Journal of Immunology Research

New Advances in Drug Hypersensitivity Research and Treatment

Lead Guest Editor: Yi-Giien Tsai
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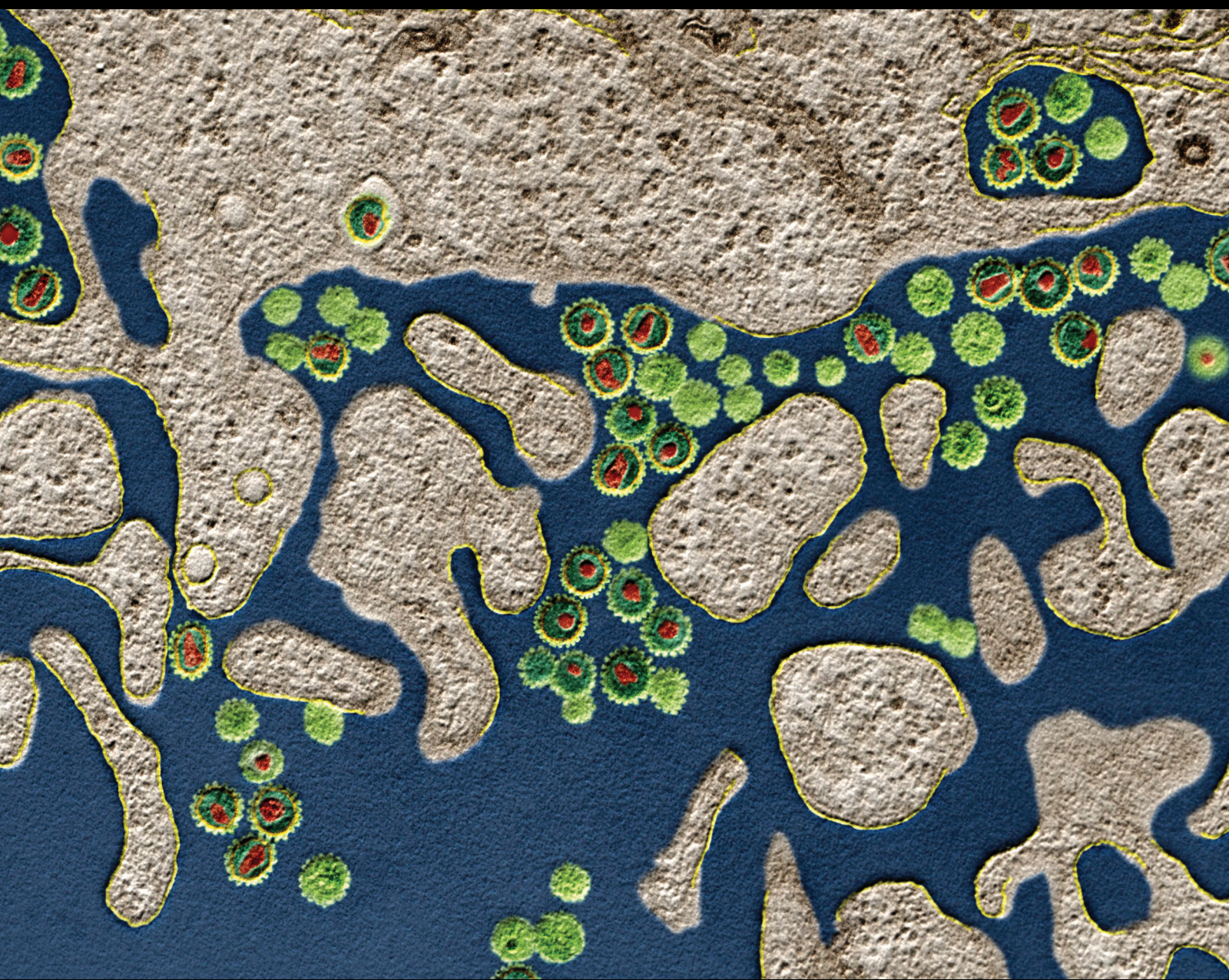

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Editorial Board

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Editorial

New Advances in Drug Hypersensitivity Research and Treatment

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Drug hypersensitivity remains an important clinical issue which is common and can be fatal with long-term complications. Severe cutaneous adverse reaction (SCAR) is T-cell-mediated delayed-type hypersensitivity, including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reactions with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS), and acute generalized exanthematous pustulosis (AGEP). These spectra of drug hypersensitivity are challenging in clinical practice and associated with the high rate of morbidity and mortality. This special issue focuses on new advances in drug hypersensitivity research and treatment. We have invited some papers to address such issues.

The first paper of this special issue provides a general overview on recent advances in the epidemiologic, genetic factors, immune mechanisms, diagnostic tools, and therapeutic approaches of drug hypersensitivity [1]. Specific immune molecules involved in SCAR, such as IL-15 in SJS/TEN or the characteristic immunohistopathological features of SJS/TEN, DRESS, and AGEP, were also reviewed in this special issue. A better illustration of the histopathological features could improve the accuracy of diagnosis and lead to give essential insight into the pathomechanism of drug hypersensitivity reactions or SCAR. This review shows an updated knowledge of drug hypersensitivity that can help clinical practice or research in this field.

To broaden our understanding of the situation of SCAR in different countries, the special issue includes epidemiologic studies of SCAR from different Asian countries, including Japan, China, and Thailand. More and more reports show anticancer drugs, especially new targeting or immune therapeutic drugs which may also cause SCAR; this special issue also includes a literature review of SJS/TEN related to anticancer drugs, including chemotherapy, targeted therapy, and immunotherapy. The rapid development of variable targeting or immunologic anticancer drugs may potentially contribute to a new threat of SCAR in the future. This article also increases clinician awareness of the differential diagnosis between immune-related hypersensitivity reactions or direct skin toxicity related to anticancer drugs that can further improve the managements of SCAR in cancer patients.

Recent advancement in pharmacogenomics reveals genetic links to SCAR. There are 3 papers in this special issue demonstrating the association between single-nucleotide polymorphisms and HLA-B alleles with adverse drug reactions, including anticonvulsant or antihyperuricemic agent-induced hypersensitivity reactions or drug-induced liver injury. Furthermore, different techniques used to screen HLA alleles or predict drug hypersensitivity reactions in new drug users were also reviewed in one paper.

There is still no consensus-specific treatment for SCAR. Due to the rarity of SCAR, there were only few well-designed and implemented large-scale randomized control trials of treatment for patients with SCAR. Systemic corticosteroid is still controversial for the management of SJS/TEN. There are more evidences showing beneficial therapeutic effects of cyclosporine and biologic anti-TNF alpha blockade on patients with SJS/TEN. In this special issue, one paper gives a concise review on the management of each SCAR based on current clinical evidences.

Authors' Contributions

Yi-Giien Tsai and Wen-Hung Chung contributed equally to this work.

Yi-Giien Tsai
Wen-Hung Chung
Riichiro Abe
Wichittra Tassaneeyakul

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Review Article

Recent Advances in Drug-Induced Hypersensitivity Syndrome/ Drug Reaction with Eosinophilia and Systemic Symptoms

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Drug-induced hypersensitivity syndrome (DIHS), also termed as drug reaction with eosinophilia and systemic symptoms (DRESS), is a multiorgan systemic reaction characterized by a close relationship with the reactivation of herpes virus. Published data has demonstrated that among patients with DIHS/DRESS, 75–95% have leukocytosis, 18.2–90% show atypical lymphocytes, 52–95% have eosinophilia, and 75–100% have hepatic abnormalities. Histologically, eosinophils were observed less frequently than we expected (20%). The mainstay of DIHS/DRESS treatment is a moderate dose of systemic corticosteroids, followed by gradual dose reduction. In this review, we will emphasize that elevations in the levels of several cytokines/chemokines, including tumor necrosis factor- (TNF-) α and the thymus and activation-regulated chemokine (TARC/CCL17), during the early stage of disease, are good markers allowing the early recognition of HHV-6 reactivation. TNF-α and TARC levels also reflect therapeutic responses and may be useful markers of the DIHS disease process. Recently, the pathogenic mechanism of T-cell activation triggered by human leukocyte antigen- (HLA-) restricted presentation of a drug or metabolites was elucidated. Additionally, we recently reported that dapsone would fit within the unique subpocket of the antigen-recognition site of HLA-B*13:01. Further studies will render it possible to choose better strategies for DIHS prevention and therapy.

1. Introduction

Drug-induced hypersensitivity syndrome (DIHS), also termed drug reaction with eosinophilia and systemic symptoms (DRESS), is a multiorgan systemic reaction characterized by rashes, fever, lymphadenopathy, leukocytosis with eosinophilia and atypical lymphocytes, and liver dysfunction [1–4]. DIHS/DRESS is closely associated with the reactivation of herpes viruses, especially human herpesvirus 6 (HHV-6) and cytomegalovirus (CMV), in patients on long-term drug therapy [1–4]. DIHS/DRESS tends to exhibit a relatively later onset (≥2–8 weeks after commencing administration of the causative drug) than other types of drug eruptions. DIHS/DRESS is usually associated with only a limited number of drugs, including carbamazepine, phenytoin, phenobarbital, lamotrigine, dapsone, mexiletine, salazosulfapyridine, allopurinol, and minocycline [1–4]. Published works and our investigations indicated that oxidative metabolites of trichloroethylene, which may include trichloroacetylated protein adducts, can also induce a hypersensitivity syndrome quite similar to DIHS/DRESS [5]. The estimated risk at the first or second prescription of an aromatic antiepileptic drug is 2.3–4.5 in 10,000 [6]. This review explains the catachrestic features of DIHS/DRESS, the markers allowing early recognition of HHV-6 reactivation, and the recent advances in the genetics of DIHS/DRESS.

2. Criteria for DIHS/DRESS

DRESS, first defined in 1996 by Bocquet et al. [2], presents with a constellation of symptoms and signs, the main features being a cutaneous eruption after exposure to the culprit drug, associated with fever and organ involvement (Table 1(a)). Hematologic (lymphadenopathy, eosinophilia, and atypical lymphocytosis) and hepatic (elevation of serum transaminases) manifestations are frequently reported [2]. Subsequently, inclusion criteria for HSS/DRESS were defined in RegiSCAR, a research group investigating severe cutaneous adverse reactions (SCAR), and a scoring system for classifying DRESS cases was established (Table 1(b)) [7]. In 2006, a

Table 1

(a) Diagnostic criteria for drug reaction with eosinophilia and systemic symptoms (DRESS) [2].

Diagnosis of DRESS is confirmed by the presence of all of the following criteria:
(1) Cutaneous drug eruption
(2) Adenopathies ≥ 2 cm in diameter or hepatitis (liver transaminases ≥ 2 times upper limit of normal) or interstitial nephritis or interstitial pneumonitis or carditis
(3) Hematologic abnormalities: eosinophilia ≥ $1.5 \times 10^9\ L^{-1}$ or atypical lymphocytes

(b) Criteria for potential cases of drug reaction with DRESS by RegiSCAR [7].

(1) Hospitalization
(2) Reaction suspected to be drug-related
(3) Acute skin rash*
(4) Fever above 38°C*
(5) Enlarged lymph nodes in at least two sites*
(6) Involvement of at least one internal organ*
(7) Blood count abnormalities
(i) Lymphocytes above or below the laboratory limits*
(ii) Eosinophils above the laboratory limits*
(iii) Platelets below the laboratory limits*

*Three or more criteria required. RegiSCAR: research group investigating severe cutaneous adverse reactions (SCAR) [7].

(c) Diagnostic criteria for drug-induced hypersensitivity syndrome (DIHS) established by a Japanese consensus group [3].

(1) Maculopapular rash developing 3 weeks after starting with a limited number of drugs
(2) Prolonged clinical symptoms 2 weeks after discontinuation of the causative drug
(3) Fever (≥38°C)
(4) Liver abnormalities (alanine aminotransferase ≥ 100 $U \cdot L^{-1}$)[a]
(5) Leukocyte abnormalities (at least one present)
(a) Leukocytosis (≥$11 \times 10^9\ L^{-1}$)
(b) Atypical lymphocytosis (≥5%)
(c) Eosinophilia (≥$1.5 \times 10^9\ L^{-1}$)
(6) Lymphadenopathy
(7) Human herpesvirus 6 reactivation

The diagnosis is confirmed by the presence of the seven criteria above (typical DIHS) or of the first five (1–5) criteria (atypical DIHS). [a]This can be replaced by other organ involvement, such as renal involvement.

Japanese consensus group established a set of criteria for the diagnosis of DIHS (Table 1(c)) [3]. The diagnosis of the typical syndrome requires all seven criteria. Importantly, a series of >60 patients diagnosed by clinical findings consistently showed detection of HHV-6 reactivation in the vast majority of patients who satisfied the other six criteria and showed clinical manifestations consistent with those reported by Bocquet et al. [2], but not in those with other types of drug eruption such as papillomacular rash, Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). In contrast, HHV-6 reactivation is rarely detected in patients with a tendency toward milder disease. Thus, it appears that patients fulfilling the criteria of DIHS may represent those with a more severe form of DRESS [3].

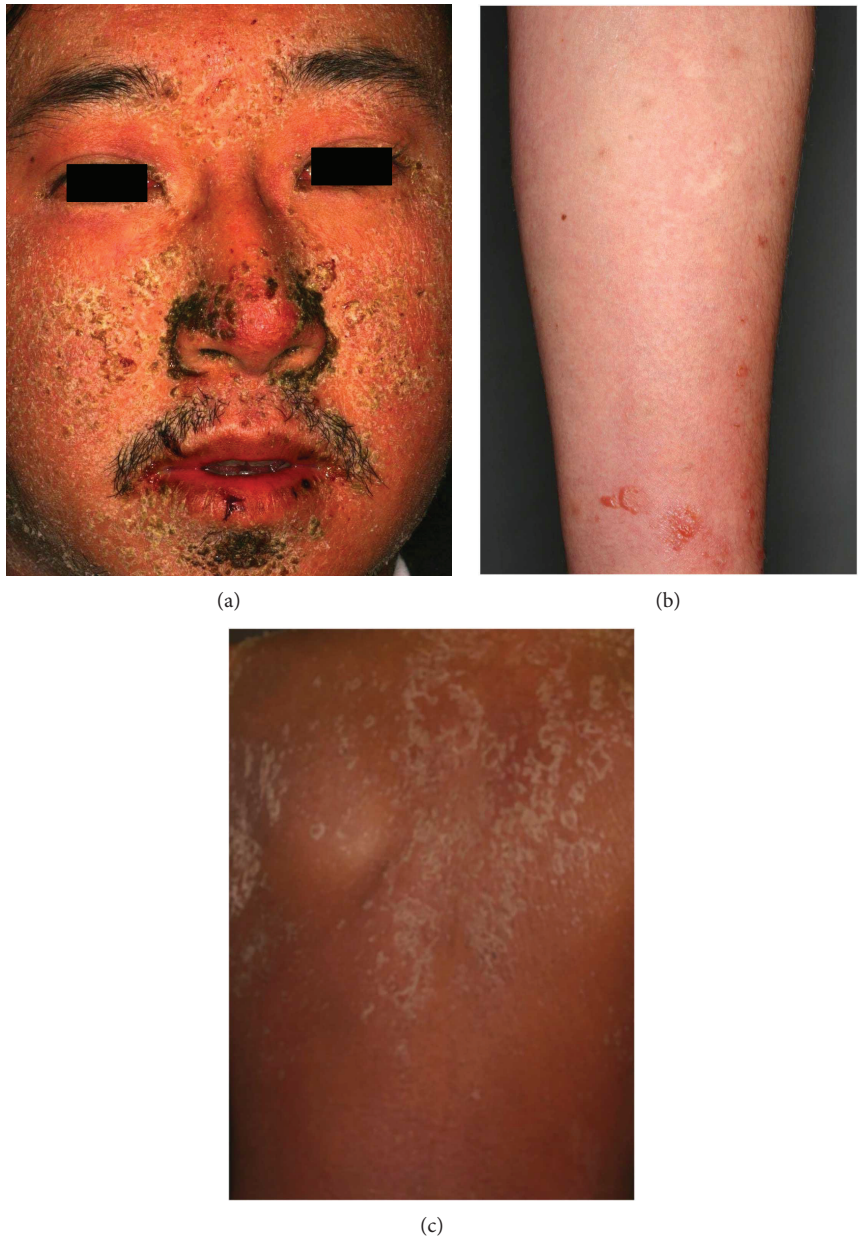
3. Clinical Findings

DIHS/DRESS commonly commences with a fever, followed soon by a maculopapular rash that is usually pruritic, and a variable degree of lymphadenopathy [1–4]. The rash often generalizes to become severe exfoliative dermatitis or erythroderma [1, 2]. Symptom onset is highly variable; usually, patients develop two or three symptoms followed by the stepwise development of other symptoms [1, 2]. In many severe cases, the symptoms continue to deteriorate, and/or several flare-ups occur, in the weeks after the offending drug is stopped [1–4].

The skin manifestations of DIHS are maculopapular rash, erythema multiforme, exfoliative dermatitis, acute generalized exanthematous pustular dermatosis-like eruption, and erythroderma [1–4]. We recently reviewed 20 patients with DIHS/DRESS, including 7 with maculopapular rash type, 5 with EM type, and 8 with erythroderma [8]. Initially, the upper trunk, face, and upper extremities are affected, followed by the involvement of lower extremities. Periorbital, facial edema with erythema and numerous scales and crusts around the nose and lips are characteristic features of DIHS/DRESS at the early stage (Figure 1(a)) [1, 5]. In some cases, bullous lesions are found on the forearm, which are also characteristic features of DIHS/DRESS (Figure 1(b)) [5]. The rash often generalizes into severe exfoliative dermatitis or erythroderma (Figure 1(c)) [1, 2, 5]. There is usually no mucocutaneous involvement, which helps distinguish DIHS/DRESS from other forms of severe drug eruptions, such as SJS and TEN [1].

4. Laboratory Data

Leukocytosis with atypical lymphocytes and eosinophilia of varying degree is a prominent feature of the syndrome [1]. Leukocytosis was observed in 99 of 104 (95%) patients reported by the RegiSCAR study group [4] and 15 of 20 (75%) Japanese patients reported by us [8]. The presence of atypical lymphocytes was demonstrated in 68 of 102 (67%) cases reported by the RegiSCAR study group [4], 38 of 60 (63%) reported from Taiwan [9], 18.5% patients reported from Thailand [10], 4 of 22 (18.2%) reported from Singapore [11], and 18 of 20 (90%) Japanese cases reported by us [8]. Eosinophilia was observed in 108 of 114 (95%) cases reported by the RegiSCAR study group [4], 31 of 60 (52%) reported from Taiwan [9], 70.4% patients reported from Thailand [10], 22 out of 27 (81.5%) reported from Singapore [11], and 13 of 20 Japanese patients (65%) reported by us [8]. Eosinophilia may often be delayed for 1 to 2 weeks and may occur even after the elevations in liver enzyme levels return to baseline [1]. In DIHS/DRESS, elevation of liver



(a) (b)

(c)

Figure 1: Clinical findings in patients with drug-induced hypersensitivity syndrome (DIHS). (a) Edema and erythema with scaling were observed on the face. Crusts were seen on the lateral surfaces of the nose and around the lips. (b) A diffuse erythematous rash and blisters were seen on the forearm. (c) Diffuse erythema with scaling on the trunk was consistent with erythroderma.

enzyme levels, the most common finding related to internal organ involvement [1], was found in 86 of 114 (75%) cases reported by the RegiSCAR study group [4] and 26 of 27 (96.3%) reported by both Singapore and Thailand [10, 11]; 48 (80%) cases in Taiwan had levels double that of normal [9]. We reported that all 20 Japanese patients with DIHS/DRESS had hepatic abnormalities (alanine aminotransferase (ALT) above the normal range of 5–25 IU/L and 14 patients [70%] had a serum ALT > 100 IU/L) [8]. Renal involvement was found in 40 of 108 (37%) cases reported by the RegiSCAR study group [4], 24 of 60 (40%) reported from Taiwan [9], 4 of 27 (14.8%) reported from Singapore [11], and 7 of 20 (35%) Japanese patients reported by us [8]. It is well known that the frequency of renal involvement is higher in patients with DIHS due to allopurinol [1].

5. Histopathology of DIHS

It is crucial for the diagnosis of SJS/TEN to examine histopathological findings to determine whether apoptotic keratinocytes are scattered in the epidermis [12]. On the other hand, it is noteworthy that none of the criteria of DIHS/DRESS [2, 3, 7] rely on histopathology. Until recently, few examinations of histopathological findings of DIHS/DRESS

were reported. Ortonne et al. [13] conducted a retrospective study on 50 skin biopsies from 36 patients with DIHS/DRESS and demonstrated that patients with DIHS/DRESS frequently show foci of interface dermatitis, involving cutaneous adnexa. Eosinophils were seen in only 20% and neutrophils in 42% of cases. Eczematous, interface dermatitis, and acute generalized exanthematous pustulosis-like and erythema multiforme-like patterns were observed in skin biopsy samples from patients with DIHS/DRESS. The association of two or three of these patterns in a single biopsy was significantly more frequent in DRESS than in a series of nondrug-induced dermatoses and appeared to be more marked in DRESS with severe cutaneous lesions than in DRESS with less severe lesions. Interestingly, higher proportions of CD8+ and granzyme B+ lymphocytes were observed in DRESS with severe cutaneous eruptions. Furthermore, FoxP3+ regulatory T cells were found within the skin infiltrates in the acute phase of DRESS; however, these cells were not numerous [13]. In addition, they found apoptotic keratinocytes in 60% of DRESS syndrome cases [13]. This observation was consistent with the report by Walsh et al. [14], which showed that the presence of apoptotic keratinocytes correlated with a more aggressive phenotype with liver injury and an erythema multiforme-like cutaneous condition. Chi et al. [15] also found that skin biopsies of DIHS/DRESS displayed various inflammatory aspects and showed that interface dermatitis with apoptotic keratinocytes was more frequent in DIHS/DRESS than in maculopapular rash.

6. Treatment

The mortality rate of DIHS has recently been estimated to be 2–14% [7, 9]. The mainstay of treatment is systemic corticosteroids [1]. Wei et al. reviewed 91 cases with DRESS in Taiwan [9]. Patients treated with systemic corticosteroids lived longer than those not treated with corticosteroids (average 36.3 versus 12.7 days). In the survival group, approximately three-quarters of the patients received systemic corticosteroids, but their resolution time was 8 days longer than those without. A study from Singapore demonstrated that 25 of 27 (92.6%) patients with DIHS/DRESS received systemic corticosteroids, with no deaths resulting from DIHS/DRESS during the follow-up period in their case series [11].

Systemic corticosteroids, recommended for most cases of DIHS/DRESS, should be initiated at a dose of 40–60 mg prednisone equivalent daily, followed by a gradual dose reduction of prednisone given over 10 weeks to prevent rapid reconstitution of valid immune responses against various pathogens; however, the mild form can resolve spontaneously over a period of weeks [1, 17]. The development of autoimmune diseases, such as lupus erythematosus and autoimmune thyroiditis, along with the generation of autoantibodies, was preferentially observed in the noncorticosteroid treatment group in the late phase (>6 months) of DIHS/DRESS [16, 17]. Severe liver damage and noncorticosteroid therapy during the acute stage were associated with the subsequent generation of autoantibodies against plakin family proteins [16]. Therefore, corticosteroids, especially if administered in the acute stage, may improve the long-term outcome [17]. Recently, Leman et al. [18] described the successful treatment of a case of DIHS/DRESS with a tumor necrosis factor- (TNF-) α inhibitor containing lithium carbonate. However, this is the only report of DIHS/DRESS treatment with a TNF-α inhibitor, and further clinical studies are required.

7. Biomarkers of Disease Severity and HHV-6 Reactivation in DIHS/DRESS

A major clinical focus during the diagnosis of DIHS and the selection of the most appropriate treatment is whether the reactivation of members of the Betaherpesvirinae subfamily, including HHV-6, develops subsequently to the drug hypersensitivity reaction [1–4]. HHV-6 DNA is detected in serum about 3–5 weeks after disease onset, followed by dramatic rises in anti-HHV-6 IgG titers [1, 17]. Shiohara et al. performed a sequential analysis of viral loads and found that the cascade of reactivation events initiated by HHV-6 or EBV extended, after some delay, to HHV-7 also and eventually to CMV [1]. In our previous study, when both HHV-6 and CMV became reactivated in the same DIHS patients, HHV-6 DNA was detected 21–35 days after disease onset and followed 10–21 days later by CMV DNA; the CMV IgG antibody titer also increased 10–21 days after elevation of the HHV-6 antibody titer [8]. In the cited study, 80% of DIHS patients exhibited HHV-6 reactivation [8]. The magnitudes of 2HHV-6 reactivation as evidenced by the increases in HHV-6 DNA levels correlated well with the severities of the inflammatory responses [1]. However, no useful predictive marker of HHV-6 reactivation has yet been widely accepted. Moreover, useful biomarkers of the DIHS disease process have not yet been reported.

7.1. Tumor Necrosis Factor-α. We recently conducted comparative assessments of, and detailed examinations on, patients with DIHS and measured their serum protein levels [8]. We found that the serum levels of TNF-α before treatment were significantly higher in the HHV-6 reactivation group than in the non-HHV-6 reactivation group. In that, a TNF-α level of 12 pg/mL allowed the detection of HHV-6 reactivation [8]. Increased levels of proinflammatory cytokines including TNF-α and IL-6 have been reported in patients with HHV-6 infections (severe cases of exanthema subitum) and CMV infections [19, 20]. However, the exact mechanisms of the reactivation of these viruses have not been fully elucidated. On the basis of both molecular and biological analyses, HHV-6, which is very similar to CMV, is the prototypic member of the Betaherpesvirinae [21, 22]. Numerous *in vitro* and *in vivo* studies have sought to elucidate the mechanisms of CMV reactivation and have reported that cytokine production, particularly of TNF-α, was implicated in reactivation [23–25]. TNF-α induces the expression of CMV immediate early (IE) gene products, potentially initiating viral replication from the latent state [26]. Expression of CMV IE genes is controlled by IE promoter/enhancer regions, which contain binding sites for NF-κB, ATF (CREB), and Sp1. The NF-κB and ATF (CREB) sites are critical in

terms of the regulation of IE gene expression [26, 27]. In contrast, the R3 region of HHV-6 contains multiple putative binding sites for cellular transcription factors, including PEA3, NF-κB, and AP-2. Via interactions with NF-κB, this region strongly enhances the promoter activity of the U95 gene, a potential homolog of the murine CMV IE2 gene [21]. These observations and our finding that the serum levels of TNF-α were significantly higher in the HHV-6 reactivation group than in the non-HHV-6 reactivation group of DIHS patients suggest that TNF-α may play a crucial role in HHV-6 reactivation (Figure 2). Moreover, an increase in the level of TNF-α before the commencement of treatment may be an especially good biomarker allowing early recognition of HHV-6 reactivation in patients with DIHS. Consistent with this finding, it was reported that the TNF-α level was higher in hematopoietic stem cell transplantation recipients exhibiting HHV-6 reactivation than in those who did not exhibit reactivation. Kamijima et al. recently investigated 28 patients with trichloroethylene hypersensitivity syndrome and recorded the times of reaction onset after exposure to trichloroethylene/other drugs, the clinical manifestations, blood data, and the duration of virus reactivation [28]. It was found that an elevated TNF-α level on admission correlated significantly with an increase in HHV-6 DNA during the clinical course. This supports our suggestion that an increased level of TNF-α prior to the commencement of treatment may be an excellent biomarker allowing early recognition of HHV-6 reactivation in patients with DIHS [8]. Moreover, in our earlier study, the TNF-α levels decreased significantly in parallel with the responses to treatment only in the DIHS group. To date, no widely accepted biomarkers of the DIHS disease process are available. Yoshikawa et al. reported elevated levels of TNF-α and IL-6 levels in four of six DIHS patients at the time of disease onset [29], indicating that the serum level of this protein reflected DIHS development. However, this report included only a small number of DIHS/DRESS cases ($n = 6$), making it difficult to discuss or compare these results with ours.

7.2. Interferon-Induced Protein 10. C-X-C motif chemokine 10 (CXCL10), also known as interferon- (IFN-) γ-induced protein 10 kDa (IP-10), plays an important role in the recruitment of antiviral-specific cytotoxic T lymphocytes into the target tissue [30]. Serum and/or tissue expression of IP-10 is increased in organ-specific autoimmune diseases and in interface dermatitis [30]. Contrary to other reports [8, 29], Chen et al. [31] demonstrated that many proinflammatory cytokines and chemokines, including interleukin- (IL-) 1β, IL-2, IL-6, IFN-γ, and TNF-α, were significantly lower in DIHS/DRESS patients with HHV-6 reactivation when compared to those without HHV-6 reactivation. In addition, these mediators were significantly lower before and during HHV-6 reactivation, compared to cytokine levels after HHV-6 reactivation in the same patients [31]. These findings suggest the importance of the timing of sample collection and that the influence of systemic corticosteroids in patient treatment should be considered carefully. Future investigations using larger numbers of samples will be needed.

7.3. Thymus and Activation-Regulated Chemokine and Other Th2-Type Cytokines/Chemokines. Ogawa et al. recently reported that the serum thymus and activation-regulated chemokine (TARC) levels were markedly higher in patients with DIHS/DRESS than in patients with other forms of drug eruption including SJS/TEN and maculopapular erythema [32]. It was found that the serum TARC levels of patients in the acute stage of DIHS correlated with disease activity and that the serum TARC levels in patients exhibiting HHV-6 reactivation were significantly higher than those in patients not exhibiting HHV-6 reactivation [33]. Interestingly, the serum TARC levels correlated with the RegiSCAR group diagnostic score for DRESS [33]. Such findings led us to suggest a pathogenic link between serum TARC levels and HHV-6 reactivation. Although the precise mechanism remains largely unknown, one possible explanation is that immunosuppression triggers HHV-6 reactivation via regulatory T cell activation induced by elevated TARC levels. Another possibility is that elevated TARC levels directly activate HHV-6 via the chemokine receptor homologues of HHV-6 [33].

Yawalkar et al. [34] examined skin sections from patients with characteristic, acute, drug-induced, maculopapular exanthem to determine the potential role of IL-5 and distinct chemokines in the recruitment and activation of eosinophils into the skin. They demonstrated that drug-induced maculopapular exanthems express significantly increased amounts of IL-5 and eotaxin [34]. However, whether these Th2 cytokines/chemokines are involved in the reactivation of HHV-6 in DIHS/DRESS has not yet to be determined.

7.4. Plasmacytoid Dendritic Cells. Plasmacytoid dendritic cells (pDCs) play a defensive role against viruses [35]. Previously, we demonstrated that pDCs accumulate in the skin of patients with DIHS/DRESS and that the number of pDCs in circulation decreases significantly around the time of viral reactivation. Upon viral infection, stimulated pDCs are prompted to differentiate into DCs by autocrine IFN-α and TNF-α and to prime naive CD4+ T cells to produce IFN-γ and IL-10 [36]. In addition, pDCs preferentially secrete the proinflammatory chemokine macrophage inflammatory protein- (MIP-) 1α, which recruits mostly Th1-type effector cells and causes the production of other proinflammatory cytokines [37]. Therefore, decreased levels of proinflammatory cytokines/chemokines may result from decreased levels of pDCs and depress the antiviral capacity in patients with DRESS. After reactivation, HHV-6 may further modulate the release of these cytokines from peripheral blood mononuclear cells, including IFN-γ, TNF-α, and IL-1β, as reflected by their increased levels in the blood [31].

7.5. High-Mobility Group Box-1. Damage-associated molecular pattern molecules (DAMPs) released from damaged cells are signals for initiating immune responses in various organs through their activation after interacting with pattern recognition receptors and/or Toll-like receptors, thereby promoting rapid recruitment of bone marrow-derived leukocytes to the target tissues for inflammation and regeneration under various aseptic inflammatory conditions [38, 39]. High-

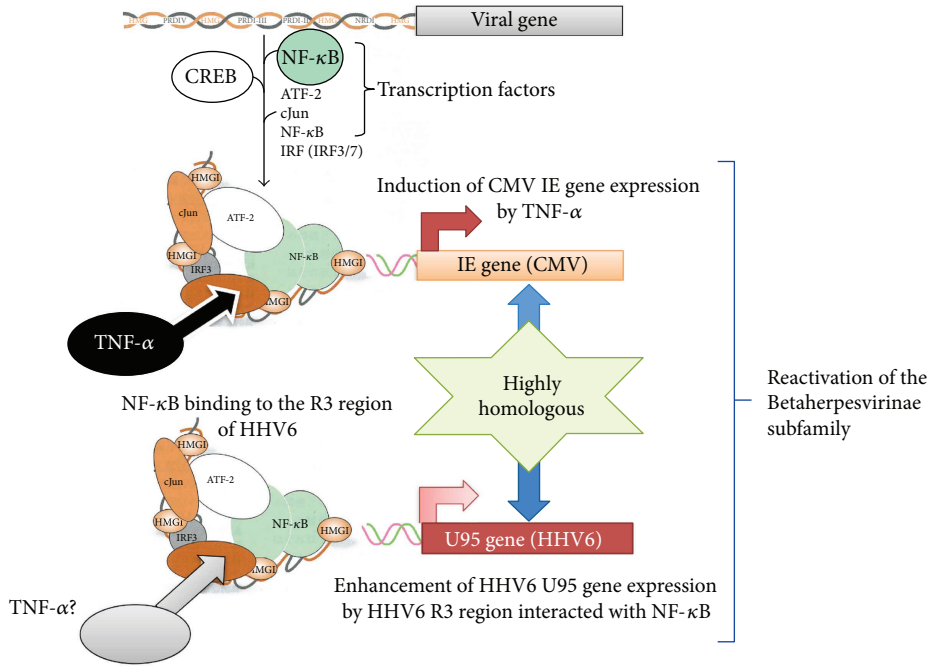


Figure 2: Possible involvement of tumor necrosis factor- (TNF-) α in the reactivation of cytomegalovirus (CMV) and human herpesvirus (HHV)-6. TNF-α may play a role in reactivation of Betaherpesvirinae subfamily members, including CMV and HHV-6. TNF-α enhances the expression of CMV immediate early gene products. Enhancement of HHV-6 U95 gene expression by the R3 region of HHV-6 might interact with nuclear factor- (NF-) κB by TNF-α.

mobility group box (HMGB)-1, one of the most well-known DAMP members, is a nonhistone protein with dual functions: intercellular transcriptional regulation by loose binding to chromatin and extracellular high potency signaling of inflammation to attract and activate various immunocompetent cells including monocytes and myeloid cells [39]. Hashizume et al. [40] demonstrated that the circulating monomyeloid precursors in patients with DIHS were mostly CD11b+ CD13+ CD14 $CD16^{high}$ and showed substantial expression of skin-associated molecules, such as CCR4. CD13+ CD14 cells were also found in DIHS skin lesions, suggesting skin recruitment of this cell population. High levels of HMGB-1 were detected in blood and skin lesions in the active phase of patients with DIHS, and recombinant HMGB-1 showed functional chemoattractant activity for monocytes/monomyeloid precursors *in vitro*. HHV-6 infection of the skin-resident CD4+ T cells was confirmed by the presence of its genome and antigen. This infection was likely mediated by monomyeloid precursors recruited to the skin, as normal CD4+ T cells gained HHV-6 antigen after *in vitro* coculture with highly virus-loaded monomyeloid precursors from patients. Hashizume et al. [40] suggested that monomyeloid precursors harboring HHV-6 are navigated by HMGB-1 released from damaged skin and likely cause HHV-6 transmission to skin-infiltrating CD4+ T cells, which is an indispensable event for HHV-6 replication. Another group also reported increased HMGB-1 levels during the acute stage of DIHS [41]. However, contrary to those reports, Nakajima et al. showed that the serum level of HMGB-1 in SJS/TEN was higher than that of DIHS [42]. Further investigations are needed.

8. Pharmacogenomic Features of Severe Cutaneous Adverse Reactions Including DIHS/DRESS

To date, genetic factors have been shown to play important roles in several types of drug eruptions, including DIHS/DRESS. For example, the human leucocyte antigen- (HLA-) B*15:02 allele was identified as an important predictor of risk for the development of both carbamazepine-induced SJS and TEN in a southeast Asian population [43]; in contrast, the HLA-A*31:01 allele was found to be relevant in European [44] and Japanese populations [45]. Many other pharmacogenomic features of SCAR have been discovered, some of which are ethnically specific. For example, HLA-B*57:01 is associated with abacavir hypersensitivity in Caucasians; HLA-B*58:01 with allopurinol-SCAR (both SJS/TEN and DIHS) in Chinese, Japanese, Koreans, Thais, and Europeans; HLA-A*31:01 with CBZ-SCAR (DIHS) in Han Chinese, Europeans, Japanese and Koreans; HLA-B*15:02 with phenytoin-SJS/TEN in Han Chinese; and HLA-B*B*59:01 and CW*01:02 with methazolamide-SJS/TEN in Koreans and Japanese (Table 2) [46].

The immunogenic complexes involved in T cell-mediated adverse drug reactions contain three components: an HLA protein, a peptide, and a drug [47]. To date, three principal models for this interaction have been developed, based on differences in the roles played by cellular metabolism and antigen processing [48–51]. These are the hapten/prohapten pharmacological interaction with an immune receptor model (the p.i. model) and the altered peptide repertoire model. Illing et al. recently suggested that abacavir hypersensitivity

Table 2: Specific human leucocyte antigen (HLA) types and associated drugs in severe drug eruptions.

Associated drug	HLA allele	Ethnicity
Abacavir	B*57:01	Caucasian, Thai, Cambodian
Allopurinol	B*58:01	Han Chinese, Thai, Japanese, Korean
Carbamazepine	B*15:02	Han Chinese, Thai, Indian, Malaysian
	B*15:11	Japanese, Korean, Han Chinese
	B*59:01	Japanese
	A*31:01	Japanese, Han Chinese, European, Korean
Cold medicine	A*02:06	Japanese, Korean
Dapsone	B*13:01	Han Chinese, Thai
Methazolamide	B*59:01	Korean, Japanese, Han Chinese
Nevirapine	DRB1*01:01	Australian, French
	B*14:02 (or Cw*08:02)	European
	B*35:05	Thai
Phenobarbital	Cw*08:01/Cw*08:02	Sardinian, Japanese
	HLA-A*01:01	Thai
	HLA-B*13:01	Thai
Phenytoin	B*15:02	Han Chinese, Thai
	HLA-B*13:01	Thai
	HLA-B*56:02/04	Thai
Sulfamethoxazole	B*38	European

This table is modified from [46].

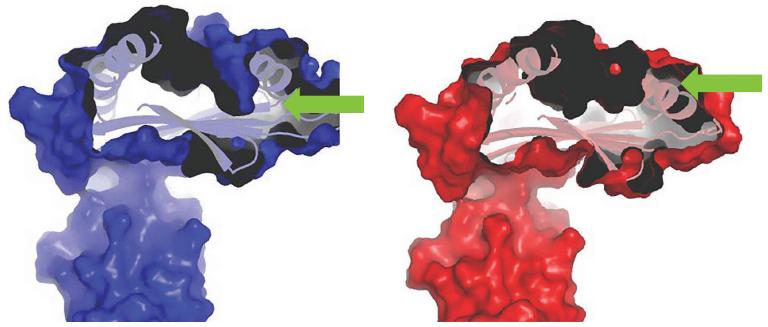


Figure 3: An extra-deep subpocket around the F-pocket of the antigen-binding site of HLA-B*13:01, which was not observed in HLA-B*13:02. HLA-B*13:01 (blue) had an extra-deep subpocket (green arrows) absent from HLA-B*13:02 (red).

syndrome could be explained by reference to the altered peptide repertoire model [47, 48].

Recently, an HLA class I allele, HLA-B*13:01, has been identified as a marker of susceptibility to DIHS attributable to dapsone (dapsone hypersensitivity syndrome) [52–54]. It was initially unclear how dapsone interacted with HLA-B*13:01.

9. Computational Analyses of the Dapsone/HLA-B*13:01 Interactions

It was most surprising that HLA-B*13:01 exhibited a strong association with DIHS attributable to dapsone (dapsone hypersensitivity) but HLA-B*13:02 did not. Only three amino acid residues of 338 differ between HLA-B*13:01 and HLA-B*13:02 [55]. These correspond to $I^{94}I^{95}R^{97}$ in HLA-B*13:01 and $T^{94}W^{95}T^{97}$ in HLA-B*13:02. When we compared the molecular surface representations of the antigen-binding sites, we found that HLA-B*13:01 had an extra, and deep, subpocket around the F-pocket of the antigen-binding site, which was not present in HLA-B*13:02 (Figure 3) [55]. The size of the extra subpocket seemed appropriate to accommodate the aniline group, suggesting that dapsone binds tightly to HLA-B*13:01 using this unique subpocket (Figure 4). In fact, Illing et al. recently suggested that abacavir hypersensitivity syndrome could be explained by reference to the altered peptide repertoire model [47, 48]. In the altered peptide repertoire model, the drug interacts with the antigen-binding cleft of a specific HLA allele and alters the binding of self-peptides to the HLA molecule. This results in a T cell

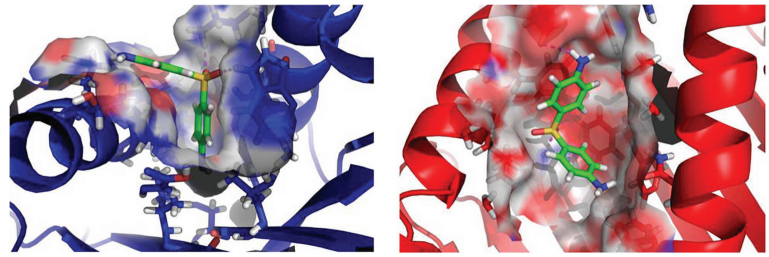


Figure 4: Dapsone binds more tightly to HLA-B*13:01 than to 13:02. Binding models before molecular dynamic simulations for dapsone–HLA-B*13:01 (blue) and dapsone–HLA-B*13:02 (red), based on observations of the stick representation of their HLA three-dimensional homology models. Dapsone (green) inserts are deeper in HLA-B*13:01 (blue) than in HLA-B*13:02 (red).

response. X-ray crystallography revealed that abacavir was specifically bound in the vicinity of the F-pocket of the antigen-binding cleft of the HLA-B*57:01 allele. This region was identified as a marker of susceptibility to abacavir hypersensitivity syndrome. From these findings, an "altered peptide repertoire" model involving the binding of dapsone to HLA-B*13:01 may also be appropriate analogous to the abacavir allergy model.

10. Conclusion

During the course of DIHS, HHV-6 reactivation triggers symptom recurrence and may be fatal by causing serious dysfunctions including liver failure. Therefore, it is essential to identify factors predictive of virus reactivation. In this review, we have emphasized that several cytokines/chemokines including levels of TNF-α and TARC are good biomarkers of virus reactivation; however, further investigations are required. Moreover, the association between causative drugs and genetic factors, including HLA polymorphisms, renders it possible to choose appropriate treatments and improve patient outcomes.

Conflicts of Interest

The author declares that he has no conflicts of interest.

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Review Article

An Updated Review of the Molecular Mechanisms in Drug Hypersensitivity

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Drug hypersensitivity may manifest ranging from milder skin reactions (e.g., maculopapular exanthema and urticaria) to severe systemic reactions, such as anaphylaxis, drug reactions with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS), or Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). Current pharmacogenomic studies have made important strides in the prevention of some drug hypersensitivity through the identification of relevant genetic variants, particularly for genes encoding drug-metabolizing enzymes and human leukocyte antigens (HLAs). The associations identified by these studies are usually drug, phenotype, and ethnic specific. The drug presentation models that explain how small drug antigens might interact with HLA and T cell receptor (TCR) molecules in drug hypersensitivity include the hapten theory, the p-i concept, the altered peptide repertoire model, and the altered TCR repertoire model. The broad spectrum of clinical manifestations of drug hypersensitivity involving different drugs, as well as the various pathomechanisms involved, makes the diagnosis and management of it more challenging. This review highlights recent advances in our understanding of the predisposing factors, immune mechanisms, pathogenesis, diagnostic tools, and therapeutic approaches for drug hypersensitivity.

1. Introduction

Drug hypersensitivity reactions are an important public health problem due to their potential to cause life-threatening anaphylaxis and rare severe cutaneous adverse reactions (SCAR). Drug hypersensitivity can be induced by immunologically mediated reactions (referred as drug allergies) as well as nonallergic direct mast cell-mediated drug reactions. Immunologic reactions have been divided into four categories according to the classical Gell and Coombs system: type I reactions, which are immediate in onset and mediated by IgE and mast cells and/or basophils;

type II reactions, which are delayed in onset and caused by antibody- (usually IgG) mediated cell destruction; type III reactions, which are delayed in onset and caused by IgG drug immune complex deposition and complement activation; and type IV reactions, which are delayed in onset and are T cell mediated [1]. According to the World Allergy Organization (WAO), drug hypersensitivity reactions can also be categorized into immediate reactions and delayed reactions based upon the timing of the appearance of symptoms [2].

Immediate-type reactions usually occur within minutes or hours of drug exposure. The clinical manifestations range from pruritus, urticaria, angioedema, and bronchospasm to anaphylaxis. Type I reactions require the presence of drug-specific IgE or the portion of the drug that forms a hapten complex. Drug-specific IgE is produced upon the first exposure to the drug antigen, and then, it binds to basophils or mast cells with the high-affinity Fc receptor. Upon the next exposure to the same drug, two or more IgE molecules on the basophil or mast cell surface may then bind to one multivalent antigen molecule, initiating a series of cellular activation events. This activation causes the extracellular release of granules with preformed inflammatory mediators, including histamine, leukotrienes, prostaglandins, heparin, and other cytokines [3]. IgE-mediated immunologic drug allergy represents a smaller fraction of drug hypersensitivity compared with nonimmunologic drug hypersensitivity [4]. According to the WAO classification system, immunologic anaphylaxis can be caused by an IgE-mediated or non-IgE-mediated mechanism, whereas nonimmunologic anaphylaxis involves direct mast cell activation [2]. Regardless of the underlying mechanism, however, the clinical symptoms of both types of anaphylaxis are similar and often indistinguishable. The mechanism of immediate-type reactions is explained more fully later in this article. In this review, the terminology used to categorize "immediate" or "delayed" drug hypersensitivity is in accordance with the WAO classification system. At the same time, the immediate-type reactions discussed herein are composed of both IgE-mediated reactions as defined by the Gell and Coombs system, as well as non-IgE-mediated and nonimmunologic anaphylactic reactions.

Delayed-type reactions consist primarily of type IV reactions, which are T cell-mediated delayed-type drug hypersensitivity reactions. These reactions usually take several days or even weeks to manifest following drug exposure. These manifestations range from mild maculopapular exanthema (MPE), contact dermatitis, chronic allergic rhinitis, chronic asthma, nephritis, hepatitis, and fixed drug eruptions (FDEs) to life-threatening SCAR. SCAR includes drug reactions with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS), Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP) [5]. The MPE phenotype consists of self-limited diffuse erythematous macules and papules without systemic involvement [6]. DRESS syndrome, meanwhile, is characterized by cutaneous involvement with typical skin eruptions (e.g., exfoliative dermatitis and generalized maculopapular exanthema), fever, atypical lymphocytosis, eosinophilia, lymphadenopathy, and systemic involvement (e.g., liver involvement and kidney involvement). This hypersensitivity syndrome was first named after many different terms had already been used to describe the syndrome, with those terms, such as "anticonvulsant hypersensitivity syndrome," "allopurinol hypersensitivity syndrome," and "sulfone syndrome," primarily depending on the culprit drug involved [7, 8]. The term "DRESS" was initially proposed by Bocquet et al. in 1996 in order to provide a more concise description of the syndrome and decrease the ambiguity resulting from the various terms previously used to refer to it [9]. That said, it should be noted that DRESS is also termed "DIHS" by Japanese experts, with the criteria of DRESS as defined by the RegiSCAR group and the criteria of DIHS as defined by Japanese experts being similar, except that HHV-6 reactivation is included in the diagnostic criteria for DIHS [10]. This nosology is somewhat confusing; however, there is a consensus that DRESS and DIHS are likely within the same disease spectrum. Specifically, patients with typical DIHS may represent a severe form of DRESS syndrome [11]. SJS and TEN (SJS/TEN) are characterized as a rapidly progressing blistering exanthema of purpuric macules and target-like lesions accompanied by mucosal involvement and skin detachment. SJS is defined as involving less than 10% body surface area skin detachment, SJS-TEN overlap as involving 10–29%, and TEN as involving more than 30% [12]. AGEP, meanwhile, typically presents as a sudden eruption of small nonfollicular pustules on a background of erythema with systemic involvement along with fever and neutrophilia [13].

Most forms of drug hypersensitivity involve T cell-mediated immune responses against specific drug/peptide antigens, leading to various clinical phenotypes. T cell receptor (TCR), $CD4^+$, and $CD8^+$ T cells are involved in the different delayed-type drug hypersensitivity reactions [14]. The molecular mechanisms and checkpoints for drug hypersensitivity include T cell activation and immune responses, cytotoxic proteins and cytokine/chemokine secretion, specific TCR clonotypes, impaired drug metabolism or clearance (e.g., the strong association of cytochrome P450 family 2 subfamily C member 9*3 *(CYP2C9*3)* with phenytoin-induced SCAR), and the cell death mechanisms (e.g., miR-18a-5p-induced apoptosis and annexin A1 and formyl peptide receptor 1-induced necroptosis in keratinocytes). In addition, genetic polymorphisms and specific *HLA* loci also play an important role (e.g., *HLA-B*15:02* for carbamazepine- (CBZ-) induced SJS/TEN, *HLA-B*58:01* for allopurinol-induced SCAR, and *HLA-B*57:01* for abacavir-induced hypersensitivity reactions). Moreover, environmental factors, autoimmune disorders, and patients with a prior medical history of viral infection have also been reported to be implicated in susceptibility to drug hypersensitivity.

2. Clinical Perspectives and Variabilities in Severe Drug Hypersensitivity

2.1. Immediate-Type Hypersensitivity. Immediate-type hypersensitivity reactions may range from urticaria and

angioedema to severe fatal reactions, such as bronchospasm and anaphylaxis. Anaphylaxis is a life-threatening systemic hypersensitivity reaction mainly mediated by mast cells and basophil activation via IgE-mediated, non-IgE-mediated, or nonimmunologic mechanisms. Drugs are the most common anaphylaxis triggers in adults, while foods are the most common triggers in children and teenagers [15]. The incidence of drug-induced anaphylaxis has been reported to range from 0.04 to 3.1%, with a mortality rate of around 0.65% [2]. NSAIDs are the main culprits, followed by beta-lactam antibiotics [16, 17]. Perioperative anaphylaxis also remains an issue due to the administration of various combinations of neuromuscular blocking agents (NMBAs), induction agents (e.g., propofol, etomidate, midazolam, and ketamine), and antibiotics [18, 19]. Nonsteroidal anti-inflammatory drugs (NSAIDs) (with the exception of pyrazolones) are believed to rarely be among the causes of IgE-mediated anaphylaxis, but such anaphylaxis is more commonly related to an aberrant arachidonic acid metabolism [20–22]. The non-IgE-mediated immunologic mechanisms can be mediated by IgG antibodies, as well as by complement or contact system activation, but non-IgE-mediated anaphylaxis is clinically indistinguishable from IgE-mediated anaphylaxis [23, 24]. The causes of non-IgE-mediated immunologic anaphylaxis include biologics, lipid incipients, and dextran [2]. In contrast, nonimmunologic anaphylaxis, previously regarded as a form of pseudoallergic drug reaction, involves the direct stimulation of mast cell degranulation. These reactions are limited to certain groups of drugs, including NSAIDs, such as aspirin, as well as opiates, vancomycin, quinolones, and NMBAs [24, 25]. For radiocontrast media-induced anaphylaxis, the mechanisms are not entirely clear and several mechanisms may be involved, including IgE-mediated or direct stimulating histamine release or the activation of the complement cascades [24, 26, 27].

Due to the complexity of NSAID-induced drug hypersensitivity, a panel of experts from the European Academy of Allergy and Clinical Immunology (EAACI) has proposed a classification and practical approach to cases of drug hypersensitivity caused by NSAIDs [28]. The most frequently occurring type of these cases is cross-reactive hypersensitivity, for which the mechanism is not immunological but, rather, is primarily linked to cycloxygenase-1 inhibition. This immunological type of NSAID-induced hypersensitivity includes NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD), and NSAID-induced urticaria/angioedema (NIUA) [28]. NSAIDs can also induce immunological (noncross-reactive) hypersensitivity reactions, including IgE-mediated single-NSAID-induced urticaria/angioedema or anaphylaxis (SNIUAA), and T cell-mediated single-NSAID-induced delayed hypersensitivity reactions (SNIDHR). Both cross-reactive reactions and SNIUAA are immediate-type reactions [28].

2.2. Delayed-Type Hypersensitivity

2.2.1. Drug Reactions with Eosinophilia and Systemic Symptoms (DRESS)/Drug-Induced Hypersensitivity Syndrome (DIHS). There have been no large epidemiologic studies of DRESS/DIHS, a shortcoming which could be due to the fact that the term "hypersensitivity syndrome" was instead used before [5]. It could also be explained by the difficulty of diagnosing DRESS/DIHS, which presents with a complex natural course, a wide diversity of manifestations, and various laboratory abnormalities, and also because there is no specific code for this condition [29]. The incidence of anticonvulsant-related DRESS/DIHS is about one per 1000 to one per 10,000 new users [30]. DRESS/DIHS can occur in pediatric patients, but is more common in adults [31]. Antiepileptic agents and allopurinol are the most commonly reported offending medications [32]. The symptoms often begin 2 to 6 weeks after drug incubation [9]. Damage to multiple systemic organs may occur during the course of DRESS/DIHS syndrome. The liver is most commonly involved among the organs, with liver involvement having been found in 51–84% of patients [33, 34]. Renal involvement also occurs frequently, having been reported in 10–57% of patients [33, 34]. Lung involvement is the third most common type of systemic involvement and may present in various forms ranging from nonspecific symptoms to interstitial pneumonitis, pleuritis, and acute respiratory distress syndrome [35, 36]. Cardiac involvement, meanwhile, has been reported in 4–27% of patients with DRESS/DIHS [37]. This complication is likely associated with the fatal outcomes of the condition, especially when acute necrotizing eosinophilic myocarditis occurs [38]. Several other systemic organs can also be involved in DRESS/DIHS, including the gastrointestinal tract, pancreas, central nervous system, and thyroid, while multiple organ failure associated with disseminated intravascular coagulation or hemophagocytic syndrome may also occur [31, 39]. The overall mortality rate of DRESS/DIHS is around 10% [32]. The likelihood of mortality in cases of DRESS/DIHS is primarily determined by the degree of systemic involvement [35]. Tachycardia, leukocytosis, tachypnea, coagulopathy, gastrointestinal bleeding, and systemic inflammatory response syndrome (SIRS) have also been found to be associated with poor outcomes in DRESS/DIHS patients [33].

2.2.2. Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN). Large epidemiologic investigations of SCAR, especially SJS/TEN, have been performed in Europe beginning 30 years [40, 41]. The reported incidence rates of SJS/TEN for various countries and ethnicities have included 0.93–1.89 cases (Germany), 1.2 cases (France (TEN)), 1.4 cases (Italy), 5.76 cases (United Kingdom), 8.0 cases (Han Chinese), and 12.7 cases (United States) per million people per year [5, 40–45]. The large variation among these rates of incidence might be due to differences in the studies reporting them, including differences in the populations studied, generational differences, differing diagnostic criteria, and differing methodologies (such as the use of registration databases or electronic nationwide healthcare databases). SJS/TEN can occur in different age groups, but the incidences of SJS, SJS-TEN, and TEN appear to be lower in US children than in adults [46]. Racial disparities in SJS/TEN incidence were first reported by a large population-based study, which found that SJS/TEN is more strongly associated

with people of nonwhite ethnicities, particularly Asians and blacks [42]. Pharmacogenetic studies, meanwhile, have pointed out that the strength of genetic associations is related to the prevalence with which susceptibility alleles are carried in different ethnic populations, such as *HLA-B*15:02* and *HLA-B*58:01* in Asians [47, 48]. Although the above classical examples partially explain the phenomenon of specific drug hypersensitivity in specific ethnicities with specific genetic factors, not all cases of drug hypersensitivity can be fully elucidated using this approach.

Cases of SJS/TEN are primarily induced by medications, but *Mycoplasma pneumonia* infection, viral infection, and collagen vascular diseases have also been found to account for a small portion of such cases [49–52]. The European ongoing case-control surveillance of the SCAR (EuroSCAR) group used a case-control study to identify the drugs carrying a high risk of such reactions and found that they included sulfonamides, aromatic convulsants, allopurinol, oxicam nonsteroidal anti-inflammatory drugs, and nevirapine [53]. Newly developed drugs, such as anticancer target therapies, also have the potential to induce SJS/TEN [54]. SJS/TEN induced by monoclonal antibodies targeting the coinhibitory immune checkpoint with antiprogrammed death-1 (PD-1) (nivolumab) and anticytotoxic T-lymphocyte-associated protein 4 (CTLA-4) (ipilimumab) has likewise been reported [55, 56]. Proton pump inhibitors, meanwhile, have been known to induce type I hypersensitivity reactions, but they carry some risk of inducing life-threatening type IV hypersensitivity reactions as well [57]. That risk, however, is mostly confined to the first 8 weeks drug exposure, after which the onset of SCAR is much less likely [53]. Meanwhile, the ALDEN (ALgorithm for Drug causality in Epidermal Necrolysis) has been used to provide structured assistance for the assessment of culprit drugs in SJS/TEN patients [58].

The mortality rates of the various forms of SJS/TEN are high, at approximately 10% for SJS, 30% for overlapping SJS/TEN, and 50% for TEN, for an overall rate of about 25% [34, 59]. Indeed, the mortality rate for cases of TEN has remained high, with reported rates of 15.8%–49.0%, even with the overall improvements to health care in recent decades [42, 44, 60]. A disease severity scoring system called SCORTEN (SCORe of Toxic Epidermal Necrolysis) built on seven independent variables (age > 40 years; presence of malignancy; body surface area involved > 10%; serum urea nitrogen level > 28 mg/dL; glucose level > 252 mg/dL; bicarbonate [HCO_3] level < 20 mEq/L; and heart rate > 120 beats per minute) can be used to help predict mortality in individual cases of SJS/TEN [61, 62]. Modified versions of this scoring system may be needed for specific populations, like pediatric patients [63].

2.2.3. Acute Generalized Exanthematous Pustulosis (AGEP). The annual incidence of AGEP is estimated to be one to five per million [64]. The EuroSCAR group conducted a large case cohort study of 97 validated cases of AGEP [13]. The mean age of the patients was 56 years (range: 4–91 years) [13]. The list of drugs reported to have been involved is extensive, but certain medications such as aminopenicillins, pristinamycin, quinolones, terbinafine, diltiazem, antimalarials, and Chinese herbs are known to be associated with higher risks of AGEP [13, 65]. The mortality rate of AGEP has been reported to be about 4%, a relatively low rate compared to those of SJS/TEN and DRESS/DIHS [13].

3. Genetic Factors in Drug Hypersensitivity

3.1. Genetic Factors in Immediate-Type Drug Hypersensitivity. Genetic predisposing factors have been reported in cases of immediate-type drug hypersensitivity resulting from the use of beta-lactams, aspirin, and other NSAIDs. Interestingly, HLA class II genes (*HLA-DRA* and the *HLA-DRA*|*HLA-DRB5* interregion) have been linked to immediate reactions to beta-lactams (Table 1) [66]. The genetic variants of proinflammatory cytokines (*IL4*, *IL13*, *IL10*, *IL18*, *TNF*, and *IFNGR1*), the cytokine receptor (*IL4R*), the genes involved in the IgE/FceRI pathway (the galectin-3 gene (*LGALS3*)), and nucleotide-binding oligomerization domain (*NOD*) gene polymorphisms are also strongly associated with beta-lactam-induced immediate reactions (Table 2) [67–73].

The involvements of *HLA-DRA*, *ILR4*, *NOD2*, and *LGALS3* have also been further validated by a replication study [72]. *HLA-DRB1*13:02* and *HLA-DRB1*06:09* are associated, meanwhile, with aspirin-induced urticaria/angioedema [74]. In addition, *HLA-B44* and *HLA-Cw5* have also been reported to be associated with chronic idiopathic urticaria associated with aspirin- and/or NSAID-induced hypersensitivity [75]. Several genetic predisposing factors have been reported to be associated with immediate-type aspirin hypersensitivity, with those factors involving cytokines (TGFB1, TNF, and IL18) and the production and release of mediators (LTC4S, TBXA2R, PTGER4, FCER1A, MS4A2, FCER1G, and HNMT) [76, 77]. Immediate-type hypersensitivity to NSAIDs has also been reported to be associated with genes belonging to the arachidonic acid pathway (*ALOX5*, *ALOX5AP*, *ALOX15*, *TBXAS1*, *PTGDR*, and *CYSLTR1*) [72, 78]. However, the association of common genetic variations in histamine receptor genes was not found in patients with hypersensitivity to NSAIDs [79].

3.2. Genetic Factors in Delayed-Type Drug Hypersensitivity. Recently, the number of pharmacogenetic studies of HLA-associated drug hypersensitivity and related drug-induced syndromes, such as fixed drug reaction, delayed rash, lupus erythematosus, drug-induced liver disease, DRESS/DIHS, SJS, and TEN, has been increasing. These associations are usually drug and ethnic specific (Table 1), which implies that specific HLA molecules may have higher binding affinities for specific drug antigens and present the drug antigens to specific TCRs, causing a series of T cell activations and adverse immune responses.

3.2.1. Aromatic Anticonvulsants. Aromatic anticonvulsants, such as carbamazepine (CBZ), phenytoin (PHT), oxcarbazepine (OXC), and lamotrigine (LTG), are known to carry higher risks of inducing SCAR. A strong genetic association between *HLA-B*15:02* and CBZ-induced SJS/TEN was found in 2004 in Han Chinese (corrected P value $= 3.1 \times 10^{-27}$, odds ratio (OR) = 2504, and 95% confidence interval

Table 1: HLA association with various phenotypes of drug hypersensitivity in different populations.

Associated drug	HLA allele	Hypersensitivity reactions	Ethnicity	Reference
Aromatic anticonvulsants				
Carbamazepine	*B*15:02*	SJS/TEN	Han Chinese, Thai, Indian, Malaysian, Vietnamese, Singaporean, Hong Kongese	[45, 82, 83, 226–230]
	*A*31:01*	DRESS	Han Chinese, European, Spanish	[86, 87, 231]
	*A*31:01*	DRESS/SJS/TEN	Northern European, Japanese, Korean	[88–90]
	*B*15:11*	SJS/TEN	Han Chinese, Japanese, Korean	[89, 232, 233]
	*B*59:01*	SJS/TEN	Japanese	[234]
	*B*38:01*	SJS/TEN	Spanish	[231]
	*B*15:02*	SJS/TEN	Han Chinese, Thai	[81, 84]
	*B*15:02*	SJS/TEN	Han Chinese, Thai	[81, 83]
Oxcarbazepine Phenytoin	*B*15:02*, *B*13:01*, *B*51:01*	SJS/TEN	Han Chinese, Japanese, Malaysian	[91]
	*A*33:03*, *B*38:02*, *B*51:01*, *B*56:02*, *B*58:01*, *C*14:02*	SJS/TEN	Thai	[235]
	*B*51:01*	DRESS	Thai	[235]
	*B*15:13*	DRESS/SJS/TEN	Malaysian	[236]
	*CYP2C9*3*	DRESS/SJS/TEN	Han Chinese, Japanese, Malaysian	[91]
	*CYP2C9*3*	SJS/TEN	Thai	[235]
Phenobarbital Lamotrigine	*B*15:02*	SJS/TEN	Han Chinese	[81, 85, 237]
	*B*38; B*58:01*, *A*68:01*, *Cw*07:18*	SJS/TEN	European	[93, 238]
	*B*38:01*	SJS/TEN	Spanish	[231]
	*A*31:01*	SJS/TEN	Korean	[239]
	*A*24:02*	DRESS/SJS/TEN	Spanish	[231]
Allopurinol	*B*58:01*	DRESS/SJS/TEN	Han Chinese, Thai, Japanese, Korean, European	[92–96]
Antiretroviral drugs				
Abacavir	*B*57:01*	HSS	European, African	[98, 99]
Nevirapine	*DRB1*01:01*	DRESS	Australian	[240]
	*B*35:05*	DRESS	Thai	[101]
	*B*14:02*, *Cw*08:01*, *Cw*08:02*	HSS	Sardinian, Japanese	[102, 241]
	*C*04:01*	DRESS/SJS/TEN	Malawian	[242]
Antibiotics				
Beta-lactam	*DR9*, *DR14.1*, *DR17*, *DR4*	Immediate-type drug hypersensitivity	Chinese	[243]
	DRA rs7192, *DRA* rs8084	Immediate-type drug hypersensitivity	Spanish, Italian	[66]
Cotrimoxazole	*B*15:02*, *C*06:02*, *C*08:01*	SJS/TEN	Thai	[244]
Dapsone	*B*13:01*	HSS	Han Chinese	[105]
Sulfamethoxazole	*B*38:02*	SJS/TEN	European	[93]
Sulfonamide	*A*29*, *B*12*, *DR*7*	TEN	European	[245]
NSAIDs				
Aspirin	*DRB1*13:02*, *DRB1*06:09*	Urticaria/angioedema	Korean	[74]
Aspirin and other NSAIDs	*DRB1*11*	Urticaria/angioedema and hypotension/laryngeal edema	Spanish	[246]
Aspirin and other NSAIDs	*B*44*, *Cw*5*	Chronic idiopathic urticaria	Italian	[75]

Table 1: Continued.

Associated drug	HLA allele	Hypersensitivity reactions	Ethnicity	Reference
Oxicam NSAIDs	*B*73:01*	SJS/TEN	European	[93]
Other drugs				
Methazolamide	*B*59:01*, *CW*01:02*	SJS/TEN	Korean, Japanese	[108]

DRESS: drug reaction with eosinophilia and systemic symptoms; HSS: hypersensitivity syndrome; MPE: maculopapular exanthema; NSAIDs: nonsteroidal anti-inflammatory drugs; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis.

Table 2: Genetic association with pathogenetic pathways in immediate-type drug hypersensitivity.

Associated drug	Ethnicity	Cytokines/chemokines	Production and release of mediators	Drug metabolism	Others	Reference
Beta-lactam antibiotics	Korean	—	*MS4A2*	—	—	[247, 248]
	Chinese	*IL4R*, *IL4*, *IL10*, *IL13*, *IFNGR1*, *STAT6*	—	—	—	[69, 70, 249–252]
	Italian	*IL4R*, *IL13*, *NOD2*	*LGALS3*	—	—	[66, 68, 73]
	French	*IL4R*, *IL10*	—	—	—	[253]
	American	*IL4R*, *IL4*	—	*LACTB*	—	[67]
	Spanish	*IL4R*, *TNF*, *NOD2*	*LGALS3*	—	—	[66, 73, 254, 255]
Aspirin	Korean	*IL18*, *TGFB1*, *TNF*	*ALOX5*, *FCER1A*, *FCER1G*, *HNMT*, *TBXA2R*, *PTGER4*	—	—	[76, 256–263]
	Poles	—	*LTC4S*	—	*GSTM1*	[264]
	Venezuelan	—	*LTC4S*	—	—	[265]
NSAIDs	Spanish	—	*ALOX5*, *ALOX5AP*, *ALOX15*, *CTSLTR1*, *DAO*, *PPARG*, *PTGDR*, *TBXAS1*	—	*CEP68*	[78, 266, 267]
	French	—	*ALOX5*, *PTGER1*	—	—	[268]
	Brazilian	*IL4R*, *IL10*	*DAO*	—	*CTLA4*	[269]

(CI) = 126–49,522) and has further been validated in cohorts of various other Asian populations including Thai, Indian, Malaysian, Vietnamese, Singaporean, and Hong Kongese cohorts [45, 80]. The *HLA-B*15:02* allele has also been identified as the common risk factor for SJS/TEN caused by other aromatic antiepileptic drugs [81], such as PHT [82, 83], OXC [84], and LTG [85]. The association between *HLA* alleles and CBZ-induced SCAR is phenotype and ethnic specific. The *HLA-A*31:01* allele is as specific predictor of CBZ-induced DRESS but not CBZ-induced SJS/TEN in Europeans and Han Chinese [86, 87]. In contrast, a strong association with *HLA-A*31:01* was found in CBZ-induced cutaneous adverse drug reactions (cADR) but not only in DRESS/DIHS in Northern Europeans, Japanese, and Koreans [88–90]. In addition to HLA alleles, a genome-wide association study showed a strong association of CYP2C9*3 with PHT-induced SCAR in patients from Taiwan, Japan, and Malaysia and this finding was further supported by evidence indicating the delayed clearance of plasma PHT levels in PHT-induced SCAR [91].

3.2.2. Allopurinol. Allopurinol is a first-line drug used to treat gouty arthritis and urate nephropathy. In 2005, Hung et al. reported that *HLA-B*58:01* was the genetic risk marker for allopurinol-induced hypersensitivity in Han Chinese (corrected P value $= 4.7 \times 10^{-24}$, OR = 580.3, and 95% CI = 34.4–9780.9) [92]. This correlation was subsequently validated among different populations, including various Asian and European populations [93–96]. The gene dosage effect of *HLA-B*58:01* also influences the development of allopurinol-induced hypersensitivity (OR = 15.3 for *HLA-B*58:01* heterozygotes and OR = 72.5 for homozygotes), and the strength of the *HLA-B*58:01* association has been found to be correlated with the disease severity of allopurinol-induced hypersensitivity (OR = 8.5 for MPE, OR = 44.0 for SCAR) [97].

3.2.3. Antiretroviral Drugs, Antibiotics, and Other Drugs. The antiretroviral drugs, such as abacavir and nevirapine, are also known to cause hypersensitivity reactions. The association with abacavir was first found in 2002 due to the significant association between the *HLA-B*57:01* and abacavir-induced hypersensitivity reactions (corrected P value < 0.0001, OR = 117, and 95% CI = 29–481). The positive predictive value of *HLA-B*57:01* for abacavir hypersensitivity reactions has been reported to be 55% in Caucasians [98, 99]. Nevirapine, meanwhile, has been associated with nevirapine-induced hypersensitivity or DRESS in patients with *HLA-DRB1*01:01* in Western Australia [100], *HLA-B*35:05* in Thailand [101], and *HLA-Cw8* in Japan [102]. In addition, several antibiotic-induced hypersensitivity reactions and pharmacogenomic associations have also been reported,

such as sulfonamide-induced allergic reactions [103], penicillin-induced SCAR [104], *HLA-B*13:01* and dapsone-induced hypersensitivity syndrome in Chinese [105], *HLA-B*57:01* and flucloxacillin-induced liver injury [106], and *HLA-A*02:01* and *HLA-DQB1*06:02* and amoxicillin-clavulanate hepatitis [107]. Other pharmacogenomic associations include *HLA-B*59:01* and methazolamide-induced SJS/TEN in Koreans and Japanese [108], *HLA-B*73:01* and oxicam-induced SJS/TEN in Europeans [93], and *ABCB11*, *C-24T*, *UGT2B7*2*, and *IL-4 C-590-A* and diclofenac-induced liver disease in Europeans [109, 110].

4. Cellular Immunology and Immune Mechanisms in Drug Hypersensitivity

4.1. Antigen Presentation and Processing. Drugs are considered to be foreign antigens and bind to the HLA/peptide/TCR complex to trigger immune and hypersensitivity reactions. There are four hypotheses regarding drug presentation mechanisms that have been proposed to explain how small drug antigens might interact with HLA and TCR in drug hypersensitivity: (1) the hapten theory, (2) the pharmacological interaction with immune receptors (p-i) concept, (3) the altered peptide repertoire model, and (4) the altered TCR repertoire model [111–115].

First, the hapten theory states that the culprit drugs or their reactive metabolites are too small to be immunogenic on their own, whereas they covalently bind to the endogenous peptides to form an antigenic hapten-carrier complex. The hapten-carrier complex is presented to the HLA molecule and then recognized by TCR, resulting in the induction of drug-specific cellular or humoral immune responses. The hapten theory has been shown to be valid in cases of penicillin-induced cADR [111, 116]. Second, the pharmacological interaction with immune receptor (p-i) concept postulates that drugs may directly, reversibly, and noncovalently bind to the HLA and/or TCR protein and bypass the classic antigen-processing pathway in antigen-presenting cells. Wei et al. previously found that CBZ/aromatic antiepileptic drugs can directly interact with *HLA-B*15:02* protein. No intracellular antigen processing or drug metabolism was involved in the *HLA-B*15:02* presentation of CBZ [112]. Oxypurinol, the reactive metabolite of allopurinol, provides another example of the p-i concept in that it can directly and immediately activate drug-specific T cells via the preferential use of *HLA-B*58:01* without intracellular processing [113]. Third, the altered peptide repertoire model states that the culprit drugs occupy the position in the peptide-binding groove of the HLA protein, changing the binding cleft and the peptide specificity of HLA binding. Abacavir-induced hypersensitivity has been found to belong to this model, as the crystal structure of *HLA-B*57:01* has been found to form complexes with abacavir and peptides [114, 115]. These studies showed that abacavir binds to the F-pocket of *HLA-B*57:01* and alters the shape and chemistry of the antigen-binding cleft, thereby altering the repertoire of endogenous peptides and resulting in polyclonal T cell activation and autoimmune-like systemic reaction manifestations. Finally, the altered TCR repertoire model suggests that some drugs, such as sulfamethoxazole, directly interact with TCR, but not with the peptides or HLA molecules. The drug antigens bind to specific TCRs and alter the conformation of those TCRs, giving them the potential to bind to HLA-self peptide complexes to elicit immune reactions [117]. In this model, TCR is regarded as an initial drug interaction molecule, suggesting that TCR is as crucial as HLA molecules and contributes to the occurrence of drug hypersensitivity. Furthermore, viruses have also been proposed to participate in HLA/drug/TCR interactions, in that they may provide exogenous peptides for drug presentation and play important roles in cADR [116].

4.2. Cellular Immunology and Immune Molecules Involved in Drug Hypersensitivity

4.2.1. Immediate-Type Drug Hypersensitivity. Immediate-type drug hypersensitivity can be mediated by IgE-mediated or non-IgE-mediated mechanisms [118]. IgE-mediated mechanisms are mediated by drug-specific IgE via an immune response to a hapten/carrier complex. In the primary drug sensitization, drug-specific IgE is formed when plasma cells are transformed from activated B cells and interact with T cells. In an allergic reaction, drug allergens bind to mast cells or basophils with high-affinity Fc receptors, to which drug-specific IgE is bound, causing degranulation of the mast cells or basophils that results in the release of various mediators, such as histamine, leukotrienes, prostaglandins, and cytokines [3]. Degranulation has recently been proposed to occur in two main forms that are related to reaction severity and progression: piecemeal degranulation and anaphylactic degranulation [2, 119]. Piecemeal degranulation is mediated through the upregulation of CD203c on basophils via the formation of small vesicles from the histamine-containing granules quickly shuttling to the plasma membrane to cause more severe and rapid reactions [120]. Anaphylactic degranulation results in the fusion of the main histamine-containing granules with the plasma membrane, releasing the entire contents of granules to the extracellular space and exposing CD63 on the surface of basophils [120].

The non-IgE-mediated immunologic mechanisms are mediated by IgG antibodies or by complement activation [23, 24]. IgG-mediated anaphylaxis has been established in mouse models, wherein the use of drugs with specific IgG bound to FcγRIII stimulates the release of platelet-activating factor (PAF) by basophils, macrophages, or neutrophils [24]. Although the IgG-mediated anaphylaxis mechanism has not been fully demonstrated in humans, some studies have shown that PAF is an essential mediator in such anaphylaxis [121]. In addition, a novel gain-of-function splice variant of FcγR FcγRIIA has been identified with the presence of IgG anti-IgA antibodies in patients with common variable immunodeficiency who developed anaphylaxis after intravenous immunoglobulin infusion [122]. Moreover, biological agents with IgA and infliximab have been shown to induce anaphylaxis in the absence of specific IgE but with high levels of specific IgG [123–125]. These observations also provide some additional evidence

for IgG-mediated anaphylaxis. Furthermore, complement activation can be induced through the absence of agent-specific IgE or IgG antibody immunocomplexes [24]. This condition can be observed in patients undergoing hemodialysis with a new dialysis membrane, protamine neutralization of heparin, and polyethylene glycol infusion [23, 126]. Drugs solubilized in therapeutic liposomes and lipid-based excipients (such as Cremophor EL used as the diluent for older preparations of propofol and paclitaxel) can form large micelles with serum lipids and cholesterol to stimulate the complement system [23, 126]. This activation of complement mechanisms further causes the release of C3a, C5a, and C5b-9, which trigger, in turn, the activation of mast cells, basophils, and other cells via their specific receptors, resulting in degranulation and mediator release [24].

The nonimmunologic-type hypersensitivity reaction directly activates mast cell degranulation without involving the activation of the immune system. There are several specific agents that induce different mechanisms beyond the direct immunoglobulin-mediated activation or complement activation. Oversulfated chondroitin sulfate-contaminated heparin was found to have caused various cases of anaphylaxis around 2007-2008 via the direct activation of the kinin system with increased production of bradykinin, C3a, and C5a [127]. The triggering of factor XII-driven contact system activation-mediated bradykinin formation also plays a key role in anaphylaxis [24]. NSAIDs, including aspirin, can result in anaphylactic reactions via the inhibition of cyclooxygenase with a decrease in the production of prostaglandins and the increased generation of cysteinyl leukotrienes [23]. Vancomycin can directly activate mast cells and/or basophils, leading to the release of histamine [128]. This mechanism was suggested to be mediated via the calcium-dependent activation of phospholipase-C and phospholipase-A2 pathways [128]. Opiates (e.g., meperidine, codeine, and morphine) also cause histamine release via direct mast cell degranulation [129]. Recently, it was proposed that nonimmunologic hypersensitivity reactions may also be mediated through the MAS-related G protein-coupled receptor-X2 (MRGPRX2) in cases involving specific drugs, such as icatibant, neuromuscular blocking drugs, and quinolone antibiotics [25]. The interaction of certain drugs with this mast cell receptor can stimulate degranulation and the release of TNF-α and prostaglandin D2 (PGD2), among other molecules, leading to nonimmunologic anaphylactic reactions [25]. The mouse counterpart of MRGPRX2 that participates in peptidergic drug-induced pseudoallergic reactions has been newly identified and could potentially be applied in preclinical screening models [25, 130].

4.2.2. Delayed-Type Drug Hypersensitivity. The main concept used to explain the pathomechanisms of delayed-type drug hypersensitivity consists of the view that specific T lymphocytes or natural killer (NK) cells are activated upon antigen recognition or Fas/FasL interaction and that various cytotoxic proteins, including perforin/granzyme B, and granulysin, are then released to attack keratinocytes or other cells, inducing skin rash or epidermal necrosis. In addition, several other cytokines/chemokines, including TNF-α, IFN-γ, GM-CSF, TARC/CCL17, IL-6, IL-8/CXCL8, IL-15, and IL-36, are also known to participate in the immune reactions of drug hypersensitivity. These cytokines/chemokines have been found to be highly expressed in the skin lesions, blister fluids, blister cells, peripheral blood mononuclear cells (PBMC), or plasma of patients. These immune mediators are responsible for the trafficking, proliferation, regulation, or activation of T lymphocytes and other leukocytes, thereby affecting the clinical presentations of drug hypersensitivity in various ways (Table 3).

(1) Fas-FasL Interaction. Fas ligand (FasL) belongs to the tumor necrosis factor (TNF) family. The binding of Fas and FasL plays an important role in regulating the immune system and is involved in the apoptosis of epidermal cells in patients with drug hypersensitivity. Briefly, upon Fas–FasL interaction, the Fas-associated death domain protein (FADD) is recruited and binds to the Fas–FasL complex. The FADD then recruits procaspase 8, bringing multiple copies of procaspase 8 together, which in turn autoactivate to become caspase 8, triggering the caspase cascade and resulting in intracellular DNA degradation [131]. Viard et al. proposed that a suicidal interaction between Fas and FasL, which are both expressed by keratinocytes, leads to the extensive necrosis of epidermal cells in individuals with SJS/TEN [132].

(2) Perforin/Granzyme B. A controversial hypothesis suggests that perforin and granzyme B play more important roles in the keratinocyte death in SJS/TEN than does the Fas–FasL interaction [133]. Granzymes are serine proteases that are released by cytoplasmic granules and can induce programmed cell death in the target cells. Upon activation, drug-specific cytotoxic T lymphocytes (CTL) and NK cells produce perforin, which can bind to and punch a channel through the cell membrane, promoting the entry of granzyme B into the target cells to activate the caspase cascade and the succeeding apoptosis [134]. Delayed reactions to drugs have shown that increasing levels of perforin and granzyme B are related to the disease severity of drug hypersensitivity [131].

(3) Granulysin. Granulysin is a cytolytic protein mainly released by CTL and NK cells. It functions to create holes in the cell membranes and thereby destroy target cells. In 2008, Chung et al. reported that 15 kDa secretory granulysin serves as a key mediator for the disseminated keratinocyte apoptosis seen in SJS/TEN [135]. In that study, the increased level of granulysin in blister fluids from the skin lesions of SJS/TEN patients was much higher than the levels of other cytotoxic proteins, such as perforin, granzyme B, and FasL, and depleting the granulysin reduced the cytotoxicity [135]. Further studies demonstrated that granulysin is strongly expressed in patients with drug-induced FDE, DRESS/DIHS, and SJS/TEN but not MPE [136–138].

(4) TNF-α, IFN-γ, TARC, IL-15, and Other Cytokines/Chemokines in SJS/TEN, DRESS/DIHS, and AGEP. TNF-α is a major proinflammatory cytokine and is produced by

Table 3: Delayed-type drug hypersensitivity-related cytokines and chemokines.

Phenotype	Cytokines/chemokines	Skin or blister	Plasma	PBMC	References
DRESS/DIHS	TNF-α		+		[160]
	IFN-γ	+	+	+	[270–272]
	IL-2			+	[270]
	IL-4			+	[270]
	IL-5			+	[270]
	IL-6		+		[160]
	IL-13			+	[270]
	IL-15		+		[138]
	TARC/CCL17		+		[273]
SJS/TEN	TNF-α	+	+	+	[131, 138, 141–143, 274, 275]
	IFN-γ	+		+	[131, 142, 143, 274]
	IL-2	+		+	[131, 143]
	IL-5	+			[143]
	IL-6	+	+	+	[143, 153, 154, 138]
	IL-8/CXCL8		+		[138]
	IL-10	+	+	+	[142, 153]
	IL-12	NS			[142]
	IL-13	+			[143]
	IL-15	NS	+		[142, 138]
	IL-18	+			[142]
	CCR3	+			[143]
	CXCR3	+			[143]
	CXCR4	NS			[143]
	CCR10			+	[152]
AGEP	IL-8/CXCL8	+			[145, 146]
	IL-36	+			[147, 148]
	GM-CSF			+	[145]

AGEP: acute generalized exanthematous pustulosis; CCR: C–C chemokine receptor; CXCR: CX chemokine receptor; DIHS: drug-induced hypersensitivity syndrome; DRESS: drug reactions with eosinophilia and systemic symptoms; IFN-γ: interferon-γ; IL: interleukin; NS: not significant; SJS/TEN: Stevens–Johnson syndrome and toxic epidermal necrolysis; TNF-α: tumor necrosis factor-α.

macrophages, T lymphocytes, NK cells, neutrophils, mast cells, and eosinophils. It regulates immune responses through the induction of cell apoptosis, activation, differentiation, and inflammation [139]. TNF-α was highly expressed and suggested to be responsible for the extensive necrosis of skin lesions of SCAR patients [140, 141]. IFN-γ is critical for both innate and adaptive immunity against viral and bacterial infection, and it is predominantly produced by $CD4^+$ T helper cells, $CD8^+$ CTL, and NK cells. IFN-γ was found to be increased in the skin tissue, blister cells, and plasma of patients with erythema multiforme, SJS, TEN, and DRESS/DIHS [131, 142, 143]. The immune mechanism of AGEP is not yet well understood. However, high levels of IL-8/CXCL8 production and the recruitment of neutrophils have been observed in the skin lesions of AGEP patients [144–146]. Mutations in the *IL36RN* gene encoding the IL-36 receptor antagonist (IL-36Ra) have also been identified in AGEP patients [147, 148]. DRESS/DIHS is characterized by leukocytosis with atypical lymphocytosis or eosinophilia [149]. Serum thymus and activation-regulated chemokine (TARC) was identified as a potential biomarker for early indication of the disease and a predictor of disease activity in DRESS/DIHS [150, 151]. Compared to patients with MPE and SJS/TEN, the TARC levels in patients with DRESS/DIHS are significantly higher during the acute phase and are correlated with skin eruptions [151]. Interleukin-15 (IL-15) is a cytokine that can induce the proliferation of NK cells and other leukocytes, and it has been found to be associated with the disease severity and mortality of SJS/TEN [138]. IL-15 has also been shown to enhance the cytotoxicity of cultured NK cells and blister cells from TEN patients [138]. In addition, other cytokines and chemokine receptors, including IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-18, CCR3, CXCR3, CXCR4, and CCR10, have been found to be upregulated in the skin lesions, blister fluids, PBMC, or plasma of drug hypersensitivity patients and to participate in the immune regulation of drug hypersensitivity [131, 138, 142, 143, 152–154].

(5) Syndrome-Specific Effector Cells. SJS/TEN is characterized by profound necrosis localized to the epidermis. Cytotoxic CD8 T cells, natural killer cells, and natural killer T cells

producing the cytotoxic molecules, especially granulysin, which causes extensive keratinocyte death, are enriched in blister fluid samples from the skin lesions of patients with SJS/TEN. Granulysin serum levels are correlated with the severity of acute disease and mortality [135, 155]. These cytotoxic cells mediate the disease pathogenesis. It is shown that the function of regulatory T cells (Tregs) in SJS/TEN is inadequate, although present in normal frequency [156]. Immunological changes of DRESS/DIHS are characterized by the increase of atypical lymphocytes or eosinophils [149, 157]. Eosinophilia can be observed in 60–95% of DRESS/DIHS patients at the early stage of the illness [32, 157]. Most of DRESS patients had increased numbers of $CD4^+$ T cells in the acute stage, which was associated with the severity of clinical symptoms, such as the extent of skin rash and reactivations of virus [158]. In addition, Tregs play important roles in DRESS/DIHS pathogenesis. Dramatic expansions of functional Tregs are found in the acute stage of DRESS/DIHS [156]. It is hypothesized that $CD4^+FoxP3^+$ T cells that are home to skin serve to limit the severity of acute disease by regulating the cytotoxic effector T cell responses. However, Treg responses eventually exhaust and this might contribute to ongoing viral replication and intermittent recurrence of clinical symptoms [156, 159]. In patients with AGEP, it is shown that the increased neutrophilic inflammatory processes are regulated by T lymphocytes, which is important in the pathogenesis. The recruitment of neutrophils was observed in the skin lesions of the patients with the late phase of disease development [144, 145].

5. Environmental Factors and Viral Infections in Drug Hypersensitivity

In addition to drug antigens, hypersensitivity reactions may be induced by other pathogens, such as *Mycoplasma pneumonia*, or viral infections. Virus-drug interactions associated with viral reactivation may also exist. For example, it is well known that human herpesvirus-6 (HHV-6) plays an important role in DRESS/DIHS. HHV-6 reactivation in patients with DRESS/DIHS may increase T cell activity after the initiation of the drug eruption and induce the synthesis of proinflammatory cytokines, including TNF-α and IL-6, which may in turn modulate the T cell-mediated responses [160]. Shiohara et al. reviewed the associations between viral infections and drug rashes, as well as the mechanisms by which viral infections induce drug rashes. The sequential reactivations of several herpes viruses (HHV-6, HHV-7, Epstein-Barr virus (EBV), and cytomegalovirus (CMV)) were found to be coincident with the clinical symptoms of drug hypersensitivity reactions [161]. Chung et al. reported that a new variant of coxsackievirus A6 (CVA6) acting as the causative agent may induce widespread mucocutaneous blistering reactions mimicking the features of erythema multiforme major or SCAR [52]. In addition, the virus may also provide exogenous peptides for drug presentation and participate in HLA/drug/TCR interactions. White et al. recently proposed that some patients may acquire primary infection via HHVs or other pathogens that in turn induce drug hypersensitivity [116]. The presence of HHV peptides in patients with high-risk HLA alleles may trigger the activation of cytotoxic T cells, thereby resulting in the development of SCAR. The pathogenic factors underlying the unusual presentations of drug hypersensitivity related to viral infections need to be further investigated.

6. Diagnostic Tools for Drug Hypersensitivity

6.1. Diagnostic Tools for Immediate-Type Drug Hypersensitivity. The most commonly used laboratory test for confirming a diagnosis of anaphylaxis consists of determining the patient's total serum tryptase level [162]. Serial measurements of tryptase levels can be taken during an anaphylactic episode, although measurements of the baseline level are considered to be most useful. In fact, while serial measurements of tryptase levels taken during an anaphylactic episode can serve as useful markers for evaluating these reactions, this approach is not used so widely in clinical practice due to the limitations involved in measuring tryptase during the acute phase of an episode. Elevated levels of histamine, the first mediator released by mast cells, in plasma or urine are also consistent with anaphylaxis [2]. However, plasma histamine levels are only transiently elevated, making them of little utility if the patient is evaluated more than 1 hour after onset of the episode [163]. At the same time, normal levels of tryptase or histamine do not preclude a diagnosis of drug hypersensitivity [15]. Other newly identified biomarkers, such as PAF and carboxypeptidase A3, bring hope for enhancing diagnostic accuracy, although their use remains experimental [15, 164].

For IgE-mediated hypersensitivity reactions, serum drug-specific IgE (sIgE) quantification and the basophil activation test (BAT) are frequently used to assess the culprit drug. The tests used to conduct sIgE immunoassays consist of radioallergosorbent testing (RAST), enzyme-linked immunosorbent assays (ELISAs), and fluoroenzyme immunoassays (FEIAs) [165]. While RAST or ELISAs are usually conducted using in-house techniques, FEIAs can be performed using commercial products, such as the ImmunoCAP-FEIA system [166–168]. Only a few products are available, meanwhile, for some drugs, particularly beta-lactam antibiotics [167, 169]. The sensitivity of the various immunoassays used has been found to average 62.9%, while the average specificity, PPV, and NPV are 89.2%, 83.3%, and 77.8%, respectively [168]. The average NPV is also relatively low in order to exclude allergic reactions and determine whether to perform a provocation test [170]. In comparison, the BAT test provides a higher average specificity (94.6%) and PPV (93.4%) than immunoassays [168]. The test uses flow cytometry after drug stimulation to determine the levels of basophil activation or degranulation markers; the upregulation of CD63 and CD203c is also usually measured [171]. Of note, the results of the BAT for aspirin/NSAID-induced hypersensitivity remain inconclusive due to the fact that they encompass both IgE-mediated allergic reactions and nonimmunological intolerances, limiting the use of the BAT in assessing non-IgE-mediated reactions [172]. Mediator release assays, meanwhile, measure the mediator released (histamine or leukotriene 4) in a supernatant upon cell activation after

drug stimulation, but these assays have exhibited sensitivity and specificity levels too low for them to be recommended for the purposes of diagnosis [169, 173].

6.2. Diagnostic Tools for Delayed-Type Drug Hypersensitivity. The discovery of biomarkers for drug hypersensitivity is crucial for clinical purposes, including the early diagnosis and better prediction of this disease in order to prevent complications. We previously found granulysin to be a key cytotoxic molecule responsible for disseminated keratinocyte necrosis through the action of cytotoxic lymphocytes or NK-cell-mediated cytotoxicity with no direct cellular contact [135]. A significant correlation between the granulysin levels in blister fluids and clinical severity was also found [135]. In addition, the serum granulysin levels in patients with SJS/TEN have also been found to be significantly elevated before the development of skin detachment or mucosal lesions but then to drop rapidly within 5 days of disease onset [136]. As a potential marker for the early phase of SJS/TEN, a simple rapid immunochromatographic test for elevated serum granulysin was developed for immediate clinical use. Additionally, prolonged elevation of serum granulysin has also been found in DIHS patients, indicating that such elevation could possibly be used for the purposes of early diagnosis and predicting disease prognosis [174]. Furthermore, the levels of IL-15 were correlated with the disease progression and mortality of SJS/TEN at early stage [138]. Serum IL-15 levels can be further utilized as a marker for early diagnosis and prognosis monitoring [138]. For DRESS/DIHS, serum TARC levels in patients with DRESS/DIHS have been reported to be significantly higher than those in patients with SJS/TEN and MPE during the acute phase and to be correlated with skin eruptions [151]. TARC was thus identified as a potential biomarker for the early indication and disease activity of DRESS/DIHS and also for determining the prognosis of systemic severity of inflammation in drug eruptions other than SJS/TEN [150, 151]. For AGEP, meanwhile, no specific markers for diagnosing or predicting the disease have been identified at present [175].

Drug rechallenge is considered the gold standard for confirming a potential offending drug; however, its use is not practical due to the possible life-threatening consequences. As such, there is still no standard method for the confirmation of drug causality. Nonetheless, since HLA genotyping has been useful in screening for populations at risk for SCAR, HLA genotyping might be helpful for identifying culprit drugs via specific HLA alleles in at-risk populations [48, 176]. Several *in vitro* tests can be used to assist in the confirmation of drug causality, but the exact sensitivity and specificity of such tests are not well known [177, 178]. There are several tests currently available: the lymphocyte transformation test (LTT), ELISpot (Enzyme-linked immunospot assay) intracellular cytokine staining, and the enzyme-linked immunosorbent assay (ELISA) for the secretion of cytotoxic mediators including inflammatory cytokines, chemokine–chemokine receptors, IFN-γ, Fas–Fas ligand, perforin, granzyme B, and granulysin [179]. The LTT is a reproducible test for measuring the enhanced proliferative response of PBMC after the sensitization of T cells to a drug [180]. However, the sensitivity of the test has reportedly varied among various studies involving various drugs and clinical phenotypes and different timings for use of the test [181, 182]. The relevance of using the LTT in testing for SJS/TEN was relatively lower those using than DRESS/DIHS and AGEP [182]. Several modifications can help to increase the sensitivity of the LTT or ELISPOT, including stimulation with anti-CD-3/CD28 antibody-coated microbeads with IL-2, depletion of Treg/CD25hi cells, or the combined addition of anti-CTLA4 and anti-programmed cell death ligand 1 (PD-L1) antibodies to PBMC cultures [183–185]. IFN-γ-ELISpot showed a similar sensitivity (67%) and specificity in DRESS, but a higher sensitivity (71%) in SJS/TEN [179]. The data for an ELISA-based test used to detect granulysin showed better sensitivity (86%) in SJS/TEN, but the evidence was limited due to the small number of cases in the study [186]. Further larger studies will thus be needed to confirm both the sensitivity and specificity.

In vivo patch tests provide a low-risk method for reproducing delayed hypersensitivity with moderate reexposure of patients to suspected offending drugs [187]. The value of patch testing depends on the phenotypes and drugs involved. The sensitivity of such testing is generally <70%, but higher sensitivities have been reported for AGEP and for some selected populations such as abacavir-hypersensitivity, carbamazepine-induced SJS/DRESS, and fixed drug eruption patients [178, 187, 188]. The skin tests involving a prick or intradermal testing are considered to be crucial tools for evaluating drug hypersensitivity reactions, including IgE-mediated or delayed-type hypersensitivity, in both the European and American guidelines [22, 189–191]. However, these skin tests are usually not suggested for SCAR patients due to the risk of relapse, although late-reading intradermal tests are of value for AGEP patients and negative patch tests are of value for SCAR patients [187, 192].

7. Therapeutic Approaches in Drug Hypersensitivity

7.1. Therapeutic Approaches in Immediate-Type Drug Hypersensitivity. Anaphylaxis is a medical emergency and epinephrine is the treatment of choice for anaphylaxis to prevent its progression to a life-threatening condition [15, 193]. Epinephrine should be administered as soon as possible without delay to avoid mortality [194]. The intramuscular injection of epinephrine into the middle of the outer thigh is recommended to treat anaphylaxis in most settings and in patients of all ages [195]. Glucagon is indicated for patients receiving beta-blockers with refractory symptoms [196]. The use of corticosteroids was previously believed to decrease the risk of biphasic and protracted reactions; however, a systematic review of the literature failed to retrieve any randomized controlled trials to confirm their effectiveness [197]. An emergency department-based study also failed to find a decrease in the rates of return visits or biphasic reactions among patients treated with glucocorticoids [198]. These adjunctive therapies, including corticosteroids, antihistamines, and bronchodilators, could help to relieve symptoms,

but should not be substituted for epinephrine or delay the use of epinephrine [199, 200].

7.2. Therapeutic Approaches in Delayed-Type Drug Hypersensitivity. For the treatment of severe delayed-type drug hypersensitivity, such as SJS/TEN, there are no optimal treatment guidelines. Thus far, in fact, only a few randomized trials that could be regarded as references to guide treatment have been conducted. The efficacy of systemic immunosuppressants or immunomodulatory treatments (e.g., corticosteroids, cyclosporine, intravenous immunoglobulins (IVIg), and plasmapheresis) still remains controversial. Systemic corticosteroids could be the most common treatment option, but the prior use of corticosteroids was found to prolong disease progression with no definite benefit in terms of survival [60, 201–203]. IVIg is one of the most commonly utilized therapies for SJS/TEN and is frequently the adjunctive therapy used for severe cases or pediatric patients [204]. In a meta-analysis, however, IVIg, even high doses of IVIg, failed to achieve statistically significant results supporting the conclusion that it is clinically beneficial [204, 205]. IVIg has been found to yield better outcomes in pediatric patients, but children with TEN usually have lower rates of mortality and better prognoses than adult patients [204, 206]. Cyclosporine, has been found to decrease the mortality rate and the progression of detachment in adults in an open-label phase II trial [207]. However, one recent cohort study revealed a statistically insignificant survival benefit for cyclosporine therapy compared to supportive care [208]. In contrast, the first meta-analysis of 7 studies regarding the effect on mortality of cyclosporine in the treatment of SJS/TEN showed a beneficial effect [209]. A trend identified in the same study also indicated that cyclosporine demonstrated better survival than IVIg [209]. There have also been an increasing number of case reports regarding the benefit of treatment with anti-TNF-α biologic agents for patients with TEN [210–215]. One recent systemic review showed that glucocorticosteroids and cyclosporine are the most promising therapies in terms of survival benefit, but no such benefits were observed for IVIg, plasmapheresis, thalidomide, cyclophosphamide, hemoperfusion, tumor necrosis factor inhibitors, or granulocyte colony-stimulating factor [216]. Meanwhile, IL-15 was demonstrated to be a major cytokine orchestrating SJS/TEN, indicating that further novel therapeutics including IL-15 blockers, the mammalian target of rapamycin (mTOR) inhibitors, and Janus kinase/signal transducers and activators of transcription (JAK/STAT) inhibitors hold promise for impacting various therapeutic targets [138, 217]. That said, further prospective, randomized controlled studies are needed to provide more definitive conclusions regarding treatment in patients with SJS/TEN.

Systemic corticosteroids have been considered the treatment of choice for patients with DRESS/DIHS, but they may be associated with an increased risk of complications such as opportunistic infections [218]. CMV and HHV-6 viral loads were also reported to be increased in patients receiving systemic corticosteroids, while EBV loads were higher in patients not receiving systemic corticosteroids [219]. Antiviral medications such as ganciclovir can be given in addition to steroids and/or IVIg in cases of severe disease with confirmation of viral reactivation [220]. Several previous studies have reported the effectiveness of treatment with IVIg [221]. However, the premature discontinuation of a prospective study regarding the role of IVIg treatment occurred due to severe adverse effects [222]. Plasmapheresis and other immunosuppressive drugs, such as cyclophosphamide, cyclosporine, interferons, muromonab-CD3, mycophenolate mofetil, and rituximab, may also be potential therapies [221]. Among the above treatments, the use of cyclosporine was successful in 2 recent cases with rapid response, and so, its use could be considered for patients with concerns about using longer courses of systemic corticosteroids [223]. Supportive treatment with topical steroid-based treatments for AGEP is suggested due to the mostly benign and self-limiting course of the condition [224, 225]. Meanwhile, the administration of systemic steroids for a short period can be considered for severe and refractory cases [175].

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors' Contributions

Yi-Giien Tsai and Wen-Hung Chung contributed equally to this work.

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Research Article

The Epidemiology of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in China

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Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are life-threatening disease. However, there are only few epidemiologic studies of SJS/TEN from China. To analyze the clinical characteristics, causality, and outcome of treatment for SJS/TEN in China, we reviewed case reports of patients with SJS/TEN from the China National Knowledge Infrastructure (CNKI) and Wanfang database from 2006 to 2016 and patients with SJS/TEN who were admitted to the First Affiliated Hospital of Fujian Medical University during the same period. There were 166 patients enrolled, including 70 SJS, 2 SJS/TEN overlap, and 94 TEN. The most common offending drugs were antibiotics (29.5%) and anticonvulsants (24.1%). Carbamazepine, allopurinol, and penicillins were the most common single offending drugs (17.5%, 9.6%, and 7.2%). Chinese patent medicines accounted for 5.4%. There were 76 (45.8%) patients receiving systemic steroid and intravenous immunoglobulin (IVIG) in combination therapy, especially for TEN (80.3%), and others were treated with systemic steroids alone. Mortality rate of combination treatment comparing with steroid alone in TEN patients had no statistical significance. In conclusion, carbamazepine and allopurinol were the leading causative drugs for SJS/TEN in China. Combination of IVIG and steroids is a common treatment for TEN, but its efficacy in improving mortality needs further investigation.

1. Introduction

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a well-known severe cutaneous adverse reaction (SCAR) belonged to type IV hypersensitivity, mediated by immunological effect [1]. This hypersensitivity reaction is recognized as a dysregulation of cellular immunity [2], caused by a release of various cytotoxic signals including granulysin [3], perforin/granzyme B, and Fas/Fas ligand [4] which were activated by cytotoxic T lymphocytes and natural killer cells. SJS/TEN refers to a spectrum with widespread epidermal detachment and mucocutaneous involvement [5]. Different total body surface areas (TBSA) of detached or detachable skin lesions as <10%, 10–30%, and >30% are representing Stevens-Johnson syndrome (SJS), SJS/TEN overlap (SJS-TEN), and toxic epidermal necrolysis (TEN) [6]. SCORTEN disease severity scoring system is widely used in assessing the mortality of SJS/TEN [7]. The mortality rates of SJS, SJS-TEN, and TEN were 5–10%, 30%, and 50%, respectively [2, 5]. Recently, IL-15 has been found to be useful in predicting severity and monitoring prognosis [2]. A global population-based study had previously reported that the incidence of SJS and TEN is estimated 1.0 to 6.0 per million and 0.4 to 1.2 per million, respectively [8]. However, Frey et al. [9] estimated that Asian patients were at a 2-fold risk of SJS/TEN when compared with Caucasian patients in their recent study. There are few English literatures related to SJS/TEN studies from China so far.

In this study, we analyzed case reports of SJS/TEN from Chinese literatures and cases from a tertiary referral medical center from the past 10 years. The clinical characteristics, common drug causality, and outcome of treatments were analyzed.

2. Methods

We reviewed cases of SJS/TEN from the China National Knowledge Infrastructure (CNKI) and Wanfang Data [10–37] from January 2006 to December 2016. CKNI and Wanfang Data were well-known large comprehensive network full-text databases in China, established, respectively, since 1999 and 2000. Data from online database were searched by the key word of Stevens-Johnson syndrome and toxic epidermal necrolysis. All cases from databases were published in Chinese journals. We only enrolled cases which had detailed description of skin lesions, photographs, or histopathologic findings.

In addition, we also analyzed admission database from the First Affiliated Hospital of Fujian Medical University (FJMU) during 2006 to 2016. This hospital is the major tertiary referral medical center in Fujian Province and had total 4006 dermatology inpatients during this period. Data from admission database were searched by the diagnosis of Stevens-Johnson syndromes and toxic epidermal necrolysis. One patient from the FJMU has been published as a case report in Chinese literature.

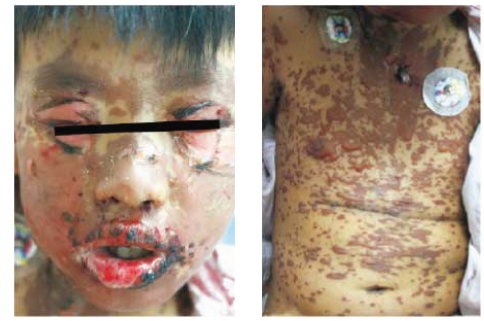
All cases of SJS/TEN enrolled for this analysis from the CNKI, Wanfang Data, and FJMU fulfilled with RegiSCAR (European Registry of Severe Cutaneous Adverse Reactions) criteria of probable to definite cases. They were carefully assessed by at least two dermatologists and further validated by the Taiwan-SCAR consortium [38–40]. All cases met the criteria of SJS/TEN from databases, and the hospital had been double checked by sex, age, and causality to exclude overlapping. The drug causalities of enrolled cases were assessed by the ALDEN algorithm, only with probable or definite (ALDEN score ≥ 4), and were included as drug-induced SJS/TEN.

All cases in this study were Han Chinese. We analyzed the detailed information collected from reviewed literatures or medical records, including patient demographics (sex and age), offending drugs, underlying medical diseases, treatments, and outcomes. We also further compared the causality of SJS/TEN in China and Southeast Asia [41].

Statistical analyses were performed using SPSS for Windows version 21.0 (IBM, Armonk, NY). Fisher's exact tests were used for analysis. Odds ratio (OR) and 95% confidence interval (CI) were also calculated. $P < 0.05$ (two-tailed) was considered to be statistically significant.

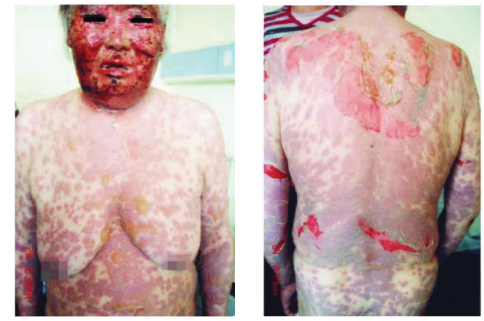
3. Results

There were total 230 SJS/TEN cases collected from reported Chinese literatures and admission database from the First Affiliated Hospital of FJMU between 2006 and 2016. Totally, 166 met the criteria of probable to definite cases of SJS/TEN, including 94 cases from literatures and 72 cases from the hospital (incidence rate of hospital population was 1.8%). Among them, there were 70 (42.2%) as SJS, 2 (1.2%) as SJS-TEN, and 94 (56.6%) as TEN. Typical cases of SJS and TEN from Chinese literature were shown in Figures 1 and 2.



(a) (b)

Figure 1: Typical cases of SJS from Chinese literature [20]. (a) Detachment of the eyelids, erosions and crusts of lips, and brownish macules on face and neck with scattered skin detachment. (b) Brownish macules with blisters and detachment on the trunk.



(a) (b)

Figure 2: Typical cases of TEN from Chinese literature [12]. (a) Widespread reddish to purplish macules and bullae on the trunk and upper limbs, with erosions on swollen face. (b) Macules and large skin detachment on the lateral trunk and upper limbs.

3.1. Demographic Data, Treatment, and Prognosis of Patients with SJS/TEN. The demographic and characteristics are summarized in Table 1. The age of the onset of SJS/TEN ranged from 1 to 94 years. Mean age of both SJS/TEN is over 40 years, with SJS or SJS-TEN in 43.4 years, and TEN in 43.6 years. There were 46 (63.9%) males and 26 (36.1%) females diagnosed with SJS or SJS-TEN and 54 (57.4%) male and 40 (42.6%) females diagnosed with TEN. There were 4 patients that were found to have HIV positive. All the enrolled patients received systemic corticosteroid, mostly methylprednisolone (67.8 ± 38.4 mg/d). Among these 166 cases, 76 (45.8%) patients had additional intravenous immune globulin (IVIG) (0.5 ± 0.3 g/kg/d), 11 patients received steroid pulse therapy (methylprednisolone 300–500 mg/d), 1 patient had cyclophosphamide, and 1 patient had plasmapheresis.

Table 1: Demographic data, treatment, and prognosis patients with SJS/TEN.

	SJS or SJS-TEN ($n = 72$)	SJS ($n = 70$)	SJS-TEN ($n = 2$)	TEN ($n = 94$)	Total ($n = 166$)	Odds ratio (95% CI)	P values
Age, y							
Mean ± SD	43.4 ± 21.7	43.5 ± 21.9	40.5 ± 11.5	43.6 ± 22.7	43.5 ± 22.3	—	0.967
Median (range)	48 (1–93)	48 (1–93)	40.5 (29–52)	44.5 (1–94)	45 (1–94)	—	—
Sex, *n* (%)							
Male	46 (63.9)	46 (65.7)	0 (0)	54 (57.4)	100 (60.2)	0.427 (0.406–1.435)	0.763
IVIG in combination, *n* (%)	15 (20.8)	14 (20.0)	1 (50)	61 (64.9)	76 (45.8)	7.024 (3.456–14.275)	<0.001
Pulse therapy	4 (5.6)	3 (4.3)	1 (50)	7 (7.4)	11 (6.6)	0.731 (0.206–2.600)	0.758
Death, *n* (%)	1 (1.4)	1 (1.4)	0 (0)	8 (8.5)	9 (5.4)	6.605 (0.807–54.071)	0.079

IVIG: intravenous immune globulin; SJS: Stevens-Johnson syndrome; SJS-TEN: SJS/TEN overlap; TEN: toxic epidermal necrolysis.

3.2. Causality of SJS/TEN. We categorized the causality into 9 groups in Table 2. The commonest causative drug category for SJS/TEN was antibiotics in 49 (29.5%) patients, and 75.5% of them were diagnosed with TEN. The largest proportion of the identified single offending antibiotics was penicillins (7.2%), followed by cephalosporins (4.2%) and quinolones (3.6%). Many of the patients had concomitant use with multiple antibiotics (4.8%). The second common offending drug category was anticonvulsants ($n = 40$, 24.1%), which the leading cause was carbamazepine (17.5%), followed by lamotrigine (4.2%), oxcarbazepine (1.2%), phenobarbital (0.6%), and phenytoin (0.6%). Three patients among them had undergone HLA genotyping, one carbamazepine-TEN and one oxcarbazepine-SJS carried the risk *HLA-B*15:02* allele, and the other carbamazepine-SJS carried *HLA-B*51:01/15:11* without *HLA-B*15:02*. Allopurinol contributed 16 (9.5%) patients, 2 of them had received HLA genotyping and revealed *HLA-B*58:01* positive.

Chinese patent medicines accounted for 9 (5.4%) cases, mostly were compound preparations. Three were for cold or clearing heat, including cough granule (containing loquat, opium poppy husk, stemona, mulberry bark, swallowwort rhizome, etc.), bupleurum granule (containing bupleurum, *Pinellia ternata* with ginger, radix scutellariae, *Codonopsis pilosula*, etc.), and extract of *Andrographis paniculata*. Others were sleeping capsule (containing lilium, *Acanthopanax senticosus*, caulis polygoni multiflori, Albizia julibrissin durazz, mother-of-pearl, etc.), Gutong capsule (containing ginseng, resina draconis, scorpion, bungarus minimus, etc.), and Honghua tablet (containing *Emilia sonchifolia*, *Hedyotis diffusa*, caulis spatholobi, etc.), and the last three were unspecified.

There were 8 (4.8%) cases caused by nonsteroidal anti-inflammatory drugs (NSAIDs), including diclofenac, ibuprofen, analgin, and some compound which contained paracetamol, caffeine, and aspirin, or aminopyrine, or phenacetin. Ten (6.0%) patients have taken multiple drugs concomitantly for treating common cold, including different combinations of antibiotics, anticonvulsant, NSAIDs, and Chinese patent drugs. There were 3 (1.8%) patients caused by industrial chemicals, which were acetochlor, naphthalenedisulfonic acid dimethyl ester, and trichloroethylene. Finally, 12 (7.2%) patients were caused by other drugs, including methazolamide ($n = 8$), dobesilate ($n = 1$), antifungals ($n = 1$), antidepressant ($n = 1$), and antituberculosis drugs ($n = 1$). One patient using methazolamide had HLA genotyping and was found to be *HLA-B*59:01* positive. However, 19 (11.4%) patients had no offending drug identified and no known infections.

The distribution of offending drugs causing SJS/TEN in northern or southern China was similar in which antibiotics (30.4% versus 29.2%) and anticonvulsants (28.3% versus 22.5%) were of most causative categories. However, there were more cases of allopurinol-related SJS/TEN in southern China (11.7% versus 4.3%) and more NSAID-related cases in northern China (8.7% versus 3.3%) (Table 3).

We further compared the drug causality of SJS/TEN in China to that in Southeast Asia, and the result was shown in Table 4. The proportion of antibiotics or anticonvulsant-related SJS/TEN of Malaysia (27.8% and 33.3%) and Singapore (28.9% and 29.6%) was similar to that of China (29.5% and 24.1%), Thailand had higher percentage of antibiotic-related SJS/TEN (66.7%), and the Philippines had higher percentage of anticonvulsant-related SJS/TEN (42.9%). Penicillins were the most common causative antibiotics in China in our study (7.2%), which are similar to Singapore (11.9%) and Thailand (31.7%), whereas sulfonamide being the largest group of antibiotics in Malaysia (17.3%) and the Philippines (7.1%). Carbamazepine was the most common causative anticonvulsant in our study (17.5%) and also in other Southeast Asian countries (Table 4). Allopurinol was also one of the leading causes for SJS/TEN in Asian countries (China: 9.6%, Philippines: 21.4%, and Singapore: 20.4%). Interestingly, Chinese patent medicines, or herbal medicines, which are still common traditional therapeutics in Chinese society, caused 7.5% SJS/TEN in Singapore, 5.4% of our study in China, and 3.6% and 2.5% in the Philippines and Malaysia, respectively.

3.3. Mortality of SJS/TEN. There were 9 (5.4%) deceased patients (Table 5), 1 was SJS, and 8 were TEN. Patient diagnosed with SJS was a 51-year-old male, with underlying disease of chronic renal failure and diabetes, and had cardiorespiratory arrest before admission. Other 8 patients diagnosed with TEN mostly had cardiovascular disease, diabetes, and nephropathy. Besides a child with age of 3

Table 2: Drug causality of SJS/TEN in China.

	SJS or SJS-TEN, *n* (%) (*n* = 72)	TEN, *n* (%) (*n* = 94)	Total, *n* (%) (*n* = 166)	Death, *n* (*n* = 9)
Culprit drug				
Allopurinol	**11 (15.3)**	**5 (5.3)**	**16 (9.6)**	**2**
Antibiotics	**12 (16.7)**	**37 (39.4)**	**49 (29.5)**	**5**
Penicillins[a]	2	10	12	1
Cephalosporins[b]	1	6	7	1
Carbapenems[c]	0	3	3	0
Quinolones[d]	3	3	6	0
Sulphonamides[e]	3	1	4	0
Others[f]	2	4	6	0
Unspecified[g]	1	2	3	1
Multiple drugs[h]	0	8	8	2
Anticonvulsants	**19 (26.4)**	**21 (22.3)**	**40 (24.1)**	**0**
Carbamazepine	12	17	29	0
Lamotrigine	4	3	7	0
Others[i]	3	1	4	0
Chinese patent medicines[j]	**6 (8.3)**	**3 (3.2)**	**9 (5.4)**	**0**
Industrial chemicals[k]	**0 (0)**	**3 (3.2)**	**3 (1.8)**	**0**
NSAIDs[l]	**3 (4.2)**	**5 (5.3)**	**8 (4.8)**	**0**
Multiple drugs[m]	**3 (4.2)**	**7 (7.4)**	**10 (6.0)**	**1**
Others[n]	**7 (9.7)**	**5 (5.3)**	**12 (7.2)**	**1**
Nondrugs[o]	11 (15.3)	8 (8.5)	19 (11.4)	0

NSAIDs: nonsteroidal anti-inflammatory drugs; SJS: Stevens-Johnson syndrome; SJS-TEN: SJS/TEN overlap; TEN: toxic epidermal necrolysis. [a]Penicillins including amoxicillin ($n = 5$), amoxicillin with clavulanic acid ($n = 1$), ampicillin ($n = 1$), penicillin ($n = 1$), piperacillin ($n = 1$), and piperacillin-tazobactam ($n = 3$). [b]Cephalosporins including cefalexin ($n = 1$), cefaclor ($n = 1$), cefuroxime ($n = 2$), cefoperazone sulbactam ($n = 2$), and cefotaxim ($n = 1$). [c]Carbapenems including imipenem-cilastatin ($n = 2$) and meropenem ($n = 1$). [d]Quinolones including ciprofloxacin ($n = 1$) and levofloxacin ($n = 5$). [e]Sulphonamides including sulfasalazine ($n = 2$), sulfamethoxazole ($n = 1$), and compound of sulfonamides ($n = 1$). [f]Others in antibiotics including azithromycin ($n = 1$), clarithromycin ($n = 1$), lincomycin ($n = 2$), doxycyclin ($n = 1$), and vancomycin ($n = 1$). [g]Unspecified as not available, unspecified in contained group. [h]Multiple drugs in antibiotics as concomitant use of multiple antibiotics. [i]Others in anticonvulsants including oxcarbazepine ($n = 2$), compound of phenobarbital and scopolamine ($n = 1$), and phenytoin ($n = 1$). [j]Chinese patent medicines including extract of *Andrographis paniculata* ($n = 1$), bupleurum granule (containing bupleurum, *Pinellia ternata* with ginger, radix scutellariae, *Codonopsis pilosula*, etc.) ($n = 1$), cough granule (containing loquat, opium poppy husk, stemona, mulberry bark, swallowwort rhizome, etc.) ($n = 1$), Gutong capsule (containing ginseng, resina draconis, scorpion, bungarus minimus, etc.) ($n = 1$), Honghua tablet (containing *Emilia sonchifolia*, *Hedyotis diffusa*, caulis spatholobi, etc.) ($n = 1$), sleeping capsule (containing lilium, *Acanthopanax senticosus*, caulis polygoni multiflori, Albizia julibrissin durazz, mother-of-pearl, etc.) ($n = 1$), and unspecified ($n = 3$). [k]Industrial chemicals including acetochlor ($n = 1$), naphthalenedisulfonic acid dimethyl ester ($n = 1$), and trichloroethylene ($n = 1$). [l]NSAIDs including analgin ($n = 1$), diclofenac sodium eye drops or tablets ($n = 3$), compound of paracetamol, aspirin and caffeine ($n = 1$), compound of paracetamol, aminophenazone, caffeine, and chlorphenamine maleate ($n = 1$), compound of paracetamol, aminopyrine, phenacetin, caffeine, and phenobarbital ($n = 1$), and ibuprofen ($n = 1$). [m]Multiple drugs as different classification of drugs in concomitant use, including NSAID concomitant with antibiotic and anticonvulsant ($n = 4$), Chinese patent drug concomitant with antibiotic ($n = 1$), Chinese patent drug concomitant with unknown cold medicine ($n = 2$), and concomitant with multiple unknown cold medicine ($n = 3$). [n]Others including calcium dobesilate ($n = 1$), methazolamide ($n = 8$), multiple antifungals (itraconazole and voriconazole) ($n = 1$), multiple antidepressant (amitriptyline and estazolam) ($n = 1$), and multiple antituberculosis drugs ($n = 1$). [o]Nondrugs as absence of medication using history before onset.

years, all patients were older than 40 years, ranging from 51 to 94. Among 9 deceased patients, 4 patients received systemic steroids in combination with IVIG, 3 in the early stage and 1 in the late stage, and 5 patients received systemic steroids only.

3.4. Treatment with Combination of Steroid and IVIG versus Steroid Alone. There were 90 (54.2%) patients of SJS/TEN who received systemic steroids alone and 76 (45.8%) patients who had IVIG in combination with systemic steroids. Combination treatment was more commonly used in TEN patients than in SJS patients (64.9% versus 20.8%) (Odds ratio: 7.024; $P < 0.001$) (Table 1). In 76 patients who received systemic steroids with IVIG in combination, 61 (80.3%) of them were TEN, and the mortality rate of TEN cases receiving combination treatment was 6.6% (4/61). In 90 patients who received systemic steroids alone, 33 patients (36.7%) were TEN, and 12.1% (4/33) of these TEN cases underwent steroid alone deceased. On the other hand, 57 patients with SJS and SJS-TEN received systemic steroids alone and only 1 (1.8%) died. There were 15 SJS and SJS-TEN patients who received combination treatment, and all survived. Mortality rate between using IVIG and steroid in combination or steroid alone had no statistical significance (Table 6).

Table 3: Comparison of the common drug causality between northern and southern China.

	Northern China, *n* (%) (*n* = 46)	Southern China, *n* (%) (*n* = 120)	Total, *n* (%) (*n* = 166)
Antibiotics	14 (30.4)	35 (29.2)	49 (29.5)
Penicillins	3 (6.5)	9 (7.5)	12 (7.2)
Cephalosporins	1 (2.2)	6 (5.0)	7 (4.2)
Quinolones	2 (4.3)	4 (3.3)	6 (3.6)
Others	8 (17.4)	16 (13.3)	24 (14.5)
Anticonvulsants	13 (28.3)	27 (22.5)	40 (24.1)
Carbamazepine	9 (19.6)	20 (16.7)	29 (17.5)
Lamotrigine	2 (4.3)	5 (4.2)	7 (4.2)
Others	2 (4.3)	2 (1.7)	4 (2.4)
Nondrug	1 (2.2)	18 (15.0)	19 (11.4)
Allopurinol	2 (4.3)	14 (11.7)	16 (9.6)
Multiple drugs	6 (13.0)	4 (3.3)	10 (6.0)
Herbal medication	2 (4.3)	7 (5.8)	9 (5.4)
NSAIDs	4 (8.7)	4 (3.3)	8 (4.8)
Others	4 (8.7)	11 (9.2)	15 (9.0)

NSAIDs: nonsteroidal anti-inflammatory drugs.

4. Discussion

In this study, we enrolled a total 166 Han Chinese patients diagnosed with SJS, SJS-TEN overlap, and TEN from a tertiary medical center and Chinese literatures during 2006 to 2016. We evaluated underlying condition, causation, treatment, and clinical outcome. Mean age of SJS/TEN was 43.5 years, with little difference between SJS or SJS-TEN overlap and TEN. There was a male predominance in SJS or SJS-TEN overlap (male-to-female ratio 1.77 : 1) and TEN (male-to-female ratio 1.35 : 1). This observation was opposite to what Mohammed et al. found in Egypt and different from an earlier study which showed equally affected by male and female [42, 43].

There were 88.6% of SJS/TEN patients had drug relationship, and the major contribution was antibiotics, followed by anticonvulsants and allopurinol. The difference between the antibiotics and anticonvulsants was small. This result was similar to the comparison of Malaysia and Singapore in a review of Southeast Asia [41], only different in sequence of antibiotics and anticonvulsants, whereas Huang et al. found anticonvulsants as the most common drug which caused SJS/TEN in China, followed by allopurinol, antipyretics/analgesics, and cephalosporins [44]. Similarly, Li and Ma reported anticonvulsants and antibiotics to be the most common single drug in SJS and traditional Chinese medicines in TEN [45]. It is known that allopurinol, aromatic anticonvulsants, sulfonamide antibiotics, oxicam NSAIDs, and nevirapine have higher risk to induced SCARs [46]. Nevertheless, there were only some sulphonamides and none oxicam type of NSAIDs induced SJS/TEN in this study. This may due to prescribing habits of antibiotics in China and Taiwan, causing more penicillins and cephalosporins than the others [47–50]. Similarly, oxicam type of NSAIDs is less commonly seen in Chinese literatures of case series [48, 49]. Allopurinol was found to be a less common causality to induce SJS/TEN in this study, especially in northern China. From previous reports, *HLA-B*58 : 01* was found positive in 93.3–100% of patients with allopurinol-induced SCARs whether in northern or southern China [51–54]. Moreover, the prevalence of carrying the risk *HLA-B*58 : 01* allele was 0.0515–0.085 in China [55]. The discrepancy of the percentages between this study and literature needs further investigation. Chinese patent medicines were unique causative drugs to induce SJS/TEN in the Asian region [43, 56–59]. In our study, 5.4% of the SJS/TEN cases were related to Chinese patent medicine. Previously, Singapore was also reported to have more herbal medicine-induced SJS/TEN cases [41]. However, there are possibilities of adulteration with Western medicine in the component of Chinese patent medicine [60–62], which makes it hard to identify the exact causality and may cause bias. Patients also tend to received multiple drugs, including compound preparations of Western medicine or even antipyretic and analgetic in Chinese patent medicine [45]. Both of these would increase the possibility of adverse drug reaction and enhance difficulty of identifying offending drug.

In our study, 19% of patients did not have definite or possible relationship with drug according to ALDEN scoring system. The cause may be infection or idiopathic, and unfortunately there were no validation via further examinations. The annual incidence of SJS/TEN in the HIV-positive population is approximately 1000-fold higher than in the general population [63], and 4 patients with suspected causative drugs were HIV positive in our study. Infections are possible causations besides drugs. Reactivations of human herpesvirus 6 (HHV6) and cytomegalovirus were found in SJS/TEN [64, 65]. A case has been reported of a teenage boy diagnosed with SJS and primary Epstein-Barr virus infection without any attributing medication [66]. In addition, *Mycoplasma pneumoniae* infection may also be an additional cause of SJS. Watkins et al. and Olson et al. have reported *Mycoplasma pneumoniae* infection outbreak associated with SJS in children [67, 68]. Although there were some reports with malignancy-related SJS [69, 70], none of our non-drug-induced-SJS/TEN patients were found to have malignancy.

Withdrawal of offending drugs or treatment of causative infection, timely supportive treatment, immunomodulation, and management of complications and consequences are the most common suggested treatments [71]. In this study, all of the patients received systemic corticosteroid. Despite systemic corticosteroids remain a controversial treatment for SJS/TEN, it is the most commonly used medication across Asia [72–75].

Massive keratinocyte apoptosis induced by the intercellular death receptor Fas and Fas ligand is now considered to be the pathogenesis of SJS/TEN [76], yet IVIG inhibits keratinocyte apoptosis by inhibiting the FAS receptor [77]. IVIG was prescribed as an additional management in 45.8% of our patients, whether at the early or late stage of SJS/TEN, especially with much higher percentage in TEN (80.3%) compared to SJS or SJS-TEN overlap (19.7%). Apparently IVIG is a common option of treating SJS/TEN in China, especially in TEN for their extensive skin lesion involvement, and is

Table 4: The comparison of the common drug causality from cases in China with other populations in Southeast Asia*.

Culprit drug	China ($n = 166$)	Malaysia ($n = 162$)	Singapore ($n = 159$)	Thailand ($n = 60$)	Philippines ($n = 28$)
Antibiotics	49 (29.5)	45 (27.8)	46 (28.9)	40 (66.7)	5 (17.9)
Penicillins	12 (7.2)	14 (8.6)	19 (11.9)	19 (31.7)	1 (3.6)
Sulfonamide	4 (2.4)	28 (17.3)	11 (6.9)	9 (15.0)	2 (7.1)
Others	33 (19.9)	3 (1.9)	16 (10.1)	12 (20.0)	2 (7.1)
Anticonvulsants	40 (24.1)	54 (33.3)	47 (29.6)	9 (15.0)	12 (42.9)
Carbamazepine	29 (17.5)	34 (21.0)	29 (18.2)	4 (6.7)	4 (14.3)
Lamotrigine	7 (4.2)	7 (4.3)	2 (1.3)	0 (0)	0 (0)
Phenytoin	1 (0.6)	13 (8.0)	14 (8.8)	4 (6.7)	5 (17.9)
Allopurinol	16 (9.6)	33 (20.4)	23 (14.5)	1 (1.7)	6 (21.4)
NSAIDs	8 (4.8)	10 (6.2)	14 (8.8)	4 (6.7)	3 (10.7)
Herbal medications	9 (5.4)	4 (2.5)	12 (7.5)	0 (0)	1 (3.6)

*We compared the common drug causality from cases in China with other populations in Southeast Asia according to the previous literature report (41).

Table 5: Information of the deceased patients with SJS/TEN in this study ($n = XXX$).

Phenotype	Sex	Age, y	Underlying disease	SCORTEN	Culprit drugs	Treatment
SJS	M	51	Chronic renal failure, diabetes	4	Allopurinol	Systemic steroids
TEN	M	70	Nil	6	Antibiotics	Systemic steroids
TEN	F	58	Aneurysm, subarachnoid hemorrhage	NA	Antibiotics	Systemic steroids
TEN	F	67	Rheumatic heart disease, mitral insufficiency	NA	Antibiotics and compound with aminopyrine, phenacetin, caffeine, phenobarbital	Systemic steroids with IVIG use in the late stage
TEN	F	71	Coronary heart disease, hypertension, diabetes, diabetic nephropathy	4	Calcium dobesilate	Systemic steroids with IVIG use in the early stage
TEN	M	62	Hypertension, diabetes	NA	Antibiotics	Systemic steroids with IVIG use in the early stage
TEN	M	94	Coronary heart disease, cardiac insufficiency, hypertension, diabetes, interstitial lung disease	NA	Antibiotics	Systemic steroids with IVIG use in the early stage
TEN	M	62	Hypertension, diabetes, chronic renal failure, hyperuricemia	NA	Allopurinol	Systemic steroids
TEN	M	3	Nil	2	Antibiotics	Systemic steroids

IVIG use in the early stage ≤ 7 days of onset; IVIG use in the late stage ≥ 7 days of onset. NA: not available.

Table 6: A comparison of mortality rate between combination treatment of steroid with IVIG versus steroid alone.

Mortality	Steroids with IVIG ($n = 76$)	Steroids alone ($n = 90$)	Odds ratio (95% CI)	P values
TEN, n (%)	4/61 (6.6)	4/33 (12.1)	0.509 (0.119–2.183)	0.445
SJS and SJS/TEN, n (%)	0/15 (0.0)	1/57 (1.8)	—	1.000
Total cases, n (%)	4/76 (5.3)	5/90 (5.6)	0.944 (0.244–3.650)	1.000

usually in combination of systemic steroids instead of using alone. A score-based comparison study of clinical outcomes found that corticosteroid therapy combined with IVIG may lead to lower mortality when compared to corticosteroid alone [78]. However, several studies have shown limited success of IVIG in the clinical settings [79–82]. In our study, mortality rate in patients with TEN who received systemic steroids with IVIG comparing to those who received systemic steroids alone was 6.6% and 12.1%. However, this difference of mortality rate was not statistically significant. Application of intravenous immunoglobulins or systemic corticosteroids also did not improve the outcome of SJS and TEN in a study in Singapore [83]. Similarly, Lee et al. [84] demonstrated that the use of IVIG does not yield survival benefits in SJS/TEN overlap and TEN, even when corrected for IVIG dosages. Until now, the usage of IVIG in the treatment of SJS/TEN

is still controversial. Recent studies have shown that immunosuppressive treatment with tumor necrosis factor-alpha (TNF-α) inhibitors may be helpful [85] and cyclosporin A is also safe and may contribute to rapid reepithelialization in patients with SJS/TEN [86–88]. The efficacy of using cyclosporin in treating SJS/TEN has recently validated with the decreased mortality rate both in adults and children [89–92].

There are several limitations in this study. First, we enrolled case reports only with careful checkup to prevent overlapping cases. However, ruling out the articles with case series also led to underestimation of SJS/TEN patients. Second, the mortality rate in our study is lower than international literatures which ranged from 10% to 70% [93, 94]. The possibility of lower mortality in this study may be due to underreported deceased cases of SJS/TEN from the Chinese literatures. In addition, the underlying severity of SJS/TEN in our study is unknown due to the lack of complete data of SCORTEN factors; hence, the efficacy of treatment needs to be further elucidated.

5. Conclusion

SJS/TEN is life-threatening drug adverse reaction, with higher prevalence rate in Asian than in Western populations in literature review. The most common offending drugs in our study are antibiotics, anticonvulsants, and allopurinol. IVIG in combination with systemic steroids is a common option especially for TEN in China. There was no significant difference in the mortality rate of TEN patients with or without IVIG adjuvant treatment.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Review Article

Anticancer Drugs Induced Severe Adverse Cutaneous Drug Reactions: An Updated Review on the Risks Associated with Anticancer Targeted Therapy or Immunotherapies

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Cutaneous adverse drug reactions are commonly seen in patients with anticancer drug treatment. Anticancer drugs, including chemotherapy, target therapy, and recent immunotherapy causing skin reactions ranging from mild skin rash to life-threatening severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN) with increase morbidity and mortality while they are receiving cancer treatments, have been proposed to be a result of direct skin toxicity or drug hypersensitivity reactions (these are proposed mechanism, not definite). Differentiating SCARs from other more commonly seen reactions with a better outcome help prevent discontinuation of therapy and inappropriate use of systemic immunosuppressants for presumable allergic reactions, of which will affect the clinical outcome. In this article, we have reviewed published articles from 1950 to August 2017 for SJS/TEN associated with anticancer drugs, including chemotherapy, targeted therapy, and immunotherapy. We aimed to provide an overview of SJS/TEN associated with anticancer drugs to increase clinician recognition and accelerate future studies on the pathomechanism and managements.

1. Introduction

The advancement in cancer detection and development of anticancer drug therapy has led to increased incidence of cutaneous adverse reactions following anticancer drug therapy. Conventional chemotherapy and targeted or immunotherapy that are thought to be well tolerated and may cause various cutaneous adverse reactions ranging from nonlife-threatening skin toxicities such as paronychia, acneiform eruption, and alopecia to life-threatening severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These drug eruptions are thought to be immunologically mediated reactions that are termed type B adverse reaction [1]. However, the pathomechanism of SCARs reactions in anticancer drugs including chemotherapy, targeted therapy, and immunotherapy is poorly understood and the literatures were still limited.

SJS/TEN are a spectrum of fatal mucocutaneous adverse reactions characterized by rapidly progressing purpuric atypical target-like rashes with blisters, cutaneous sloughing, and mucosal involvement. SJS and TEN are differentiated by the degree of skin detachment: SJS involves less than 10% body surface area skin detachment, TEN more than 30%, while SJS/TEN overlap involves body surface area of 10–30% [1, 2]. Despite their rare occurrence, the overall mortality was generally high in accordance with the body surface involve, ranging from 10% for SJS to approximately

Table 1: Anticancer chemotherapy-related severe cutaneous adverse drug reactions from the English literature (year: 1950–2017).

Drug class	Drug	Pharmacology	References	Total (n)	Mortality	SJS	SJS/TEN	TEN
Alkylating agents	Treosulfan	Alkysufonates	[6]	1	1	0	0	1
	Chlorambucil	Mustard gas derivatives	[7, 8]	2	0	0	0	2
	Mechlorethamine (topical)	Nitrogen mustard	[9]	1	0	1	0	0
	Temozolomide	Hydrazines and triazines	[10]	1	0	0	1	0
	Procarbazine	Hydrazines and triazines	[11–13]	3	0	0	0	3
Plant alkaloids	Paclitaxel	Taxanes	[14]	1	0	1	0	0
	Docetaxel	Taxanes	[15–19]	5	2	3	0	2
	Etoposide	Podophyllotoxins	[20]	1	0	1	0	0
Anthracyclines	Doxorubicin		[21]	1	1	0	0	1
Antimetabolites	Methotrexate	Folic acid antagonists	[22–26]	5	2	2	0	3
	Cytarabine	Pyrimidine antagonist	[27, 28]	2	2	0	0	2
	Fludarabine	Adenosine deaminase inhibitor	[29]	1	1	1	0	0
	Gemcitabine	Pyrimidine antagonist	[30–32]	3	0	2	1	0
	Capecitabine	Pyrimidine antagonist	[33]	1	0	1	0	0
	Cladribine	Purine antagonist	[34, 35]	2	NA	1	0	1
	6-Mercaptopurine	Purine antagonist	[36]	1	NA	0	0	1
	TS-1 (tegafur-gimeracil-oteracil potassium)		[37, 38]	2	0	1	0	1
	Pemetrexed	Multitarget antifolate	[39, 40]	2	0	0	0	2
Antitumor antibiotics	Bleomycin		[41, 42]	2	1	0	0	2
	Peplomycin		[43]	1	0	1	0	0
	Mithramycin		[44, 45]	2	0	0	0	2
Miscellaneous	Lenalidomide		[46–48]	14	2	12	1	1
	Thalidomide		[49–53]	5	1	1	0	4
	Asparaginase		[54]	1	0	0	0	1
			Total	**60**	**13**	**28**	**3**	**29**

NA: not available.

50% for TEN, and can cause irreversible sequelae to the eyes, skin, and lungs [2–5]. Hence, increased recognition and improved management are of paramount importance, especially at early stages. Furthermore, in clinical practice, the conjectural association of anticancer drugs with SCAR event may lead to alterations in therapy, affects clinical outcome, and may cause physician and patient distress. This review aimed to provide an overview of the current evidence of anticancer drug-related SCARs to assist clinicians in early recognition and management.

To synthesize current literature, relevant English literatures were identified through searches of PubMed, EMBASE, Web of Science, SCOPUS, and OVID from 1950 to August 2017 using the terms Stevens-Johnson syndrome, toxic epidermal necrolysis, cancer drug therapy, and target therapy drugs. We did not constrain our research on publication types but limited the search only in indexed, peer-reviewed journals so as to ensure quality publications. Primary case reports, case series, reports from clinical trials, or as part of postmarketing surveillance were included. Histopathologic diagnosis of SJS/TEN was not required for the inclusion criteria. Clinical course, type of anticancer drugs, and mortality were analyzed and summarized according to the respective anticancer drug classifications of chemotherapy [6–54] (Table 1), targeted therapy [55–80] (Table 2), and immunotherapy [81–87] (Table 3). Cases with multiple concomitant medications used during the same period of time and/or with questionable diagnosis were excluded.

2. Chemotherapy

Chemotherapy is the most widely used anticancer drug in oncology field. The administration of chemotherapy may lead to many cutaneous findings, ranging from allergic reactions to infectious complications caused by disrupted immunity. From the search of peer-review articles, a total of 60 reports of SJS/TEN associated with 23 chemotherapeutic anticancer drugs were identified [6–54] (Table 1). The most common drugs to cause chemotherapy-induced SJS/TEN are lenalidomide ($n = 14$; SJS = 12, SJS/TEN = 1, and TEN = 1), methotrexate ($n = 5$; SJS = 2 and TEN = 3), docetaxel ($n = 4$; SJS = 3 and TEN = 1), and thalidomide ($n = 5$; SJS = 1 and TEN = 4). Most patients were exposed to drugs either concomitantly or within 8 weeks of the anticancer agent. Although there were a few cases with exceedingly short duration of onset with questionable diagnosis [28, 31], the report descriptions and causality indicators (course of treatment, duration and timing between exposure and event, blood levels, etc.) were not consistently

Table 2: Anticancer targeted therapy-related severe cutaneous adverse drug reactions from the English literature (year: 1950–2017).

Drug class	Drug	Pharmacology	References	Total (n)	Mortality	SJS	SJS/TEN	TEN
EGFR inhibitor	Afatinib	Monoclonal antibody to EGFR	[55, 56]	2	0	2	0	0
	Cetuximab	Monoclonal antibody to EGFR	[57–59]	4	1	1	1	2
	Erlotinib	TKI specific to EGFR	[60]	1	0	1	0	0
	Gefitinib	TKI specific to EGFR	[61, 62]	2	1	0	0	2
	Panitumumab	Monoclonal antibody to EGFR	[122]	1	0	1	0	0
	Vandetanib	Less specific multikinase inhibitors	[63]	2	0	0	1	1
KIT and BCR-ABL inhibitors	Imatinib	KIT, BCR-ABL, PDGFR	[64–72]	11	1	11	0	0
Antiangiogenic agents	Sorafenib	Nonselective antiangiogenesis multikinase agents	[73–76]	3	0	2	0	1
Proteasome	Bortezomib		[77]	2	1	1	0	1
CD30	Brentuximab vedotin	CD30	[78]	2	0	1	0	1
CD20	Rituximab	Monoclonal antibody to CD20	[79]	5	2	2	2	1
BRAF inhibitors	Vemurafenib	A/B/C-Raf and B-Raf (V600E)	[80]	7	1	1	0	6
			Total	**42**	**7**	**23**	**4**	**15**

Table 3: Anticancer immune therapy-related adverse drug reactions from the English literature (year: 1950–2017).

Drug class	Drug	Pharmacology	References	Total	Mortality	SJS	SJS/TEN	TEN
Immunomodulators	Aldesleukin	Recombinant interleukin-2	[81, 82]	2	1	0	0	2
	Ipilimumab	CTLA-4 inhibitors	[83]	1	0	1	0	0
	Nivolumab	PD-1 inhibitors	[84, 85]	2	1	0	0	2
	Pembrolizumab	PD-1 inhibitors	[86, 114, 116]	4	0	4	0	0
	Denileukin	Recombinant interleukin-2 and diphtheria toxin	[87]		1	0	0	1
			Total	9	3	5	0	5

reported in these articles. Some articles enclose pictures that are not very suggestive of SJS/TEN but of an alternative diagnosis, including erythema multiforme, GVHD, and toxic erythema of chemotherapy. For instance, methotrexate-induced epidermal necrosis is a distinct entity that closely mimics SJS/TEN but exhibits distinct clinicopathological features from SJS/TEN [88]. Many of the reported articles did not obtain skin biopsy for pathology examination and hence, it is difficult to draw to a definitive diagnosis of SJS/TEN. Another clinical mimic of SJS/TEN associated with chemotherapy is toxic erythema of chemotherapy (TEC), characterized by painful erythematous eruptions with edema and/or blisters which involves the acral part, intertriginous areas, pressure points, and less often ears, knees, and elbows [89, 90]. TEC is a toxic phenomenon with minimal inflammatory infiltrates despite the dramatic clinical appearance, hence studies have hypothesized that the erythema is secondary to keratinocyte damage with release of cytokines leading to vasodilation [90, 91]. Most cases involve the use of either antimetabolites or alkylating agents that interferes RNA or DNA synthesis, including methotrexate, cytarabine, 5-fluorouracil, and mercaptopurine. By contrast, SJS/TEN is an immune-driven type 4 allergic reaction, where cytotoxic T lymphocytes and natural killer cells are activated. Clinical recognition and differentiation of SJS/TEN from toxic erythema are of importance because it helps prevent the inappropriate use of systemic immunosuppressants for presumed allergic reactions, precludes subsequent dosing, and affects the patient's clinical outcome.

3. Targeted Anticancer Therapy

From the literature review, a roster of 42 reports of SJS ($n = 23$), SJS/TEN ($n = 4$), or TEN ($n = 15$), associated with 12 targeted anticancer drugs, were identified, including EGFR inhibitors (afatinib, cetuximab, erlotinib, gefitinib, panitumumab, and vandetanib), MKI (imatinib, regorafenib, and sorafenib), recombinant IL-2 (aldesleukin), proteasome (bortezomib), anti-CD20 (rituximab), anti-CD30 (brentuximab vedotin), and BRAF inhibitor (vemurafenib) (Table 2). The most common drugs to cause SJS/TEN reported are imatinib ($n = 11$), EGFR inhibitors ($n = 10$), and vemurafenib ($n = 7$). The response of cancer control is hard to analyze because it was not fully mentioned in the reports. All cases were treated with immunosuppressant, including steroid, IVIG, and there was one TEN case with promising outcome after etanercept (anti-TNF α) treatment. In these reports, nine patients underwent drug rechallenge test with recurrences, confirming the notoriety of exposed targeted anticancer drugs [67–72, 74, 80].

3.1. EGFR Inhibitors. EGFR inhibitors are approved as the drug for the treatment of non-small cell lung, colorectal, breast, pancreatic, head, and neck cancers with EGFR mutations [92]. The incidence of EGFR inhibitor-induced cutaneous adverse drug reactions (cADRs) is high (36%–80%) [93], of which most were papulopustular eruptions, xerosis, paronychia, mucositis, and photosensitivity [94]. In this article, we have identified 13 cases of SJS/TEN induced by EGFR inhibitors. Though rare, SJS/TEN should be distinguished from EGFR inhibitor-related mucositis, particularly when the patient present with constitutional symptoms and widespread atypical target spots with blisters that extend beyond mucosa to the skin. Cross-reactivity between EGFR inhibitors was reported. It is hypothesized that the pathomechanism of SJS/TEN associated with EGFR inhibitors could be caused by to the irreversible inhibition of EGFR, of which hinders epidermal differentiation and reepithelialization and causing extensive erosions [95].

3.2. KIT and BCR-ABL Inhibitors. Imatinib, a tyrosine kinase inhibitor, is the standard treatment in chronic myeloid leukemia and gastrointestinal stromal tumors (GIST) [96, 97]. In this article, imatinib accounts one of the most common causative targeted anticancer drug to induce SJS, with a roster of 12 cases. This must be differentiated from other more commonly seen cutaneous adverse effects of imatinib, maculopapular rashes, and facial edema [98], of which has a better prognosis and dose-dependent pharmacologic effect rather than hypersensitivity reaction [99]. For maculopapular rash/facial edema associated with imatinib, temporary discontinuation or dose reduction may be applied if the patient's cancer is susceptible to the drug. By contrast, reintroducing the culprit drug with a dose reduction is usually not suggested [100, 101].

3.3. Multikinase Inhibitors. Multikinase inhibitors (sunitinib, sorafenib, pazopanib, and vandetanib) are small molecule inhibitors of the tyrosine kinase of the VEGF, and also differential binding capacities to other tyrosine kinases, including PDGFR, EGFR, KIT, RET, FLT-3, CSF-1R, and RAF [102]. They were approved for treatment of patients with renal cell cancer, gastrointestinal stromal tumors, and hepatocellular cancer. These drugs can cause hand-foot skin reaction, hair change, maculopapular eruptions, stomatitis, genital erosions, and bleeding [103, 104], especially in patients using sorafenib. These more common cutaneous toxicities are thought to be caused by direct VEGF inhibition, which result in vessel regression, and impact on vascular repair capacities [74]. Other research has also shown that Fas/FasL interaction mediates keratinocyte death in sunitinib-induced HFSR [75]. Recently, one recent study identified SLC22A20 (OAT6) as an uptake carrier of sorafenib and subsequently sorafenib enters the keratinocyte through OAT6 and then inhibits mitogen-activated protein kinase MAP3K7 (TAK1) leading to cytotoxicity and keratinocyte injury [76]. Interestingly, erythema multiforme, a spectrum of delayed type hypersensitivity, induced by sorafenib was around 19–25% in Japanese population, which is much higher than the Caucassian population [105]. This could imply a possible genetic role in the pathogenesis of adverse drug reactions. The different incidence of cutaneous adverse reactions among different ethnicities need to be further investigated.

3.4. BRAF Inhibitors. Vemurafenib is a selective inhibitor of BRAF-kinase approved for the treatment of metastatic melanoma with BRAF mutation. Skin toxicity, such as photosensitivity and maculopapular eruptions, and secondary skin malignancy (keratoacanthoma and squamous cell carcinoma) were estimated to affect more than 90% of patients [106, 107]. One vemurafenib-TEN underwent a lymphocyte transformation test (LTT) assay to confirm the causality of vemurafenib and also show positive cross-reactivity for dabrafenib [108]. On the contrary, another case reported a successful switch from vemurafenib-induced cutaneous adverse reactions to dabrafenib [109]. Furthermore, cross-reactivity was also found between vemurafenib and sulfonamide antibiotics—sulfamethoxazole—based on LTT reports. These data suggested that there might be clinical cross-reactivity between BRAF inhibitors and sulfonamides. Predisposing factors to sulfonamide-related adverse cutaneous drug reactions could be implied in the pathomechanism studies of vemurafenib-associated SJS/TEN [108].

3.5. mTOR Inhibitors. Mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus, everolimus, and temsirolimus, are emerging drugs, increasingly applied in oncology and in the prevention of rejection in patients receiving solid organ transplantation [110]. The most common cutaneous side effects are oral ulcers, acne-like eruptions, and morbilliform drug eruptions [111]. Oral ulcer is a very frequent (72%) adverse reaction and is often recurrent and chronic following everolimus treatment in 25% of patients. The adverse event was found to be dose dependent [112].

Severe drug eruptions of life-threatening lingual angioedema after initiation of everolimus in heart transplant recipients have also been reported in a case series. In these patients, lingual edema occurs predominantly within the first weeks after initiation of everolimus therapy and disappears without recurrences in majority patients after adequate symptomatic treatment [113].

There were otherwise no SCAR (SJS/TEN, DRESS) event being reported in the literature.

4. Immunotherapy

Immunotherapy is the latest breakthrough in anticancer drug development with immunomodulatory therapeutic antibodies, targeting inhibitory receptors expressed by T cell as CTLA-4 and PD-1. They are used to treat advance stage cancer with metastasis or unresectable tumor such as melanoma and lung cancer. In this section, older immunotherapy such as interleukin-2 was also included in Table 3. These therapeutic options are most widely used in advanced and late cancer stages. From literature reviews, we have identified one ipilimumab-SJS, two nivolumab-TEN, and four pembrolizumab-SJS. All of the patients were

advanced melanoma patients, and the onset of epidermal necrolysis varies from 2.5 weeks to 3 months. In one case of pembrolizumab-associated SJS, concomitant phenytoin for epilepsy was used; hence, the exact culprit drug is hard to define. Two cases of pembrolizumab-SJS were being reported by Saw et al. [114]. Interestingly, there was a striking demarcation of epidermal detachment along the radiotherapy field aside from typical mucocutaneous findings of SJS. Such findings, although rarely, have also been reported in previous traditional culprit drugs and targeted therapy. A total of 3 cases were found with interleukin-2 immune therapy with 2 fatalities [81, 82, 87]. One of the authors suggested that IL-2 may increase patient's susceptibility to allergy of other medication [87]. An increased expression of PD-L1 in the epidermis by immunohistochemistry (IHC) was found, and they hypothesized that the use of anti-PD-1 therapy could provoke the expression of PD-L1 of keratinocytes and permit the activated $CD8^+$ cytotoxic T cells to target keratinocytes leading to keratinocyte apoptosis [86]. PD-1 knockout mouse often exhibits symptoms related to adverse cutaneous reactions. It has been reported in a mouse model that PD-L1 expressed on keratinocytes presenting self-antigens regulates autoreactive $CD8^+$ T cell activity and prevents the development of cutaneous autoimmune disease [115]. Goldinger et al. had demonstrated that the gene expression analysis of TEN-like lesional skin from anti-PD-1-treated patients revealed an upregulation of major inflammatory chemokines, such as CXCL9, CXCL10, and CXCL11, of cytotoxic mediators such as PRF1 and GZMB and proapoptotic FASLG and upregulation of PD-L1 [116]. These gene expression profiles resembling SJS/TEN suggest that PD-1/PD-L1 interaction is required to preserve epidermal integrity during inflammatory skin reactions. Interestingly, there was a case with preceding nivolumab treatment followed by vemurafenib who developed TEN [117]. The authors suggest that nivolumab predispose patients to drug hypersensitivity reactions through activation of $CD8^+$ cells [84, 85].

In spite of being uncommon, SJS/TEN are severe life-threatening cutaneous diseases that should be concerned in patients treated with anticancer drugs. The typical presentation and diagnosis often require proper drug exposure documentation, photography, and skin biopsies. Currently, there are many different classifications and models with detail and validated diagnostic criteria to assist clinical diagnosis and can help predict patients' mortality [118, 119]. Standard reporting method is important for subsequent investigation and analysis of these rare events. In addition, diagnosis of culprit drug is often challenging, the drug notoriety scoring systems including ALDEN score, Naronjo score and in vitro test with lymphocyte transformation test (LTT) are useful tests for the diagnosis of drug hypersensitivity and cross-reactivity and helped to better understand these reactions [120, 121]. Current evidence on the pathomechanism of this complication was limited. Further research is warranted to elucidate the pathophysiology as well as help clinician coping with this notorious adverse event, advancing towards personalized medicine in oncology treatment.

Conflicts of Interest

The authors declared no conflicts of interests.

Authors' Contributions

Chau Yee Ng and Chun-Bing Chen contributed equally to this work.

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Clinical Study

Association between HLA-B Alleles and Carbamazepine-Induced Maculopapular Exanthema and Severe Cutaneous Reactions in Thai Patients

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The *HLA-B* ∗ *15:02* allele has been reported to have a strong association with carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) in Thai patients. The *HLA-B* alleles associated with carbamazepine-induced maculopapular exanthema (MPE) and the drug reaction with eosinophilia and systemic symptoms (DRESS) among the Thai population have never been reported. The aim of the present study was to carry out an analysis of the involvement of *HLA-B* alleles in carbamazepine-induced cutaneous adverse drug reactions (cADRs) in the Thai population. A case-control study was performed by genotyping the *HLA-B* alleles of Thai carbamazepine-induced hypersensitivity reaction patients (17 MPE, 16 SJS/TEN, and 5 DRESS) and 271 carbamazepine-tolerant controls. We also recruited 470 healthy Thai candidate subjects who had not

taken carbamazepine. *HLA-B ∗ 15:02* showed a significant association with carbamazepine-induced MPE ($P = 0.0022$, odds ratio (OR) (95% confidence interval [CI]) = 7.27 (2.04–25.97)) and carbamazepine-induced SJS/TEN ($P = 4.46 \times 10^{-13}$; OR (95% CI) = 70.91(19.67–255.65)) when compared with carbamazepine-tolerant controls. Carbamazepine-induced SJS/TEN also showed an association with *HLA-B ∗ 15:21* allele ($P = 0.013$; OR (95% CI) = 9.54 (1.61–56.57)) when compared with carbamazepine-tolerant controls. *HLA-B ∗ 58:01* allele was significantly related to carbamazepine-induced MPE ($P = 0.007$; OR (95% CI) = 4.73 (1.53–14.66)) and DRESS ($P = 0.0315$; OR (95% CI) = 7.55 (1.20–47.58)) when compared with carbamazepine-tolerant controls. These alleles may serve as markers to predict carbamazepine-induced cADRs in the Thai population.

1. Introduction

Hypersensitivity reactions such as maculopapular exanthema (MPE), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) are common with carbamazepine therapy [1]. MPE is characterized by a diffuse cutaneous erythema which can evolve into severe forms, presenting as vesicles and papules [2]. SJS and TEN, being severe and fatal hypersensitivity reactions, are characterized by epidermal necrosis and skin detachment [3]. The percentage of body surface involvement in SJS is <10%, SJS/TEN overlap is 10%–30%, and TEN is >30% [4]. DRESS includes serious maculopapular eruptions, fever, pharyngitis, eosinophilia, and systemic symptoms with an estimated mortality rate of up to 10% [5–7]. SJS and TEN are bullous reactions, whereas MPE and DRESS are nonbullous reactions [8].

Investigators have found strong phenotype- and ethnicity-specific associations between carbamazepine-induced hypersensitivity reactions and human leukocyte antigen (*HLA*) genes [9–11]. In 2004, Chung et al. reported a very strong association between carbamazepine-induced SJS and *HLA-B ∗ 15:02* allele in Han Chinese patients [12]. This study did not discuss *HLA* association with other cADRs associated with carbamazepine. The Food and Drug Administration (FDA) of the USA and the Clinical Pharmacogenetics Implementation Consortium (CPIC) have recommended screening for the *HLA-B ∗ 15:02* allele prior to initiating treatment with carbamazepine in patients with Asian ancestry [13, 14]. The association of the *HLA-B ∗ 15:02* allele with carbamazepine-induced SJS and TEN was reported in a systematic review and meta-analysis of the relationship between the *HLA-B ∗ 15:02* allele and carbamazepine-induced SJS and TEN among Han Chinese, Thai, and Malaysian populations [15]. Grover and Kukreti, in a meta-analysis study exploring the relationship between *HLA* alleles and carbamazepine-induced cutaneous adverse drug reactions (cADRs) among Asian patients treated with carbamazepine, showed an association of cases of carbamazepine-induced SJS and TEN with *HLA-B ∗ 15:02* and *HLA-B ∗ 15:11* alleles [16]. The authors also showed an association between cases of MPE, DRESS, and SJS/TEN caused by carbamazepine and the *HLA-A ∗ 31:01* allele. The *HLA-A ∗ 31:01* allele was reported to be associated with carbamazepine-induced hypersensitivity reactions among the subjects of European descent [17]. The *HLA-A ∗ 31:01* allele was significantly associated and was a distinct genetic predictor of carbamazepine-induced DRESS but not for carbamazepine-induced SJS/TEN in Chinese and Europeans [18]. Patients with carbamazepine-induced MPE/DRESS showed an association with the *HLA-A ∗ 31:01* and *HLA-B ∗ 51:01* alleles in a study performed in Han Chinese patients [19].

The association between the occurrence of carbamazepine-induced cADRs and the *HLA* allele among the Thai population has been reported previously in only one study. In a case-control study in a Thai population, Tassaneeyakul et al. found a strong association between the presence of the *HLA-B ∗ 15:02* allele and SJS/TEN induced by carbamazepine [20]. More recently, a Thai patient with carbamazepine-induced SJS did not show the presence of the *HLA-B ∗ 15:02* allele but showed the presence of the *HLA-B ∗ 15:21* allele [21]. There is no published data of genetic association of carbamazepine-induced MPE and DRESS within the Thai population. In the present study, we sought to investigate the *HLA-B* allele-phenotype correlations in carbamazepine-induced MPE, DRESS, and SJS/TEN in Thai subjects.

2. Materials and Methods

2.1. Subjects and Characteristics. This study was carried out as a retrospective and prospective case-control study. From 2011 to 2016, patients with carbamazepine-induced cADRs were retrospectively and prospectively enrolled from the Faculty of Medicine Ramathibodi Hospital, Mahidol University, the Faculty of Medicine, Chulalongkorn University, Prasart Neurological Institute, and the Thai Severe Cutaneous Adverse Drug Reaction (THAI-SCAR) research group, Bangkok, Thailand. Among them, 38 patients with carbamazepine-induced cADRs were categorized into MPE (17 cases), SJS/TEN (16 cases), and DRESS (5 cases). Meanwhile, patients who had been taking carbamazepine for more than 6 months without evidence of cutaneous adverse effects were recruited as carbamazepine-tolerant controls ($n = 271$). In addition, 470 healthy Thai subjects were recruited who were not taking carbamazepine. The study was approved by the Ethical Review Committee on Research Involving Human Subjects, Faculty of Medicine, Ramathibodi Hospital, Mahidol University.

2.2. Diagnosis of Carbamazepine-Induced Cutaneous Adverse Drug Reactions. Hypersensitivity reactions were classified according to the criteria of the RegiSCAR study, and a dermatologist and an allergist confirmed the diagnoses on the basis of the photographs, pathological slides, clinical morphology of the skin damage, and medical records [22].

MPE was defined as cutaneous fine pink macules and papules and lesions without mucosal or systemic symptoms [23]. SJS/TEN cases were defined according to the detached

body surface area as SJS (3–10%) and SJS/TEN overlap (10–30%) with or without associated systemic symptoms but not fulfilling the criteria of DRESS [22]. DRESS was defined as follows: presence of fever, maculopapular rash with internal organ involvement, and hematologic abnormalities [24].

2.3. DNA Isolation and HLA-B Typing. DNA extraction (MagNA Pure Compact nucleic acid purification kit, Roche Diagnostics Ltd., USA) was performed based on magnetic bead technology. DNA was aliquoted and stored at −20°C before *HLA* typing. *HLA-B* alleles were analyzed by the polymerase chain reaction-sequence-specific oligonucleotide probe (PCR-SSOP) assay and Luminex™ Multiplex Technology with well-established protocols [22]. In brief, PCR products were hybridized against a panel of oligonucleotide probes coated on polystyrene microspheres that have sequences complementary to stretches of polymorphic sequence within the target *HLA-B* alleles. The amplicon-probe complex was visualized using a colorimetric reaction and fluorescence detection technology. Data analysis for the *HLA-B* assays was performed with HLA fusionTM2.0 software.

2.4. Statistical Analysis. Statistical analysis was performed with SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Allele case-control comparisons were analyzed by Fisher's exact test. A two-sided P value < 0.05 was considered to be statistically significant.

3. Results

3.1. Subjects. Table 1 summarizes the clinical manifestations and demographic variables of the 38 cases and 271 carbamazepine-tolerant controls. Most cases received carbamazepine to treat epilepsy (29 cases), except for 9 patients who received carbamazepine to treat trigeminal neuralgia (5 cases), neuropathic pain (2 cases), bipolar disorder (1 case), and paroxysmal kinesigenic and nonkinesigenic dyskinesia (1 case). The mean treatment dose of carbamazepine in the carbamazepine-induced cADR patients was 325 ± 75 mg/day (mean ± standard deviation). There was no significant differences between the case and tolerant group in treatment dose of carbamazepine. The mean duration for the onset of cADR was 16 ± 7 days (mean ± standard deviation).

3.2. Association of HLA-B Alleles with Carbamazepine-Induced cADRs. Of the 38 patients who had carbamazepine-induced cADRs, 17 (44.74%) were found to carry the *HLA-B ∗ 15:02* allele. The *HLA-B ∗ 15:02* allele was observed in 4.06% (11/271) of carbamazepine-tolerant controls and 15.11% (71/470) of the general Thai population (Table 2). Our analysis of all subjects with cADRs and clinical control subjects showed a significant allelic association with *HLA-B ∗ 15:02* ($P = 7.35 \times 10^{-12}$), generating an odds ratio (OR) of 19.13 (95% confidence interval [CI], 7.94–46.09). A comparison of all 38 carbamazepine-induced cADR subjects with 470 general Thai subjects produced an OR of 4.55 (95% CI, 2.29–9.05, $P = 3.44 \times 10^{-6}$). Two patients with carbamazepine-induced cADRs carried *HLA-B ∗ 15:21*, while the other *HLA-B* serotypes 75 were not detected in this study.

3.3. Association between HLA-B Alleles and Various Types of Carbamazepine-Induced cADRs. We analyzed the *HLA-B* association between 17 patients with carbamazepine-induced MPE and 271 carbamazepine-tolerant controls. We found two *HLA-B* alleles, *HLA-B ∗ 15:02* and *HLA-B ∗ 58:01*, as significant in the carbamazepine-induced MPE (Table 3). The *HLA-B ∗ 15:02* allele was observed in 23.53% (4/17) of patients with carbamazepine-induced MPE, but only in 4.06% (11/271) of the carbamazepine-tolerant controls, giving a significant association with carbamazepine-induced MPE ($P = 0.002$; OR (95% CI) = 7.27 (2.04–25.97)). The *HLA-B ∗ 58:01* allele appeared in 29.41% (5/17) of patients with carbamazepine-induced MPE, which was more frequent than in carbamazepine-tolerant controls (8.12%, 22/271; $P = 0.007$; OR (95% CI) = 4.73 (1.53–14.66)). In the included general population, the carrier rates of *HLA-B ∗ 15:02* and *HLA-B ∗ 5801* were 12.34% (58/470) and 12.13% (57/470), respectively. Comparing the difference of the *HLA-B ∗ 58:01* allele frequencies between the 17 patients with carbamazepine-induced MPE and 470 general subjects, *HLA-B ∗ 58:01* showed the significant association with carbamazepine-induced MPE ($P = 0.045$; OR (95% CI) = 3.02 (1.03–8.88)). As for the carbamazepine-induced SJS/TEN, the *HLA-B ∗ 15:02* and *HLA-B ∗ 15:21* alleles were most significantly detected (Table 4). 75% (12/16) of carbamazepine-induced SJS/TEN patients carried *HLA-B ∗ 15:02*, which was more frequent than in carbamazepine-tolerant controls (4.1%, 11/271; $P = 4.46 \times 10^{-13}$; OR (95% CI) = 70.91 (19.67–255.65)). The *HLA-B ∗ 15:02* allele was present in 15.11% (71/470) of the general population and when we compared the difference of *HLA-B ∗ 15:02* frequency between carbamazepine-induced SJS/TEN patients and the general population, *HLA-B ∗ 15:02* showed a significant association with carbamazepine-induced SJS/TEN ($P = 6.9 \times 10^{-8}$; OR (95% CI) = 18.26 (5.79–57.61)). *HLA-B ∗ 15:21* was significantly associated with carbamazepine-induced SJS/TEN appearing in 12.5% (2/16) of cases as compared to 1.48% (4/271) and 0.43% (2/470) in carbamazepine-tolerant controls and general Thai subjects, respectively.

As shown in Table 5, the *HLA-B ∗ 58:01* allele was detected as significant in the carbamazepine-induced DRESS group when compared with the carbamazepine-tolerant control group ($P = 0.032$; OR (95% CI) = 7.55 (1.20–47.58)). The *HLA-B ∗ 58:01* allele was present in 40.00% (2/5) of the DRESS patients, but in only 8.12% (22/271) of the carbamazepine-tolerant controls and 12.13% (57/470) of the general population.

4. Discussion

HLA-B alleles are reported to be associated with hypersensitivity reactions during the clinical usage of carbamazepine [25]. Pharmacogenetic screening of *HLA-B* alleles before initiating carbamazepine therapy can prevent the risk of severe and life-threatening cutaneous adverse drug reactions. This study recruited patients with carbamazepine-induced hypersensitivity reactions, such as MPE, DRESS, and SJS/TEN and carbamazepine-tolerant patients from

Table 1: Clinical characteristic of patients with carbamazepine-induced cutaneous adverse drug reactions and carbamazepine-tolerant controls.

Demographic data	Cases ($n = 38$)	Tolerant controls ($n = 271$)	P value
Gender (n/%)			0.145
Male	24/63.15	137/50.6	
Female	14/33.84	134/49.4	
Age (mean/range)	44/24–64	32/10–54	0.010
Indication (n/%)			
Epilepsy	29/75.31	108/39.85	2.26×10^{-5}
Neuropathic pain	2/5.26	23/8.5	0.752
Trigeminal neuralgia	5/13.2	62/22.88	0.173
Bipolar disorder	1/2.6	10/3.7	1.000
Paroxysmal kinesigenic and nonkinesigenic dyskinesia	1/2.6	7/2.6	1.000
Autism	—	35/12.9	0.012
Schizophrenia	—	18/6.6	0.143
Others	—	8/3.0	0.602
Dose of carbamazepine; mg/day (mean ± SD)	325 ± 75	418 ± 19	0.397
Onset of cADRs; days (mean ± SD)	16 ± 7	—	—
cADRs (n/%)			
MPE	17/45	—	—
SJS/TEN	16/42	—	—
DRESS	5/13	—	—

cADRs: cutaneous adverse drug reactions; SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis; DRESS: drug reaction with eosinophilia and systemic symptoms; MPE: maculopapular exanthema.

Thailand. We found the association between *HLA-B* alleles (*B ∗ 15:02* and *B ∗ 58:01*) and carbamazepine-induced MPE. Further, the *HLA-B ∗ 15:02* and *HLA-B ∗ 15:21* alleles were strongly associated with carbamazepine-induced SJS/TEN, and carbamazepine-induced DRESS had significant association with *HLA-B ∗ 58:01* allele.

The evidence of association of different types of carbamazepine-induced cADRs was shown by Hung et al. in Han Chinese patients [3]. In their study, the *HLA-A ∗ 31:01* allele was associated with MPE ($P_c = 2.2 \times 10^{-3}$; OR (95% CI) = 17.5 (4.6–66.5)) and *HLA-B ∗ 15:02* was the susceptible allele for SJS/TEN ($P_c = 1.6 \times 10^{-41}$; OR (95% CI) = 1357 (193.4–8838.3)). Few studies have been conducted in the Thai population regarding the involvement of *HLA* alleles in carbamazepine-induced cADRs. The *HLA-A ∗ 31:01* allele has been mainly associated with carbamazepine-induced DRESS and MPE in Han Chinese population, Japanese, and European populations [17, 19, 26]. Our study did not perform *HLA-A* typing, and we might have missed the potential association between the *HLA-A ∗ 31:01* allele and carbamazepine-induced hypersensitivity reactions.

In 2008, Locharernkul et al. first identified that the *HLA-B ∗ 15:02* allele was strongly associated with carbamazepine-induced SJS ($P = 0.0005$) in the Thai population [27]. A consistent association of the cases of carbamazepine-induced SJS/TEN were reported among the carriers of the *HLA-B∗15:02* allele in this Thai population [20, 28]. Our findings justify the strongest association of the *HLA-B ∗ 15:02* allele in the prediction of carbamazepine-induced SJS/TEN. In our study, we observed that the *HLA-B ∗ 15:02* allele was not specific for carbamazepine-induced SJS/TEN only, but it was also significantly associated with carbamazepine-induced MPE. However, a previous study by Hung et al. reported the phenotype-specific *HLA* association of carbamazepine-induced cADRs [3]. This discrepancy might be due to the different study populations. We observed the first evidence of a significant association of the *HLA-B ∗ 15:21* allele with carbamazepine-induced SJS/TEN in Thai subjects. *HLA-B∗15:21* allele belongs to the HLA-B75 family, which consists of the *HLA-B ∗ 15:02* allele as well [29]. Jaruthamsophon et al. reported that *HLA-B ∗ 15:21* was associated with carbamazepine-induced SJS in different populations and that a patient without the *HLA-B ∗ 15:02* allele may be at a risk of carbamazepine-induced SJS due to the presence of the *HLA-B ∗ 15:21* allele, another HLA-B75 serotype marker [21]. We can conclude that the presence of alternative forms of *HLA* alleles belonging to the same subfamilies of serotypes might contribute to the susceptibility to cADRs. These observations imply that members of the HLA-B75 serotype encode proteins sharing a similar conformation for carbamazepine binding and presentation and trigger the immune response of SJS caused by carbamazepine [19].

In our study, we also found the association of the *HLA-B ∗ 58:01* allele with carbamazepine-induced MPE and DRESS. In contrast to our finding, Cheung et al. noted

Table 2: Association of *HLA-B* alleles with carbamazepine-induced cADRs.

HLA-B alleles	Carbamazepine-induced cADRs ($n = 38$)	Controls ($n = 271$)	Thai population ($n = 470$)	Carbamazepine-induced cADRs cases versus tolerant controls		Carbamazepine-induced cADRs cases versus Thai population	
				OR (95% CI)	*P* value	OR (95% CI)	*P* value
B∗07:05	3 (7.89%)	12 (4.43%)	24 (5.11%)	1.85 (0.50–6.88)	0.357	1.59 (0.46–5.55)	0.4649
B∗13:01	1 (2.63%)	37 (13.65%)	54 (11.49%)	0.17 (0.02–1.28)	0.063	0.21 (0.03–1.55)	0.106
B∗13:02	1 (2.63%)	6 (2.21%)	20 (4.26%)	1.19 (0.14–10.19)	1.000	0.61 (0.08–4.66)	1.000
B∗15:01	1 (2.63%)	10 (3.69%)	5 (1.06%)	0.71 (0.09–5.67)	1.000	2.51 (0.29–22.08)	0.374
B∗15:02	17 (44.74%)	11 (4.06%)	71 (15.11%)	19.13 (7.94–46.09)	7.35×10^{-12}*	4.55 (2.29–9.05)	3.44×10^{-6}*
B∗15:21	2 (5.26%)	4 (1.48%)	2 (0.43%)	3.71 (0.66–20.97)	0.161	13.00 (1.78–95.01)	0.030*
B∗18:01	4 (10.53%)	29 (10.70%)	36 (7.66%)	0.98 (0.33–2.97)	0.974	1.42 (0.48–3.22)	0.529
B∗18:15	2 (5.26%)	0 (0.00%)	0 (0.00%)	15.06 (1.33–170.25)	0.041*	26.11 (2.31–294.90)	0.016*
B∗27:04	2 (5.26%)	12 (4.43%)	19 (4.04%)	1.20 (0.26–5.58)	0.685	1.32 (0.30–5.89)	0.665
B∗27:06	1 (2.63%)	8 (2.95%)	12 (2.55%)	0.89 (0.11–7.31)	1.000	1.03 (0.13–8.15)	1.000
B∗40:01	5 (13.16%)	41 (15.13%)	58 (12.34%)	0.85 (0.31–2.31)	0.749	1.08 (0.40–2.87)	0.883
B∗44:03	3 (7.89%)	20 (7.38%)	42 (8.94%)	1.08 (0.30–3.81)	0.910	0.47 (0.14–1.59)	0.223
B∗46:01	8 (21.05%)	64 (23.62%)	122 (25.96%)	0.86 (0.38–1.98)	0.718	0.77 (0.34–1.72)	0.524
B∗51:01	5 (13.16%)	21 (7.75%)	40 (8.51%)	1.80 (0.64–5.11)	0.267	1.63 (0.60–4.41)	0.337
B∗56:04	1 (2.63%)	1 (0.37%)	12 (2.55%)	7.30 (0.45–119.17)	0.231	1.03 (0.13–8.15)	1.000
B∗57:01	1 (2.63%)	9 (3.32%)	11 (2.34%)	0.79 (0.10–6.39)	1.000	1.13 (0.14–8.98)	0.611
B∗58:01	8 (21.05%)	22 (8.12%)	57 (12.13%)	3.02 (1.24–7.38)	0.015*	1.93 (0.85–4.42)	0.119

cADRs: cutaneous adverse drug reactions; OR: odds ratio; 95% CI: confidence interval 95%. *P value less than 0.05.

Table 3: Association of *HLA-B* alleles with carbamazepine-induced MPE.

HLA-B alleles	Carbamazepine-induced MPE ($n = 17$)	Controls ($n = 271$)	Thai population ($n = 470$)	Carbamazepine-induced MPE cases versus tolerant controls		Carbamazepine-induced MPE cases versus Thai population	
				OR (95% CI)	*P* value	OR (95% CI)	*P* value
B∗07:05	1 (5.88%)	12 (4.43%)	24 (5.11%)	1.44 (0.18–11.81)	0.533	1.234 (0.16–9.78)	0.576
B∗13:02	1 (5.88%)	6 (2.21%)	20 (4.26%)	2.94 (0.33–26.05)	0.334	1.50 (0.19–11.93)	0.512
B∗15:02	4 (23.52%)	11 (4.06%)	71 (15.11%)	7.27 (2.04–25.97)	0.002*	2.30 (0.36–4.67)	0.721
B∗18:01	1 (5.88%)	29 (10.70%)	36 (7.66%)	0.19 (0.03–1.40)	0.098	0.80 (0.10–6.26)	1.000
B∗18:15	1 (5.88%)	0 (0.00%)	0 (0.00%)	18.07 (1.08–303.14)	0.108	31.33 (1.87–525.19)	0.065
B∗27:04	1 (5.88%)	12 (4.43%)	19 (4.04%)	1.44 (0.18–11.81)	0.533	1.58 (0.20–12.61)	0.495
B∗40:01	3 (17.65%)	41 (15.13%)	58 (12.34%)	1.30 (0.35–4.74)	0.720	1.64 (0.45–5.93)	0.438
B∗44:03	2 (11.77%)	20 (7.38%)	42 (8.94%)	1.72 (0.37–8.11)	0.369	1.46 (0.32–6.62)	0.648
B∗46:01	3 (17.65%)	64 (23.62%)	122 (25.96%)	0.69 (0.19–2.49)	0.574	0.66 (0.18–2.35)	0.772
B∗51:01	3 (17.65%)	21 (7.75%)	40 (8.51%)	2.55 (0.69–9.60)	0.166	2.30 (0.65–8.35)	0.204
B∗57:01	1 (5.88%)	9 (3.32%)	11 (2.34%)	1.94 (0.23–16.34)	0.442	2.78 (0.34–22.96)	0.334
B∗58:01	5 (29.41%)	22 (8.12%)	57 (12.13%)	4.74 (1.53–14.66)	0.007*	3.03 (1.03–8.88)	0.045*

MPE: maculopapular exanthema; OR: odds ratio; 95% CI: confidence interval 95%. *P value less than 0.05.

Table 4: Association of *HLA-B* alleles with carbamazepine-induced SJS/TEN.

HLA-B alleles	Carbamazepine-induced SJS/TEN ($n = 16$)	Controls ($n = 271$)	Thai population ($n = 470$)	Carbamazepine-induced SJS/TEN cases versus tolerant controls OR (95% CI)	*P* value	Carbamazepine-induced SJS/TEN cases versus Thai population OR (95% CI)	*P* value
B∗07:05	2 (12.50%)	12 (4.43%)	24 (5.11%)	3.08 (0.63–12.13)	0.165	2.65 (0.57–12.35)	0.213
B∗13:01	1 (6.25%)	37 (13.65%)	54 (11.49%)	0.40 (0.05–3.07)	0.709	0.48 (0.06–3.70)	0.707
B∗15:01	1 (6.25%)	10 (3.69%)	5 (1.06%)	1.63 (0.20–13.55)	0.494	5.81 (0.64–52.67)	0.193
B∗15:02	12 (75.00%)	11 (4.06%)	71 (15.11%)	70.91 (19.67–255.65)	4.46×10^{-13} *	18.26 (5.79–57.61)	6.9×10^{-8} *
B∗15:21	2 (12.50%)	4 (1.48%)	2 (0.43%)	9.54 (1.61–56.57)	0.013*	19.14 (2.51–146.09)	0.004*
B∗18:01	2 (12.50%)	29 (10.70%)	36 (7.66%)	1.19 (0.26–5.51)	0.822	1.72 (0.38–7.88)	0.483
B∗18:15	1 (6.25%)	0 (0.00%)	0 (0.00%)	16.94 (1.01–183.39)	0.114	29.38 (1.76–490.97)	0.069
B∗44:03	1 (6.25%)	20 (7.38%)	42 (8.94%)	0.78 (0.10–6.22)	1.000	0.37 (0.05–2.89)	0.484
B∗46:01	4 (25.00%)	64 (23.62%)	122 (25.96%)	1.08 (0.34–3.46)	0.899	0.96 (0.30–3.03)	0.947
B∗56:04	1 (6.25%)	1 (0.37%)	12 (2.55%)	16.88 (1.01–282.35)	0.115	2.39 (0.29–19.48)	0.374
B∗58:01	1 (6.25%)	22 (8.12%)	57 (12.13%)	0.71 (0.09–5.59)	1.000	0.45 (0.06–3.48)	0.707

SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis; OR: odds ratio; 95% CI: confidence interval 95%. *P value less than 0.05.

Table 5: Association of *HLA-B* alleles with carbamazepine-induced DRESS.

HLA-B alleles	Carbamazepine-induced DRESS ($n = 5$)	Controls ($n = 271$)	Thai population ($n = 470$)	Carbamazepine-induced DRESS cases versus tolerant controls		Carbamazepine-induced DRESS cases versus Thai population	
				OR (95% CI)	*P* value	OR (95% CI)	*P* value
B∗15:02	1 (20.00%)	11 (4.06%)	71 (15.11%)	5.91 (0.61–57.36)	0.126	1.41 (0.16–12.75)	0.562
B∗18:01	1 (20.00%)	29 (10.70%)	36 (7.66%)	2.09 (0.23–19.30)	0.440	3.01 (0.33–27.68)	0.325
B∗27:04	1 (20.00%)	12 (4.43%)	19 (4.04%)	5.40 (0.56–52.04)	0.216	5.93 (0.63–55.68)	0.194
B∗27:06	1 (20.00%)	8 (2.95%)	12 (2.55%)	8.22 (0.82–82.09)	0.154	9.54 (0.99–91.90)	0.130
B∗40:01	2 (40.00%)	41 (15.13%)	58 (12.34%)	3.74 (0.61–23.08)	0.174	4.74 (0.78–28.94)	0.122
B∗51:01	1 (20.00%)	21 (7.75%)	40 (8.51%)	2.98 (0.32–27.85)	0.339	2.69 (0.29–24.63)	0.382
B∗58:01	2 (40.00%)	22 (8.12%)	57 (12.13%)	7.55 (1.20–47.58)	0.032*	4.83 (0.79–29.53)	0.088

DRESS: drug reaction with eosinophilia and systemic symptoms; OR: odds ratio; 95% CI: confidence interval 95%. *P value less than 0.05.

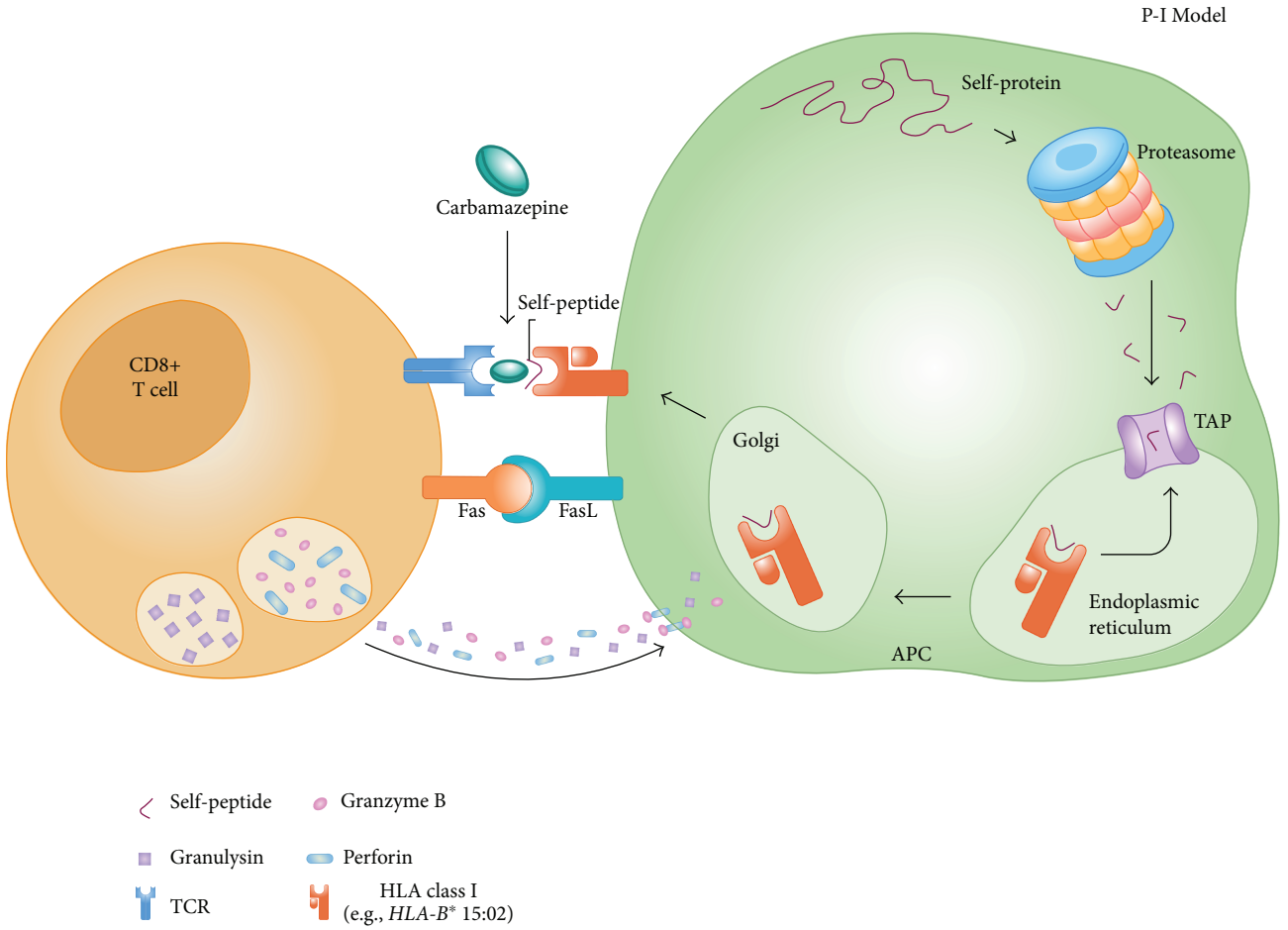

Figure 1: The "pharmacological interaction with immune receptors (p–i)" model of immune activation during carbamazepine-induced hypersensitivity reactions.

in Han Chinese that the presence of the *HLA-B ∗ 58:01* allele appears to be protective against the development of carbamazepine-induced SJS/TEN [30]. A meta-analysis investigating the association of *HLA-B* alleles and carbamazepine-induced SJS/TEN also found that the *HLA-B ∗ 58:01* allele was a protective marker among Asian populations [31]. From these observations, we can conclude that genetic susceptibility to carbamazepine-induced cADRs is phenotype-specific. The *HLA-B ∗ 58:01* allele is mainly associated with allopurinol-induced MPE, DRESS, and SJS/TEN in the Thai population [22, 32]. There are structural dissimilarities between carbamazepine and allopurinol; therefore, the details of the mechanism, including how exactly the *HLA-B ∗ 58:01* allele interacts with each drug and exhibits the immune response, should be explored in future studies. Genetic screening of the *HLA-B ∗ 15:02* allele in isolation will fail to prevent carbamazepine-induced MPE/DRESS. The association of the *HLA-B ∗ 58:01* allele with carbamazepine-induced MPE and DRESS indicates the role of multiple *HLA-B* alleles, and the genetic testing of these alleles will improve the prevention of carbamazepine-induced cADRs. The *P* value for the association of the *HLA-B ∗ 58:01* allele with carbamazepine-induced DRESS is just below the margin of significance ($P = 0.032$). This finding must be considered preliminary and further studies are required to confirm this association of the *HLA-B ∗ 58:01* allele with carbamazepine-induced DRESS.

The pathogenesis of these carbamazepine-induced hypersensitivity reactions needs further research, due to the role of genetic and host factors in carbamazepine-induced cADRs. The role of carbamazepine-specific T cells and its T cell receptors (TCRs) in the pathogenesis of carbamazepine-induced cADRs must be documented to evaluate the mechanism of carbamazepine-induced cADRs [33]. As illustrated in Figure 1, the "pharmacological interaction with immune receptors (p–i)" concept is a useful model to explain how carbamazepine triggers an immune-mediated hypersensitivity reactions [10].

Our study has provided substantial evidence of the development of MPE, SJS/TEN, and DRESS among carbamazepine-treated patients with *HLA* risk alleles. Screening of the risk alleles before carbamazepine use in the Thai population will significantly reduce cADRs with the exclusion of high-risk patients. We did not carry out an analysis of the involvement of *HLA-A* and *HLA-C* alleles in carbamazepine-induced hypersensitivity reactions, so this

might limit the scope of the application of our findings in clinical settings. Therefore, further studies should include association analysis of *HLA-A* and *HLA-C* variants with cADRs in Thai population. The adjusted significance level after Bonferroni's correction is 0.003 with 17 *HLA-B* alleles tested. Only the *HLA-B* ∗ *15:02* allele remained significant with $P < 0.003$ after Bonferroni adjustment. Because, the smallest P value in Tables 2–5 is >0.003, no other alleles are deemed significant after Bonferroni adjustment.

5. Conclusions

We found a strong association between the *HLA-B* ∗ *15:02* allele and carbamazepine-induced SJS/TEN and MPE in Thai patients. We also reported an association of the *HLA-B* ∗ *15:21* allele with carbamazepine-induced SJS/TEN providing a new perspective of the pharmacogenetic linkage. In addition, the *HLA-B* ∗ *58:01* allele was also found to be a significant predictor of carbamazepine-induced MPE and DRESS in Thai patients. These findings may need to be confirmed before clinical interpretation and usage with the inclusion of larger sample sizes in further studies. Testing multiple related *HLA* alleles will aid in more reliable evaluation of the risks for developing SJS/TEN and MPE in patients prior to taking carbamazepine.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Treatments for Severe Cutaneous Adverse Reactions

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Severe cutaneous adverse reaction (SCAR) is life-threatening. It consists of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and generalized bullous fixed drug eruptions (GBFDE). In the past years, emerging studies have provided better understandings regarding the pathogenesis of these diseases. These diseases have unique presentations and distinct pathomechanisms. Therefore, theoretically, the options of treatments might be different among various SCARs. However, due to the rarity of these diseases, sufficient evidence is still lacking to support the best choice of treatment for patients with SCAR. Herein, we will provide a concise review with an emphasis on the characteristics and treatments of each SCAR. It may serve as a guidance based on the current best of knowledge and may shed light on the directions for further investigations.

1. Introduction

Drug hypersensitivity may result in several different kinds of reactions. In most of the cases, drug hypersensitivity presents as generalized maculopapular exanthema, which is mild and almost self-limited after withdrawing the causative agents. However, in a small fraction of the cases, drug hypersensitivity would show up as a severe drug reaction. These severe reactions are life-threatening and termed as severe cutaneous adverse reactions (SCARs).

SCARs consist of some different disease entities, including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and generalized bullous fixed drug eruptions (GBFDE) [1]. All of them harbor considerable rates of morbidities and mortalities. However, each SCAR has its own characteristic cutaneous presentations, causative drugs, clinical courses, pathomechanisms, and possible treatment modalities. Therefore, being familiar with SCARs and providing prompt treatments are important to manage these diseases and to reduce the adverse impacts. For this purpose, in this review, we will summarize concise descriptions regarding the characteristics of each SCAR with an emphasis on the options of treatment for each SCAR.

2. Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

2.1. Basic Characteristics. SJS and TEN are among the most important and well-known SCARs. The incidence of SJS/TEN has been reported to be 1.5–1.8/per million persons per year [2]. They are usually caused by a limited number of drugs, including anticonvulsants, sulfa-containing drugs, antibiotics, nonsteroidal anti-inflammatory drugs, and uric acid-lowering agents [3]. Patients with SJS/TEN usually develop mucosal erosions or ulcers with variable extents of skin detachment after ingesting causative agents for a period of 1–3 weeks [4]. The mucosal lesions may include the oral cavity, lips, conjunctivae, and genital areas. Skin lesions are usually widespread with a predilection on the trunk and consist of atypical flat target lesions, which may become confluent or result in the formation of blisters [5]. Systemic symptoms may develop, which include fever, general malaise, flu-like symptoms, and possible internal organ involvement [6].

SJS and TEN are thought be a spectrum of the same disease. They are classified, by the definition, using the extent of blistering or detachment in relation to the body surface area (BSA) [5]. In SJS, skin detachment is limited to less than 10% of BSA, while in TEN, it is more than 30%. For those skin detachments between 10 and 30% of BSA, they are classified as SJS/TEN overlap. The mortality rate of SJS/TEN is quite high but varies depending on the severity of the disease. It is usually between 1 and 5% in SJS but may be up to 25–30% in TEN [7]. The severity-of-illness score for TEN (SCORTEN) has been widely used to predict mortality of patients with SJS/TEN [8]. The SCORTEN consists of seven variables: (1) age > 40 years, (2) skin detachment > 10% of BSA, (3) heart rate > 120 per minute, (4) presence of malignancy, (5) blood urea nitrogen level > 28 mg/dl, (6) blood glucose level > 252 mg/dl, and (7) blood bicarbonate level < 20 mEq/l. Each item gets one point if it presents. A higher score of the SCORTEN correlates with a higher mortality rate [8].

Histopathological examination is important to confirm the diagnosis of SJS/TEN. It is characterized by numerous apoptotic keratinocytes or forming confluent epidermal necrosis, basal layer vacuolarization, and scarce superficial dermal and perivascular lymphohistiocytic infiltrations [9]. Several mediators have been shown to account for the development of apoptosis of keratinocytes and to be involved in the pathogenesis of SJS/TEN. These include tumor necrosis factor- (TNF-) α [10, 11], Fas/Fas ligand [12–14], perforin/granzyme B [15–17], and granulysin [18]. Among them, granulysin exhibits potent toxic effects on keratinocytes and is thought to be the most important mediator in SJS/TEN by far. Granulysin is produced by intraepidermal natural killer (NK) cells and cytotoxic $CD8^+$ T-cells in the early phase of SJS/TEN [18]. A rapid test for granulysin has been shown to be an aid for making the diagnosis [19].

In addition to the high mortality rate, several short-term and long-term sequelae have also been reported [20, 21]. Cutaneous and ocular problems were the most common sequelae with an incidence of 44% [22]. The common cutaneous problems include chronic eczema, pigmentary changes, and nail changes. The common ophthalmic complications include dry eye syndrome, chronic conjunctivitis, trichiasis, corneal erosions, and symblepharon [20–22].

2.2. Treatment

2.2.1. General Management. Correct identification and prompt withdrawal of the culprit drug are the most important steps in treating patients with SJS/TEN [23]. A useful algorithm has been designed to assess drug causality in SJS/TEN (algorithm of drug causality for epidermal necrolysis (ALDEN)) [24], which could be very helpful to determine the culprit drug.

Supportive care is basically the most important and fundamental treatment for patients with SJS/TEN (Table 1) [25]. Supportive care should include assessment and management of skin wounds, fluid and nutrition status, electrolyte balance, renal and airway function, and adequate pain control [26]. For skin wound care, an antishear handling should be applied to minimize further skin damages. Some experts suggest that the detached skin should be left in situ to act as a biological dressing to protect the underlying dermis, while others argue that the detached skin must be debrided to remove all the potentially infected materials and then covered by biosynthetic dressings [25]. Both approaches are widely used with no good evidence to differentiate which is better. A guideline proposed by the UK experts suggests that debridement may be considered when failure of conservative treatment, presence of wound infection, or delayed healing occurs [27]. Adequate covering of the denuded skin can improve skin barrier function, reduce transepidermal water and protein loss, limit microbial colonization, improve pain control, and promote reepithelialization. Currently, no evidence supports which dressing is superior.

Keeping the fluid balance is an important measurement to prevent end-organ hypoperfusion [27]. It could be monitored daily by a urine output or when necessary by intra-arterial hemodynamic monitoring [27]. A urine output of 0.5–1.0 ml/kg/hr should be maintained [28]. Adequate nutrition support is mandatory because of a hypermetabolic status and large amounts of protein loss in SJS/TEN. It has been suggested to provide up to 20–25 kcal/kg/day in the early phase and up to 25–30 kcal/kg/day in the recovery phase of SJS/TEN by oral intake or nasogastric feeding [27]. Analgesia is necessary and should be adjusted according to the degree of pain. In mild cases, acetaminophen may be adequate, while in severe cases, opiate-based analgesics may be considered [27].

2.2.2. Specific Treatments. There is still a lack of well-designed randomized controlled trial to assess treatment efficacy in SJS/TEN because of rarity of the disease. However, recently, new evidences support that compared to supportive care, some treatments may provide more benefits to the patients. In the following section, we will discuss these commonly used treatments.

(1) Corticosteroids. Corticosteroid is by far the most commonly used treatment in SJS/TEN other than supportive care [29]. In the past years, many studies showed noninferiority of systemic corticosteroids compared to the supportive care in treating patients with SJS [30, 31]. Kakourou et al. even found that corticosteroids were significantly associated with decreased fever length and duration of skin lesions [32]. For patients with TEN, there are controversies regarding the usage of corticosteroids. Despite that more studies showed survival benefits on patients with TEN receiving systemic corticosteroids, some studies reported a lack of efficacy or even increased mortality [33, 34]. A high dose of systemic corticosteroids has been shown to be effective in patients with TEN and is recommended by Japanese experts [35]. Araki et al. has reported successfully the use of corticosteroid pulse therapy with a dose of methylprednisolone 500 mg/day for 3 days in 5 patients with TEN [36]. All of them survived. Hirahara et al. have reported similar results in 8 patients with TEN using a dose of methylprednisolone 1000 mg/day for 3 days [37]. A recent published meta-analysis, which collected studies from 1990 to 2012, showed a trend toward survival

Table 1: Treatments for severe cutaneous adverse reactions (SCARs).

SCARs	Comments
SJS/TEN	
Supportive care	It is the most important and fundamental treatment and should include assessment and management of skin wounds, fluid and nutrition status, electrolyte balance, renal and airway function, and adequate pain control.
Systemic corticosteroids	They are the most commonly used treatment in SJS/TEN other than supportive care. There are controversies regarding the usage of corticosteroids. There is a trend toward survival benefits of systemic corticosteroids compared to supportive care (odds ratio: 0.54; 95% CI: 0.29–1.01).
IVIG	The results were conflicting. A recently published meta-analysis showed no differences in mortality when comparing patients receiving IVIG to those receiving supportive care.
Cyclosporine	Three recent meta-analysis studies showed a significant and beneficial effect of cyclosporine compared with supportive care on mortality.
Anti-TNF-α agents	There is an unexpected increase in mortality in the patients receiving thalidomide. Several case reports and one case series showed positive results of infliximab or etanercept in the treatment of SJS/TEN.
Plasmapheresis	Plasmapheresis may remove toxic and harmful mediators from the patients and has been shown to provide rapid and dramatic improvement in some reports.
DRESS	
Supportive care	It might have a higher rate of detectable autoantibodies and a higher rate of autoimmune long-term sequelae. Further studies are needed.
Systemic corticosteroids	They are the mainstay treatment. They may reduce the occurrence of disease flare-ups and decrease the probability of the development of autoimmune sequelae. Individual adjustments are needed.
IVIG	Results are conflicted. It should not be used as monotherapy.
Others	These include cyclosporine, cyclophosphamide, mycophenolate mofetil, and rituximab. Antiviral therapies such as ganciclovir have been proposed in addition to systemic corticosteroids or IVIG in patients with severe disease and viral reactivation.
AGEP	
Supportive care	It includes identification and removal of the possible culprit drugs.
Topical corticosteroids	They were correlated with a decreased median duration of hospitalization.
Systemic corticosteroids	The beneficial effects of the usage of systemic corticosteroids need further investigations.
GBFDE	
Supportive care	It includes prompt identification and removal of the possible culprit drugs.
Systemic corticosteroids	There is a lack of sufficient evidence.

AGEP: acute generalized exanthematous pustulosis; DRESS: drug reaction with eosinophilia and systemic symptoms; GBFDE: generalized bullous fixed drug eruption; IVIG: intravenous immunoglobulin; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; TNF: tumor necrosis factor.

benefits of systemic corticosteroids compared to supportive care (odds ratio: 0.54; 95% CI: 0.29–1.01) and suggested that systemic corticosteroids are one of the most promising immunomodulating therapies for SJS/TEN [38].

(2) Intravenous Immunoglobulin. Intravenous immunoglobulin (IVIG) has attracted much attention since the very first report showing the activation of Fas-Fas ligand in SJS/TEN and the success of treatment with IVIG [12]. Since then, many studies emerged; however, the results were conflicting. Some reports showed survival benefits [39–42], while others did not [43–46]. Dosages of IVIG may have influences on the results of treatment [47]. For those studies with survival benefits, the dosages of IVIG were at least 2.8 g/kg and even up to 4 g/kg. For studies that failed, the dosages of IVIG were mostly 2 g/kg or even lower [47]. Huang et al. performed the first meta-analysis on efficacy of IVIG for the treatment of TEN [48]. They found a significant lower mortality in patients treated with high-dose IVIG compared to those treated with low-dose IVIG (18.9% versus 50%, P value = 0.022). However, this trend did not exist after multivariate logistic regression (high versus low dose: odds ratio 0.494; 95% CI: 0.106–2.300, P value = 0.369). Lee et al. have reported a retrospective study, which is the largest one till now, analyzing 64 patients with SJS/TEN overlap or TEN treated with IVIG [49]. They found that the use of IVIG does not have survival benefits on SJS/TEN overlap and TEN, even when corrected for IVIG dosages. A recently published meta-analysis also confirmed this observation and showed no differences in mortality when comparing patients receiving IVIG to those receiving supportive care [38].

(3) Cyclosporine. Cyclosporine is an immunosuppressive agent inhibiting $CD8^+$ cytotoxic T-cells and harboring an antiapoptotic effect through the inhibition of Fas ligand [12] and TNF-α [10]. All these cells and mediators play an important role in the pathogenesis of SJS/TEN. It is reasonable to use cyclosporine for the treatment of SJS/TEN. Valeyrie-Allanore et al. conducted a pilot study recruiting 29 patients with SJS/TEN [50]. These patients were treated

with cyclosporine 3 mg/kg for 10 days with gradual tapering over 1 month. They found that both mortality rate and progression of skin detachment were lower than expected and suggested a possible usefulness of cyclosporine in SJS/TEN. Recently, Lee et al. reported a retrospective case-control study including 44 patients with SJS/TEN [51]. Among these patients, 24 patients received cyclosporine treatment, while others received supportive care. In the group treated with cyclosporine, 3 deaths were observed. The number of observed death was fewer than that of the SCORTEN-predicted death. Compared to the control group, the standardized mortality ratio of cyclosporine treatment was 0.42 (95% CI: 0.09–1.22). The authors suggested that the use of cyclosporine may improve mortality in SJS/TEN. Recently, Chen et al. performed a meta-analysis on the efficacy of cyclosporine in SJS/TEN [52]. They found that the observed mortality was significantly lower than the SCORTEN-predicted mortality in patients receiving cyclosporine (odds ratio: 0.42; 95% CI: 0.19–0.95) and suggested that cyclosporine harbored a beneficial effect on mortality. Another meta-analysis conducted by Zimmermann et al. also found a similar result showing a significant and beneficial effect of cyclosporine compared with supportive care on mortality [38]. A most recently published study [53] has used three different approaches (case-control, case series, and meta-analysis approaches) to analyze the efficacy of cyclosporine on SJS/TEN. They found that all these three approaches showed consistently a reduction in mortality in SJS/TEN patients receiving cyclosporine. Although the use of cyclosporine in SJS/TEN is not quite popular [4], it seems to be a promising treatment. Further large-scale randomized controlled studies are needed to confirm this observation.

(4) Anti-TNF-α Agents. Increased expressions of TNF-α in skin specimens [54], in blister fluid, and in serum [17] of SJS/TEN patients justified the strategy of anti-TNF-α treatment. With this regard, thalidomide had been chosen as one of the options because of its anti-TNF-α property. Wolkenstein et al. had conducted a double-blind, randomized, placebo-controlled trial to evaluate the efficacy of thalidomide [55]. However, it terminated earlier as an unexpected increase in mortality in the patients receiving thalidomide. Nevertheless, the failure of thalidomide did not reject the rationale of anti-TNF-α therapy. After the launch of anti-TNF-α biologics, several case reports showed positive results of infliximab or etanercept in the treatment of SJS/TEN [56–60]. Paradisi et al. published a case series regarding the use of etanercept in TEN [61]. They recruited 10 consecutive patients with TEN (median SCORTEN: 3, range: 2–6) and treated them with a single subcutaneous injection of 50 mg etanercept. All patients survived and responded well with complete reepithelialization. The median time to healing was 8.5 days. Although it is a preliminary study, the result shows that anti-TNF-α therapy may be an effective treatment for SJS/TEN. Further studies are absolutely needed.

(5) Plasmapheresis. Plasmapheresis may remove toxic and harmful mediators from the patients and has been shown to provide rapid and dramatic improvement in some reports [62–65]. Narira et al. have demonstrated the usefulness of plasmapheresis in patients who were refractory to conventional therapies and have shown a correlation between disease severity and serum cytokine levels before and after treatment with plasmapheresis [66]. In these patients, serum levels of interleukin- (IL-) 6, IL-8, and TNF-α decreased after plasmapheresis. Plasmapheresis is now a recommended treatment option by Japanese experts for patients with TEN who are refractory to high-dose corticosteroids [66].

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

3.1. Basic Characteristics. DRESS, which is also named as drug-induced hypersensitivity syndrome (DiHS) by Japanese experts, is a life-threatening disease presenting with fever, cutaneous eruptions, and internal organ involvement [67]. The mortality rate of DRESS is about 10% [68]. Skin lesions in patients with DRESS have some common features, including an extent greater than 50% of BSA, presences of infiltrative papules and plaques with markedly purpuric change, development of facial edema, and occurrence of desquamation in the stage of resolution [67]. Mucosal lesions may be found in more than 50% of the patients with mouth and lips being the most common site [69]. Systemic symptoms usually present with variable organ/systems involved. Among the hematological abnormalities, eosinophilia is the most common one, being present in 66–95% of the patients, followed by atypical lymphocytosis, which could be found in 27–67% of the patients [69]. In addition, lymphadenopathy can be found in 54% of the patients by physical examinations or image studies [69]. For internal organ involvements, the liver is the most frequently encountered one with a rate of 75–94% of the patients, followed by the kidney, lung, and heart [67]. The duration between the start of the culprits and development of the disease is long with a range usually between 3 and 8 weeks [67]. The list of the causative drugs is long, but most of which are limited to a few categories of drugs, including anticonvulsants, anti-infectious (antibiotics, antituberculosis, and antiviral) agents, sulfonamides, and uric acid-lowering medications [67]. The clinical courses of DRESS usually lasted for more than 15 days with a predilection of protracted and prolonged courses [67]. Waves of recurrence of clinical symptoms may sometimes be encountered possibly accompanied by episodic reactivations of human herpes viruses (HHVs) [70, 71]. Reactivations of HHVs, especially HHV-6, are observed in certain patients during the acute stage and subsequent periods of flare-ups. Therefore, it has been suggested that both antidrug and antiviral immune responses contribute to the development of the disease [67]. In addition to a considerable mortality rate in the acute stage of the disease, there have been certain sequelae reported in the literature [72]. These sequelae included permanent renal dysfunction with a requirement of dialysis, fulminant type 1 diabetes mellitus, thyroid disorders, and autoimmune diseases [72, 73].

3.2. Treatment. For treatments of patients with DRESS, there is still insufficient clinical evidence because most of the suggestions are derived from case series or experts' opinions [67]. Immediate withdrawal of the culprit drugs is unsurprisingly the most important thing to do in the management of patients with DRESS. There have been several options of systemic treatments suggested in the literature (Table 1).

3.2.1. Supportive Care Only. Supportive care only may be considered a treatment option for patients with DRESS. A few case series supported this notion. Uhara et al. have reported 12 patients with DiHS who received hydration with or without topical steroids [74]. All the patients recovered well within 7 to 37 days after the withdrawal of the culprit drugs. Ushigome et al. have also presented 17 cases of DiHS treated with only supportive care [75]. All of them recovered smoothly except for those with a higher rate of detectable autoantibodies and a higher rate of autoimmune long-term sequelae. However, the number of patients with DRESS or DiHS treated with only supportive care is still limited. Further studies including a larger number of patients are needed to confirm the observation.

3.2.2. Corticosteroids. Systemic corticosteroids are the mainstay treatment for patients with DRESS. There is still a lack of consensus regarding the dosage and the duration of systemic corticosteroids. A starting dose of 0.5–1.0 mg/kg/day of prednisolone with a gradual tapering over 2-3 months has been suggested by some experts [67]. This approach may reduce the occurrence of disease flare-ups and decrease the probability of the development of autoimmune sequelae [67]. Nevertheless, a prolonged duration of systemic corticosteroid usage may be associated with a higher rate of opportunistic infections and with the possibility of many complications. Funck-Brentano et al. have reported a retrospective study of 38 patients with DRESS [76]. Among these patients, some received supportive care with topical steroids, while others received systemic steroids. The authors found higher rates of infections, septicemia, and the need for intensive care in patients receiving systemic steroid and suggested that systemic steroids should be reserved for those with severe presentations. Thus, individual adjustments are needed for each case based on the severity of the disease and underlying comorbidities. One group of the French Society of Dermatology has recommended that the use of systemic corticosteroids may be considered when 5-fold elevation of serum transaminase levels or involvement of any other organs, such as the kidney, lung, and heart, occurs [77].

3.2.3. Intravenous Immunoglobulin. The results of the use of IVIG in the treatment of patients with DRESS are conflicting. Several studies have reported the successful results [78, 79]. On the other hand, Joly et al. reported their unfavorable experience of using IVIG treatment in 6 DRESS patients [80]. Among them, 5 of the patients had severe adverse effects, with 4 patients requiring systemic corticosteroids due to the adverse effects of IVIG or uncontrolled diseases. Therefore, the authors suggested that IVIG should not be used as monotherapy in treating DRESS syndrome. Obviously, the use of IVIG in the treatment of DRESS needs further investigations.

3.2.4. Other Treatments. Anecdotal reports have shown the treatment effectiveness of several immunosuppressive agents other than those of corticosteroids. These include cyclosporine [81], cyclophosphamide [82], mycophenolate mofetil, and rituximab [67]. Antiviral therapies such as ganciclovir have been proposed in addition to systemic corticosteroids or IVIG to be used in patients with severe disease and confirmation of viral reactivation [77]. However, such treatment should be thoroughly considered by the judgment between benefits and harms.

4. Acute Generalized Exanthematous Pustulosis (AGEP)

4.1. Basic Characteristics. AGEP is characterized by a sudden onset of at least dozens and often hundreds of sterile, nonfollicular pustules on an edematous erythema with a predilection at the major folds [83]. Sometimes, facial edema, blisters, or atypical target lesions may develop. Mucosal lesions are rare and usually mild. Fever and leukocytosis are commonly accompanied by cutaneous eruptions. Systemic involvements have been reported to develop in less than 20% of the patients with AGEP [84]. Liver involvement is the most common one, followed by the kidney, lung, and bone marrow. Although AGEP may result from viral infections [85], it is primarily a hypersensitivity reaction to drugs. The most strongly associated drugs are pristinamycin, ampicillin/amoxicillin, quinolones, hydroxychloroquine, anti-infective sulfonamides, terbinafine, and diltiazem based on a multinational case-control EuroSCAR study [86]. The latent periods between the drug intake and development of the disease showed two different patterns [86]. For those exposed to antibiotics, the median duration was 1 day, while for those using other medications, the median duration was 11 days. The explanation for these differences is largely unexplored. The prognosis of AGEP is generally very good. Most of the patients recovered without sequelae.

4.2. Treatment. The mainstay of treatment for AGEP is the identification and removal of the possible culprit drugs (Table 1) [83]. Recovery and resolution of the skin eruptions usually develop within several days after withdrawal of the culprit drugs [83]. The mean durations between the resolution of the pustules and cessation of the culprit drugs have been reported to be 6 days [87] and 7.6 days [88] in two different studies, respectively. Hospitalization may be required in some patients, especially those with extensive cutaneous eruptions, altered general condition, and systemic involvement. Topical corticosteroid may be used and has been correlated with a decreased median duration of hospitalization [89]. Systemic corticosteroids have been used in some patients with AGEP [88]. However, because of the benign courses in most of the patients with AGEP,

the beneficial effects of the usage of systemic corticosteroids need further investigations.

5. Generalized Bullous Fixed Drug Eruption (GBFDE)

5.1. Basic Characteristics. GBFDE is a rare and severe form of fixed drug eruption (FDE). It is characterized by large areas of well-demarcated erythematous or hyperpigmented patches with blisters or erosions developed soon after administrating the culprit drugs [90]. It exhibits typical features of FDE but may resemble the presentations of SJS/TEN. To differentiate these two diseases is important. One previous study identified that patients with GBFDE had a shorter latent period and less mucosal involvement compared to those with SJS/TEN [90]. The mean duration of the latent period was 3.2 days in GBFDE. Mucosal involvements were only identified in 43% of the patients. Upon histopathological examination, skin specimens of patients with GBFDE showed more eosinophil infiltration and more dermal melanophages. Lesional infiltrates in GBFDE had more dermal $CD4^+$ cells including $Foxp3^+$ cells, less intraepidermal $CD56^+$ cells, and fewer intraepidermal $granulysin^+$ cells compared to those in SJS/TEN. The serum level of granulysin in GBFDE was significantly lower than that in SJS/TEN [90]. These features may help to differentiate the two diseases when skin lesions are ambiguous. The common culprit drugs in GBFDE were antibiotics, including cephalosporins, penicillins, and anti-infective sulfonamides, followed by nonsteroid anti-inflammatory drugs [90]. Traditionally, the prognosis of GBFDE is thought be better than that of SJS/TEN. However, a large retrospective case-control study including 58 patients with GBFDE and 170 patients with SJS/TEN matched for age and extent of skin detachment failed to support this traditional concept [91]. The authors found that the mortality rate was slightly but not significantly lower for patients with GBFDE than for controls (22% versus 28%, multivariate odds ratio: 0.6, 95% CI: 0.3–1.4). Although some selection bias may exist in this study, the observation highlights the nature of GBFDE as SCAR might be overlooked before.

5.2. Treatment. Currently, there is still a lack of reports regarding the treatment of patients with GBFDE. Just like all other drug reactions, prompt identification and removal of the possible culprit drugs are the most important steps to manage the disease (Table 1). Skin lesions of GBFDE patients usually recover gradually after withdrawal of the causative drugs as that usually seen in patients with conventional FDE. However, for those patients with extensive areas of skin detachment, intensive supportive care should be applied as that used in treating patients with SJS/TEN. Systemic corticosteroids may be used as a treatment option for GBFDE and may be considered effective. Our own unpublished data consisting of 32 patients with GBFDE showed only one death occurring during the acute stage of the disease. Most of these patients were treated with systemic corticosteroids. Nevertheless, due to a lack of sufficient evidence regarding the treatments of GBFDE, further investigations are needed.

6. Conclusion

The rarity of SCAR cannot dampen the importance of management of these diseases. All these diseases, including SJS/TEN, DRESS, AGEP, and GBFDE, harbor considerable rates of morbidities and mortalities, which could not be overlooked. However, indeed, the low incidence of SCAR limits the execution of large-scale randomized trials, which in turn, leads to a lack of sufficient clinical evidence in the management of these diseases. Except the existence of some meta-analyses in the treatment of patients with SJS/TEN, for patients with other SCARs, there is a big gap between clinical practice and evidence-based management. Further efforts are needed on these issues to improve the knowledge of SCAR management.

Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Research Article

Comparison between the *HLA-B*58:01* Allele and Single-Nucleotide Polymorphisms in Chromosome 6 for Prediction of Allopurinol-Induced Severe Cutaneous Adverse Reactions

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Severe cutaneous adverse drug reactions (SCARs) are life-threatening reactions. The strong association between the *HLA-B*58:01* allele and allopurinol-induced SCARs is well recognized. Screening for *HLA-B*58:01* allele before prescribing allopurinol in some populations has been recommended. Several single-nucleotide polymorphisms (SNPs) in chromosome 6 have been found to be tightly linked with the *HLA* allele, and these SNPs have been proposed as surrogate markers of the *HLA-B*58:01* allele. This study aimed to evaluate the association between three SNPs in chromosome 6 and allopurinol-induced SCARs in a Thai population. The linkage disequilibrium between the *HLA-B*58:01* allele and these SNPs was also evaluated. Results showed that three SNPs including rs9263726, rs2734583, and rs3099844 were significantly associated with allopurinol-induced SCARs but with a lower degree of association when compared with the *HLA-B*58:01* allele. The sensitivity, specificity, PPV, and NPV of these SNPs were comparable to those of the *HLA-B*58:01* allele. Although detection of the SNP is simpler and less expensive compared with that of the *HLA-B*58:01* allele, these SNPs were not perfectly linked with the *HLA-B*58:01* allele. Screening using these SNPs as surrogate markers of the *HLA-B*58:01* allele to avoid SCARs prior to allopurinol administration needs caution because of their imperfect linkage with the *HLA-B*58:01* allele.

1. Introduction

Allopurinol, a uric acid-lowering agent, is one of the most common culprit drugs for severe cutaneous adverse drug reactions (SCARs). These reactions range from Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) to drug reaction with eosinophilia and systemic symptoms (DRESS). Although the incidence of allopurinol-induced SCARs is rare, they are life-threatening reactions. Data from systematic reviews shows that although the prevalence of gout in Asian population is lower than that in Caucasian populations, the hypersensitivity caused by allopurinol reported in Asians was about 73% of the reported cases [1]. In Taiwan, the annual incidence rates for allopurinol hypersensitivity were 4.68 per 1000 new users, 2.02 per 1000 new users for related hospitalization, and 0.39 per 1000 new users for related mortality [2]. The mortality rate of allopurinol hypersensitivity in Taiwan was about 8.3% [2]. Similarly, the incidence rate of allopurinol-induced SCARs in Thailand reported from the biggest hospital in Thailand was about 2.13 per 1000 new users [3]. Compared with that of other drug-induced SCARs, the mortality rate of allopurinol-induced SCARs observed in a Thai population is the highest up to 11% [4].

Although allopurinol-induced SCARs are considered as idiosyncratic reactions, current studies have identified several risk factors of such fatal reactions that include both genetic and nongenetic factors [4–6]. For genetic factors, the specific allele of the human leukocyte antigen (HLA), namely, the *HLA-B*58:01* allele, is the first genetic marker that was found to be strongly associated with allopurinol-induced SCARs in a Taiwanese population [7]. This association has been confirmed in Thai [4, 8, 9] and Han Chinese [10, 11] populations. Unlike the *HLA-B*15:02* allele which is specific to Chinese and Southeast Asian population, the associations between the *HLA-B*58:01* allele and allopurinol-induced SCARs were also demonstrated in Japanese [12, 13], Korean [14], and Caucasian populations [15]. The strength of association ranges from an odds ratio (OR) of 39 to 696 [16], and the sensitivity and specificity of the *HLA-B*58:01* allele for the prediction of allopurinol-induced SCARs were 93% (95% CI: 85–97%) and 89% (95% CI, 87–91%) across Asian and Caucasian populations [16]. To date, the American College of Rheumatology recommends the testing for the *HLA-B*58:01* allele in certain ethnicities with a high frequency of this allele and showing an elevated risk for allopurinol-induced SCARs in *HLA-B*58:01* allele carriers such as Han Chinese, Thai, and Korean populations [17].

Due to the highly polymorphic nature of the *HLA* gene, a specific method is required in order to determine a specific *HLA* allele, particularly the *HLA-B* alleles in which exon 2 and 3 regions exhibit the highest variability. Several molecular techniques including specific sequencing primers (SSP) PCR, sequence-specific oligonucleotide (SSO) probes, and sequencing-based typing (SBT) have been demonstrated to be specific methods for the determination of *HLA* genotype; however, these techniques are quite expensive, time-consuming, and not commonly available in hospital laboratories. A recent genome-wide association study in a Japanese population has discovered a number of single-nucleotide polymorphisms (SNPs) in chromosome 6 that were strongly associated with allopurinol-induced SCARs [13]. These SNPs included rs2734583 in the *HLA-B-associated transcript 1* (*BAT1*) gene, rs3099844 in the *HLA complex P5* (*HCP5*) gene, and rs9263726 in the *psoriasis susceptibility 1 candidate 1* (*PSORS1C1*) gene. Due to the absolute linkage disequilibrium between rs9263726 and the *HLA-B*58:01* allele found in 27 Japanese patients who suffered from allopurinol-induced SCARs, the rs9263726 has been proposed as a surrogate marker for allopurinol-induced SJS/TEN [18]. Similarly, an absolute linkage disequilibrium between the rs9263726 and allopurinol-induced SCARs has also been recently reported in 17 Eastern Chinese patients [19]. Ethnic specificity of the associations between *HLA* alleles and drug-induced SCARs is well recognized [20]. Whether these SNPs are good surrogates of allopurinol-induced SCARs in other ethnic societies or not needs to be evaluated. The present study aimed to evaluate the degree of relationship between the three selected SNPs in chromosome 6 including rs9263726, rs2734583, and rs3099844 and allopurinol-induced SCARs in a Thai population that has a relatively high frequency of the *HLA-B*58:01* allele. In addition, the sensitivity and specificity for these selected SNPs for the prediction of allopurinol-induced SCARs and their linkage disequilibrium with the *HLA-B*58:01* allele are characterized in the present study.

2. Materials and Methods

2.1. Study Population Assessment and Enrollment. A total of 96 allopurinol-induced SCARs patients including 23 DRESS and 73 SJS/TEN patients were recruited for the study. These patients had been diagnosed with allopurinol-induced SCARs within the first 3 months of allopurinol exposure. The phenotype of SCARs in an individual patient was scored and assessed by the ALDEN [21] or the RegiSCAR algorithms [22] whereas the assessment of causative drugs was performed using Naranjo's algorithm [23]. All of the SCARs patients who represented at least a probable score were recruited for the study.

For the control cohort comparison, 193 patients were recruited from patients who had used allopurinol for more than 6 months without any evidence of cutaneous reactions. Written informed consent was obtained from each patient. The study protocol within the hospital network of Khon Kaen University was approved by the Khon Kaen Ethics Committee for Human Research, Khon Kaen University, Thailand (HE510837). The study protocol was also approved by each hospital, where IRB function was available.

2.2. Genomic DNA Preparation. Leukocytes were separated from peripheral blood by centrifugation at 3500 rpm for 15 min or buccal swab. Genomic DNA (gDNA) was isolated from leukocytes using a QIAamp DNA Blood mini kit (QIAGEN GmbH, Hilden, Germany). The quantity and quality of gDNA were checked by a Nano Drop machine (Thermo Scientific NanoDrop 2000c) and kept at −20°C until used.

*2.3. Detection of the HLA-B*58:01 Allele.* The *HLA-B*58:01* allele was detected using a commercial PG5801 DNA detection kit (Pharmigene Inc., Taipei, Taiwan) as described previously [8]. The *HLA-B* genotypes of patients who had the *HLA-B*58:01* allele were confirmed using the PCR sequence-specific oligonucleotide probe method as has been described in a previous study [24].

2.4. Detection of rs9263726, rs2734583, and rs3099844 SNPs. The rs9263726 in the *PSORS1C1* gene was detected using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay as previously described [18]. The PCR conditions were set at 94°C for 5 min followed by 35 cycles of amplification at 94°C for 30 sec, 60°C for 45 sec, and 72°C for 45 sec and final extension of 72°C for 7 min. The 260 bp length PCR products were digested with Fok I endonuclease (New England Biolabs, Beverly, MA, USA), and the DNA fragments were detected by agarose gel electrophoresis.

The rs2734583 in the *BAT1* gene (assay ID: C__26778946_20) and the rs3099844 in the *HCP5* gene (assay ID: C__27455402_10) were detected by TaqMan® SNP Genotyping Assays (Life Technologies, Carlsbad, CA, USA).

2.5. Statistical Analysis. Two-tailed Student's *t*-test and Fisher's exact test were used to compare the differences among SCARs and tolerant control demographic data (SPSS for Windows; IBM Corp., New York, USA). The risks for allopurinol-induced SCARs were calculated using the dominant model and univariate logistic regression analysis by SPSS software (IBM Corp., New York, USA). The Haldane modification of Woolf's formula was used among samples containing zero. The Bonferroni-corrected *P* value (Pc-value) was calculated by multiplying *P* value by 4 which is the number of multiple comparisons to account for the observed SNPs in this study, and Pc-value less than 0.05 was considered statistically significant. The individual sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) of the *HLA-B*58:01* allele or the selected SNPs for the screening of allopurinol-induced SCARs were calculated.

The estimated linkage disequilibrium coefficients (D') and coefficient of correlation (r^2) between the *HLA-B*58:01* allele and the selected SNPs were calculated using the PLINK (V1.07) program.

3. Results

*3.1. Comparisons of the Associations between the HLA-B*58:01 Allele and the Selected SNPs with Allopurinol-Induced SCARs.* Ninety-six allopurinol-induced SCARs (i.e., 23 DRESS and 73 SJS/TEN patients) and 193 allopurinol-tolerant controls were recruited for the study. The demographic and clinical characteristics of the case and the control groups are shown in Table 1.

Of ninety-six allopurinol-induced SCARs patients, 90 patients (93.75%) carried the *HLA-B*58:01* allele including 21/23 (91.30%) patients in the DRESS group and 69/73 (94.52%) patients in the SJS/TEN group (Table 2). Compared with the SCARs group, only 23 of 193 (11.92%) patients in the tolerant control group carried this allele (Table 2). Results from the univariate analysis show that the *HLA-B*58:01* allele was strongly associated with allopurinol-induced SCARs with an OR of 110.87 (95% CI = 43.57–282.15, Pc-value = 2.05×10^{-22}) (Table 2). The risk of allopurinol-induced DRESS was 77.61-fold (95% CI = 17.07–352.85, Pc-value = 7.12×10^{-8}) in the patients who carried the *HLA-B*58:01* allele compared with those did not carry this allele. Similar to that observed in SJS/TEN, the risk of allopurinol-induced SJS/TEN in the *HLA-B*58:01* allele carriers was 127.50-fold (95% CI = 42.53–382.27, Pc-value = 1.99×10^{-17}) (Table 2).

Among the three selected SNPs in chromosome 6, the rs2734583 in the *BAT1* gene showed the strongest association with allopurinol-induced DRESS with an OR of 64.56 (95% CI = 14.31–291.16, Pc-value = 2.35×10^{-7}) followed by the rs3099844 in the *HCP5* gene (OR = 59.38, 95% CI = 13.21–266.97, Pc-value = 4.04×10^{-7}) and the rs9263726 in the *PSORS1C1* gene (OR = 22.21, 95% CI = 7.10–69.46, Pc-value = 3.91×10^{-7}) (Table 2). In contrast, the strongest association between allopurinol-induced SJS/TEN was observed with rs9263726 (OR = 63.60, 95% CI = 23.85–169.56, Pc-value = 4.22×10^{-16}). When considering both DRESS and SJS/TEN as SCARs, these three SNPs were significantly associated with SCARs induced by allopurinol with the strength of association ranging from 45 to 60 (Table 2). All of these SNPs in the study populations were followed the Hardy–Weinberg equilibrium.

The sensitivity, specificity, NPV, and PPV of the *HLA-B*58:01* allele compared with the three selected SNPs in chromosome 6 for the prediction of both DRESS and SJS/TEN caused by allopurinol are shown in Table 3. These parameters of the *HLA-B*58:01* allele for the prediction of DRESS or SJS/TEN were the highest. The sensitivity, specificity, PPV, and NPV of these three SNPs for the prediction of SJS/TEN as well as SCARs were quite similar (Table 3). It should be noted that these values of the rs9263726 for the prediction of DRESS were relatively lower than those of the other two SNPs (Table 3).

Concerning the haplotypes of these three selected SNPs (rs9263726-rs2734583-rs3099844), 69.57% (16/23) of the patients in the DRESS group and 83.56% (61/73) of the patients in the SJS/TEN group carried the GA-TC-CA haplotype compared with 12.44% (24/193) in the controls (Table 2). About 80.83% (156/193) of the control patients carried the GG-TT-CC haplotype. A small number of patients in the case and the control groups carried other haplotypes (data not shown). Compared with the GG-TT-CC haplotype, the risk of allopurinol-induced DRESS in the patients who carried the CA-TC-GA haplotype was about 52.00-fold (95% CI = 11.24–240.51, Pc = 1.17×10^{-6}) whereas that of allopurinol-induced SJS/TEN was about 99.13-fold (95% CI = 33.03–297.52, Pc = 9.90×10^{-16}) (Table 2). Sensitivity, specificity, PPV, and NPV of the CA-TC-CA haplotype screening for the prediction of DRESS and SJS/TEN are shown in Table 3.

Table 1: Demographic and clinical characteristics of allopurinol-induced SCARs and tolerant control patients.

Characteristic data		DRESS ($n = 23$)	SJS/TEN ($n = 73$)	SCARs ($n = 96$)	Control ($n = 193$)
Age (year)	Mean (SD)	65 (14)	65 (12)	65 (12)	64 (12)
	Median (range)	68 (28–82)	68 (38–84)	68 (28–84)	66 (29–91)
Gender	Female; *n* (%)	10 (43.48)	40 (54.79)*****	50 (52.08)*****	49 (25.39)
Onset of SCARs (day)	Mean (SD)	29 (13)	19 (11)	21 (13)	—
	Median (range)	30 (10–60)*****	18 (2–60)*****	20 (2–60)*****	—
Allopurinol dose (mg)	Mean (SD)	171 (78)	182 (106)	179 (99)	194 (90)
	Median (range)	200 (100–300)	100 (50–600)	100 (50–600)	200 (100–600)
Indication of allopurinol	Hyperuricemia; *n* (%)	11 (47.83)*****	13 (17.81)*****	24 (25.00)*****	3 (1.55)
	Gouty arthritis; *n* (%)	12 (52.17)	60 (82.19)	72 (75.00)	190 (98.45)
Baseline kidney function					
Blood urine nitrogen (mg/dL)	*n*	*14*	*26*	*40*	*129*
	Mean (SD)	29.79 (21.14)	24.85 (20.09)	26.58 (20.33)	18.63 (10.40)
	Median (range)	21.35 (11.00–80.00)	18.50 (10.00–105.00)	21.00 (10.00–105.00)*	16.20 (3.00–70.00)
Serum creatinine (mg/dL)	*n*	*19*	*65*	*84*	*174*
	Mean (SD)	2.20 (2.20)	1.54 (1.05)	1.69 (1.40)	1.47 (1.46)
	Median (range)	1.40 (0.90–9.60)	1.30 (0.50–8.82)	1.30 (0.50–9.60)	1.20 (0.70–14.80)
Estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2)[a]	*n*	*19*	*65*	*84*	*174*
	Mean (SD)	44.05 (21.99)	48.61 (21.95)	47.58 (21.91)	58.01 (20.41)
	Median (range)	46.00 (6.54–88.61)**	45.27 (4.62–127.17)**	45.65 (4.62–127.17)***	57.45 (3.12–112.49)
	eGFR < 30.00; *n* (%)	4 (17.39)	14 (19.18)**	18 (21.43)**	13 (7.47)
	30.00 ≤ eGFR < 60.00; *n* (%)	11 (47.83)	37 (50.68)*	48 (57.14)	78 (44.83)
	eGFR ≥ 60.00; *n* (%)	4 (17.39)*	14 (19.18)***	18 (21.43)****	83 (47.70)

[a]eGFR: estimated glomerular filtration rate (expressed as mL/min/1.73 m^2) calculated by Modification of Diet in Renal the Disease (MDRD) study equation [39]. Indicated significant difference between case and tolerant control. *P value < 0.05, **P value < 0.01, ***P value < 0.001, ****P value < 0.0001, and *****P value < 0.00001.

Table 2: Univariate analysis of the association between *HLA-B*58:01* allele and SNPs with allopurinol-induced SCARs.

Allele/SNPs		Control ($n = 193$)	DRESS ($n = 23$)		SJS/TEN ($n = 73$)		SCARs ($n = 96$)	
		n (%)	n (%)	OR [95% CI] Pc-value	n (%)	OR [95% CI] Pc-value	n (%)	OR [95% CI] Pc-value
*HLA-B*58:01*	Negative	170 (88.08)	2 (8.70)	Reference	4 (5.48)	Reference	6 (6.25)	Reference
	Positive	23 (11.92)	21 (91.30)	77.61 [17.07–352.85] 7.12×10^{-8}	69 (94.52)	127.50 [42.53–382.27] 1.99×10^{-17}	90 (93.75)	110.87 [43.57–282.15] 2.05×10^{-22}
rs9263726 (G/A)	Negative (GG)	159 (82.38)	4 (17.39)	Reference	5 (6.85)	Reference	9 (9.38)	Reference
	Positive (GA/AA)	34 (17.62)	19 (82.61)	22.21 [7.10–69.46] 3.91×10^{-7}	68 (93.15)	63.60 [23.85–169.56] 4.22×10^{-16}	87 (90.63)	45.21 [20.73–98.60] 3.92×10^{-21}
rs2734583 (T/C)	Negative (TT)	166 (86.01)	2 (8.70)	Reference	7 (9.59)	Reference	9 (9.37)	Reference
	Positive (TC/CC)	27 (13.99)	21 (91.30)	64.56 [14.31–291.16] 2.35×10^{-7}	66 (90.41)	57.97 [24.07–139.60] 5.51×10^{-19}	87 (90.63)	59.43 [26.76–131.97] 4.24×10^{-23}
rs3099844 (C/A)	Negative (CC)	164 (84.97)	2 (8.70)	Reference	7 (9.59)	Reference	9 (9.38)	Reference
	Positive (CA/AA)	29 (15.03)	21 (91.30)	59.38 [13.21–266.97] 4.04×10^{-7}	66 (90.41)	53.32 [22.26–127.71] 1.82×10^{-18}	87 (90.63)	54.67 [22.77–120.66] 1.58×10^{-22}
SNPs haplotypes (rs9263726-rs2734583-rs3099844)	GG-TT-CC	156 (80.83)	2 (8.70)	Reference	4 (5.48)	Reference	6 (6.25)	Reference
	GA-TC-CA	24 (12.44)	16 (69.57)	52.00 [11.24–240.51] 1.17×10^{-6}	61 (83.56)	99.13 [33.03–297.52] 9.90×10^{-16}	77 (80.21)	83.42 [32.74–212.55] 7.43×10^{-20}

Pc-value: Bonferroni-corrected P value, calculated by multiplying P value by 4 which is the number of detected SNPs.

Table 3: Properties of proposed genetic screening tests for prediction of allopurinol-induced SCARs in a Thai population.

Allele/SNPs	Sensitivity (%)			Specificity (%)			PPV (%)			NPV (%)		
	DRESS	SJS/TEN	SCARs	DRESS	SJS/TEN	SCARs	DRESS	SJS/TEN	SCARs	DRESS	SJS/TEN	SCARs
*HLA-B*58:01*	91.30	94.52	93.75	88.08	88.08	88.08	47.73	75.00	79.65	98.84	97.70	96.59
rs9263726 (G/A)	82.61	93.15	90.63	82.38	82.38	82.38	35.85	66.67	71.90	97.55	96.95	94.64
rs2734583 (T/C)	91.30	90.41	90.63	86.01	86.01	86.01	43.75	70.97	76.32	98.81	95.95	94.86
rs3099844 (C/A)	91.30	90.41	90.63	84.97	84.97	84.97	42.00	69.47	75.00	98.80	95.91	94.80
SNPs haplotypes (rs9263726-rs2734583-rs3099844)												
GA-TC-CA	69.57	83.56	80.21	87.56	87.56	87.56	40.00	71.76	76.24	96.02	93.37	89.89

Data presented as percentage. PPV: positive predictive value; NPV: negative predictive value.

Table 4: Concordance between selected SNPs and *HLA-B*58:01* allele in allopurinol-induced SCARs.

SNP	Disequilibrium coefficient (D')				Coefficient of correlation (r^2)			
	DRESS ($n = 23$)	SJS/TEN ($n = 73$)	SCARs ($n = 96$)	Control ($n = 193$)	DRESS ($n = 23$)	SJS/TEN ($n = 73$)	SCARs ($n = 96$)	Control ($n = 193$)
rs9263726	1.0000	1.0000	1.0000	1.0000	0.4524	0.7884	0.6444	0.6327
rs2734583	1.0000	1.0000	1.0000	1.0000	1.0000	0.5466	0.6444	0.8318
rs3099844	1.0000	1.0000	1.0000	1.0000	1.0000	0.5466	0.6444	0.7651

*3.2. Concordance between the HLA-B*58:01 Allele and the Selected SNPs in Chromosome 6.* Results from linkage disequilibrium (LD) analysis in the study population (combining data from the case group and the control group, $n = 289$) showed that each SNP showed strong linkage disequilibrium with the *HLA-B*58:01* allele with D' values of more than 0.90 and r^2 values of more than 0.8 (Table 4). Subgroup analysis of LD in the DRESS group revealed that these three SNPs were a complete LD with the *HLA-B*58:01* allele ($D' = 1.0$) but perfect LD with an r^2 of 1.0 was found only for the rs2734583 and rs3099844 but not for rs9263726 ($r^2 = 0.4524$) (Table 4). For the SJS/TEN and the SCARs groups, these three SNPs were complete LDs with the *HLA-B*58:01* allele (D' = 1.0) but the r^2 values were less than 0.8 (Table 4).

4. Discussion

Allopurinol is an effective and cheap drug for the treatment of gout; however, allopurinol-induced SCARs may be life-threatening adverse drug reactions. Therefore, prediction for patients who may be at risk of these reactions is necessary to increase the safety of the drug. In line with previous reports, the results from this study clearly show that the *HLA-B*58:01* allele was strongly associated with both phenotypes of SCARs including DRESS and SJS/TEN caused by allopurinol. High sensitivity and high specificity of the *HLA-B*58:01* allele for the prediction of these life-threatening reactions were observed (93.75% and 88.08%) with the PPV and NPV of 79.65% and 96.59%. Compared with the *HLA-B*58:01* allele, the selected SNPs in chromosome 6 showed relatively low sensitivity and specificity as well as low PPV and NPV for the prediction of allopurinol-induced SCARs. In contrast to previous reports in a Japanese population, the rs9263726, rs2734583, and rs3099844 SNPs were not complete and perfect LDs with the *HLA-B*58:01* allele in a Thai population.

Results from univariate analysis revealed that the *HLA-B*58:01* allele was strongly associated with both DRESS and SJS/TEN caused by allopurinol (Table 2). The OR of the *HLA*58:01* allele for the SJS/TEN was about 1.6-fold higher than that of DRESS. The overall OR of this *HLA* allele for the prediction of both phenotypes of allopurinol-induced SCARs was 110.87 (95% CI = 43.57–282.15, $Pc = 2.05 \times 10^{-22}$). It is noteworthy that 86 patients of the SJS/TEN and 182 patients in the control groups are the same patients as reported in the previous study [4]. A lower OR between the *HLA-B*58:01* and allopurinol-induced SCARs observed in the present study and a previous study was due to the absence of the *HLA-B*58:01* allele in some of the SCARs patients that were currently recruited for the present study. Due to the high sensitivity, high specificity, high PPV, and high NPV observed in the present study and in other previous studies [5, 7, 15, 25], the *HLA-B*58:01* allele screening has been proposed as a valid genetic marker for screening patients who may be at a high risk of allopurinol-induced SCARs. To date, guidelines and recommendations for *HLA-B*58:01* allele screening prior to allopurinol administration particularly in certain ethnicities with a high frequency of *HLA-B*58:01* allele carriers such as Han Chinese, Thai, and Korean populations have been released [17, 26]. Moreover, data from several countries including Thailand and Taiwan suggest that the *HLA-B*58:01* allele screening is a cost-effective intervention for preventing allopurinol-induced SCARs [27, 28].

A recent study using a genome-wide association study in a Japanese population (including 14 allopurinol-related SJS/TEN patients and 991 ethnically matched controls) has discovered a set of SNPs in chromosome 6, particularly rs9263726 in the *PSORS1C1* gene, rs2734583 in the *BAT1* gene, and rs3094011 in the *HCP5* gene that were closely

linked with the *HLA-B*58:01* allele [13]. Moreover, results from a Chinese population revealed that among the three SNPs including rs9263726, rs2734583, and rs309984, the rs9263726 showed the highest degree of association with allopurinol-induced SJS/TEN (OR = 108.8, 95% CI = 13.9–850.5, Pc-value = 1.1×10^{-7}) which was the same value as that of the *HLA-B*58:01* allele [19]. Different to a report of a Chinese population, the OR values of the rs9263726 for the prediction of allopurinol-induced SCARs both DRESS and SJS/TEN in a Thai population were 2- to 3.5-fold lower than that of the *HLA-B*58:01* allele (Table 2). Sensitivity, specificity, PPV, and NPV of the rs9263726 for the prediction of allopurinol-induced SCARs in a Thai population were relatively lower than those of the *HLA-B*58:01* allele (Table 3).

The rs9263726 in the *PSORS1C1* gene has been reported to be complete LD ($D' = 1$) and perfect LDs ($r^2 = 1$) with the *HLA-B* 58:01* allele in a Japanese population ($n = 206$) [13]. Similarly, a recent study in 120 Chinese from the Eastern region of China ($n = 120$) showed a complete LD between the *HLA-B*58:01* allele and rs9263726 ($D' = 1$) but their LD was not perfect ($r^2 = 0.92$) [19]. In contrast, it has been reported in an Australian admixture population that the rs9263726 was not linked with the *HLA-B*58:01* allele ($D' = 0.059$; $r^2 = 0.001$) suggesting that these two alleles within nearby genes are inherited independently from each other in an Australian admixture population [29]. It should be noted that results from the present study showed that although the rs9263726 was in complete LD ($D' = 1$) with the *HLA-B*58:01* allele in DRESS, SJS/TEN, SCARs, and the tolerant control groups but this SNP appeared to be not perfect LD with the *HLA-B*58:01* because the r^2 values were less than 1 (range from 0.4524 to 0.7884, Table 4). The lowest r^2 values of this SNP were found with the allopurinol-induced DRESS. These results suggest that the rs9263726 may not be a good surrogate marker or good tag SNP of the *HLA-B*58:01* allele for screening patients who are at risk of SCARs, particularly DRESS induced by allopurinol.

In comparison with the *HLA-B*58:01* allele, it was found that the strength of association between allopurinol-induced DRESS and allopurinol-induced SJS/TEN and the rs2734583 or the rs3099844 were about 1.3–2.39-fold lower (Table 2). The sensitivity, specificity, PPV, and NPV of these two SNPs were comparable to those of the *HLA-B*58:01* allele (Table 3). Although these two SNPs were complete ($D' = 1$) and perfect LDs ($r^2 = 1$) with the *HLA-B*58:01* allele in the allopurinol-induced DRESS, they were not perfect LD (r^2 of 0.5466–0.8318) with the *HLA-B*58:01* allele in SJS/TEN and tolerant control groups (Table 4). These results suggest that neither the rs2734583 nor the rs3099844 is a good surrogate marker of the *HLA-B*58:01* allele for screening Thai patients who are at risk of SCARs. The rs2734583 and the rs3099844 appeared to be complete and perfect LDs in the SCARs group but not perfect LDs in the control group (data not shown). Detecting the haplotypes of these three SNPs was not significantly increased for the sensitivity, specificity, PPV, and NPV for the prediction of allopurinol-induced SCARs than single SNP detection (Table 3).

To date, the definite role of these SNPs in the pathogenesis of drug-induced SCARs is still unknown. The *PSORS1C1* gene encodes a psoriasis susceptibility 1 candidate gene 1 protein. Although the function of this protein is not clear, the *PSORS1C1* gene polymorphism has been reported to be associated with the susceptibility to psoriasis, hyper proliferative skin disorder [30, 31], and rheumatoid arthritis [32] whereas the *BAT1* gene encodes a protein that downregulated inflammatory cytokine production in splicing and RNA export mechanism such as tumor necrosis factor (TNF), interleukin-1, and interleukin-6 [33]. The polymorphism of the *BAT1* gene has been reported to be associated with rheumatoid arthritis [34]. The *HCP5* gene encodes a human endogenous retroviral element that sequences homology to retroviral *pol* genes. The *HCP5* was expressed in lymphocytes and suggested to control retrovirus proliferation via antisense mechanism [35]. Of interest, *HCP5* genetic polymorphism has previously been reported to be associated with nevirapine-induced SJS/TEN [36] and abacavir hypersensitivity [37]. It should be noted that the three SNPs investigated in the present study are located in chromosome 6p21.3 which is the same region as the MHC molecule well recognized as a key element for the pathogenesis of several drug-induced SCARs [38]. It is likely that the strong association between these three SNPs and allopurinol-induced SCARs may be due to linkage disequilibrium with the *HLA-B*58:01* allele.

In summary, the three selected SNPs, rs926372, rs2734583, and rs3099844, were significantly associated with DRESS and SJS/TEN caused by allopurinol but the degree of associations was lower than that of the *HLA-B*58:01* allele. The sensitivity, specificity, PPV, and NPV of these SNPs were comparable to those of the *HLA-B*58:01* allele; however, these SNPs were not perfect LDs with the *HLA-B*58*:01 allele. Although the detection of the single SNP is more simple and less expensive compared with the detection of such polymorphic gene like the *HLA-B*58:01* allele, results obtained from screening for the risk of allopurinol-induced SCARs using these SNPs as surrogate makers of the *HLA-B*58:01* allele need to be carefully interpreted.

Conflicts of Interest

All authors declare no conflict of interest.

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Review Article

HLA Association with Drug-Induced Adverse Reactions

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Adverse drug reactions (ADRs) remain a common and major problem in healthcare. Severe cutaneous adverse drug reactions (SCARs), such as Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) with mortality rate ranges from 10% to more than 30%, can be life threatening. A number of recent studies demonstrated that ADRs possess strong genetic predisposition. ADRs induced by several drugs have been shown to have significant associations with specific alleles of human leukocyte antigen (HLA) genes. For example, hypersensitivity to abacavir, a drug used for treating of human immunodeficiency virus (HIV) infection, has been proposed to be associated with allele 57:01 of *HLA-B* gene (terms *HLA-B*57:01*). The incidences of abacavir hypersensitivity are much higher in Caucasians compared to other populations due to various allele frequencies in different ethnic populations. The antithyroid drug- (ATDs-) induced agranulocytosis are strongly associated with two alleles: *HLA-B*38:02* and *HLA-DRB1*08:03*. In addition, *HLA-B*15:02* allele was reported to be related to carbamazepine-induced SJS/TEN, and *HLA-B*57:01* in abacavir hypersensitivity and flucloxacillin induced drug-induced liver injury (DILI). In this review, we summarized the alleles of HLA genes which have been proposed to have association with ADRs caused by different drugs.

1. Introduction

Major histocompatibility complex (MHC) are a group of cell surface proteins that can bind to foreign molecules in order to be recognized by corresponding T cells followed by inducting immune systems. MHC is highly conserved and presents in all vertebrate species. In human, MHC is also known as human leukocyte antigen (HLA) complex, which consists more than 200 genes on chromosome 6 and can be categorized into three subgroups: class I, class II, and class III. Class I MHC, being recognized by CD8+ T cells, consists of three main genes, that is, *HLA-A*, *HLA-B*, and *HLA-C*. Class II MHC, being recognized by CD4+ T cells, consists of 6 main genes, that is, *HLA-DPA1*, *HLA-DPB1*, *HLA-DQA1*, *HLA-DQB1*, *HLA-DRA*, and *HLA-DRB1*.

HLA class I molecules are expressed in almost all the cells and are responsible for presenting peptides to immune cells. Generally, old proteins in the cells will be broken down consistently in order to synthesize new peptides. Some of these broken peptide pieces attach to the MHC molecules and are further recognized by immune cells as "self." In another situation, if a cell is infected by pathogens, pathogenic peptides attached to MHC molecules will be recognized as "nonself" and further trigger the downstream immune responses against the antigens [1]. *HLA* genes are found to be numerous and highly polymorphic in order to bind various kinds of peptides originated from self or foreign antigens. A total of more than 1500 alleles of *HLA-B* gene have been identified [2]. Variations in the *HLA* genes play an important role in determining the susceptibility to autoimmune disease and

infections; they are also critical in the field of transplant surgery where the donors and the recipients must be HLA-compatible [3].

In rare cases, some drugs are capable of inducing immune responses through interactions with MHC molecules, known as adverse drug reactions (ADRs). ADRs are one of the most common causes of hospitalization and mortality in healthcare. The definition of an ADR has been changed from time to time. In the 1970s, the World Health Organization (WHO) has first defined that an ADR is "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" [4]. However, in most cases, the ADRs might not result in effects as severe as harms or injuries like the word "noxious" addressed by WHO. Therefore, Edwards and Aronson [5] suggested to use an alternative definition; that is, an ADR is "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product." It is also defined as "an undesirable effect, reasonably associated with the use of the drug that may occur as a part of the pharmacological action of a drug or may be unpredictable in its occurrence."

2. ADRs Associated with Immunological Reactions

Several studies showed that ADRs are a major public health problem worldwide, which account for about 6.5% of all hospitalizations in the United States, Canada, and the United Kingdom, and it also resulted in a mortality rate approximate to 0.13% [6–8]. ADRs could be categorized into 6 different types [5]. Among them, type B, also known as non-dose-related or bizarre, is unpredictable and results in a high mortality rate oftentimes. This type of ADRs is usually associated with immunological reactions involving different HLA alleles and resulted in skin injury, hepatic failure, or dramatically reduced numbers of white blood cells.

Skin injury includes various kinds of spectrum such as mild rash maculopapular exanthema (MPE), fixed drug eruption (FDE), acute generalized exanthematous pustulosis (AGEP), and life-threatening severe cutaneous adverse drug reactions (SCARs) including drug reactions with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) [9]. Patients who developed MPE are usually observed with generalized, widespread mild skin rashes with red macular (not elevated) or papular (elevated) eruptions. FDE can be diagnosed by observing one or more local annular or oval erythematous patches without hyperpigmentation. The term "fixed" is considered as its recurrent lesion due to reexposure of the same culprit drug, and the lesions always occur at the same locations on the skin. AGEP is a rare, acute eruption characterized by the rapid development of many numerous pustules, which are nonfollicular sterile pustules, and is located in the epidermis. Fever, leukocytosis, and eosinophilia are usually present in AGEP patients.

SJS, SJS, and TEN overlap (SJS/TEN) and TEN are classified as the same disease spectrum with increasing severity and with extent of widespread epidermal detachment, known as SCARs [10]. All of them usually present with a variety of skin lesions, including patches, atypical targetoid macules, and erythematous or violaceous macules. In addition, SJS/TEN often has mucocutaneous involvement, which is the characteristic feature of SJS/TEN. In addition, the oral mucosa is more commonly involved than the ocular, genital, or anal mucosa. The degree of skin detachments of SJS, SJS/TEN, and TEN are defined as less than 10%, 10–30%, and 30% of body surface area, respectively. Full-thickness epidermal necrosis is a typical pathological feature of SJS/TEN. The clinical characteristics of DRESS are different from SJS/TEN. DRESS usually presents less or no skin detachment and no mucocutaneous involvement but with more internal organ involvement and hematological abnormalities such as typical eosinophilia, atypical lymphocytes, hepatitis, and high fever with frequent reactivation of human herpesvirus. Histopathological characters of DRESS are epidermal spongiosis, dyskeratosis, and interface vacuolization.

Other than skin injury, hepatic failure, such as drug-induced liver injury (DILI), is rare but life threatening. DILI is different from drug overdose toxicity in which the risk and severity of such kind of liver injury usually increases with the dose taken. DILI accounts for 7–15% of the cases of acute liver failure in Europe and the United States [11–13]. Up to 10% of DILI can progress to acute liver failure in the US and European studies, and the incidence is estimated to be 2.4 per 100,000 person-years (in a retrospective population-based study of 1.64 million UK subjects) [14] to 13.9 per 100,000 inhabitants (in a prospective analysis in France) [15].

Agranulocytosis, also known as agranulosis or granulopenia, is an acute condition involving a severe and dramatic decreasing of white blood cell counts, which is life threatening. It is recently reported to be induced by antithyroid drugs in rare situations and is associated with HLA alleles [16].

3. Hypothesis of Immune Response

Drugs or its reactive metabolites are considered as foreign antigens that bind to T cell receptors (TCR) and further activate immune response. Four hypotheses have been proposed to explain how the immune system is activated in a HLA molecule-dependent manner: (i) the "hapten/prohapten" theory, (ii) the "p-i" concept, (iii) the "altered peptide repertoire" model, and (iv) the "altered TCR repertoire" model [17, 18].

The "hapten/prohapten" theory proposes that a drug or its reactive metabolite may bind covalently to an endogenous peptide to form an antigenic hapten-carrier complex. In this model, the covalent bonds are established among the drug (or its metabolite), self-peptides, and HLA molecule. It then results in the induction of drug-specific immune responses.

The "pharmacological interaction with immune receptors (p-i)" concept postulates that a drug or its reactive metabolite may directly, reversibly, and noncovalently bind to the HLA and/or TCR without binding to the antigenic peptide. In this "p-i" model, the classic antigen-processing pathway in antigen-presenting cells may be bypassed.

The "altered peptide repertoire" model proposes that a drug could strongly bind to the self-peptide repertoire and alter the conformation of this peptide repertoire presented to HLA and TCR. In the "altered peptide repertoire" model, the drug may not directly bind to HLA.

Finally, the "altered TCR repertoire" model suggests that the drug (e.g., sulfamethoxazole) binds to the specific TCR and alters the conformation of TCR, which has the potential to bind a HLA-self peptide complex to elicit immune reaction. In the "altered TCR repertoire" model, the TCR serves as an initial drug interaction molecular. With the binding of an offending drug presented to the HLA molecule or TCR, the HLA-drug-TCR complex may trigger a series of activations of cell signaling and result in an expansion of cytotoxic T lymphocytes (CTL), cytotoxic protein secretions, and keratinocyte death in patients with SJS/TEN. A recent study has shown the importance of TCR in the pathogenic mechanism of SJS/TEN onset by clarifying the shared and restricted TCR use in carbamazepine-induced SJS/TEN patients [19]. Additionally, another interesting study demonstrated that the endogenous peptide-bound *HLA-B*15:02* molecule presents carbamazepine to TCR of CTL to initiate the immune reactions in carbamazepine-induced SJS/TEN [20].

4. Drugs and HLA Alleles

A couple of drugs have been proposed to induce *HLA*-associated ADRs (Table 1). In this section, we summarized some of the well-known drugs and the *HLA* alleles associated with ADRs induced by these drugs. For more detailed information, please see the list in Table 1.

*4.1. Abacavir Hypersensitivity and HLA-B*57:01 (Skin).* Abacavir is a nucleotide reverse transcriptase inhibitor used as part of adjuvant therapy in human immunodeficiency virus- (HIV-) infected patients. In 5–8% of treated patients, abacavir can cause hypersensitivity responses. More than 90% of the patients with hypersensitive syndrome start within 6 weeks of treatment and require immediate cessation of the medication. Re-exposure of the abacavir leads to rapid appearance of symptoms and higher chance to induce more severe symptoms [21]. Symptoms reported including fever, rash, malaise/fatigue, and gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Respiratory symptoms occurred in 30% of cases including dyspnea, cough, and pharyngitis. In very rare cases, abacavir might result in more severe reaction such as SJS/TEN [22, 23].

In 2002, two publications first proposed that abacavir hypersensitivity was significantly associated with the presence of allele *HLA-B*57:01* in Australian and British cohorts [24, 25]. Saag et al. [26] further demonstrated that there is a higher chance of developing hypersensitivity in Caucasians than African-Americans who were treated with abacavir. Among those suffered from abacavir hypersensitivity, 44% of Caucasians and 100% of African-Americans showed positive of *HLA-B*57:01* allele. Recently, *HAL-B*57:01* was screened in other populations (summarized in Martin et al. [27]). In general, the frequency of *HLA-B*57:01* allele is much higher in Caucasians than in other populations. In Taiwan, abacavir hypersensitivity is less frequent, as it occurs in approximately 0.3% of HIV-infected patients who undergo abacavir-containing combination antiretroviral therapy (a total of 320 patients studied). The possible reason might be the low frequency of the *HLA-B*5701* allele in Taiwanese population [28].

The mechanisms of abacavir hypersensitivity is better studied compared to other drug-induced ADRs. It is thought that short peptide fragments, derived from either the drug or its metabolites, form a peptide-HLA complex specifically with *HLA-B*57:01*. This complex activates CD8+ T cells, which release inflammatory cytokines and start the hypersensitivity response. More recently, it has been shown that abacavir might occupy a space below the region of HLA that presents peptides, which leads to an altered peptide presentation and trigger an autoimmune reaction [29]. By using X-ray crystallography and structural analysis, Yerly et al. further proposed that the hypersensitivity reaction is due to both types of T cells that recognize self-peptide/*HLA-B*57:01* complexes and cross react with viral peptide/*HLA-B*57:01* complexes due to similarity in drug-specific T cell receptors contact residues [30].

As genetic screens for *HLA-B*57:01* could significantly reduce the incidence of abacavir hypersensitivity in Caucasians, the European Medicines Agency and US Food and Drug Administration (FDA) recommend prospective screening for *HLA-B*57:01* for patients who are considered to undergo abacavir treatment [27, 31].

*4.2. Carbamazepine and Oxcarbazepine Hypersensitivity and HLA-B*15:02, HLA-B*15:11, and HLA-A*31:01 (Skin).* Carbamazepine is an important drug used in the treatment of epilepsy, trigeminal neuralgia, and bipolar disorder [32–34]. In 2004, Carbamazepine was first reported to be strongly associated with allele *HLA-B*15:02* by studying patients developed SJS/TEN in Taiwan (OR > 1000) [35]. This association was validated in different populations, including those in Thailand, Malaysia, Singapore, and India [36–38]. A large scale of prospective study including almost 5000 participants from 23 hospitals in Taiwan showed that 7.7% of the subjects are *HLA-B*15:02* positive. These subjects carrying *HLA-B*15:02* were then advised to take alternative drugs other than carbamazepine [39]. Consequently, taking the alternative drug greatly reduced the change of developing SCARs, especially SJS/TEN. Based on the findings from these studies, the genetic screening of *HLA-B*15:02* prior to the use of carbamazepine for certain Asian populations are recommended by different health regulatory agencies [40].

*HLA-B*15:02* association and carbamazepine-induced SJS/TEN is also proposed to be ethnic specific. It is likely due to different genetic background as the allele frequency varies among different populations. It is relatively high in

Table 1: Drug-induced ADRs and HLA allele associations.

Drug	HLA allele	Phenotype	Population	Reference
Abacavir	B*57:01	HSS	Australian	[25]
			African American	[26]
			Brazilian	[79]
			British	[24]
			Indian	[80]
			Iranian	[81]
Carbamazepine	B*15:02	SJS/TEN	Taiwanese	[35, 82]
			Han Chinese	[83]
			Thai	[37]
			Malaysian	[44]
			Asian	[46]
	A*31:01	MPE, HSS, SJS/TEN	Han Chinese	[49, 82]
			Caucasian	[48]
			Japanese	[50]
	B*15:11	SJS/TEN	Japanese	[47, 84]
Allopurinol	B*58:01	SJS/TEN	Han Chinese	[53]
			Caucasian	[57]
			Thai	[59]
			Japanese	[59]
		SCARS	Taiwanese	[85]
Dapsone	B*13:01	HSS		[60]
Phenytoin	B*15:02	SJS/TEN	Han Chinese	[83]
			Thai	[37]
Lamotrigine	A*31:01	HSS	British	[86]
	B*15:02	SJS/TEN	Han Chinese	[83]
Nevirapine	DRB1*01:01	DRESS	Hispanics, African	[87]
	B*14:02	HSS	Sardinian	[88, 89]
Sulphamethoxazole	B*38	SJS/TEN	European	[57]
Methazolamide	B*59:01, CW*01:02	SJS/TEN	Korean and Japanese	[84]
Amoxicillin-clavulanate	DRB1*15:01-DQB1*06:02	DILI	Caucasian	[64]
Flucloxacillin	B*57:01	DILI	Caucasian	[65]
Lumiracoxib	DRB1*15:01	DILI	Not available	[90]
Ticlopidine	A*33:03	DILI	Japanese	[91]
Antithyroid drugs	B*38:02-DRB1*08:03	Agranulocytosis	Taiwanese	[16]

Han Chinese (0.057–0.145), Malaysians (0.12–0.157), and Thai (0.085–0.275) compared to Japanese (0.002), Koreans (0.004), and Europeans (0.01–0.02) [41–47].

In the populations with lower frequency of *HLA-B*15:02*, that is, Northern Europeans, Japanese, and Koreans, more recent genome-wide association studies (GWAS) showed that *HLA-A*31:01* allele has relatively stronger association with carbamazepine-induced hypersensitivity (OR = 25.93, 10.8, and 7.3 in the three populations, resp.) [41, 48–50]. In addition, *HLA-B*15:11* allele was shown to be associated with carbamazepine-induced SJS/TEN in Japanese and Korean populations as well (OR = 9.8 and 18.1 in the two populations, resp.) [41, 47]. The different strength and specificity of HLA association with carbamazepine-induced SCARs further suggest that it is necessary to perform different genetic tests for different populations.

Oxcarbazepine is also an important drug used in the treatment of epilepsy. Oxcarbazepine-induced cutaneous ADRs presented with less clinical severity including limited skin detachment (all ≦ 5%) and no mortality compared to carbamazepine. Therefore, it is commonly used as an alternative to carbamazepine. A most recent study which enrolled 50 patients in Taiwan and Thailand from 2006 to 2014 identified a significant association between *HLA-B*15:02* and SJS/TEN (OR = 27.90; $P = 1.87 \times 10^{-10}$). The results of study suggested that although oxcarbazepine is used as an alternative due to the less severity of drug reactions, genetic test should also be considered further,

particularly for the populations with higher frequency of *HLA-B*15:02* [51].

*4.3. Allopurinol Hypersensitivity and HLA-B*58:01 (Skin).* Allopurinol is a xanthine oxidase inhibitor used in the treatment of gout and hyperuricemia. A study comparing the data in 2005 and in 2011 from Taiwan's National Health Insurance Research Database, which belongs to the nationwide population database with more than 23 million insured enrollees, demonstrated that allopurinol hypersensitivity happened in about 0.4% of the new users every year. About half of them required hospitalization [52]. Patients who underwent hospitalization had very high mortality rate (0.39/1000 new users). In 2005, the first case-control study in Taiwan showed that *HLA-B*58:01* allele is the genetic marker of allopurinol-induced SCARs in Han Chinese ($OR = 580.3$, $P = 4.7 \times 10^{-24}$) [53]. This association was then validated in different populations, such as Thailand, Japan, South Korea, Hong Kong, Australia, Portugal, and Europe [54–59]. Currently, *HLA-B*58:01* is considered as a useful genetic marker for allopurinol-SCARs in multiple ethnic populations worldwide [31]. The American College of Rheumatology guideline thus recommends the *HLA-B*58:01* genetic screening for allopurinol new users in Asia populations since 2012.

A most recent study in Taiwan further enrolled a large number of patients with allopurinol-induced ADRs in order to investigate the associations between *HLA-B*58:01*, renal function, gene dosage, and drug dosage with the risk of allopurinol-induced ADRs development [58]. The authors showed that *HLA-B*58:01* was strongly associated with ADRs ($OR = 44.0$; $P = 2.6 \times 10^{-41}$) and was also highly correlated with disease severity. That is, patients carrying *HLA-B*58:01* had much higher chance to develop SCARs comparing to MPE, particularly those individuals with homozygous *HLA-B*58:01*. Furthermore, coexistence of *HLA-B*58:01* and renal impairment increased the risk and predictive accuracy of allopurinol-induced ADRs. This study suggests that patients with the coexistence of *HLA-B*58:01* and renal impairment should be cautious and avoid to use allopurinol.

*4.4. Dapsone Hypersensitivity and HLA-B*13:01 (Skin).* Dapsone alone or in-combination with other drugs are effective for the treatment or prevention of infectious diseases (e.g. leprosy, malaria and pneumocystis pneumonia). However, about 0.5–3.6% of persons who were treated with dapsone developed hypersensitivity reactions. A recent genome-wide association study involving 872 participants (39 participants showed dapsone hypersensitivity syndrome and 833 controls) identified that SNP rs2844573, located between the HLA-B and MICA loci, was significantly associated with the dapsone hypersensitivity ($OR = 6.18$; $P = 3.84 \times 10^{-13}$) [60]. The authors further confirmed that *HLA-B*13:01* is associated with the dapsone hypersensitivity ($OR = 20.53$; $P = 6.84 \times 10^{-25}$). The allele showed a sensitivity of 85.5% and a specificity of 85.7% for dapsone hypersensitivity from this study and thus can be used as a marker of dapsone hypersensitivity. However, the hypersensitivity has not been studied in other ethnic populations.

4.5. Amoxicillin-Clavulanate-Induced DILI and HLA Haplotypes. Amoxicillin-clavulanate (AC) is one of the most commonly prescribed antimicrobial drugs worldwide. However, it is a known cause of DILI and accounts for 10–13% of hospitalizations. Hautekeete et al. first reported a strong association between HLA and AC-induced DILI in Europeans [61]. The authors observed a much higher frequency of *DRB1*15:01-DRB5*01:01-DQB1*06:02* haplotype in patients with AC-induced DILI compared to normal healthy controls (57.1% in cases versus 11.7% in controls, $P < 10^{-6}$). The association was further validated in two UK populations ($OR = 2.3$ and 9.3 for the two populations, resp.) [62, 63]. A recent study by performing GWAS in 201 patients further confirmed the association of AC-induced DILI with *DRB1*15:01* allele ($OR = 4.2$; $P = 4.6 \times 10^{-10}$) [64]. In addition, the study further identified two novel HLA alleles as risk factors of AC-induced DILI: *HLA-A*02:01* in all patients ($OR = 2.2$; $P = 1.8 \times 10^{-10}$) and *HLA-B*18:01* with nominal significance independently of *HLA-A*02:01* and *HLA-DQB1*06:02* in Spanish patients only.

*4.6. Flucloxacillin-Induced DILI and HLA-B*57:01 Association.* Flucloxacillin is an antibiotic belonging to penicillin class and is used widely for the treatment for staphylococcal infection in Europe. Flucloxacillin is a common cause of DILI and is also reported to be associated with cholestatic liver disease. A GWAS study enrolling 51 patients showed a strong association between flucloxacillin-induced DILI and a marker, rs2395029[G]. This marker is in complete linkage disequilibrium with *HLA-B*5701* ($P = 8.7 \times 10^{-33}$) [65]. The authors further performed MHC genotyping and confirmed the association of flucloxacillin induced DILI with *HLA-B*5701* ($OR = 80.6$, $P = 9.0 \times 10^{-19}$). This is an interesting finding because *HLA-B*57:01* is also associated with abacavir hypersensitivity, but these patients were not reported to develop liver injury. It still remains unclear whether it resulted from the binding of different drugs/metabolites to the same HLA allele and subsequent initiation of immune responses or it is merely a coincidental event. As the positive predictive value of *HLA-B*57:01* is as low as 0.12% [31], the genetic screening for *HLA-B*57:01* before the prescription of flucloxacillin to new users may not be clinically relevant.

*4.7. Antithyroid Drug-Induced Agranulocytosis and HLA-B*38:02-HLA-DRB1*08:03 Haplotype.* Other than skin and liver injures, drug reactions could also affect the immune system directly. Antithyroid drugs (ATDs) have been the cornerstones treatment of Graves' disease (GD), which is the leading cause of hyperthyroidism. It has been reported that ATDs may induce agranulocytosis resulting in lower number of white blood cells and is likely to be life threatening. However, the genetic risk factors have not been identified until recently. Chen et al. conducted both classic genotyping and GWAS to elucidate the genetic association between ATD-induced agranulocytosis and HLA genes in Taiwan [16]. First of all, they performed direct HLA genotyping including 6

Table 2: Available genetic tests.

Platform	Technology	Specificity	Advantage	References
PCR	Sequence specific oligonucleotides (SSO)	>95%	Commercial kits available	[66, 92]
PCR	sequence-specific primer (SSP) PCR	>97%	More specific than SSO	[66, 68, 69]
Real-time PCR	Hydrolysis probe (TaqMan)	>99%	Mismatch in the probe region seems to be more sensitive than those in the primer region	[73]
Flow cytometry	HLA-B17 specific monoclonal antibody	~80%		[93]
Patch testing		60–70%	Safe and inexpensive	[75, 76]

classical loci for a total of 42 agranulocytosis cases and about 1200 GD controls. The results showed strong associations of ATD-induced agranulocytosis with two alleles: *HLA-B*38:02* ($P = 6.75 \times 10^{-32}$) and *HLA-DRB1*08:03* ($P = 1.83 \times 10^{-9}$), which are in independent LD blocks. From GWAS, two more markers were further identified in the genomic region of HLA genes (6q21): rs17193122 ($P = 4.29 \times 10^{-27}$), which is in LD block with *HLA-B*38:02*, and rs116869525 ($P = 1.27 \times 10^{-8}$). The two markers are in the same LD block with *HLA-DRB1*08:03*. The authors further showed that the patients who carried both alleles have much higher chance to develop agranulocytosis compared to those who had only one allele. This is an interesting finding similar to the observation in amoxicillin-clavulanate-induced DILI: class I and class II HLA confer genetic susceptibility to the same drug adverse effect, as we mentioned above.

5. Different Techniques Used to Screen HLA Alleles or Predict Hypersensitivity Reactions in New Drug Users

As the association between HLA alleles and the chance of developing SCARs has been shown in many studies, it is important and advised to have the genetic test for new users of the drugs mentioned above. Systematic and large-scale genetic testing is mostly available for *HLA-B*57:01* through commercial laboratories in the US as this allele has the highest frequency in Caucasians. These kits typically offer single allele testing with a short turnaround time. The genotype results are either "positive" (*HLA-B*57:01* being present in one or both copies of the *HLA-B* gene) or "negative" (no copies of *HLA-B*57:01* are present). There are no intermediate phenotypes because *HLA-B* is expressed in a codominant manner [27]. Although most of the technologies were developed based on the purpose of detecting *HLA-B*57:01* allele, the concept can also be applied to test other alleles. Therefore, in the following paragraph, we summarize the technologies developed to genotype HLA on the purpose of screening new drug users to avoid potential ADRs (Table 2).

5.1. PCR-Based Assays. Sequence-specific oligonucleotide (SSO) assays for HLA typing was one of the first PCR-based HLA typing methods [66, 67]. The technique amplifies a particular HLA gene locus such as HLA-A, HLA-B, or HLA-DRB1. Primers are generally designed in exons 2 and 3 for HLA class I and exon 2 for HLA class II—regions known to carry the most variations. Amplifications of all the alleles of a particular HLA locus can be performed in one PCR tube. PCR products of a particular HLA locus is then hybridized with labelled oligonucleutides specifically to a particular HLA allele or a group of alleles. Recently, several commercial kits have been developed based on SSO but can get the results in a shorter period of time such as LIFECODES HLA-B SSO Typing Kit (Immucor Transplant Diagnostics).

However, with the very high number of possible heterozygous HLA allele combinations, SSO is not sufficient to resolve all ambiguities as the method does not distinguish between *cis* and *trans* polymorphisms. Therefore, when the subjects are *HLA-B*57* positive, sequence specific primer- (SSP-) PCR will be advised to further determine the specific genotype [68, 69]. Comparing to SSO, SSP-PCR has higher resolution and sensitivity as it uses sequence-specific primers.

More recently, new assays were developed for *HLA-B*57:01* typing on a quantitative polymerase chain reaction (qPCR) platform [70–72]. This enables detection of primer specificity through differentiating Cq values by SYBR Green quantitative (q)PCR or analysis of allele-specific PCR by high-resolution melting. Implementation of these assays on a qPCR platform significantly decreases the processing and reaction time as well as reagent costs. Jung et al. further designed primers and probes based on DNA polymorphisms using hydrolysis probes (oftentimes referred to TaqMan technology) [73]. In their study, not only the primers but also the probes were designed for generating PCR products specifically from the *HLA-B*57:01* allele. Although these primers may also generate products from other *HLA-B* alleles that do not induce hypersensitivity reactions, hydrolysis probes can differentiate these products and only give fluorescence signals if the *HLA-B*57:01* allele is present. To reduce false-positive detection, additional probes are incorporated into a single multiplex reaction. The authors also developed PCR-restriction fragment length polymorphism (RFLP) assay for genotyping *HLA-B*57:01*. In this assay, two pairs of primers, one specific to 57:01 allele and another pair is for control, selectively amplify genomic DNA followed by digestion with restriction enzymes NlaIII or RsaI. PCR products amplified from two different pairs of primers resulted in different sizes of fragments that can be visualized easily on the agarose gel.

5.2. Non-PCR-Based Techniques. Using monoclonal antibody to differentiate alleles *HLA-B*57* and *HLA-B*58* was first

proposed by Kostenko et al. [74]. Monoclonal *HLA-B17* antibodies (mAb 3E12), which recognized both *HLA-B*57* and *HLA-B*58* allotypes (members of the group specificity, HLA-B17), was labelled with phycoerythrin while anti-CD45 labelled with FITC were incubated with blood from subjects. Lymphocytes were gated based upon scatter and CD45 bright expression, and mean fluorescence intensity for *HLA-B17* expression was then measured by flow cytometry. Although this is an inexpensive and rapid approach to detect the presence of two allotypes, it is proposed to be less specific and sensitive than PCR-based approaches. The subjects who test positive by mAb screening are recommended to proceed with high-resolution gold-standard typing, such as SSO and SSP-PCR, to ascertain the presence of *HLA-B*5701* or *HLA-B*5801*.

Patch testing is also used to predict hypersensitivity reaction of abacavir [75] and carbamazepine [76]. Giorgini and others performed patch testing on 100 subjects including 20 cases who had experienced a hypersensitivity reaction when treated with highly active antiretroviral therapy including abacavir. Among the cases with positive patch testing results, about 50% of them carry *HLA-B*57:01* allele. More recently, Lin et al. proposed to use patch testing to predict carbamazepine induced hypersensitivity. They showed that about 60–70% of the cases who developed SJS/TEN and DRESS to carbamazepine had positive reactions in the patch testing. Although drug patch testing is a safe and inexpensive method for the identification of hypersensitivity, the sensitivity and specificity is not as good as PCR-based approaches.

6. Conclusion

In this review, we summarize the HLA alleles associated with ADRs induced by different drugs. From the literature, we learned that most of the HLA-associated ADRs have ethnic specificity. It is likely due to the different allele frequency between populations. Gonzalez-Galarza et al. summarize the allele frequencies of all the HLA genes and showed that the frequencies differ a lot [77]. For example, HLA-B*57:01 has the highest frequency in Ireland, but has the lowest frequency in Cuba (African populations). The frequencies can of each allele in different populations be found in the public database (http://www.allelefrequencies.net/default.asp) [78].

Other than the HLA-associated ADRs being ethnic specific, there are also two interesting questions: (1) why one locus contributes to different ADRs as we have observed on *HLA-B*57:01* in abacavir hypersensitivity and flucloxacillin-induced DILI. (2) How different loci contribute to the same ADRs as we have seen in antithyroid drug-induced agranulocytosis and amoxicillin-clavulanate-induced DILI. As class I and class II HLA genes have different structures, cell-type distributions, and functional roles in the immune system, the genetic susceptibility from both classes for a phenotype are expected to be intriguing. How both class I and class II HLA genes confer genetic susceptibility to the same ADR requires further pathophysiological investigations.

Abbreviations

ADR: Adverse drug reactions
HLA: Human leukocyte antigen
DRESS: Drug reaction with eosinophilia and systemic symptoms
SCAR: Severe cutaneous adverse drug reactions
SJS: Stevens–Johnson syndrome
TEN: Toxic epidermal necrolysis.

Conflicts of Interest

The authors declare no conflict of interest.

Authors' Contributions

Wen-Lang Fan, Meng-Shin Shiao, Rosaline Chung-Yee Hui, Shih-Chi Su, Chuang-Wei Wang, and Ya-Ching Chang contributed to the conception and writing of the manuscript. Wen-Hung Chung reviewed the manuscript. Wen-Lang Fan and Meng-Shin Shiao contributed equally to this work.

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Review Article

Immunohistopathological Findings of Severe Cutaneous Adverse Drug Reactions

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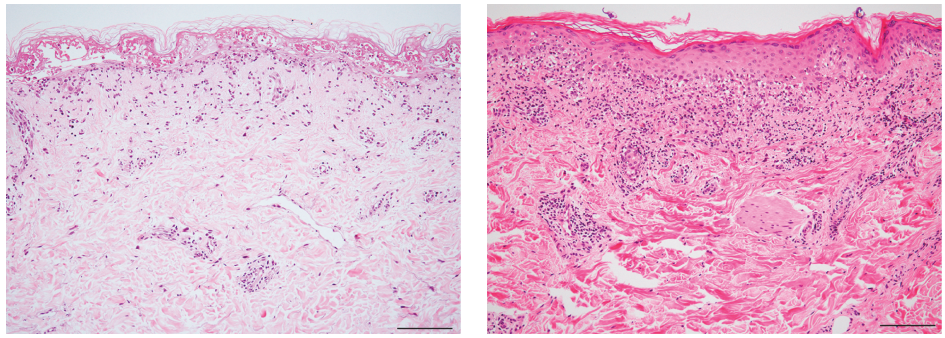
Diagnosis of severe cutaneous adverse drug reactions should involve immunohistopathological examination, which gives insight into the pathomechanisms of these disorders. The characteristic histological findings of erythema multiforme (EM), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) provide conclusive evidence demonstrating that SJS/TEN can be distinguished from EM. Established SJS/TEN shows full-thickness, extensive keratinocyte necrosis that develops into subepidermal bullae. Drug-induced hypersensitivity syndrome (DIHS) and exanthema in drug reaction with eosinophilia and systemic symptoms (DRESS) each display a variety of histopathological findings, which may partly correlate with the clinical manifestations. Although the histopathology of DRESS is nonspecific, the association of two or more of the four patterns—eczematous changes, interface dermatitis, acute generalized exanthematous pustulosis- (AGEP-) like patterns, and EM-like patterns—might appear in a single biopsy specimen, suggesting the diagnosis and severe cutaneous manifestations of DRESS. Cutaneous dendritic cells may be involved in the clinical course. AGEP typically shows spongiform superficial epidermal pustules accompanied with edema of the papillary dermis and abundant mixed perivascular infiltrates. Mutations in *IL36RN* may have a definite effect on pathological similarities between AGEP and generalized pustular psoriasis.

1. Introduction

Typical cutaneous adverse drug reactions (cADRs), such as maculopapular eruptions (MPEs), often show varying degrees of vacuolar interface dermatitis associated with nonspecific eosinophilic and/or neutrophilic infiltrates [1]. Nonetheless, the histopathologies of most of the severe cADRs are unique to each condition. The following reviews the immunohistopathological features of several severe cADRs.

2. Stevens–Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)

The general histological findings of SJS/TEN are subepidermal bullae with overlying confluent necrosis of the epidermis and a few perivascular lymphocytic infiltrates (Figure 1(a)) [2]. In the early stages of SJS/TEN, scattered necrotic keratinocytes appear in the lower layer of the epidermis, histologically resembling a feature of erythema multiforme (EM) major: necrotic keratinocytes spread around the epidermis with vacuolization at the epidermal-dermal junction (Figure 1(b)) [3, 4]. In established SJS/TEN, extensive full-thickness keratinocyte necrosis is seen, which results in the formation of subepidermal bullae. The epidermis exhibits major epidermal necrosis in SJS/TEN, whereas in EM major, the epidermis exhibits less necrosis, with changes appearing predominantly in the basal layer. The Japanese diagnostic criteria for SJS/TEN propose that at least ten necrotic keratinocytes be seen at a magnification of 200x. In the upper dermis, perivascular inflammatory infiltrates and exocytosis are minimal to absent. SJS/TEN tends to show less dermal inflammation than is seen in the pronounced dermal infiltration and extravasation of erythrocytes in EM major [5, 6]. By



(a) (b)

Figure 1: Hematoxylin-eosin (HE) sections of toxic epidermal necrolysis (TEN) (a) and erythema multiforme (EM) (b). (a) Subepidermal bullae under full-thickness epidermal necrosis. Note: the cell-poor dermal inflammation. (b) An interface reaction pattern with infiltrates of lymphocytes and scattered necrotic keratinocytes. Lymphocyte infiltrates are much denser in EM than in TEN. Bar = 100 μm.

contrast, the degree of inflammation was shown in a study of 37 TEN patients to correlate with a worse prognosis, with the quantification of dermal mononuclear cell infiltration approximately as accurate as the TEN-specific severity-of-illness score (SCORTEN) in predicting patient outcome [7].

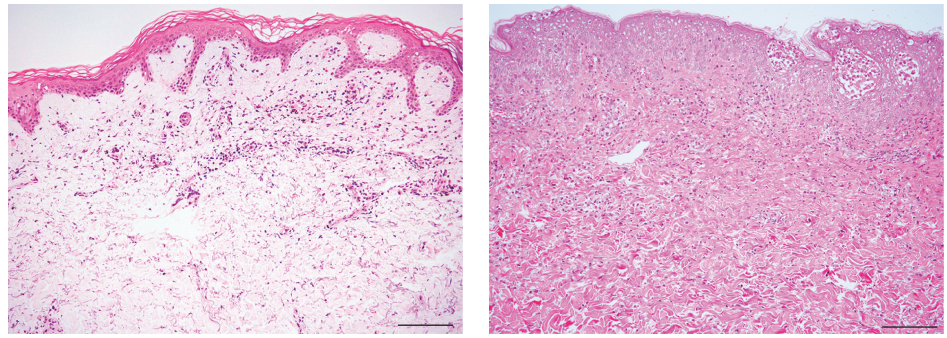
In SJS/TEN patients showing EM-like lesions, the initial diagnosis and prediction of disease activity can benefit from information gleaned from snap-frozen, immediately cryostat-sectioned hematoxylin and eosin-stained skin specimens [8].

Differential diagnoses other than EM major include staphylococcal scalded skin syndrome (SSSS), linear immunoglobulin A (IgA) bullous dermatosis, acute graft-versus-host disease (GVHD), and generalized bullous fixed drug eruption (GBFDE). SSSS displays only superficial, rather than full-thickness, epidermal necrosis, and the pathogenesis is staphylococcal exfoliative toxins that cleave a specific peptide bond on desmoglein 1 [9]. Linear IgA bullous dermatosis can be clinically similar to TEN, although the former shows no necrotic epidermis [10–12]. Complete epidermal necrosis may point to the need to distinguish severe acute GVHD from TEN. The most conspicuous epidermal change of acute GVHD is satellite cell necrosis comprising apoptotic keratinocytes adjacent to lymphocytes in the epidermis; however, when the epidermal necrosis is prominent, it can be hard to distinguish between the two diseases [13]. If the early exanthema of acute GVHD displays erythematous follicular papules showing folliculotropic infiltrates accompanied by basal vacuolization and satellite cell necrosis, the papules might help distinguish severe acute GVHD from TEN [14]. GBFDE also displays apoptotic keratinocytes throughout the epidermis, whereas infiltrating eosinophils and dermal melanophages are more frequently found in GBFDE than in SJS/TEN. Compared with SJS/TEN, the dermal $CD4^+$ T cells, including $Foxp3^+$ regulatory T cells, infiltrate to a greater extent in GBFDE. Additionally, both serum granulysin levels and the number of intraepidermal granulysin-expressing cells are much lower in GBFDE [15].

3. Drug-Induced Hypersensitivity Syndrome (DIHS)/Exanthema in Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Histopathological investigation is not critical for the diagnosis of DIHS according to diagnostic criteria established by a Japanese consensus group [16, 17], nor is it critical for the diagnosis of DRESS according to diagnostic criteria proposed by the European registry of severe cutaneous adverse reaction to drugs group (EuroSCAR/RegiSCAR) [16].

The heterogeneous histopathology of DRESS entails no specific diagnostic feature. Frequently reported findings include spongiosis, various degrees of basal vacuolization, necrotic keratinocytes, dense and diffuse dermal-epidermal infiltrates with lymphocytic exocytosis, dermal edema, and superficial perivascular infiltrates of mostly lymphocytes with or without eosinophils (Figures 2(a) and 2(b)) [18–20]. Clinicopathological investigations of DRESS have suggested that an association between two or more of four patterns—eczematous alterations, interface dermatitis, acute generalized exanthematous pustulosis- (AGEP-) like pattern, and EM-like pattern—in a single biopsy specimen may lead to the diagnosis and suggest the risk of severe cutaneous manifestations. These characteristics are remarkably more prominent in DRESS cases than in MPE cases [21]. Apoptotic keratinocytes have been shown to be more closely related to liver and/or renal complications [21–24]. Additionally, a recent study has demonstrated a close relationship between interface changes and cholestatic-type liver injury, which might imply an immunoallergic reaction in cholestatic-type liver injury in DRESS [25]. The intensity of the dermal lymphocytic infiltrates could correlate with DRESS severity [26]. Conversely, epidermal spongiosis correlates with the absence of renal complications and with nonsevere forms of DRESS [23]. Immunohistochemically, the number of plasmacytoid dendritic cells, a subset of leukocytes with the ability to produce interferon-α upon viral infection, increases in DIHS skin, and the number of these cells in the peripheral



(a) (b)

Figure 2: HE sections of drug-induced hypersensitivity syndrome/exanthema in drug reaction with eosinophilia and systemic syndrome. Two cases that are associated with liver function deficiency show different histopathologies: intermittent interface change, few necrotic keratinocytes, and slight spongiosis in (a); diffuse interface change, several necrotic keratinocytes, and considerable spongiosis with spongiotic bullae in (b). Bar = 100 μm.

blood is diminished around the viral reactivation period [27]. Thymus and activation-regulated chemokine (TARC), a family of CC chemokines known to be vital for Th2-type immune response and to potentially reflect the activity of skin eruptions in DRESS, is expressed on $CD11c^+$ dendritic cells in the dermis of the lesion site [28]. This indicates that such cells may be a major cause of TARC in DRESS [28].

The clinical features of SJS/TEN and AGEP may be similar to those of DRESS [29, 30]. However, the histopathology of DRESS differs substantially from that of TEN and AGEP; DRESS presents neither full-thickness necrosis nor sterile subcorneal pustules [31–33]. In our clinical experience, none of the following have been found to associate with DRESS severity: interface dermatitis, spongiosis, the degree of necrotic keratinocytes, and vascular damage (unpublished data). A recent publication showed that the coexistence of three patterns—eczematous, vascular, and interface dermatitis—was frequently observed in definite DRESS cases with high grades of cutaneous and hematological abnormalities [34]. The differences between our observations and those of this study might be due to our smaller sample. Differences in DRESS case definitions and the skin lesions' stages of evolution may account for the differences observed among diverse case reports and clinical studies [2]. The various clinical appearances, such as MPE-like and EM-like eruptions, might be responsible for the wide variety of histopathological findings observed in DRESS patients. In performing biopsies, it is recommended that the type of biopsy lesion—that is, macular or confluent erythema, purpura, papule, or pustule—be described in detail, for more than one area, and at several points in time. The relation between the onset of the skin eruption and the time of biopsy should be mentioned in terms of hours or days, instead of "early" or "late."

The reactivation of several viruses, such as human herpesvirus- (HHV-) 6, HHV-7, cytomegalovirus (CMV), and Epstein-Barr virus, sometimes occurs over the prolonged clinical course [35]. Cutaneous lesions emerging as late systemic manifestations of CMV tend to be rare, presenting as ulcerated erythematous papules that histopathologically exhibit intranuclear inclusion [36]. Because cutaneous manifestations are associated with fatal gastrointestinal complications, early identification of CMV reactivation is crucial for effective management.

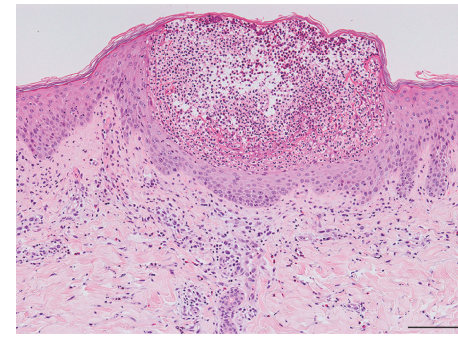


Figure 3: An HE section of acute generalized exanthematous pustulosis shows spongiform superficial intraepidermal pustules and polymorphous perivascular infiltrates containing mostly neutrophils. Bar = 100 μm.

4. Acute Generalized Exanthematous Pustulosis (AGEP)

The histopathology of AGEP is typically spongiform subcorneal and/or superficial intraepidermal pustules accompanied with edematous papillary dermis and large amounts of perivascular infiltrates (Figure 3) [37, 38]. A large series of AGEP cases revealed several unique features: a higher prevalence of necrotic keratinocytes (67%), which was described as a major epidermal feature, and a conspicuously high prevalence of dermal infiltrates (93–100%) containing neutrophils (100%) as well as eosinophils (81%) [31]. The prevalence of leukocytoclastic vasculitis ranges from less than 1% to 20% of cases [39]. This difference might be attributed to misinterpreting erythrocyte extravasation as vasculitis [31].

AGEP and generalized pustular psoriasis (GPP) share common clinical manifestations: diffuse pustules over the entire body and systemic symptoms of high fever and

neutrophil-predominant hyperleukocytosis [39]. Morphology of the spongiotic pustules is indistinguishable between that seen in AGEP or the acute phase of GPP. In one study of 43 cases of AGEP and 24 cases of GPP, AGEP was successfully differentiated from GPP by necrotic keratinocytes, mixed neutrophil-rich interstitial and middermal perivascular infiltrates, the presence of eosinophils in the pustules or dermis, and the absence of tortuous or dilated blood vessels. Furthermore, chronic GPP with pustules on prolonged existing lesions displays significant epidermal psoriasiform changes, such as hyperkeratosis and parakeratosis [32]. These pathological similarities between AGEP and GPP might stem from a mutually occurring mutation in *IL36RN* encoding the interleukin-36 receptor antagonist. Several cases of patients with AGEP with homozygous or heterozygous *IL36RN* mutations have been reported, particularly in patients presenting with intraoral involvement, which might underlie the defect in some forms of AGEP [40–42].

5. Conclusion

SJS/TEN might present particular histopathological findings if the condition is because of viral infection. Secondary cutaneous eruptions following immune checkpoint blockade therapy appear to show many histological findings distinct from those of classic cADRs [43].

Evaluating the histopathological features of these diseases, in combination with their severity, can lead to accurate diagnoses.

Conflicts of Interest

The author declares that there is no conflict of interest regarding the publication of this article.

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