in which 8 countries participated: Austria,

Table 1. Retrospective studies addressing severe cutaneous adverse reactions (SCARs) and drug-induced liver injury (DILI).

	Han, Koh and Wong, 2019[26] Singapore, Pediatric population	**Fang *et al*, 2018[11] Australia**	**Hiransuthi-kul *et al*, 2016[27] Thailand**	**Skowron *et al*, 2015[23] France**	**Lin *et al*, 2015[13] Taiwan**	**Lee *et al*, 2013[12] Korea**	**Su *et al*, 2014[25] Singapore**	**Chen *et al*, 2010[24] Taiwan**	**Ang *et al*, 2010[34] Singapore**	**Eshki *et al*, 2009[35] France**
Years	2006 – 2016	2004-2014	2004-2014	2005-2013	2000-2013	2008-2011	2007-2011	1998-2008	2003-2008	1995-2006
N of SCARs	10	104	52	45	72	136	42	60	27	15
Total DRESS cases, N N, (%) with liver injury	10 10 (100%)	12 6 (50%)	52 49 (94.2%)	45 24 (53%)	72 62 (86%)	33 29 (70%)	2 2 (100%)	60 48 (80%)	27 26 (96.3%)	15 9 (60%)
Total SJS/TEN cases, N N, (%) with liver injury	-	76 23 (36%)	-	-	-	30 11 (30%)	30 4 (13%)	-	-	-
DRESS manifesta-tions										
Time to onset days, mean (range)	19.6 (5 - 42)	ND	16 (median) (9-27)	ND	ND	ND	22.5 (15-30)	20.7 (3-37)	26.7 (3-84)	ND
Acute skin eruption (%)	Rash (100%), Desquama-tion, purpura	Acute general-ised exanthe-matous pustu-losis (10.6%), Linear IgA bullous der-matosis (1.9%), Erythema multiforme (2.9%)	Rash (100%)	Spongiosis (55%) keratino-cyte damage (53%)	Skin eruption (100%)	Rash (100%)	Rash (100%)	Diffuse exanthema-tous eruption (100%); Exfoliative dermatitis (12%); Blistering or purpuric eruption (10%)	Morbilli-form cuta-neous erup-tion (81.5%)	Exanthema (100%)
Fever, (%)	Yes (100%)	ND	Yes (78.8%)	Yes (95%)	Yes (79%)	ND	ND	Yes (87%)	Yes (77.8%)	ND
Edema, (%)	Facial edema (40%) Lip swelling (20%)	ND	Facial edema (7.7%), periorbital edema (5.8%)	Facial edema (72%)	No	ND	ND	ND	Facial ede-ma (33%)	Facial edema (100%)
Eosino-philia (>500/ µL), (%)	Yes (70%) (>0.78 $\times 10^9$/L)	Yes (54%)	Yes (57.7%)	Yes (97%) (> 700/ µL)	Yes (58%) (≥ 700/ µL)	Yes (38%)	ND	Eosinophilia (52%)	Yes (81.5%)	ND

Table 1 contd....

	Han, Koh and Wong, 2019[26] Singapore, Pediatric population	**Fang *et al*, 2018[11] Australia**	**Hiransuthikul *et al*, 2016[27] Thailand**	**Skowron *et al*, 2015[23] France**	**Lin *et al*, 2015[13] Taiwan**	**Lee *et al*, 2013[12] Korea**	**Su *et al*, 2014[25] Singapore**	**Chen *et al*, 2010[24] Taiwan**	**Ang *et al*, 2010[34] Singapore**	**Eshki *et al*, 2009[35] France**
Lymphocyte activation, (%)	Atypical lymphocyte (90%) Lymphadenopathy (80%)	Periferal lymphocytosis (45.5%)	Lymphopenia (51.9%) Atypical lymphocyte (26.9%) Lymphocytosis (26.9%)	Atypical Lymphocytes (82%) Enlarged lymph nodes (51%)	Lymphocytosis (68%)	Lymphadenopathy (23%)	Leukocytosis/ eosinophilia (54.3%)	Atypical lymphocytes (63%) Lymphocytopenia (45%) Lymphocytosis (25%)	Lymphopenia (32%) Atypical lymphocytosis (18%)	Lymphadenopathy (100%)
Organ involvement other than liver, (%)	Myalgia (10%) CNS (drowsiness, rotatory nystagmus) (10%) Abdominal/epigastric pain (20%)	ND	Kidney (15.4%) Lung (3.8%) Other (1.9%)	Kidney (31%)	ND, Focused on description liver injury	Kidney (39%) Lung (11%) Pancreas (5%)	GI System (13%)	Kidney (40%) Lung (33%) Cardiac (15%) Pancreas (5%)	Kidney (14.8%)	Kidney (33%) Lung (67%)
HVV-6 reactivation	5 evaluated, 1 positive	ND	ND	Yes (16%)	No	ND	ND	No	ND	7 evaluated, 6 positive
DILI criteria	Transaminitis	(Aithal *et al*, 2011)	ND	RegiSCAR criteria	RegiSCAR criteria	AST or ALT >40 IU/L, ALP>120 IU/L, TB>1.2 mg/dL, or PT>1.3 INR	Transaminitis	Liver enzymes >2xULN	Elevation of serum transaminases	ND
DILI characteristics, N (%)										
Age, years, mean (range)	11.2 (4 – 17)	55 (median) (45-66)	33 (median) (2-86)	64 (median) (3-87)	49 (median) (6-88)	53	47 (11-71)	51 (6-90)	49 (18-86)	38 (15-71)
Female, N (%)	4 (40)	14 (42)	37 (71)	25 (55)	33 (53)	28 (46)	3 (50)	34 (56)	14 (54)	6 (67)
Time to DILI onset, days; mean (range)	ND	ND	16 (9-27)	ND	ND	22.5	ND	21 (3-76)	ND	ND

Table 1 contd....

	Han, Koh and Wong, 2019[26] Singapore, Pediatric population	**Fang *et al*, 2018[11] Australia**	**Hiransuthi-kul *et al*, 2016[27] Thailand**	**Skowron *et al*, 2015[23] France**	**Lin *et al*, 2015[13] Taiwan**	**Lee *et al*, 2013[12] Korea**	**Su *et al*, 2014[25] Singapore**	**Chen *et al*, 2010[24] Taiwan**	**Ang *et al*, 2010[34] Singapore**	**Eshki *et al*, 2009[35] France**
Jaundice, N (%)	1 (10)	8 (27)	ND	ND	ND	ND	ND	ND	ND	ND
Type of liver injury, N (%)	ND	Hep 10 (30) Mix 23 (70)	ND	ND	Hep 12 (19) Chol 23 (37) Mix 17 (27) Unknown 10 (17)	ND	ND	ND	ND	ND
Severity	ND	Severe 6 (18.2%)	ND	Identify severe (transa-minases >5 ULN)	Identify extreme group (transa-minases > 10 xULN)	38 severe liver dys-function (AST or ALT ≥80 IU/L)	ND	ND	ND	ND
Recovery (%)	100%	64%	96.1%	93%	100%	88%	100%	90%	100%	67%
ALF/Death, N	0/0	2/1	1/1	0/0	0/0	0/0	0/0	0/0	0/0	1/1
Total death, N	0	12	2	3	0	7*	1*	6	0	3
Culprit drugs, N										
SJS/TEN	-	-	-	-	-	Allopurinol (3) NSAIDs (3) Anticon-vulsants (1) Antineo-plastics (1)	Allopurinol (5) Ceftriaxone (4) Cefazolin (2) Carba-mazepine (3)	-	-	-
DRESS, hepatitis	Trimethoprim-sulfamethoxa-zole (3) carbamazepine (2), phenobarbi-tone (2), sulfasalazine (1) amoxicillin-clavulanic acid (1) Levetiracetam (1)	Cepha-losporins (8), Vancomycin (7), Penicillins (6), Nevirapine (3), Trimethoprim /sulfamethoxa zole (3) Lamotrigine (2), Phenytoin (2	Phenytoin (12) Nevirapine (9) Allopurinol (8) Cotri-moxazole (7)	Antibiot-ics (23) Antiepi-leptics (5) Allopuri-nol (5)	Allopurinol (15) Phenytoin (10) Sulfona-mides/ sulfones (13) Dapsone (8) Carba-mazepine (7)	Beta-lactam (7) Allopurinol (3) NSAIDs (2) Sulfona-mide (2) Anticon-vulsants (2)	Allopurinol (1) Phenytoin (1)	Allopuri-nol (19) Phenytoin (11) Dapsone (10) Carba-mazepine (3) Cotrimox-azole (3)	Allopurinol (6) Phenytoin (4) Carba-mazepine (4) Pyrimeth-amine and dapsone (4) Trimethoprim - sulfamethoxa-zole (4)	Al-lopurinol (3) Mino-cycline (2)
Causality assess-ment, N (%) score	ND	Naranjo *et al* ALDEN	A modifica-tion of WHO-UMC causality categories	ND	ND	WHO-UMC causality assessment	ND	Criteria of Naranjo	Based on the patient's history	ND

*Do not specify if the cause of death is liver related. DILI criteria Aithal *et al,* 2011: ALT ≥5xULN or ALP ≥ 2xULN or ALT ≥3xULN and TB ≥2 mg/dL. RegiSCAR criteria: (ALT>2xULN or TB>2 on at least 2 different dates or AST>2xULN or ALP and TB elevated on at least one date). Severe DILI: elevated ALT/ALP reaching criteria for DILI and bilirubin≥2xULN and one more of the following: INR ≥1,5; ascites and/or encephalopathy; disease during<26weeks and absence of underlying cirrhosis; Any other organ failure considered to be due to DILI. Abbreviations: ALDEN: Algorithm for Drug Causality for Epidermal Necrolysis; Chol: cholestatic.DRESS: Drug reaction with eosinophilia and systemic symptoms; GI: gastrointestinal; Hep: hepatocellular; Mix, mixed; ND: no data; RegiSCAR: International Registry of Severe Cutaneous Adverse Reactions; RUCAM: Roussel Uclaf Causality Assessment Method; SJS: Stevens Johnson syndrome: skin detachment <10%; TEN: toxic epidermal necrosis: skin detachment >30% plus widespread purpuric macules or flat atypical targets; WHO-UMC: World Health Organization-Uppsala Monitoring Center.

Table 2. Prospective studies addressing severe cutaneous adverse reactions (SCARs) and drug-induced liver injury (DILI)

	Spanish DILI Registry, 2018[22] N=920	**Latin-America DILI Registry, 2018[22] N=300**	**Indian Registry, 2016[29] N=748**	**DILIN, 2015[3] USA N=899**	**RegiSCAR, 2013[18] Multinational[≠] N=201**	**Walsh *et al,* 2013[28] UK N=27**
Years	1994-2018	2011-2018	1997-2014	2004-2013	2003-2009	2005-2011
N of SCARs	35	18	36	9	117	27
Total DRESS cases, N N, (% with liver injury)	32 32 (100%)	18 18 (100%)	-	-	117 86 (74%)	27 27 (100%)
Total SJS/TEN cases, N N, (% with liver injury)	3 3 (100%)	-	36 36 (100%)	9 9 (100%)	-	-
DRESS manifestations						
Time to onset days, mean (range)	ND	ND	24 (5-50)	ND	22 (median)	27 (10–49)
Acute skin eruption (%)	Rash (100%)	Rash (100%)	Rash (100%)	Rash (100%)	Rash (100%)	Urticated papular exanthema (48%) Erythema multi-forme-like (30%) Morbilliform erythema (11%) Exfoliative erythroderma (11%)
Fever, (%)	Yes (31%)	Yes (78%)	ND	ND	Yes (90%)	Yes (100%)
Edema, (%)	ND	ND	ND	ND	Yes (76%)	23 (85%)
Eosinophilia (>500/ µL), (%)	Yes (83%)	Yes (72%)	ND (Eosinophils 8%)	No	Yes (95%) (≥ 700/ µL)	Yes (93%) (>400/ µL)
Lymphocyte activation, (%)	Lymphopenia (46%)	Lymphopenia (22%)	ND	ND	Atypical lympho-cytes (67%), Lymphade-nopathy (54%)	Lymphadenopathy (89%)
Organ involvement other than liver, (%)	No	No	No	No	Kidney (37%) Lung (32%)	Kidney (7%) Cardiac (4%)
HVV-6 reactivation	ND	ND	ND	ND	58 evaluated, 21 positive	ND
DILI criteria	(Aithal *et al*, 2011)	(Aithal *et al*, 2011)	AST or ALT>3xULN + symptoms AST or ALT>5xULN or ALP>2xULN or TB >2 mg/dL with AST/ALT or ALP elevated	ALT or AST>5xULN or ALP>2xULN; in presence of jaundice or coagulopathy with any levels of ALT, AST, ALP	RegiSCAR criteria	Transaminase > 2xULN on two successive dates or bilirubin > 2xULN on two successive dates or AST, GGT and ALP > 2xULN at least once

(Table 2) Contd....

	Spanish DILI Registry, 2018[22] N=920	**Latin-America DILI Registry, 2018[22] N=300**	**Indian Registry, 2016[29] N=748**	**DILIN, 2015[3] USA N=899**	**RegiSCAR, 2013[18] Multinational[≠] N=201**	**Walsh *et al*, 2013[28] UK N=27**
DILI characteristics, N (%)						
Age, years, mean (range)	53 (16-82)	42 (16-76)	32	33 (11-60)	48 (median)	40 (2-68)
Female	16 (46)	10 (56)	19 (53)	7 (77)	65 (55)	17 (63)
Time to DILI onset, days; mean (range)	39 (5-121)	28 (2-60)	ND	24 (2-64)	16 (9-27)	ND
Jaundice, (%)	25 (71)	13 (72)	22 (61)	8 (89)	ND	ND
Type of liver injury, N (%)	Hep 16 (46) Chol 7 (20) Mix 12 (34)	Hep 7 (39) Chol 6 (33) Mix 5 (28)	Hep 13 (36) Mix 18 (50) Chol 5 (14)	Hep 7 (78) Mix 2 (22)	ND	ND
Severity, N (%)	Severe 2 (6)	Severe 4 (22)	Severe 21 (58)	Severe[#] 3 (33)	ND	ND
Recovery, N (%)	35 (100)	18 (100)	23 (64)	5 (56)	84 (98)	24 (89)
ALF/Death, N	0/0	0/0	4/13*	0/1	0/0	2/0
Total death, N	0	0	13*	4	2*	3*
Culprit drugs, N						
SJS/TEN	Ciprofloxacin (1) Ibuprofen (1) Carbamazepine (1)	-	Phenytoin (8) Nevirapine (6) Dapsone (5) Carbamazepine (4)	Lamotrigine (2) Azithromycin (2) Carbamazepine (1), Moxifloxacin (1), Cephalexin (1), Diclofenac (1), Nitrofurantoin (1)	-	-
DRESS, hepatitis	Amoxicillin-clavulanate (7) Carbamazepine (2) Allopurinol (2) Sulfamethoxazole and Trimethoprim (2)	Carbamazepine (3) Allopurinol (2) Lamotrigine (2)	-	-	Carbamazepine (23) Allopurinol (21) Sulfasalazine (8) Phenytoin (8) Lamotrigine (8)	Phenytoin (6) Carbamazepine (6) Minocycline (3) Sulfasalazine (3) Allopurinol (2)
Causality assessment N (%) score	RUCAM 14 (40) highly probable 17 (49) probable	RUCAM 2 (11) highly probable 10 (56) probable	RUCAM 18 (50) probable 18 (50) highly probable ALDEN 17 (47.2) probable 19 (52.7) very probable	DILIN Causality Committee 235 (22) definite 466 (43) highly likely 198 (18) probable	Expert decision by consensus 39 (33) very probable 54 (46) probable	DRESS classification scoring system 14 (52) probable 13 (48) definite

*Do not specify if the cause of death is liver related.

[≠]Multinational: Austria, England, France, Germany, Israel, Italy, Taiwan and the Netherlands.

DILI criteria Aithal *et al*, 2011: ALT ≥5xULN or ALP ≥ 2xULN or ALT ≥3xULN and TB ≥2 mg/dL. RegiSCAR criteria: (ALT>2xULN or TB>2 on at least 2 different dates or AST>2xULN or ALP and TB elevated on at least one date). Severe: elevated ALT/ALP reaching criteria for DILI and bilirubin≥2xULN and one more of the following: INR ≥1,5; ascites and/or encephalopathy; disease during<26weeks and absence of underlying cirrhosis; Any other organ failure considered to be due to DILI. [#]severe: jaundice and signs of hepatic or other organ failure

Abbreviations: ALDEN: Algorithm for Drug Causality for Epidermal Necrolysis; Chol: Cholestatic; DRESS:Drug reaction with eosinophilia and systemic symptoms; Hep, Hepato-cellular; Mix, mixed; .ND: no data; RegiSCAR: International Registry of Severe Cutaneous Adverse Reactions; RUCAM: Roussel Uclaf Causality Assessment Method; SJS: Stevens Johnson syndrome: skin detachment <10%; TEN: toxic epidermal necrosis: skin detachment >30% plus widespread purpuric macules or flat atypical targets.

England, France, Germany, Israel, Italy, Taiwan and the Netherlands. In most of the published retrospective and prospective studies analyzed, DRESS cases are more frequent than SJS/NET. In the largest cohort of SJS/TEN from a DILI Registry in India [29], only 36 patients were included. As expected, more comprehensive information on liver involvement in SCARs was reported in the prospective DILI registries (Tables **1** and **2**) except for the unique retrospective study by Lin *et al*. [13] that aimed to analyze the characteristics of liver injury in DRESS.

The causality assessment approach that was used differed among the studies. Lee *et al*. [12] used the WHO Uppsala Monitoring Centre causality categories, Chen *et al*. [24] employed the criteria of Naranjo *et al*., while Fang *et al*. [11] used both the Naranjo and ALDEN scores. However, in other studies, it was unclear which approache was used for case ascertainment.

The reported DILI prevalence varies among different types of SCARs. Consistent with the literature, in patients with DRESS, the liver was the most commonly involved organ in 50% to 100 % of the cases (Tables **1** and **2**). On the contrary, only 17% to 31% of the published showed that liver was the most affected organ in SJS/TEN patients. Noticeably, these figures were influenced by the DILI definition applied to each study.

4. CLINICAL PHENOTYPES AND OUTCOME OF DILI ASSOCIATED WITH SCARS

While acknowledging that the liver is the organ that is the most frequently involved in hypersensitivity syndromes caused by drugs, its full characterization has been relatively neglected so far in the existing literature with regard to the dominant cutaneous involvement.

4.1. Demographic Data

The mean age of patients presenting DILI associated with SCARs ranged from 32 to 64 years (Tables **1** and **2**). The lower mean age observed in the US DILIN [3] and the Indian DILI registry [29] can be explained by the inclusion of pediatric patients. In general terms, females are overrepresented compared to males in the majority of published studies, representing up to 71% of the cases. Despite that, the comparison of DRESS patients with and without liver involvement does not support the hypothesis that female sex is a risk factor for DILI [11,12] (Tables **1** and **2**).

4.2. Clinical Presentation

DRESS has a heterogeneous presentation with a broad spectrum of clinical features. Studies conducted in different geographic areas also display some individual and unique features, possibly reflecting the differences caused by diagnostic criteria, genetic factors, ethnicity, drugs involved and the healthcare systems, among others. Unfortunately, comparisons among different SCARs cohorts [28, 37] do not provide detailed information on liver involvement.

The typical course of DRESS is that it presents prodromal symptoms, such as fever and itching, followed by variable cutaneous eruptions and lymphadenopathy; subsequently, systemic symptoms occur, including gastrointestinal, hepatic, renal, cardiac, hematological, neurologic and thyroid [16, 19]. However, in the study by Lin *et al*., liver injury preceded skin eruption in 9.7% of the patients, suggesting that there might be some mild liver injury during the early prodromal phase, which could go unnoticed [13]. On the other hand, Lee *at al*. reported that patients with SJS/TEN presented hepatic involvement characterized by biochemical abnormalities without clinical jaundice. Therefore, future studies should determine the time of the onset of liver abnormalities compared to skin toxicity.

The time to the onset of DRESS (drug-rash presentation) is between 2 to 8 weeks; however, information related to the time to DILI onset is limited. The median latency reported by the prospective RegiSCAR study was 22 days (IQR 17-31), however, it has been suggested that it may vary depending on the culprit drug [18]. In prospective cohorts from DILI registries, the average time to DILI onset ranges from 28 to 39 days, but information regarding the onset of cutaneous involvement is lacking. On the other hand, SJS/TEN seems to have a shorter time to the onset of rash compared to DRESS, *i.e*. between 5 to 28 days (ALDEN causality assessment criteria). In the prospective Indian DILI cohort of SJS/TEN cases, the average time to DILI onset was 24 days, while in the US DILIN study, it was 14 days [3, 29]. Therefore, the time to DILI onset in patients with SJS/TEN is shorter than that in DILI patients without skin reactions, typically ranging for 60 to 90 days [3, 4, 38].

Information regarding the type of liver injury among patients from retrospective SCARs cohorts is very limited. Apparently, mixed/cholestatic (up to 64% of cases) pattern of liver damage is the most common among SCARs, particularly in DRESS cases [11, 13]. In the majority of prospective DILI cohorts, the predominant type of liver damage is hepatocellular (>60% of DILI cases), while cholestatic and mixed cases raised up to 40% of DILI cases (3,4). Similar to what has been described for DILI [39], SCARs patients with cholestatic-type of injury were older [13]. The pattern of liver damage reported in association with SJS/TEN has been less consistent, with a predominant mixed/cholestatic pattern (64%) in India [29], while in the US DILIN cohort it was mainly hepatocellular (78%) [3]. These differences could reflect the signature of the different culprit drugs involved in liver injury. In fact, in a limited number of cases, the liver injuries in allopurinol-DRESS and phenytoin-DRESS were of the cholestatic-type, whereas most of the patients with liver injuries in carbamazepine-DRESS and sulfonamide/sulfones-DRESS had a hepatocellular or mixed type of injuries [12, 13]. Indeed, recent data from 123 patients with DRESS provided evidence that the occurrence of hepatitis, latency period and severity of the reaction differs according to the culprit drug [40]. In addition, the type of liver injury reported partially depends on the time when the injury occurred, as hepatocellular cases tend to progress towards mixed or even cholestatic pattern later in the follow-up [41,42]. The assumption that the type of liver injury may differ according to the drug-hypersensitivity phenotype needs further research.

4.3. Severity

Characterizing the severity of the liver injury in the course of SCARs presents a challenge since it depends on the severity criteria applied and available information. Among the retrospective DRESS cohorts, the severity definitions applied were inconsistent and inappropriate as some were only based on the low transaminase elevations (Table **1**). Despite these limitations, a retrospective Korean study reported [12] that more severe and prolonged hepatocellular injuries were more frequent in DRESS compared to SJS/NET. In contrast, the definition of severity is consistent across DILI Registries and is based on the International Consensus Criteria [20], which include a category where patients must meet at least one of the following criteria: INR >= 1.5, ascites, encephalopathy or other organ failures due to liver injury. Among the DRESS patients, the frequency of severe cases ranged from 6% to 22% (Spanish DILI Registry and Latin-American DILI Registry, respectively), while in SJS/TEN, higher frequency of the severe cases was reported ranging from 33% to 58% (US DILIN and Indian registry, respectively), as well as 2 ALF cases were reported by the Indian registry (Table **2**).

It has been suggested that a relationship between dermatological features and the severity of the liver damage exists. However, this association is difficult to assess because of the heterogeneous pattern of cutaneous involvement and skin biopsy findings. In a small study, patients with histological findings of basal cell vacuolar degeneration and necrotic keratinocytes more frequently had an

erythema multiforme (EM)-like cutaneous phenotype and more severe hepatic involvement. Three patients died, in which 2 died due to unsuccessful liver transplantation [28].

Available histological information on 7 out of 16 patients with acute liver failure (ALF)-DRESS in a study showed the presence of activated and irregular lymphocytes with a cytotoxic phenotype [43], the origin of which is unclear, although the authors proposed that those observed in the peripheral blood, skin and liver were triggered by a combination of both anti-drug and anti-viral immune responses. Eosinophils were observed inconsistently, while Kupffer cell hyperplasia with erythrophagocytosis was an unexpected finding. The most extensive necrosis (40% and 90%) was observed in 2 patients who required liver transplant [43].

4.4. Outcome & Prognostic Factors

SCARs can be severe, leading not only to skin detachment and subsequent infectious complications but also to multiorgan failure and significant mortality. The estimated mortality rate of SJS patients is up to 10%, and is greater (30%) in patients with SJS/TEN overlap. The worst-case scenario included ten patients affected with extensive BSA, whose mortality rate is almost 50% [16, 44].

Whether a pre-existing liver disease is a risk factor for DILI in SCARs patients remains unclear. While in a retrospective SCARs cohort of patients from Australia, the underlying liver disease did not seem to be a risk factor for DILI, due to the small sample size and the fact that severity of liver disease was not specified precludes reaching solid conclusions [11]. In addition, in a retrospective SCARs cohort study from Taiwan, patients with HBV or HCV did not appear to have hepatic involvement [24] (Chen *et al.,* 2010). Furthermore, patients with HIV/AIDS have been shown to have an increased risk of developing SJS/TEN with DILI. Surprisingly, however, mortality was lower in patients with HIV (12.5% *vs* 36%) in a study from India [29].

In several studies, mortality was found to be higher in SCARs associated with liver injury, especially in those including patients with SJS/TEN and associated DILI, with 4 ALF cases in the Indian study [3,29]. A lower eosinophil count is another risk factor that could be associated with severe DILI [45]. In the study of Lin *et al*. [13], severe cases of serum transaminases > 10 x ULN were found to have a lower number of eosinophils in the dermis. It is possible that in such instances, a genetic background favors the reduced eosinophil count as shown in DILI patients with a low-producing IL-10 genotype, which has been associated with more severe drug-induced liver injury [45]. Furthermore, the absence of eosinophils in severe DILI has also been confirmed in biopsy samples [46].

The mortality rate of DRESS syndrome is about 10%, most commonly due to acute liver failure [19]. However, few cases due to ALF were found in the studies of Walsh *et al*. (n=2) [28], Hiransuthiku *et al.* (n=1) [27] and Eshki *et al*. (n=1) [35]. However, no instances of ALF cases (leading to liver transplantation or death) were reported in the Spanish and Latin-American DILI Registries (Table **2**). In the RegiSCAR study, 98% of the cases recovered, only two cases died and the primary cause of death was not specified [18]. These data cast doubts on the actual figures of mortality rate in DRESS. No phenotypic markers with a prognostic value are currently available for severity in DRESS [28, 43].

Limited information exists regarding DRESS presentation in children. DRESS seems to be less common in children than in adults, but liver involvement is similar to that in adults [26, 47]. In addition, children have a lower mortality rate due to DRESS syndrome than adults, regardless of the association with DILI. The reasons for these differences are unclear, however, the better outcome in children with SJS may be related to the use of lower doses of medication, lack of comorbidities and drug interactions, and different susceptibility to certain drugs [48, 49].

5. DRUGS INDUCING LIVER INJURY ASSOCIATED WITH SEVERE CUTANEOUS ADVERSE REACTIONS

Even commonly used medicines, which are considered to be safe, are involved in SCARs. Similarly, DILI is also caused by a large number of substances. However, only a restricted group of medications are deemed responsible for both DILI and SCARs. The causative drugs for either SJS/TEN or DRESS associated with liver injury in different DILI registries (Table **2**) were anti-infective, non-steroid anti-inflammatory drugs (NSAIDs), and anti-epileptic drugs. In addition, allopurinol was the culprit drug of DRESS in 27 instances, but interestingly, it was not recorded as the causative agent in any case of SJS/TEN (Tables **1** and **2**). The most common culprit drugs in SCARs may somewhat differ between different geographic regions, reflecting differences in drug prescription patterns (*i.e*. nevirapine, dapsone). However, for the DRESS syndrome, the leading drugs and the drug classes are the same in most studies. For drug classes, these are the anti-infectives (including, but not limited to, antituberculous drugs, beta-lactam antibiotics), antiepileptic drugs (importantly, aromatic anticonvulsants, but also lamotrigine), NSAIDs, and allopurinol. In the Taiwanese and Singaporean population, allopurinol was the most common causative agent for DRESS [24,25]. Moreover, allopurinol is consistently related to DRESS not only in the Asian population but also in Europeans. Allopurinol and its metabolite oxypurinol interact with T-cells, and in the carriers of the HLA-B*58:01 allele, the susceptibility to hypersensitivity of this phenotype increases [50]. It is even more likely for this reaction to occur if a high concentration of oxypurinol is present, as is the case of patients with renal insufficiency [50].

As the aromatic antiepileptic drugs (such as phenytoin, carbamazepine, oxcarbazepine, phenobarbital) have long been associated with hypersensitivity, their common involvement in SCARs is not surprising [51], having the potential for cross-reactivity. Phenytoin, phenobarbital, and carbamazepine are metabolized to hydroxylated aromatic compounds. Since arene epoxides are suggested to intermediate in the hypersensitivity reaction, it is possible that this shared reactive metabolite is responsible for the adverse effect [51]. Antiepileptic drugs were also the most frequent therapeutic group implicated in DRESS with phenytoin, carbamazepine and lamotrigine as representative drugs, followed by anti-infective and allopurinol [13, 37].

In a study including subjects who developed SCARs, and a part of them concomitantly developed DILI, a total of 59 drugs were deemed responsible for the SCARs-DILI injury. The leading group of drugs was antimicrobials, and the leading culprit drug was beta-lactam antibiotics [11]. Other agents involved were anticonvulsants (including lamotrigine, phenytoin, valproate), leflunomide, methotrexate, sulfasalazine, allopurinol, NSAIDs, and also herbals.

A recent study from India found overlaps in causative agents between SCARs with and without DILI. In their report, the anticonvulsants, sulfonamides, anti-infectives (including beta-lactams predominantly), antituberculous drugs, antiretroviral, NSAIDs (diclofenac, celecoxib) and leflunomide were also indicated as common causative agents for SCARs-DILI [29].

Data of the pediatric population is very scarce. A small cohort was identified, described retrospectively by Han *et al.* [26]. However, the drugs that were identified as culprit drugs did not differ from those described for adult populations. The identified classes were anti-infective and anti-epileptic (including levetiracetam) drugs. In a pooled analysis using data from two multicenter international case-control studies, a severe cutaneous adverse reaction study and a multinational severe cutaneous adverse reaction (EuroSCAR) study, anti-infective sulfonamides, phenobarbital, carbamazepine, and lamotrigine were the drugs with highest risk of SJS/TEN in children < 15 years of age [49]. The list of culprit drug

of SCARs and DILI is continuously growing as newer medicines, such as the anticancer drug imatinib, are being identified [52].

5.1. Immune Checkpoint Inhibitors

Immune checkpoints are crucial regulators of the immune system. Programmed cell death protein 1 (PD-1, CD279) is a cell surface receptor expressed predominantly by activated T-cells. It interacts with the programmed death-ligand (PD-L1, CD274) expressed on APCs and has a negative regulatory role that promotes T-cell apoptosis. Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is a similar cell surface receptor expressed in T cells that interacts with the CD80 and CD86 ligands expressed on APCs to downregulate T-cell activation leading to anergy [53]. The inhibition of PD-1 and CTLA-4 consequently enhances the T-cell activity. The development of immune checkpoint inhibitors, such as PD-1 (nivolumab and pembrolizumab) and CTLA-4 (ipilimumab) inhibitors, has a major impact on cancer therapy and represents a paradigm shift from targeting tumor cells to targeting immune cells. However, these agents have a distinctive set of immune-related adverse events (irAEs) in numerous locations in the body. The most common irAEs include rash, colitis and hepatitis [54]. Between 30% and 50% of patients treated with Ipilimumab or PD-1 inhibitors experience dermatologic adverse effects [55, 56]. Despite rash being a common irAE, SJS/TEN and DRESS are rarely reported with immune checkpoint-inhibiting treatments [55, 57, 58]. Due to the possibility of potentially fatal complications, it is important to keep SJS/TEN and DRESS in consideration while dealing with patients on immune checkpoint point inhibitor treatments for rash, eosinophilia, liver profile elevation or acute renal failure. Early recognition of DRESS and consequent discontinuation of the causative agent are key steps in clinical management and patient safety.

6. PHYSIOPATHOLOGY AND HOST RISK FACTORS

The exact physiopathology of idiosyncratic immune-mediated adverse reactions is still not completely understood. However, it is generally believed to be multifactorial involving drug/pharmacological, environmental and host factors that ultimately influence patient susceptibility and phenotype [7, 59]. Furthermore, T-cell mediated immune responses are thought to be an essential factor in the pathogenesis of the severe drug hypersensitivity reactions, such as DRESS and SJS/TEN [50]. This is supported by findings of a study demonstrating the drug-specificity of CD4 and CD8 T-cells cloned from blood lymphocytes or skin lesions of patients with a variety of drug hypersensitivity reactions [60, 61]. Carbamazepine-specific CD4 and CD8 T-cells displaying different effector functions and homing characteristics persist for many years after the resolution of clinical symptoms in the blood of patients who had carbamazepine hypersensitivity[62]. Furthermore, the infiltration of cytotoxic CD8 T-cells in blister fluid and the involvement of CD8 T-cells and the natural killer (NK) cells in keratinocyte damage has been demonstrated in SJS/TEN [63, 64].

The major histocompatibility complex (MHC) molecules, encoded by human leukocyte antigen (HLA) genes, have a central role in T-cell activation through antigen presentation and are believed to play a role in drug hypersensitivity through immune reactions manifesting as SJS/TEN or DRESS-related symptoms [61]. Drugs or intermediate drug metabolites are generally not immunogenic per se but can bind to endogenous molecules and subsequently trigger an immune response. Three different hypotheses have been proposed to explain drug-induced immune system activation: the hapten/prohapten model, pharmacological interaction or p-i model, and the altered peptide repertoire model [9, 65, 66] (Fig. **1**).

The haptens are small molecules that are unable to induce an immune response by themselves but can bind covalently to larger molecules, such as proteins (carrier), and trigger an immune response. The prohaptens, on the other hand, must first be metabolized by the liver to produce haptens in order to bind to a carrier [9]. In the hapten model, the offending drug or a reactive metabolite covalently binds to endogenous proteins generating hapten-protein adducts. When this complex is processed into an antigen by antigen-presenting cells (APCs), and presented on MHC molecules, these modified peptides can be perceived as foreign/pathogenic by T-cells and can elicit an immune response [65, 66]. The activation of effector T-cells results in a local response at the sites where hapten-protein adducts were generated and presented by APCs, while the activation of central memory T-cells results in lymph node involvement [9].

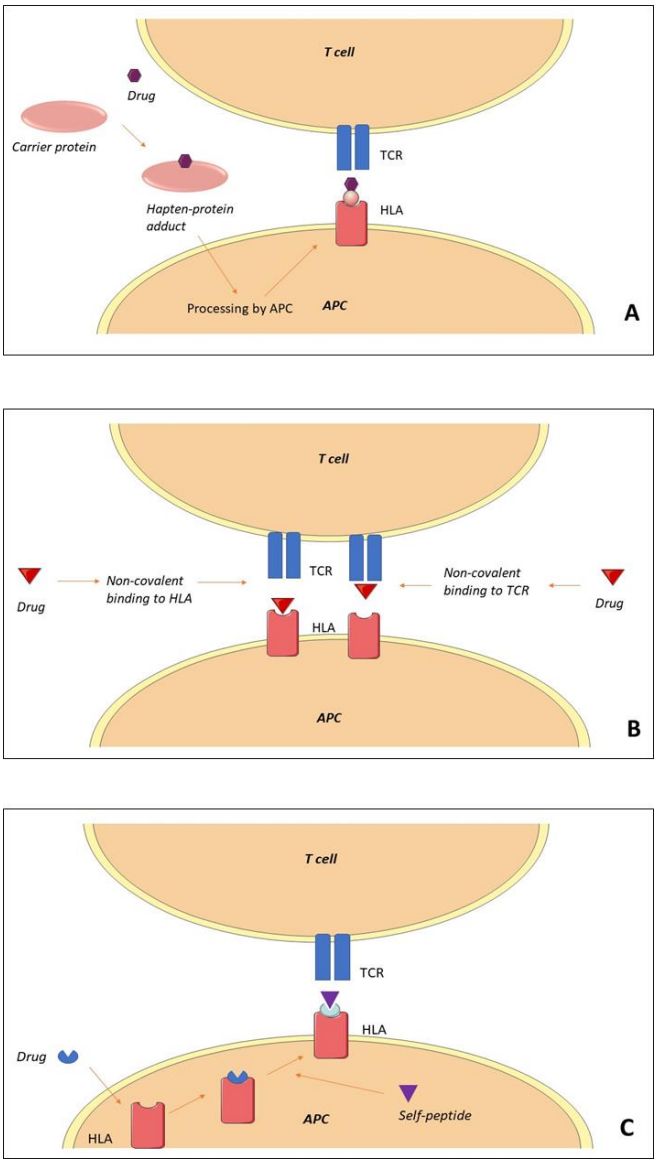

Fig. (1). Immunopathogenic models of idiosyncratic adverse reactions. (A) Prohapten/hapten model: A drug or a reactive metabolite covalently binds to an endogenous carrier protein, generating a hapten-protein complex. This complex is processed by APCs and presented to the TCR on HLA molecules. (B) Pharmacological interaction or p-i model. A drug or a metabolite binds noncovalently to either the HLA or TCR, directly eliciting a T-cell response in a peptide-independent manner. (C) In the altered peptide repertoire model, drugs are hypothesized to bind non-covalently to the HLA-binding cleft, allowing the presentation of different/new self-peptides to the T-cells. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

In the pharmacological interaction or p-i model, it is hypothesized that a drug or an intermediate drug metabolite binds non-covalently to either the MHC molecule or T-cell receptor (TCR) and directly elicits T-cell responses in a peptide-independent manner, without the need to be previously processed or metabolized.

In the altered peptide repertoire model, drugs were found to non-covalently bind to the HLA-binding cleft, thereby altering the specificities of MHC-peptide binding [65, 66]. This results in the ability of different self-peptides to bind to the modified MHC-binding cleft. Although being endogenous and not new to the cell, these peptides may have not been previously found in the MHC molecules, and therefore can be perceived as neoantigens by the T-cells.

6.1. Genetic Factors

Several pharmacogenetic studies have found associations between HLA alleles and the predisposition to adverse drug reactions (Table **3**). Regarding drug hypersensitivity with cutaneous manifestations, the specific HLA class I alleles have been identified for a number of drugs. While HLA-B*58:01 appears to be a common risk allele for allopurinol-induced SCARs, DRESS and SJS/TEN in various ethnicities, predisposition to carbamazepine-induced SJS/TEN has been found with both HLA-A*31:01 and HLA-B*15:02, potentially depending on the ethnicity and genetic background [67-75]. Interestingly, the HLA-B*15:02 allele also appears to be a risk factor for SJS/TEN caused by lamotrigine, oxcarbazepine and phenytoin in Han Chinese [76, 77]. Similarly, Han Chinese HLA-B*13:01 carriers seem to have a higher risk of developing DRESS if treated with dapsone and a higher risk of SJS/TEN when treated with phenytoin and salazosulfapyridine [36, 76, 78]. This demonstrates that there is an apparent overlap of HLA risk alleles, whereby the same allele can increase the risk of different phenotypes as well as increase the risk of hypersensitivity reactions due to different causative agents. This has also been noted for DILI. For example, the HLA class II alleles DRB1*15:01-DQB1*06:02 were found to be associated with increased risk of DILI caused by amoxicillin-clavulanate as well as lumiracoxib [79, 80]. A recent meta-analysis has found that the HLA-A*31:01 allele is a shared risk allele between the SCARs and DILI induced by carbamazepine in patients of the European ancestry. However, the association was stronger for SCARs than for DILI, which suggested a difference in antigen presentation between the skin and liver tissue [10].

HLA-B*57:01 is a well-established risk factor for abacavir hypersensitivity [81]. The same allele was later found to also increase the risk of DILI due to flucloxacillin and potential pazopanib-related alanine aminotransferase elevations as identified in recent clinical trials [82, 83]. The mechanistic role of abacavir, however, differs somewhat from that of flucloxacillin. Abacavir has been demonstrated to bind directly and specifically to the HLA-B*57:01 protein and cause an inappropriate immune response, while flucloxacillin seems to bind covalently to endogenous proteins resulting in the presentation of modified self-peptides to T cells [84, 85].

Genetic screening for HLA-B*57:01 prior to prescription has been proven to be very effective and reduces the incidence of abacavir hypersensitivity [86]. In addition to being clinically effective, prospective screening of HLA-B*57:01 is also cost-effective and mandatory for testing HLA-B*57:01 prior to abacavir prescription which has now been approved by the Foods and Drug Administration in the US and the European Medicines Agency and consequently implicated in clinical practice [87, 88]. This is not the case for the flucloxacillin DILI, which is associated with a significantly lower positive predictive value for the same HLA alleles than abacavir hypersensitivity. Hence, prospective screening for HLA-B57*01 prior to flucloxacillin prescription would have a low clinical impact and is consequently not a cost-effective way of reducing the number of flucloxacillin hepatotoxicity cases [89].

Similarly, screening for HLA-B*15:02 prior to carbamazepine prescription is mandatory, in particular, in the South East Asian population, due to the strong association between this allele and carbamazepine-induced SJS/TEN [90]. Genetic screening for HLA-A*31:01 before prescribing carbamazepine has also been demonstrated to be cost-effective, and could reduce the incidence of serious, and sometimes fatal, cutaneous adverse reactions by identifying patients at risk and select alternative therapies [91, 92]. Unlike HLA-B*15:02 which is specific for carbamazepine SJS/TEN in the South East Asian patients, HLA-A*31:01 appears to be a broader risk factor that predisposes to various phenotypic forms of carbamazepine hypersensitivity. In addition, this has been demonstrated in a number of populations, including Europeans, with varying effect sizes [92].

However, mandatory screening is not yet implicated for HLA-A*31:01, although information on the association between this allele and hypersensitivity is now included in the carbamazepine label.

6.2. Virus Reactivation in DRESS

A relationship between viral infections and DRESS development has been observed. Several studies have linked the reactivation of the human herpesvirus-6 (HHV-6) to the development of DRESS [93, 94]. A Japanese study found increased anti-HHV-6 IgG titers in 62% of patients with drug rash and systemic symptoms 2-4 weeks after the onset of the symptoms [95]. The reactivation of other herpes viruses, such as HHV-7, Epstein-Barr virus and cytomegalovirus, has also been reported in DRESS patients [94, 96, 97]. Virus reactivation in DRESS seems to have an impact on the disease progression with more severe organ involvement and potentially prolonged course [94, 95, 97, 98].

In 2010, Picard *et al*. proposed that DRESS development after carbamazepine, allopurinol or sulfamethoxazole exposure was the result of cutaneous and systemic manifestations of an immune response mainly mediated by CD8+ T lymphocytes, directed against herpes viruses [96].

CONCLUSION AND FUTURE PERSPECTIVES

In conclusion, drug-induced systemic hypersensitivity reactions associated with DRESS and SJS/TEN lack systematic collection of detailed information with regard to the time of appearance and specific type of skin rashes, histological phenotype, evolution and associated components of hypersensitivity, such as eosinophil count and lymphocyte activation, which preclude the identification of prognostic risk factors for the pattern of liver injury, severity and outcome. In addition, data analysis when the liver injury manifests in relation to skin rashes and whether resolution or progression to a worst outcome parallels the cutaneous manifestations is scarce.

Conceivably, patients would seek consult a dermatologist or a hepatologist depending on symptom predominance. Presumably, when jaundice is present, it will be the hepatologist who takes care of the patient, while if hypersensitivity reactions predominate, the patient will probably consult a dermatologist. Thus, for advancing in the characterization of clinical phenotypes, identification of risk factors and proper management of reactions affecting both the skin and the liver an interdisciplinary approach is recommended. The assessment of SCARs associated with liver injuries would improve by input from a multidisciplinary team including hepatologists, dermatologists and other specialists.

Furthermore, there is a need for the harmonization of clinical measurements, definitions, disease severity grading, and outcomes for the implementation of accurate phenotyping that would allow the comparison of these cases across DILI or SCARs registries. This would facilitate further innovative and collaborative research to identify genetic risk factors associated with liver injury related to immune-mediated cutaneous reactions and to advance our understanding of the underlying biology of these disorders [99].

Table 3. Associations between HLA alleles and predisposition for drug-induced liver injury (DILI) and severe cutaneous adverse reactions (SCARs) according to clinical phenotype and ethnicity.

Associated Drug	HLA Allele	Reaction	Study type and Cohort Population	OR (95% CI)	References
Abacavir	HLA-B*57:01	Drug hypersensitivity	CGS: 18 cases, 167 Abacavir -tolerant controls (Australia)	117 (29–481)	[81]
			CGS: 85 cases, 113 Abacavir -tolerant controls (North America)	23.6 (8.0–70.0)	[103]
			CGS: 42 cases, 28 controls (Hispanic)	30.4 (1.74-530.90)	[104]
Allopurinol	HLA-B*58:01	SCARs	CGS: 51 cases, 93 controls (Han Chinese)	393.51 (23.23–6665.26)	[67]
	HLA-B*58:01	DRESS	CGS: 19 cases, 3200 controls (European)	85.4 (32.52–224.04)	[68]
	HLA-B*58:01	SJS/TEN	CGS: 27 cases, 54 allopurinol-tolerant controls (Thai)	348.3 (19.2–6336.9)	[69]
			CGS: 6 cases, 3200 controls (European)	99.6 (17·91–553.72)	[68]
Carbamazepine	*HLA-A*31:01*	DRESS	GWAS: 27 cases, 257 controls (European)	12.41 (1.27-121.03)	[71]
			GWAS: 36 cases, 420 controls (Japanese)	9.5 (4.6–19.5)	[70]
			CGS: 10 cases, 710 controls (Han Chinese)	26.3 (7.2–96.5)	[105]
			CGS: 17 cases, 485 controls (Korean)	12.4 (4.5–34.1)	[75]
	*HLA-A*31:01*	SJS/TEN	GWAS: 6 cases, 420 controls (Japanese)	33.9 (3.9–295.6)	[70]
			GWAS: 12 cases, 257 controls (European)	25.93(4.93-116.18).	[71]
	*HLA-A*31:01*	SCARs/DILI	GWAS: 43 CBZ-SCAR cases, 12 CBZ-DILI cases (European-descent)	SCAR: 18.1 (8.03-40.88), DILI: 7.3 (2.47-23.67)	[10]
	HLA-B*15:02	SJS/TEN	CGS: 44 cases, 93 controls (Han Chinese)	895(50-15869)	[72]
			CGS: 21 cases, 300 controls (Malaysian)	16.15 (4.57-62.4)	[73]
			CGS: 6 cases, 50 controls (Thai)	25.5 (2.68–242.61)	[74]
			CGS: 7 cases, 485 controls (Korean)	18.4 (3.8–88.0)	[75]
Dapsone	*HLA-B*13:01*	HRS (DRESS) /hepatitis	GWAS: 39 cases, 833 controls (Han Chinese)	21.67 (10.41-45.12)	[36]
		SCARs	CGS: 15 cases, 986 controls (Thai)	26.11 (7.27–93.75)	[106]
Lamotrigine	B*15:02	SJS/TEN	CGS: 6 cases and 275 controls (Han Chinese)	89.25 (19.25-413.83)	[77]
	HLA-A*24:02	DRESS	CGS: 3 cases, 253 controls (European)	34.53	[107]
Nevirapine	*HLA-B*35,HLA-Cw*04*	Cutaneous adverse effects	CGS:175 cutaneous adverse events, 101 hepatic adverse events and 587 controls. (Multiple ethnicities).	Asians: 18.34 (5.10-65.99) Thai: 13.49 (3.56-52.20)	[108]
	*HLA-DRB1*01*		CGS: 6 cases, 15 tolerant controls (European)		[109]
Oxcarbazepine	*HLA-B*15:02*	SJS/TEN	CGS: 3 cases, 93 controls (Han Chinese)	80.7 (3.8–1714.4)	[76]
Phenytoin	*HLA-B*15:02*	SJS/TEN	CGS: 4 cases, 50 controls (Thai)	18.5 (1.82–188.40)	[74]
			CGS: 26 cases, 113 tolerant controls (Han Chinese)	5.1 (1.8–15.1)	[76]
	*HLA-B*13:01*	SJS/TEN	CGS: 26 cases, 113 tolerant controls (Han Chinese)	3.7 (1.4–10.0)	[76]
Salazosulfapyridine	*HLA-B*13:01*	DRESS	CGS: 6 cases, 283 controls (Han Chinese)	11.16 (1.98–62.85)	[78]
Amoxicillin-Clavulanate	*A*02:01 (rs2523822)*	DILI	GWAS: 201 cases, 532 controls (European)	2.3 (1.8-2.9)	[79]

(Table 3) Contd....

Associated Drug	HLA Allele	Reaction	Study type and Cohort Population	OR (95% CI)	References
	*DRB1*15:01,DQB1*06:02*	DILI	GWAS: 201 cases, 532 controls (European)	2.8 (2.13.8)	[79]
Lumiracoxib	*DRB1*15:01, DQB1*06:02*	DILI	GWAS: 41 cases, 176 controls (North American)	1.9 (1.0-3.9)	[80]
Antituberculosis therapy	*DQB1*02:01*	DILI	CGS: 56 cases, 209 controls (Indian)	1.9 (1.0–3.9)	[110]
			GWAS: 59 cases, 111 tolerant controls, 109 population controls (Indian)	Association not confirmed	[111]
			CGS: 55 cases, 55 tolerant controls (European)	Association not confirmed	[112]
Flucloxacillin	*HLA-B*57:01*	DILI	GWAS: 51 cases and 282 controls (European)	80.6 (22.8–284.9)	[82]
Pazopanib	*HLA-B*57:01*	DILI	2,190 patients (107 HLA-B*57:01 carriers, 2083 non carriers). (Multiple ethnicities)		[83]

CI, confidence Interval; CGS, candidate gene study; GWAS, Genome-wide association study.

Interestingly, in addition to the potential bioactivation of drugs in the skin [100], more recent experimental data suggest that DILI-associated genes related to immune and inflammatory responses are expressed in keratinocytes [101], opening the door to the identification of individuals susceptible to DILI using the patient's keratinocytes. Besides, interesting findings suggest that there might be a shared genetic risk factor associated with drugs inducing both SCARs and DILI hypersensitivity reactions. However, this concept needs to be confirmed for other drugs in further genome-wide association (GWA) studies [10].

Systemic corticosteroids remain the recommended treatment for SCARs and also for DILI-associated reactions, a practice not relying on the data from randomized trials and with inconsistent results in both recovery and mortality [13,34,43]. Nonetheless, the use of corticosteroids has been justified based on the rationale of improving regulatory T cell response and clinical symptoms in the acute phase, and to prevent the development of autoimmune responses after resolution [102].

The low prevalence of these immune-mediated systemic reactions, heterogeneous clinical phenotypes and the strong genetic developmental influence represent a strong case for the establishment of large prospective collaborations following standardized definitions and criteria. Such collaborations will advance research and understanding of these reactions that would ultimately allow the development of predictive biomarkers, better patient risk stratification and exploring new and effective treatments.

LIST OF ABBREVIATIONS

AIDS = Acquired immune deficiency syndrome
APCs = Antigen presenting cells
ALDEN = The Algorithm for Drug Causality for Epidermal Necrolysis
ALF = Acute liver failure
ALP = Alkaline phosphatase
ALT = Alanine aminotransferase
AST = Aspartate aminotransferase
BSA = Body surface area
CIOMS = The Council for International Organizations of Medical Sciences
CTLA-4 = Cytotoxic T-lymphocyte-associated protein 4
DIDMOHS = Drug-induced delayed multiorgan hypersensitivity syndrome
DIHS = Drug-induced hypersensitivity syndrome
DILI = Idiosyncratic drug-induced liver injury
DRESS = Drug reactions with eosinophilia and systemic symptoms
EM = Erythema multiforme
GWA = Genome-wide association
HBV = Hepatitis B virus
HCV = Hepatitis C virus
HIV = human immunodeficiency virus
HLA = Human leukocyte antigen
HSS = Hypersensitivity syndrome
irAEs = Immune-related adverse events
IQR = Interquartile range
MHC = Major histocompatibility complex
NAFLD = Non-alcoholic fatty liver disease
NSAID = Non-steroid anti-inflammatory drugs
PD-1 = Programmed cell death protein 1
PD-L1 = Programmed death ligand
RegiSCAR = Registry of Severe Cutaneous Adverse Reactions
RUCAM = Roussel Uclaf Causality Assessment Method
SCARs = Severe cutaneous adverse reactions
SJS = Stevens-Johnson syndrome
TEN = Toxic epidermal necrosis
TCR = T-cell receptor
ULN = Upper limit of normal

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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