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Severe cutaneous adverse reactions and their association with autoimmune disease: an update

Lydwan Pérez-Westerband[1,2], Keyun Wang[1,2], Matthew Hernandez[3], David A. Sanchez[1,2]*

[1]Downstate Health Sciences University, State University of New York, Brooklyn, NY 11203, USA
[2]Veterans Affairs New York Harbor Healthcare System, New York, NY 10010, USA
[3]Hunter College, City University of New York, New York, NY 10065, USA

***Correspondence:** David A. Sanchez, Veterans Affairs New York Harbor Healthcare System, New York, NY 10010, USA. David.sanchez4@va.gov
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Abstract

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP), are T-cell-mediated hypersensitivity reactions. Although their causative agents and acute manifestations are well characterized, limited data exist regarding their long-term sequelae, particularly the subsequent development of autoimmune disease. A comprehensive literature review was conducted using PubMed. Given the limited published evidence regarding autoimmune sequelae following SCARs, the search strategy was intentionally broad and included studies published from the 1980s through 2025. Among SCARs, DRESS demonstrated the strongest association with autoimmune disease, including type 1 diabetes mellitus, thyroiditis, bullous pemphigoid, thrombotic thrombocytopenic purpura, autoimmune hemolytic anemia, vitiligo, and systemic lupus erythematosus. Proposed pathogenic mechanisms include viral reactivation and persistent immune dysregulation. SJS/TEN has also been associated with fulminant type 1 diabetes mellitus, autoimmune thyroid disease, systemic lupus erythematosus, Sjögren's syndrome, and the development of positive antinuclear antibodies. In contrast, evidence linking AGEP to autoimmune disease remains limited and conflicting, although associations with CARD14 mutations and polyarteritis nodosa have been reported. Evidence supporting post-SCAR autoimmunity, particularly following DRESS, is growing but remains largely based on case reports and small observational studies. SCARs, particularly DRESS and to a lesser extent SJS/TEN, may predispose patients to autoimmune disease through persistent immune dysregulation and viral reactivation. In contrast, no clear association has been established between AGEP and autoimmune disease. Clinicians should remain vigilant for potential long-term autoimmune sequelae following SCARs and consider multidisciplinary follow-up when clinically appropriate. Further prospective studies are needed to better characterize the underlying mechanisms, incidence, and optimal long-term surveillance strategies associated with these conditions.

Keywords

severe cutaneous adverse reactions, autoimmunity, SJS/TEN, DRESS, AGEP

Introduction

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) are defined as delayed-type hypersensitivity reactions caused by an offending drug [1]. SCARs are a group of heterogeneous, T-cell mediated and potentially life-threatening conditions typified by skin and mucosal involvement [2]. Although extensive studies have been done to identify the responsible predisposing drugs to these diseases, not enough information is currently available regarding the long-term outcomes in affected patients and how SCARs may play a role in autoimmune disease. In this review, we present how SCARs can predispose patients to autoimmune diseases by viral re-activation, disruption of immune homeostasis, and several other potential mechanisms that are actively being explored (Table 1).

Table 1. SCARs and associated autoimmune conditions.

SCAR	Pathogenesis	Clinical features	Autoimmune conditions
DRESS	Type IV hypersensitivity reaction; herpes virus reactivation; cytokine dysregulation	2–8-week latency; fever, fatigue, and diffuse lymphadenopathy; morbilliform rash affecting the face and leading to facial edema; palms and soles usually spared; eosinophilia	Type 1 diabetes mellitus (T1DM), thyroiditis, bullous pemphigoid, thrombotic thrombocytopenic purpura (TTP), hemolytic anemia, vitiligo, Kikuchi-Fujimoto disease (KFD)/systemic lupus erythematosus (SLE)
SJS/TEN	Type IV hypersensitivity reaction; granulysin-mediated keratinocyte apoptosis	Rapidly progressive irregular purpuric macules that progress to bullae with widespread epidermal necrolysis; painful erosions of the mucus membranes; positive Nikolsky sign	Fulminant type 1 diabetes mellitus (FT1DM), thyroiditis, SLE, Sjögren's syndrome, ANA seroconversion
AGEP	Type IV hypersensitivity reaction; IL-8-neutrophil recruitment	24–48-hour latency after exposure; sterile, pruritic, non-follicular pustules that spare the mucosal membranes; elevated neutrophilia	No clear link; however, some associations with CARD 14 mutations and polyarteritis nodosa

ANA: antinuclear antibody; CARD 14: caspase recruitment domain 14; AGEP: acute generalized exanthematous pustulosis; DRESS: drug reaction with eosinophilia and systemic symptoms; SCARs: severe cutaneous adverse reactions; SJS/TEN: Stevens-Johnson syndrome/toxic epidermal necrolysis.

Materials and methods

A comprehensive literature review was conducted using PubMed. Given the limited published evidence regarding autoimmune sequelae following SCARs, our search strategy was intentionally broad, including studies published from 1985 through 2025. Search terms included "severe cutaneous adverse reactions", "SCAR", "drug reaction with eosinophilia and systemic symptoms", "DRESS", "Stevens-Johnson syndrome", "SJS", "toxic epidermal necrolysis", "TEN", "acute generalized exanthematous pustulosis", "AGEP", "autoimmune disease", "autoimmunity", "viral reactivation", and "immune dysregulation." All English-language publications reporting autoimmune manifestations following SCARs were considered, including case reports, case series, cohort studies, retrospective studies, reviews, and other relevant observational studies; non-English publications were excluded. Due to the limited available evidence on this emerging topic, all eligible studies identified through the search strategy were included. References from selected articles were also manually reviewed to identify additional relevant publications.

DRESS

Definitions and epidemiology

DRESS is a type IV hypersensitivity syndrome typically triggered by specific medications. It is characterized by prodromal symptoms, the development of a diffuse erythematous maculopapular eruption,

lymphadenopathy, and eosinophilia that can lead to significant organ damage. The term DRESS was proposed as an umbrella term in 1996 to encompass several drug-specific reactions, which had been described under a variety of names such as anticonvulsant hypersensitivity syndrome, allopurinol hypersensitivity syndrome, and dapsone hypersensitivity syndrome [3]. DRESS is more commonly seen in adults when compared to children, with recent studies demonstrating a slight female-to-male predominance [4]. Common causative agents are anticonvulsants, allopurinol, antibiotics, and NSAIDs; reactions have usually been reported three weeks to three months after initiation of therapy. This distinguishes it from other types of type IV hypersensitivity drug reactions that usually begin one to two weeks after initial exposure [3, 5, 6]. Interestingly, DRESS has been seen in connection with a variety of autoimmune diseases such as type 1 diabetes mellitus (T1DM), thyroid diseases, hematologic diseases, and rheumatologic disease.

Clinical features and laboratory findings

Patients afflicted with DRESS usually have a latency phase that occurs for two to eight weeks, marked by nonspecific systemic symptoms like fever, fatigue, and diffuse lymphadenopathy. Following the prodromal symptoms, patients typically manifest with a morbilliform rash predominantly affecting the face, upper trunk, and upper extremities, with subsequent involvement of the lower extremities [7, 8]. On occasion, there may be an upper-respiratory infection-like prodrome. Periorbital, facial, or neck erythema and edema with pustules may be present at the early stages. Mild mucosal involvement, often in the oral mucosa, rarely progresses to skin detachment in DRESS and has been documented in up to 50% of cases [7]. Palms and soles are classically spared. Lymph nodes may also become affected, with most patients developing tender lymphadenopathy at the beginning of the illness. Some patients also develop severe xerostomia, which makes swallowing difficult [6]. Leukocytosis with atypical lymphocytes and eosinophilia are prominent, and liver abnormalities with increased serum alanine aminotransferase values are characteristic. However, liver function test abnormalities frequently resolve about 3 weeks after, without sequelae. Hepatitis, interstitial pneumonia, interstitial nephritis and carditis represent eosinophilic organ infiltration in DRESS. Dramatic decreases in serum IgG, IgM, and IgA are observed at the early stages of the condition, likely secondary to decreased peripheral B-cell numbers and predominance of regulatory T cells (Tregs) leading to significant immune dysregulation [9]. Notably, IgG levels continue to decrease even after removal of the offending drug over several weeks; however, some reports describe an overshooting phenomenon that increases IgG values similar to other autoimmune conditions. Occasionally, renal involvement can also be seen, with the degree of involvement correlating with mortality. Poor prognosis is seen with eosinophil counts above 6,000 × 10^3/μL, thrombocytopenia, pancytopenia, leukocytosis, coagulopathy, and the presence of comorbidities such as CKD [3, 4, 6, 8].

Diagnostic criteria

There are various diagnostic criteria used around the world to diagnose DRESS. The Japanese Research Committee on Severe Cutaneous Adverse Reactions (J-SCAR) and RegiSCAR have both proposed diagnostic criteria that are used internationally for diagnosis of DRESS. RegiSCAR is a multinational registry of all SCARs started in 2003 with a network of hospitals in Austria, England, France, Germany, Israel, Italy, the Netherlands and Taiwan (China) [4]. For diagnosis of DRESS, three out of seven criteria must be present and the presence of the first three criteria are needed for diagnosis: acute rash, reaction is suspected to be drug-related, hospitalization, fever (> 38°C), laboratory abnormalities (at least one present-lymphocytes above or below normal, low platelets, eosinophilia), involvement of > 1 internal organ and enlarged lymph nodes > 2 sites [8]. DRESS is often a clinical diagnosis, with biopsies having a limited role in confirming the diagnosis.

Pathogenesis

T-cell mediated SCARs are believed to occur by three mechanisms: the hapten/pro-hapten model, the pharmacological interactions of drugs with immune receptors (p-i) concept, and the altered peptide repertoire model. In the hapten/pro-hapten model, it is believed that drugs are too small to be

immunogenic; thus, they must bind to an endogenous carrier and form a hapten-carrier complex. This complex will then be recognized by antigen-presenting cells (APCs) and subsequently be recognized by a T-cell receptor (TCR), forming a drug-specific immune response. In the p-i concept, it is believed that the drug will bind to HLAs/TCRs, directly stimulating the TCR and then the drug-reactive T cells. The altered peptide repertoire model suggests that a drug can bind to a pocket on an HLA and change its conformation, thereby creating a new set of self-peptides and stimulating T cells [3]. SCARs also appear to be influenced by genetic factors. HLA allele studies have shown associations between HLA-B*57:01 and abacavir-induced hypersensitivity reactions, HLA-B*15:02 and carbamazepine-induced SJS/TEN, and HLA-B*58:01 and allopurinol-induced SCARs (SJS/TEN and DRESS) [3].

SCARs, as type IV hypersensitivity reactions, can be further characterized into IVa, IVb, and IVc based on T cell subset, cytokines, and leukocyte recruitment. DRESS is considered a type IVb reaction and primarily involves T helper 2 (TH2) lymphocyte activation and viral reactivation [10]. Support for this theory arises as discontinuation of the causative drug paradoxically worsens clinical symptoms. Thus, mechanisms cannot be explained only by a drug reaction [3]. Evidence of increased HHV-6 IgG titers and HHV-6 DNA arising two to three weeks after the onset of rash has caused countries in Asia and Europe to adopt testing for the virus as the gold standard, as reactivation has only been detected in DRESS but not in other drug eruptions [11]. Studies have also demonstrated that other herpesviruses can reactivate sequentially, with reactivation events initiated by HHV-6, followed by HHV-7, and then CMV. This sequential reactivation of these herpesviruses would explain why several flares of the disease occur even after discontinuation of the culprit drug, as symptoms would be mediated by an immune response to viral replication [8, 11].

It is important to note that HHV-6 has selective tropism for CD4 T cells. CD134, also called OX40, is a member of the tumor necrosis factor (TNF) family and is expressed on CD4 T cells in acute stages of DRESS. It is a costimulatory receptor and has been identified as a receptor of HHV-6. It is believed that the up-regulation of CD134 allows entry of HHV-6 into the CD T cells in the acute stages of DRESS. CD4 and CD8 T cells play distinct roles in DRESS. CD4 T cells are drug-specific and initiate drug-induced immune responses, while CD8 T cells recognize viral antigens and launch antiviral immune responses, affecting multiple organs and amplifying immune responses [3].

Association with autoimmune diseases

T1DM

The development of T1DM in association with the development of DRESS is rare and characterized by autoantibodies such as anti-glutamic acid decarboxylase (GAD) and islet cell antibodies [12]. From our literature review, a total of three patients were found to develop autoimmune T1DM (two males and one female). The first case depicts a 50-year-old male with past medical history of Grave's disease who developed methimazole-induced drug hypersensitivity syndrome after 1.5 months of treatment, presenting with generalized exfoliative erythema and high fever; his condition improved after drug withdrawal but worsened upon rechallenge. High-dose methylprednisolone followed by prednisolone resolved his symptoms, while declining anti-HHV-6 and anti-CMV IgG titers supported reactivation of both viruses during the illness [13]. The second case identified a 44-year-old Vietnamese man who was diagnosed with DRESS likely secondary to an unknown antibiotic taken while he was in Vietnam. In his case, however, he presented nine days after discharge with hyperglycemia, altered mental status, and was admitted to the hospital for DKA. He was found to have low C-peptide and elevated GAD antibodies, indicating an autoimmune pathogenesis [5]. The third case depicts a 15-year-old female who developed DRESS after minocycline therapy for acne. Seven months after taking the medication, she presented with polydipsia and polyuria and an HbA1c of 8.1%; elevated GAD and islet-antigen 2 (IA2) were also detected [14].

Thyroiditis

Thyroid disease has been previously documented as a potential sequela of a DRESS episode. Thyroid gland abnormalities have been found, with increased free thyroxine (FT4), low thyroid-stimulating hormone

(TSH), and the production of autoantibodies such as anti-TSH, anti-thyroperoxidase (anti-TPO), and anti-thyroglobulin (anti-TG) in several patients who have experienced DRESS [12]. Various cases of Graves' disease can be seen throughout the literature. One case report detailed diffuse large goiter followed by hyperthyroidism two months after the incidence of DRESS [12]. Three additional cases have also been described in the literature. The first was a 27-year-old man who developed DRESS secondary to ampicillin medication. Thirty-six days after onset of DRESS, he developed palpitations and tremors and, based on laboratory data, was diagnosed with primary hyperthyroidism. Labs showed that FT4 was elevated, TSH was low, and elevated TSH-binding inhibitory immunoglobulin (TBII) and antithyroglobulin antibody was positive (TgAb). This patient also developed alopecia about two years after DRESS diagnosis and was diagnosed with alopecia areata [15]. The second patient was a 33-year-old woman who developed DRESS after taking carbamazepine for neuropathic pain. Nine months after her diagnosis, she began to have palpitations, insomnia, weight loss, and blurred vision. Her labs were remarkable for elevated FT4 and low TSH, indicating primary hyperthyroidism; she was subsequently diagnosed with Graves' disease [15]. Lastly, the literature also shows a 15-year-old female who developed DRESS after minocycline therapy for acne. During admission, thyroid function tests were normal and antithyroid antibodies were negative; however, upon discharge, repeat levels showed low TSH, elevated FT4, and elevated antithyroglobulin and anti-TPO. After seven weeks of taking the medication, she developed Graves' disease [14]. Hashimoto's has also been observed after the resolution of DRESS [12]. Kano et al. [16] performed a study in 2015 in 14 institutions in Japan and Taiwan (China) to detect new-onset diseases after DRESS. The most common sequelae was thyroid disease-7 out of 145 patients developed autoimmune thyroiditis (two with Graves' disease, three with Hashimoto's, and two with painless thyroiditis).

In 2013, Kano et al. [12] presented a review paper highlighting that following DRESS, thyroid disease is the most frequently detected sequelae, with an incidence of about 3.8%, about ten times higher than the expected incidence in the Chinese population. It was also shown that the presence of HHV-6 in the thyroid is significantly higher in Hashimoto's than in controls, again highlighting a possible association between viral reactivation and subsequent development of autoimmune thyroid disease [12]. Interestingly, Kano et al. [12] also describe autoantibodies such as antinuclear antibody (ANA), anti-TPO, and anti-TG antibodies that were observed without any clinical manifestations after an analysis of thirty-four cases of DRESS at their institution [12]. Therefore, one could infer that the development of these autoantibodies can lead to disease in susceptible hosts.

Bullous pemphigoid

Bullous pemphigoid is an autoimmune disease that affects the subepidermal layers of the skin and mostly affects the elderly population. In 2008, Kijima et al. [17] described the case of a 68-year-old woman who was diagnosed with DRESS after taking minocycline hydrochloride, carbamazepine, and zonisamide for one year. Nine days after incidence of DRESS, the patient developed tense bullae in the trunk and extremities. Biopsies were taken and revealed subepidermal blisters with eosinophilic and lymphocytic infiltration. Immunofluorescence showed IgG antibodies at the basement membrane consistent with a diagnosis of bullous pemphigoid [17]. Supporting the notion that autoantibody production may get triggered by DRESS, Brown et al. [14] describe a 15-year-old female who developed DRESS after minocycline therapy for acne and developed elevated titers of previously negative ANA, anti-Sjogren syndrome A and anti-smith antibodies seven months after discontinuation of minocycline.

Thrombotic thrombocytopenic purpura

Thrombocytopenic purpura (TTP) is rare and characterized by a pentad of fever, neurologic deficits, hemolytic anemia, renal impairment, and thrombocytopenia. In 2012, Sandouk et al. [18] described the case of a 50-year-old male with new onset of seizures secondary to a stroke. He was diagnosed with DRESS after one month of phenytoin use. Three months after the onset of DRESS, the patient returned to the emergency room with aphasia and altered mental status. CT head was negative for any acute stroke; however, he was found to have an acute kidney injury (AKI), anemia, thrombocytopenia, an elevated reticulocyte count, and

lactate dehydrogenase plus a low haptoglobin. A liver profile was normal, coagulation was unchanged, and the disseminated intravascular coagulation profile was negative. Schistocytes were seen in the peripheral smear, and the patient was diagnosed with thrombotic thrombocytopenia with severe ADAMTS13 deficiency [18]. TTP develops due to deficiency of ADAMTS13, as its job is cleaving aggregations of von Willebrand factor. It is possible that after DRESS, an unknown antibody developed in this patient, causing inhibition of ADAMTS13, demonstrated by his severely low levels of less than 5% [18, 19].

Hemolytic anemia

In 2013, Chen et al. [15] performed a retrospective cohort study in Taiwan (China) to establish long-term sequelae of DRESS. They describe a 35-year-old man who developed DRESS after dapsone treatment. He was also found to have progressive anemia with high lactate dehydrogenase, elevated reticulocytes, and decreased haptoglobin with a positive Coombs test, confirming autoimmune hemolytic anemia [15]. Defective suppression of Tregs was described by Mqadmi et al. [20] as a potential cause of the development of acute hemolytic anemia. Although in the acute stage of DRESS, Treg cells are upregulated, at the resolution stage they begin to become refractory [21].

Vitiligo

Kano et al. [16] showed a case of vitiligo which occurred in a patient about 4.5 months after diagnosis of DRESS. Furthermore, Lonowski et al. [22] present a case of a 45-year-old woman who developed vitiligo three weeks after diagnosis of DRESS. The case of a 59-year-old male who developed vitiligo six months after DRESS diagnosis has also been described in the literature [23]. Finally, the case of a 47-year-old woman was diagnosed with vitiligo universalis 4 months after the development of DRESS; in her particular case, PCR testing confirmed reactivation of HHV-7, HHV-6, and CMV after DRESS diagnosis [24]. As has been described previously, Treg cells are increased during the acute phase of DRESS, which causes downregulation of cytotoxic effector T cells and incites viral replication. This imbalance between Treg and T effector cells contributes to the autoimmunity. In these particular cases of vitiligo, CD8 cells secreting INF-y could be causing melanocyte apoptosis [25, 26].

Kikuchi-Fujimoto disease/systemic lupus erythematosus

Kikuchi-Fujimoto disease (KFD) was first described in 1972 by Kikuchi and Fujimoto as a benign self-limited lymphadenitis. The disease presents with fever and enlarged cervical lymph nodes. Diagnosis is typically made by biopsy, with histology showing patchy areas of necrosis with eosinophilic material and debris. KFD has been shown to have an association with the subsequent development of SLE. In 2008, Aota et al. [21, 27] described the case of a 36-year-old man who developed KFD four years after DRESS. In this specific case, the patient developed SLE immediately following KFD. Workup revealed leukopenia, positive ANA, decreased C3 and C4, and kidney biopsy was remarkable for mesangial proliferation, indicating lupus nephritis [21, 27].

It is possible that the reactivation of EBV during DRESS could have led to the subsequent development of SLE by its ability to infect and stay latent in B cells [27]. The exact mechanism remains unclear; however, Moon et al. and Gross et al. [28, 29] have discovered an increased proportion of EBV-infected B cells in SLE patients. DRESS appears to trigger latent viruses, thus leading to the reactivation of EBV and, in this case, the subsequent development of SLE. Reported autoimmune sequelae following DRESS are summarized in Table 2.

SJS and TEN

Definitions and epidemiology

SJS and TEN are rare but highly fatal clinical subtypes of SCARs typically manifesting as a hypersensitive allergic response to infections or medications. Common causative agents include antiepileptics, sulfonamides, antipyretics, antibiotics, analgesics, and allopurinol, although some cases are idiopathic [30–35]. HIV, *Mycoplasma pneumonia*, and vaccination have also been documented to predispose SJS/TEN-like

Table 2. Drug reaction with eosinophilia and systemic symptoms (DRESS).

Associated autoimmune conditions	Evidence type	Reported cases (*n*)	Time to onset	Key findings
T1DM	Case reports	3	9 days to 7 months	Low C-peptide, +GAD, +IA2
Grave's disease	Case reports	≥ 4	1–9 months	Low TSH, high FT4, high TBII, +TgAB
Hashimoto's thyroiditis	Case report; cohort study	≥ 3	Weeks to months	anti-TPO, anti-TG
Bullous pemphigoid	Case report	1	9 days	Subepidermal blisters; linear IgG immunofluorescence
Thrombotic thrombocytopenic purpura	Case report	1	3 months	Severe ADAMS13 deficiency
Autoimmune hemolytic anemia	Cohort study	1	Weeks	+Coombs, high LDH, Low haptoglobin
Vitiligo	Case report; cohort study	4	3 weeks to 6 months	Depigmentation; Increased $CD8^+$ IFN-γ
Kikuchi-Fujimoto disease/systemic lupus erythematosus	Case report	1	Years	+ANA, Low C3/C4

ANA: antinuclear antibody; anti-TG: anti-thyroglobulin; anti-TPO: anti-thyroperoxidase; FT4: free thyroxine 4; GAD: glutamic acid decarboxylase; IA2: islet antigen-2; LDH: lactate dehydrogenase; T1DM: type 1 diabetes mellitus; TgAB: thyroglobulin antibody; TBII: thyrotropin-binding inhibiting immunoglobulin; TSH: thyroid-stimulating hormone.

conditions [33–37]. These manifestations can be further complicated with hepatic, renal, and respiratory dysfunction. The estimated incidence of SJS is approximately 8–9 cases per million people annually, with a mortality rate of 4.8%, while TEN is less frequent at 1–2 cases per million but with a significantly higher mortality rate of 14.8% [30, 33, 34, 36]. Curiously, mortality increases further in SJS/TEN overlap cases, with recent studies reporting mortality as high as 19.4% [37]. Demographic factors also influence risk, with females and younger adults more commonly affected. Racial disparities have also been identified, with incidence rates highest among Black and Asian individuals, with elevated risk also noted in Hispanic, Native American, and multiracial populations compared to white individuals due to HLA-A/B association [34, 35, 37]. Additionally, SJS/TEN is associated with a spectrum of systemic comorbidities, such as malignancies including multiple myeloma, leukemia, non-Hodgkin's lymphoma, central nervous system cancers, renal and hepatic dysfunction, epilepsy, and autoimmune disorders like systemic lupus erythematosus (SLE) [35, 37].

Clinical features and laboratory findings

The diagnosis of SJS/TEN is primarily clinical, based on characteristic mucocutaneous findings and the extent of epidermal detachment. Patients may experience preliminary symptoms preceding skin involvement, characterized by fever, cough, rhinorrhea, conjunctivitis, anorexia, and malaise [35]. General cutaneous manifestations present with symmetrical facial and truncal rashes spreading to extremities, irregularly shaped and sized erythematous or purpuric macules that progress to bullae, widespread epidermal necrolysis, and painful erosions involving both the skin and mucus membranes of the mouth, eyes, and genitalia, which are commonly affected [30, 32, 35, 36, 38]. A positive Nikolsky's sign, where gentle lateral pressure causes epidermal detachment, is a hallmark clinical finding [30, 34, 35]. Blisters develop quickly, leading to the shedding of extensive areas of the epidermis and revealing the underlying, fluid-secreting dermis. Epidermal separation typically advances over five to seven days, after which a healing phase with re-epithelialization occurs over one to three weeks [35]. Symptom onset typically occurs within four to eight weeks following the initiation of a culprit medication, although latency periods as long as 30 weeks have been reported for drugs with low or atypical risk. In addition to classic high-risk medications, emerging evidence highlights agents which enhance cytotoxic T lymphocyte (CTL) activity, such as checkpoint inhibitors like CTLA-4 antagonists, EGFR inhibitors like cetuximab, and BRAF inhibitors used in melanoma, which can precipitate SJS/TEN by intensifying immune-mediated keratinocyte apoptosis [34, 39]. Management of SJS/TEN primarily involves prompt discontinuation of the offending drug, along with supportive care focused on maintaining fluid and electrolyte balance, ensuring adequate respiratory

function, providing nutritional support, controlling pain, and preventing or treating infections [34, 35]. Wound care is also essential, involving careful handling to promote re-epithelialization and prevent secondary infections. One of the most significant predictors of these conditions is the presence of multiple underlying chronic illnesses, suggesting that concurrent use of multiple medications and poor baseline health status contribute substantially to susceptibility [34, 37, 40].

Diagnostic criteria

Classification is based on total body surface area (BSA) involvement: SJS involves less than 10% BSA detachment, TEN involves more than 30%, and SJS/TEN overlap is defined by detachment between 10–30% [30, 31, 33–36, 38]. Given the importance of identifying the causative agent, the ALDEN scoring system has emerged as a valuable diagnostic tool which systematically assesses drug exposure timing, known associations, and alternative causes to classify drug causality likeliness. Another score, SCORTEN is the standard clinical score for predicting mortality in SJS/TEN, but it reflects severity at presentation rather than the underlying immune mechanism [34].

In addition to clinical and histopathological criteria, biomarkers have shown promise in early diagnosis and disease monitoring. Serum granulysin, for example, is now proposed as an early diagnostic marker, with rapid immunochromatographic tests available [34, 35]. Granulysin is one of the strongest proposed early mediators and biomarkers of SJS/TEN, while IL-15 appears to act upstream by promoting cytotoxic immune activity and granulysin production. In SLE, the main issue is diagnostic overlap: lupus can mimic SJS/TEN or rarely present with SJS/TEN-like skin disease, so careful differentiation is essential. Overall, the literature supports IL-15 and granulysin as biologically informative markers in SJS/TEN, with SCORTEN remaining the main bedside prognostic tool [34].

While the acute presentation and management of SJS/TEN are well-characterized, growing evidence indicates that survivors may not fully return to immunologic baseline. Instead, the intense immune activation and epithelial injury that define the acute phase may initiate a cascade of long-term immunological consequences. In particular, persistent immune dysregulation following resolution of the acute episode has been associated with the later development of autoimmune disorders. The following section explores the mechanisms and clinical evidence linking SJS/TEN to autoimmune sequelae.

Pathogenesis

SJS/TEN is classified as a type IVa hypersensitivity reaction, characterized by involvement of TC1 and TH1 cells, natural killer cells, and macrophages in blistering lesions, primarily directed at keratinocytes [10, 30, 34]. Histopathologically, both SJS/ TEN exhibit full-thickness epidermal necrosis involving all epidermal layers, often accompanied by a sparse inflammatory infiltrate in the dermis [34–36]. Unlike other autoimmune blistering diseases, direct immunofluorescence typically reveals no immunoglobulin deposition. Instead, the immunologic response in SJS/TEN is marked by cytotoxic CD8+ T cells (CTLs) and NK-like T cells in early blister fluid, with monocytes predominating in later phases by IFN-γ recruitment [34, 35]. In the pre-blistering phase, however, CD14+ monocytes coexpressing CD80, CD86, and CD137 can also work to promote CTL proliferation and cytotoxicity [34]. These immune cells release a variety of pro-apoptotic and inflammatory mediators that drive keratinocyte death and amplify tissue damage. Granulysin has emerged as a central cytotoxic molecule in this process, with serum levels significantly elevated during the early stages of SJS/TEN, peaking two to four days prior to the development of skin detachment and mucosal erosion symptoms [34, 35]. Similarly, serum FasL exhibits an early spike during disease onset, whereas other markers such as TNF-α, IFN-γ, sTRAIL, and TWEAK remain persistently elevated throughout the disease course. Additional biomarkers such as thymus and activation-regulated chemokine (TARC) or IL-15, which recruit and activate other immune cells, and micro-RNA-124 have been correlated with disease severity, with the latter two levels showing a direct relationship with patient mortality measured by the SCORTEN index [34].

Recent evidence also implicates reactive oxygen species (ROS) generated within keratinocytes as a key contributor to the pathogenesis of TEN, preceding pro-apoptotic pathways [35]. Oxidative stress markers such as GST-π are found in greater abundance in TEN compared to other cutaneous adverse drug reactions, suggesting impaired detoxification and accumulation of electrophilic xenobiotics leading to further ROS production, cellular damage, and activation of apoptotic processes including Fas ligand expression and TNF-α inflammatory cytokine release. Additionally, TNF-α contributes to keratinocyte apoptosis by activating caspases and enhancing Fas/FasL expression, while also stimulating nitric oxide production that disrupts mitochondrial electron transport and exacerbates ROS accumulation. These combined events drive early apoptosis followed by late necrosis, corresponding to histological findings of TEN [35].

Association with autoimmune disease

Diabetes

Among the autoimmune complications reported post-SJS/TEN, reports have highlighted fulminant T1DM (FT1DM), a subtype of T1DM describing a loss of β-cell function due to rapid autoimmune activity. A case study was reported involving a patient who developed FT1DM shortly after discontinuing a 35-day course of carbamazepine and phenytoin [30]. The individual presented with symptoms consistent with SJS/TEN overlap, including facial, thoracic, and proximal upper extremity rashes, ulceration and discharge of the ocular and oral mucosa, swollen eyelids, exfoliation, and eczematous cheilitis, all of which involved 20% of total BSA. Subsequent evaluation revealed severe hyperglycemia and high urine ketone concentrations twenty days after drug discontinuation. Extremely low fasting serum C-peptide accompanied by the absence of detectable islet autoantibodies established the diagnosis of autoimmune β-cell destruction. Furthermore, a negative result for autoimmune pathogens and no past medical history of diabetes further supported a diagnosis of FT1DM resulting from drug-induced SJS/TEN [30].

Thyroid disease

Autoimmune thyroiditis has also been reported as a sequela of SJS/TEN. In one retrospective study, a patient developed delayed Hashimoto's thyroiditis one year after an episode of SJS/TEN [31]. Although thyroid function remained normal, elevated anti-TG and anti-thyroid peroxidase antibodies were observed, consistent with an early or subclinical stage of Hashimoto's thyroiditis recently developed. This pattern supports the notion of an early or subclinical stage of Hashimoto's thyroiditis before significant thyroid dysfunction has developed.

SLE

Similar to thyroid disease, SJS/TEN has been associated with the later onset of SLE. Recent literature has described a distinct severe spectrum of vesiculobullous disease associated with lupus erythematosus (LE) termed SJS/TEN-like LE [41, 42]. This condition can closely mimic true SJS/TEN but may reflect a fundamentally different autoimmune-driven pathogenic mechanism triggered by ultraviolet exposure in patients with a predisposition to SLE. This photosensitivity promotes infiltration of autoreactive T cells and histiocytes, along with deposition of autoantibodies (IgG, IgM, IgA) and C3 complement protein, inducing hydrophobic degeneration of the epidermis and keratinocyte apoptosis, with type I interferon-mediated inflammation further amplifying the pathogenic process [41]. Additionally, the involvement of interferon-inducible chemokines such as CXCL10, and the recruitment of CXCR3+ lymphocytes contributing to basal keratinocyte damage and epidermal separation reinforces the distinction of this process [41]. Furthermore, unlike conventional SJS/TEN, SJS/TEN-like LE demonstrates distinct diagnostic features, including a positive lupus band test and histopathologic changes characteristic of lupus rather than drug hypersensitivity [41]. This distinction is critical, as cases reporting SLE-induced SJS/TEN may actually represent misidentified instances of SJS/TEN-like LS [34]. Conversely, true SJS/TEN has also been followed by the delayed onset of autoimmune diseases, including SLE. In a retrospective analysis, a patient developed SLE approximately one year after recovering from SJS. The initial assessment of SJS was accompanied by an acute exacerbation of chronic hepatitis B [31]. These findings suggest that, in this

instance, SJS/TEN may have acted as a trigger for the subsequent development of SLE, highlighting the potential for SCARs to precede and possibly predispose systemic autoimmune diseases.

Sjögren's syndrome

Among autoimmune sequelae, Sjögren's syndrome has been reported most frequently following SJS/TEN. In a retrospective series, multiple patients developed primary Sjögren's syndrome two to twelve years post-recovery [31]. Diagnosis was based on hallmark symptoms, including xerostomia and keratoconjunctivitis sicca, as well as serum positive for anti-Sjögren's-syndrome-related antigen A (SSA) or B (SSB) antibodies, and abnormal salivary gland function determined by Tc-99m sialoscintigraphy. Additionally, cases of secondary Sjögren's syndrome, characterized by undetectable SSV antibodies, were reported in individuals with comorbid rheumatoid arthritis, while others exhibited Sjögren's-like symptoms, notably abnormal sialoscintigraphy, that did not reach full diagnostic criteria. Similarly, a separate retrospective study described two patients who developed Sjögren's syndrome within two months to four years after TEN recovery [32]. Both exhibited sicca syndrome involving lacrimal and salivary glands coupled with histological findings consistent with Chisholm grade III, or lymphocytic infiltration in accessory salivary gland tissue with one nodular infiltrate of more than 50 lymphocytes. Other patients in the same cohort instead presented Sjögren's-like syndrome, evidenced by sub-diagnostic Chisholm grade II, or less than 50 lymphocytes in a 4 mm^2 field, which suggested early or incomplete autoimmune involvement [32].

Positive ANA

Recent evidence suggests that SJS/TEN may precipitate the emergence of autoimmune markers in the chronic phase of recovery, even in the absence of observable autoimmune disease during the acute illness. In a pediatric retrospective study, ANA levels were evaluated in five patients either during the acute phase of SJS/TEN or prior to onset [38]. All five patients were initially negative for ANA, but three developed positive titers during the chronic recovery phase. Importantly, thyroid autoantibodies and thyroid function tests remained negative, ruling out concurrent thyroid autoimmunity but not excluding a delayed, specific onset of autoimmune activity. Although some patients tested positive for viral markers, including VZV, HSV, CMV, and mycoplasma, at initial SJS/TEN presentation, these findings were not temporally associated with the emergence of ANA positivity and may reflect coincidental or unrelated infectious exposures. Prior evidence of Treg dysfunction in patients with TEN, describing low IFN-γ–producing Tregs persisting into the recovery phase, can explain this delayed onset of positive ANA titers [38]. A separate study of 123 adults with SJS/TEN, however, found that six patients eventually developed an autoimmune disease, three of whom were ANA-positive, supporting the idea that positive ANA status may also serve as an early serologic marker of future autoimmune pathology [38]. See Table 3 for summarized findings of SJS/TEN.

Table 3. Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN).

Associated autoimmune conditions	Evidence type	Reported cases (*n*)	Time to onset	Key findings
Fulminant type 1 diabetes mellitus	Case reports	1	~20 days	Undetectable C-peptide; absence of islet antibodies
Hashimoto's thyroiditis	Cohort study	≥ 4	1 year	anti-TPO, anti-TG
Systemic lupus erythematosus	Retrospective chart analysis	1	1 year	High-titer ANA, +dsDNA
				Distinguished from SJS/TEN-like lupus erythematosus
Sjögren's syndrome	Retrospective chart analysis	≥ 3	2 months to 12 years	Sicca symptoms; +SSA, +SSB
ANA seroconversion	Cohort study	6	Months	New ANA positivity

ANA: antinuclear antibody; anti-TPO: anti-thyroperoxidase; anti-TG: anti-thyroglobulin; C-peptide: connecting peptide; dsDNA: double-stranded DNA; SJS: Stevens-Johnson syndrome; SSA: Sjögren's-syndrome-related antigen A; TEN: toxic epidermal necrolysis.

AGEP

Definitions and epidemiology

AGEP is a T-cell mediated inflammatory condition with abrupt onset of sterile, non-follicular pustules on the background of erythema and edema [43, 44]. AGEP occurs from children to adults with a predominance in those aged 20–60 years [45–47]. There is a predominance in women, which is likely due to sex differences in pharmacokinetics affecting drug metabolism, corresponding with the finding that drug eruptions are more commonly seen in females [45, 48–52]. The majority of the reported patient race is white, followed by Black or African American [53, 54]. AGEP is rare, with a yearly incidence of one to five cases per million per year [43, 55]. Out of all drug-induced rashes such as DRESS or SJS/TEN, AGEP accounts for approximately 17% of cases [56]. Triggers for AGEP are drug-related the majority of the time; most commonly implicated antibiotics include β-lactams and quinolones [46]. Other triggers have also been reported, including allergens, infections, mercury exposures, vaccines, and insect bites [57–67]. In a cross-sectional study, Gallardo et al. [68] found that AGEP patient populations had increased body mass index and previous drug allergies compared to the DRESS patient population. While AGEP is primarily linked to specific medications, social determinants of health such as socioeconomic status and healthcare access may have effects on case incidence, given that individuals with limited access to healthcare may have higher rates of infections, leading to increased antibiotic use. Though AGEP's connection with autoimmune disorders has not been well studied, there have been studies centered around patients who developed AGEP with a past medical history of autoimmune disorders. A study by Smith et al. [69] looked at the underlying diseases in 21 patients with episodes of AGEP. Out of the 21 patients with AGEP studied, past medical histories include diagnoses of psoriasis, sarcoid, inflammatory bowel disease, autoimmune thyroiditis, and multiple sclerosis, suggesting that patients who develop AGEP appear to have a deregulatory immune T-helper-1 cytokine pattern [69].

Clinical features and laboratory findings

Classically, AGEP appears quickly after exposure to a putative offending agent, which is typically within 24 to 48 hours after drug exposure [70]. Similarly, in AGEP cases induced by other triggers including vaccines, insect bite, infection, and allergens, the mean time of onset has previously been determined to be approximately 2 days following exposure [57, 58, 65, 67]. However, a more recent 2022 review of 297 drug-induced AGEP cases found the mean time of onset to be 9.1 days with a standard deviation of 13.94 days, suggesting variability depending on individual patient factors and specific drugs involved [71]. Prodromal symptoms for AGEP include fever (> 38°C), generalized malaise, neutrophilia (> 7.5×10^9/L), eosinophilia, and hypocalcemia [54, 70, 72]. Cutaneous manifestations include sudden eruption of pustules over an edematous and erythematous background [43]. The pustules can be described as sterile, pruritic, and non-follicular [43, 73]. Areas of involvement include the trunk and intertriginous areas that often spare the mucosal membranes [70, 73]. About 18–25% of cases with AGEP can involve the mucosal membrane, most commonly lips or buccal mucosa [71, 74]. Desquamation occurs after pustules have resolved and typically occurs within a few days after discontinuation of the offending agent [70, 73].

Patients with systemic organ involvement would exhibit elevated absolute neutrophil count and C-reactive protein levels [75]. Internal organs are affected in 17–20% of cases, which commonly include pulmonary, hepatic, and renal systems [70, 75]. Hepatic systemic manifestations include either elevated aspartate aminotransferase and alanine aminotransferase to twice the normal level, or elevated alkaline phosphatase and γ-glutamyl transferase [75–77]. Ultrasound of the abdomen would reveal either hepatomegaly or steatosis [75]. Pulmonary symptoms include pleural effusions, pulmonary edema, hypoxemia, and acute respiratory failure [70, 75, 78]. Renal involvement is represented by elevated creatinine levels up to 1.5 times the baseline [76]. Bone marrow was involved in one case, showing elevated neutrophils and agranulocytosis in bone marrow aspirate [75]. While most AGEP cases resolve spontaneously, mortality is about 5% when internal organs are involved [70]. Death usually occurs due to multiple organ dysfunction and disseminated intravascular coagulation and is seen more commonly in patients with diffuse skin involvement or mucous membrane involvement [70, 79].

Diagnostic criteria

AGEP is diagnosed based on both clinical presentation and histologic pathology. The EuroSCAR project has developed a scoring system for AGEP after comparing the clinical presentation of AGEP against other similar cutaneous diseases such as pustular psoriasis, pustular vasculitis, or TEN [43]. Criteria that support AGEP include sterile non-follicular pustules, erythematous background, distribution over the trunk and intertriginous areas, post-pustular desquamation, fever, neutrophils > 7,000/mm^3, and spongiform subcorneal and/or intraepidermal pustules with papillary edema [43]. Drug patch tests can also be used when the drug agent causing AGEP is known [80]. A review by Barbaud in 2014 [80] has found that drug patch tests have been shown to be useful for AGEP in 50–58% of cases, whereas skin prick tests and intradermal tests have not shown any known value. On histology, spongiform pustules are commonly located in intracorneal, subcorneal, and/or intraepidermal regions with papillary dermal edema with both neutrophilic and eosinophilic infiltrates [43, 81–83]. Intraepidermal pustules containing eosinophils are mostly in the upper epidermis, bordering the subcorneal pustules [82]. The epidermal layer contains necrotic keratinocytes and spongiosis with neutrophil exocytosis, while the dermal layer contains neutrophilia and eosinophilia with occasional erythrocyte extravasation [81–83].

Pathogenesis

AGEP is a type IVc reaction caused by massive cell infiltrates of neutrophils in pustules and infiltration in the dermis and epidermis by TH17, ILC3s, and Tc17 [10]. The pathophysiology of AGEP is suggested to be a T-cell mediated inflammatory disease or a type IV reaction, with both CD4 and CD8 T-cells playing vital roles [84–86]. As shown through patch tests and in vitro tests, it is hypothesized that after allergen exposure, CD4 and CD8 T-cells undergo activation after binding to MHC molecules from antigen-presenting cells [70, 85–90]. Activated T-cells, or drug-specific T-cells, subsequently undergo proliferation, then migrate to the dermis and epidermis [70]. The drug-specific cytotoxic T-cells utilize proteins like granzyme B and perforin to induce apoptosis of keratinocytes, resulting in the formation of epidermal vesicles [86]. Drug-specific T-cells in AGEP patients have also been shown to produce more CXCL8/IL-8, a neutrophil chemokine, guiding neutrophils into epidermal vesicles, which form sterile pustules [85, 86, 91]. Studies have also demonstrated that increased levels of granulocyte-macrophage colony-stimulating factor (GM-CSF), INF-γ, IL-17, and IL-22 prevent neutrophil apoptosis, as well as induce further release of CXCL8/IL-8 by keratinocytes [85, 91, 92]. Peripheral blood serum of AGEP patients reveals higher levels of TH17 cells, which are responsible for the production of IL-17 and IL-22, suggesting a role of innate cells in pathophysiology [92]. Other cytokines that are found to be elevated in some AGEP cases include IL-5 and TNF-α [85, 93]. The increased levels of IL-5, a key cytokine in eosinophilic development and activation, can help explain eosinophilia that is seen in 28–52% of cases [85].

Additionally, studies have found a link between mutations in the IL-γ receptor antagonist (*IL-36RN*) gene and AGEP [94–96]. IL-36 is induced by pro-inflammatory cytokines such as IL-17 and IL-22 [94]. The *IL36RN* gene codes for the IL-36 receptor antagonist, IL-36Ra, which functions to block pro-inflammatory cytokines like IL-36a, IL-36b, and IL-36γ [95, 96]. Lack of a feedback mechanism in patients with *IL36RN* gene mutation would lead to an uncontrolled IL-36 pathway, hence increasing production of inflammatory cytokines like IL-6, IL-8, IL-1a, and IL-1 b, contributing to epidermal pustule formation [95, 97]. The initial discovery of the *IL36RN* gene was found to correlate with generalized pustular psoriasis (GPP) [94, 95]. Due to similar clinical, histological, and immunological features, several studies have attempted to identify link between *IL36RN* mutations and other GPP-related diseases, namely AGEP [94, 95]. Navarini and colleagues in 2013 found the rate of *IL36RN* gene mutations to be higher in AGEP groups compared to controls [95].

The limited literature examining potential links between AGEP and autoimmune disease may be attributable to the rarity of AGEP, given its typically self-limited clinical course, and the lack of long-term follow-up studies. Consequently, most investigations have focused on drug triggers and acute immunologic mechanisms rather than subsequent autoimmune outcomes. Current evidence suggests a shared genetic and immunologic predisposition, including *CARD14* and *IL36RN* mutations, rather than a direct AGEP-mediated autoimmune process.

Association with autoimmune disease

CARD14 mutation-related psoriatic conditions

Recent cases have suggested a genetic predisposition between *CARD14* gene mutation and AGEP. *CARD14* gene mutation is a variant that traditionally was found to associate with systemic pustular rash diseases such as psoriasis vulgaris and pityriasis rubra pilaris [94]. CARD14, or cascade recruitment domain family member 14, is a protein expressed in the skin and is most found in killer cells. CARD14 induces and activates NF-kB and MAPK signaling, resulting in downstream inflammation, which is believed as common pathophysiology for psoriatic diseases [94, 98]. The first case report of patients with *CARD14* mutation was found in 2017, when a 47-year-old man developed AGEP seven days after being treated with prednisone and dipyrone for lumbago [99]. Genetic studies later on discovered a heterozygous mutation in the *CARD14* gene [99]. In 2023, Luo et al. [98] reported a second case of a young female with a history of rheumatoid arthritis who developed AGEP after exposure to hydroxychloroquine. Genetic workup with whole-exome sequencing revealed a CARD14 gain-of-function mutation [98]. Despite these reports, current literature provides limited evidence supporting a direct association between AGEP and autoimmune disease, but instead suggests shared immunologic and genetic predisposition. Given that genetic sequencing is not a standard procedure for AGEP diagnosis, further research identifying the presence of *CARD14* mutation would be useful for clarifying the link between AGEP development and *CARD14* mutation.

Polyarteritis nodosa

In a case reported by Alkhachroum et al. [100], a 60-year-old male with a history of multiple flare-ups of polyarteritis nodosa developed AGEP due to an unidentifiable precipitant. He initially presented to the hospital due to scrotal pain and fevers and started on broad-spectrum antibiotics with vancomycin and Zosyn upon admission. He was then transitioned from Zosyn to meropenem after developing AKI; however, despite the change in antibiotics, his kidney function continued worsening, and he continued to spike fevers without a clear source of infection. His previously known macular rash progressed to involve his axilla, neck, head, and chest, followed by bullae and vesicles, finally becoming pustular and associated with fevers of up to 109°F. Dermatology was consulted, a biopsy was performed, and a diagnosis of AGEP was made [100]. Podlipnik et al. [99] reported a patient developing AGEP who also presented with low-titer positive antinuclear antibodies (1/80) in a homogeneous speckled pattern in the context of newly diagnosed polyarthritis, suggesting a possible pre-existing underlying autoimmune pathology.

History of previous autoimmune conditions

Smith et al. (2003) [69] studied 21 patients with AGEP to further understand the histopathology of the disease and any related autoimmune conditions. Out of the 21 patients, two had a history of psoriasis, two a history of sarcoidosis, two a diagnosis of IBD, one with a history of thyroiditis, and one with a history of multiple sclerosis. Creadore et al. in 2022 [54], however, found a history of psoriasis in only 7.3% of participants, which matched the known prevalence. No further evidence showing a direct link or association to the previously mentioned conditions was found during our literature search.

Conclusions

Inciting factors of SCARs have long been studied; however, prior to our review, there was limited understanding of their long-term effects, specifically their role in possibly inducing autoimmunity. In the case of DRESS, there is significant evidence that supports post-DRESS autoimmunity, likely through a combination of viral replication and Treg dysfunction, although the exact mechanisms are unclear. Takahashi et al. in 2009 [101] observed that in the acute phase of DRESS, there is an upregulation of Treg cells (CD4+, CD25+ and Foxp3+), suppressing the expansion of antiviral T cells, and allowing latent viruses to replicate. Self-antigen is released in this process, and auto-reactive T cells become primed. Towards the end of the DRESS disease course, Treg cells become refractory and lose their ability to halt T effector cells from proliferating. It is possible that this immune dysregulation could explain the reported subsequent development of autoimmune diseases following DRESS [3, 11, 21, 101].

In the case of SJS/TEN, as described above, there is also some evidence that shows subsequent autoimmune disease following SJS/TEN, although data are less robust. As with DRESS, mechanisms are unclear, and it is speculated that it is likely due to genetic susceptibility from specific HLA factors, overreactive immune responses, and Treg cell dysregulation, similar to DRESS [30, 31]. Unlike in DRESS, however, Takahashi et al. (2009) [101] did not observe the same degree of Treg expansion in the acute stage with SJS/TEN or AGEP. This difference may explain why there are fewer cases of post-SCAR autoimmunity outside of DRESS. For AGEP, current evidence does not support a clear link to induced autoimmunity or an increased risk in patients with previous history of autoimmune disease. Nonetheless, interpretation of these associations remains challenging, as viral infections, underlying genetic susceptibility, HLA-related risk factors, and pre-existing immune dysregulation may independently contribute to autoimmune disease development.

Overall, this review highlights that SCARs, particularly DRESS syndrome (and to a lesser extent SJS/TEN), may be associated with subsequent autoimmune disease development. However, further studies are needed to validate and better characterize the proposed pathogenic mechanisms underlying these associations. Current evidence remains limited by the predominance of case reports and small observational studies, particularly in DRESS-associated autoimmunity. Given the potential for delayed autoimmune sequelae following SCARs, clinicians should consider longitudinal follow-up after resolution of the acute reaction, especially in patients with DRESS. Clinicians and patients should maintain awareness of symptoms suggestive of autoimmune disease, including but not limited to polyuria, polydipsia, unexplained weight loss, sicca symptoms, fatigue, and arthralgias. Consideration may also be given to periodic thyroid function testing, assessment for diabetes mellitus, and routine hemoglobin and creatinine evaluations, which may facilitate earlier recognition of evolving disease. Furthermore, multidisciplinary collaboration among dermatology, allergy/immunology, rheumatology and primary care providers may help optimize long-term patient outcomes. Nevertheless, standardized surveillance protocols have not yet been established, highlighting the need for future prospective and longitudinal studies.

Abbreviations

AGEP: acute generalized exanthematous pustulosis

ANA: antinuclear antibody

anti-TPO: anti-thyroperoxidase

BSA: body surface area

CTL: cytotoxic T lymphocyte

DRESS: drug reaction with eosinophilia and systemic symptoms

GAD: glutamic acid decarboxylase

GPP: generalized pustular psoriasis

LS: lupus erythematosus

p-i: immune receptors

ROS: reactive oxygen species

SCARs: severe cutaneous adverse reactions

SJS: Stevens-Johnson syndrome

SLE: systemic lupus erythematosus

T1DM: type 1 diabetes mellitus

TCR: t-cell receptor

TNF: tumor necrosis factor

TSH: thyroid-stimulating hormone

TTP: thrombocytopenic purpura

Declarations

Author contributions

DAS: Conceptualization, Investigation, Supervision. LPW: Investigation, Writing—original draft, Writing—review & editing. KW: Investigation, Writing—original draft, Writing—review & editing. MH: Investigation, Writing—original draft, Writing—review & editing. All authors read and approved the submitted version.

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The authors declare that they have no conflicts of interest.

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