Severe cutaneous adverse reactions (SCARs) to drugs in Latin America: RACGRAD study

Short title: RACGRAD study

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0497
Abstract

Background: Severe cutaneous adverse reactions to drugs (SCARs), have a high morbidity, mortality and present sequelae.

Objective: To characterize patients with SCARs in eight health care institutions in Latin America.

Methods: Cross-sectional, descriptive, multicenter, Latin American study of patients diagnosed with SCARs, between January 2009 and December 2018. The analysis was made from a database in BD Clinic.

Results: Seventy cases were reported. Forty-two (60%) were women. The average age was 38.7 years. Forty-two (60%) had DRESS-DIHS, 12 (17.1%) TEN, 5 (7.1%) SJS, 6 (8.5%) AGEP, 4 (5.7%) other, not classified SCARs, and 1 (1.4%) overlapping TEN/SJS. The main causative drugs were aromatic anticonvulsants in 31 cases (44.3%), beta lactam antibiotics in 11 cases (15.7%) and non-beta lactam antibiotics in 6 cases (8.6%). In all of cases, the suspected drug was withdrawn at the first sign of a SCAR. Sixty-six patients (94.2%) received anti-inflammatory treatment, mostly systemic corticosteroids. Complications occurred in 53 cases (75.7%) and death in three patients (4.3%). Thirteen patients (18.6%) had some type of sequelae.

Conclusions: This is the first multicenter report on SCARs in Latin America. DRESS-DIHS was the most frequently reported clinical entity and anticonvulsants were the main triggers. Most of patients received systemic corticosteroids. Complications were frequent and three patients died.

Keywords: Drug eruptions. Stevens Johnson Syndrome. Toxic Epidermal Necrolysis. DRESS. Acute Generalized ExanthematousPustulosis. Latin America.
Resumen

Antecedentes: Las reacciones cutáneas graves inducidas por medicamentos (SCARs) presentan alta morbimortalidad y secuelas.

Objetivo: Caracterizar clínicamente a pacientes con SCARs en ocho instituciones de salud de Latinoamérica.

Métodos: Estudio transversal, descriptivo, multicéntrico latinoamericano, de pacientes diagnosticados con SCARs, entre enero 2009 y diciembre 2018. El análisis se realizó a partir de una base de datos en BDClínic.

Resultados: Se reportaron 70 casos. 42 (60,8%) eran mujeres. El promedio de edad fue de 38 años. 42 (60%) tenían DRESS/ DiHS, 12 (17,1%) NET, 5 (7,1%) SJS, 6 (8,5%) PEGA, 4 (5,7%) otras reacciones adversas cutáneas no clasificadas y 1 (1,4%) NET-SJS superpuestos. Los principales fármacos involucrados fueron los anticonvulsivantes en 31 casos (44,3%), los antibióticos betalactámicos en 11 (15,7%) y los antibióticos no betalactámicos en 6 (8,6%). A todos se les retiró el fármaco sospechoso ante los primeros signos de la reacción. Sesenta y seis pacientes (94,2%) recibieron tratamiento antiinflamatorio, principalmente corticosteroides sistémicos. Las complicaciones ocurrieron en 53 casos (75,7%) y la muerte en tres pacientes (4,3%). Trece pacientes (18,6%) tuvieron algún tipo de secuela.

Conclusiones: Este es el primer estudio multicéntrico sobre SCARs en Latinoamérica. El DRESS/DiHS fue la reacción más frecuente y los anticonvulsivantes fueron los principales desencadenantes. La mayoría recibieron corticosteroides sistémicos. Las complicaciones fueron frecuentes y tres pacientes fallecieron.

Palabras clave: Reacciones cutáneas graves. Síndrome Stevens Johnson. Necrolisis Epidérmica Tóxica. DRESS. Pustulosis Exantemática Aguda. Latinoamérica.
INTRODUCTION

Severe cutaneous adverse reactions induced by drugs (SCARs), cover a wide range of conditions that include Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Drug Induced Hypersensitivity Syndrome (DiHS) [1, 2]. In addition, due to the extended eruptions and outbreaks it generates, and the possibility to cause systemic symptoms, clinicians also consider Acute Generalized Exanthematous Pustulosis (AGEP) as a SCAR [2].

Although having a relatively low incidence, SCARs are potentially lethal and may be responsible for serious consequences. It is estimated that the SJS-TEN incidence is two cases per million annually, while the incidence of DRESS for those who are treated with antiepileptic drugs is 1 out of every 1,000 to 10,000 patients [3].

TEN and SJS are distinguished by damage to the epidermis and the mucosal epithelium, and often have systemic complications. Both are considered variants of the same disorder, only differentiated by the extent of body surface area involved; thus, SJS is indicated when the cutaneous damage is less than 10%, Overlap Syndrome with SJS/TEN when damage is between 10% to 30% and finally, TEN if the affected area exceeds 30%. The most common drugs involved in the SJS-TEN cases include anticonvulsants, allopurinol, antimicrobial agents, NSAIDS, and the sulfonamides, although other drugs may also be involved [4].
DRESS and DiHS are associated with fever, hepatitis and/or other internal organ complications, as well as lymphadenopathies and hematologic abnormalities (leukocytosis, hypereosinophilia and atypical lymphocytosis). Over the course of these conditions, the human herpes virus (HHV) reactivation has been described, particularly the HHV-6, and with less frequency the cytomegalovirus. The common drugs associated with DRESS-DiHS include the aromatic anticonvulsants (carbamazepine, phenytoin and phenobarbital), allopurinol, minocycline, antimicrobial sulfa drugs, and aromatic sulfonamides[5].

AGEP is probably the least severe form of the SCARs. Non-follicular pustules arising on an oedematous erythema characterize the reaction. The rash is commonly accentuated in the main folds, with palmoplantar occurring infrequently. The pustules are sterile and contain a large number of neutrophils. The most frequent causative drugs mentioned as responsible are the aminopenicillins, sulphonamides, quinolones, hydroxychloroquine, terbinafine, and diltiazem[6].

Severe cutaneous adverse reactions are considered to be delayed hypersensitivity reactions with 4 subgroups identified: IVa: mediated by lymphocytes Th1, IVb: mediated by lymphocytes Th2, (interleukins 4, 5 and 13, and the cytokine eotaxin, as occurs in DRESS), IVc: mediated by lymphocytes T cytotoxic (as occurs in SJS and TEN), and IVd: mediated by lymphocytes T and neutrophils through IL-8 and GM-CSF (as occurs in AGEP) [7].

Diagnosis of SCARs is essentially clinical, always assessing the exanthema/skin characteristics, development time, and latency between the exposure to the possible drug involved and the skin manifestations that appear, as well as the
associated symptoms (e.g. fever, pruritus, and lymphadenopathies). The management of SCARs must be carried out with these reactions in mind, since early and proper multidisciplinary treatment has been associated with lower mortality and fewer subsequent problems [2].

Although they are rare disorders, the SCARs are associated with complications such as bacterial superinfection, compromising of a target organ, multisystem organ failure, and in the case of DRESS, frequent relapses. Several epidemiologic studies have established the mortality rates of 10-40% for SJS and TEN; 1-10% for DRESS-DiHS; and 1% for AGEP [8]. Dystrophic scars, hyperpigmentation, alopecia, nail loss, eye complications caused by synechiae, dry eye and symblepharon, dental loss, genital synechiae and psychiatric disorders can result from SJS and TEN. For DRESS-DiHS, some autoimmune conditions such as lupus, thyroiditis, diabetes and scleroderma are described as some consequences of the condition[2].

Genetic factors have been associated with the predisposition to suffer from SCARs, and it is known that the genetic background of Latin American individuals is different from the European, Asian or African, which may influence the incidence of SCARs in these populations. Unfortunately, in Latin America, there is no research that identifies the incidence and clinical characteristics (clinical presentation, diagnosis, treatment and prognosis) of SCARs. Not understanding how to recognize the signs and symptoms of SCARs may lead to an increase in complications, sequelae and mortality. Based on the lack of information, the main objective of this study was to clinically define the patient with severe cutaneous
reactions induced by drugs in eight health care centers in five Latin American countries between 2009 and 2018.

METHODS

A multicenter, descriptive cross-sectional study was designed that included the participation of eight healthcare centers from five countries (Argentina, Brazil, Paraguay, Peru and Colombia). This study conformed to the international recommendations of biomedical research as stated in the Helsinki and the CIOMS agreement.

Inclusion criteria are listed below, for all the medical centers the same criteria were followed and the authors reconfirmed the cases and corroborate them by reviewing medical records and photographs.

For SJS/TEN:

This diagnosis were considered in presence of typical target-like lesions (two concentric ring surrounding an erythematous center, sharply demarcated) and according the amount of blistering or detachment of the skin, relative to the body surface area (BSA).

- SJS: detachment were below 10% of the BSA.
- Overlap SJS/TEN: detachment between 10% and 30% of the BSA.
- TEN detachment above 30% of the BSA.[9]

For AGEP:
- Several dozens of small, mostly non-follicular pustules on a background of widespread edematous erythema
- Spongiform subcorneal and/or intraepidermal pustules and perivascular infiltrate with neutrophils and edema of the papillary dermis on histology
- Blood neutrophil counts above 7x10^9/L,
- Acute evolution with spontaneous resolution of pustules in less than 15 days.

The inclusion criteria for AGEP were according to the score for validation of AGEP by Sidoroff et al. 2001[10] taking into account probable and definite cases.

For HSS/DRESS:

- Fever >38.5°C
- Enlarged lymph nodes
- Eosinophilia >10% or >700/ul
- Atypical lymphocytes
- Skin involvement suggesting DRESS
- Involvement of at least one internal organ (Liver, kidney, ling, muscle/heart, pancreas, other organ)
- Resolution ≥ 15 days
- Other causes discarded (Hepatitis S, B, C, EBV, CMV, Mycoplasmas/Chlamydia, ANA, blood culture).
The inclusion criteria for DRESS/DIHS were according to the diagnostic score for validation of DRESS/DIHS by Kardaun et al. 2007 [11] taking in count probable and definite cases.

The diagnostic information came from physicians in Allergy/Immunology Departments of the participating institutions from January 2009 to December 2018. A thorough review of the clinical record was carried out to collect the demographic characteristics, specific syndrome, drug involved, latency period, treatment established, and the prognosis. Drug causality was evaluated using ALDEN score for SJS/TEN cases [12] and Naranjo score for DRESS and AGEP[13]. Data were collected using a modified version of the questionnaire of the European Network for Drug Allergies (ENDA)[14]. The BD Clinic© software platform was used to create a data base of patients with SCARs. Patients whose clinical records were incomplete and/or had duplicate records, were excluded.

**Statistical Analysis**

A univariate analysis was carried out to determine the numeric variable distribution. The variable normality was contrasted through Shapiro-Wilk test considering a P value 0.05. The normal distribution variables were summarized using central and dispersion tendency measures as the average and the standard deviation,and were summarized with the median and interquartile range. The data analysis was carried out using the STATA v.14 statistical software.
RESULTS

Seventy-two SCARs cases were reported. Two patients were excluded due to duplication. Seventy patients were included for the analysis. The demographic characteristics are shown in Table 1. The average age was 38.7 years old (SD± 2); and 42 patients (60%) were female. Forty-four patients were from Colombia, 11 from Argentina, 9 from Brazil, 3 from Paraguay and 3 from Peru.

Of all the cases, 42 (60%) were diagnosed with DRESS-DiHS, 18 with the whole spectrum of TEN/SJS: 12 (17.1%) with TEN, 5 (7.1%) with SJS, and one (1.4%) with overlap TEN/SJS; 6 (8.5%) with AGEP and 4 (5.7%) with other non-classified cutaneous adverse reactions (Figure 1). Fifty seven percent (57.1%) of the reactions in the DRESS-DiHS presented between the 1st and 4th week after initiation of the suspected drug. This same latency period was present in 58.3% of the TEN cases, although it was shorter for AGEP where 83.3% of the cases were observed less than 1 week after starting the causative drug.

Etiology

The suspected drug(s) were identified in all the patients, 38 (54.3%) as probable, 25 (35.7%) as very probable or definite and 7 (10%) as possible. The drug type and numeric distribution is shown in Table 2. The main drugs involved were; the anticonvulsants in 31 cases (44.3%), the beta lactam antibiotics in 11 cases (15.7%) and the non-beta lactams in 6 cases (8.6%).
In those patients with DRESS-DiHS, the anticonvulsants (59.5%) and antibiotics (16.7%) were the main triggers. The most frequent anticonvulsant involved in the DRESS-DiHS was carbamazepine in 28.6% of the cases, followed by phenytoin in 26.2%. For patients exhibiting TEN, anticonvulsants were involved in 41.7% of the cases, antibiotics in 25% and allopurinol in 25%. The antibiotics were the most suspected factor in the SJS and AGEP cases (40% and 50% respectively). In 53 patients (75.7%) only one causative drug was identified, while in the other 17 (24.3%) one suspected drug was reported and a second drug, less related with SCARs was also identified.

The underlying conditions that justify the use of the causative drugs were convulsive disorders including epilepsy and structural alteration of the CNS in 20 cases (28.6%), bacterial infections in 17 cases (24.2%) and neuropathic pain in 6 cases (8.6%). In twenty-two (31.4%) of the 70 patients, a skin biopsy was performed to support the diagnosis.

**Treatment**

Once identified, the suspected causative drug was withdrawn from all of the patients. Sixty-four patients (91.4%) received systemic corticosteroids and 9 (12.8%) intravenous immunoglobulin (IVIG). Seven patients (10%) were treated with both therapies. When the patients were divided according to the SCAR type, those with DRESS-DiHS received systemic steroids, none of these patients received IVIG or cyclosporine, however, one patient received infliximab plus corticosteroid. Out of the 12 patients that presented with TEN, 10 (83.3%) were
treated with systemic corticosteroid and 6 (50%) with IVIG; of these 6 patients, 4 were also given corticosteroids, one patient was given cyclosporine and one patient was treated with infliximab. All of the patients that presented with SJS were managed with systemic corticosteroid, two with IVIG plus corticosteroid and one with cyclosporine plus corticosteroid. Of the six patients with AGEP, 4 (66.7%) received systemic corticosteroid and two were treated topically.

The median time between the beginning of the reaction and the initiation of treatment was 5 days (IQR 2-10 days), being shorter for SJS, TEN and AGEP (3 [2-15], 3.5 [2.5-5.5], 3 days [1-7], respectively) and longer for DRESS-DiHS (7 days [3-10]). In the only case of overlapping SJS/TEN, the treatment started 21 days after the reaction started.

The median of the treatment duration was 14 (IQR 7-30) days, being 21 (14-30) days for DRESS-DiHS, 6 (3-19.5) days for TEN and 10 (8-11) days for SJS. All the patients with AGEP received treatment during 14 days (Table 3).

**Prognosis**

The hospital admission characteristics, outcome and prognoses are shown in Table 4. Out of 70 patients, 59 (84.2%) required hospitalization, with a median hospitalization duration of 10 (IQR 7-23) days. Patients diagnosed with SJS and TEN had a longer stay, 12.5 (7.5-58.5) and 21.5 (8-29) days respectively. Eight patients with DRESS-DiHS, 10 patients with TEN, 3 patients with SJS, one patient with AGEP and the only patient with overlapping TEN/SJS, were transferred to ICU. The median stay in ICU was 5 (3-8), 16.5 (8-20) and 10 (3-85) days, for DRESS-DiHS, TEN and SJS respectively.
Complications occurred in 53 cases (75.7%). For the cases of DRESS-DiHS the most frequent complication was liver disease (38%) followed by fluid and electrolyte disorders (19%). Nine patients presented with sepsis as a complication, 3 of them in the DRESS-DiHS group, 5 in the TEN group and 1 in the SJS group. Three patients (4.3%) died, two of them with TEN and one with SJS/TEN overlap. Sequelae occurred in 13 cases (18.6%), with cutaneous problems being the most frequent (12.8%) followed by ophthalmological complications (4.2%) as loss of eyelashes, corneal scars, palpebral and conjunctival synechiae and persistent photophobia.

DISCUSSION

This is the first study conducted in Latin America which aimed to characterize patients with severe cutaneous adverse reactions to drugs in several countries of South America. From the evaluated patients, a slightly higher number of females affected by SCARs was observed, which is in agreement with previous studies [3, 15-20].

The median age of this study was 38.7 years old, similar to the one found by Liet al.[21] in patients with SCARs in China; however, it is lower than the report by Su et al.[22] in Singapore and in other European populations according to the multinational record EuroSCARandRegiSCAR (European Registry of Severe Cutaneous Adverse Reactions to Drugs) [3, 15, 18].

Most of patients in this study presented with DRESS or DiHS, different from other Asian and European studies [21-25], including one of the largest consortia for
the SCARs study, the project RegiSCAR, where the main reaction observed was SJS. Botelho et al. [26] in a monocentric study in Brazil, found a majority of patients with DRESS when compared to SJS-TEN. Genetic factors in the Latin American population that may predispose individuals to DRESS-DiHS should be considered in cases of SCARs. Furthermore, additional pharmacogenomics studies are required to contribute to the understanding of these issues.

Although SCARs can be caused by a diverse group of drugs, in this study, the most frequent culprits were the aromatic anticonvulsants drugs. This is in contrast to what was found in other studies that evaluated SCARs when antibiotics were the predominant responsible drugs [21, 22, 24, 25]. This could be due to the fact that there were a higher number of patients with DRESS-DiHS reported in the present study, in which the use of antiepileptic drugs was predominant. This has also been reported in several other publications where patients with this syndrome were analyzed [3, 16, 17]. The anticonvulsants responsible for the reactions were all aromatics (carbamazepine, phenytoin and lamotrigine), as has been reported elsewhere [27, 28]. Among these drugs, the carbamazepine was the most frequent due to its use not only in epilepsy but also in other painful syndromes such as trigeminal neuralgia, neuropathic pain and others. Several pharmacogenomics studies carried out in the Asian and European population [29-31] have demonstrated the importance of identifying genes associated with SCARs, especially those caused by anticonvulsants. This highlights the importance of conducting genetic marker testing in the Latin American population. This may allow us to predict the future risk of SCARs and try to prevent them. Antibiotics were the
second group of drugs associated with SCARs, especially the beta lactams (15.7%). Other studies have shown that bacterial infections were the second most common underlying condition that indicated the use of these antibiotics. This result is consistent with previous studies [21, 24]. Allopurinol has been another medication frequently implicated in SCARs, [3, 22]; however, in our study, it has been identified as a potential cause of SCARs in 6 patients (8.6%); 3 of them with TEN, 2 with DRESS or DIHS and one with AGEP. Fifty-three patients (75.7%) were exposed to only one suspected drug, 17 patients (24.2%) received two or more drugs, the additional drugs having a much lower risk of causing SCARs.

The latent period between the suspected drug intake and the reaction onset varies according to each specific syndrome [3, 22, 24]. Of the patients that presented with DRESS-DiHS, 57.1% exhibited symptoms between the 1st and 4th week after beginning treatment with the suspected drug, similar to those patients with TEN where 58.3% of the patients exhibited reactions between 1 and 4 weeks. One case with DRESS had a latency period less than 24 horas. This is unusual for this disease; however, Sahnoun et al [32] reported a 47-year-old-woman who developed DRESS syndrome two days after taking ciprofloxacin for a urinary infection, also a short latency period. In addition to this, when we calculated the ADR probability scale according with Naranjo et al [13] the probability was “possible”. The reaction time was shorter for AGEP, where 83.3% showed a reaction in less than a week after taking the causative drug, similar to that reported by Guevara et al. [33]. A total of 21 (30.2%) of the DRESS cases were documented after the 4th week of starting the treatment, including 6 patients who had no
symptoms until after two months. This longer latent period in DRESS or DiHS, suggests that the early signs and symptoms of this reaction, such as fever, adenopathy, flu symptoms, odynophagia or dysphagia, may be overlooked or confused with other more frequent conditions.

Suspending treatment with the suspected agent is the most important step in managing SCARs. In this study, for all patients, the treatment with the suspected drug was terminated at the first sign of symptoms of SCARs. There have been many published reports suggesting the benefit of certain anti-inflammatory drugs [34-37]. A total of 64 patients (91.4%) in our study received systemic corticosteroids, which is consistent previous reports [22, 24]. In the 1980’s, it was suggested that the use of corticosteroids increased morbidity and mortality, not only due to the increased risk of sepsis, but also because of a delay in re-epithelization [38]. However, a case-controlled analysis of selected patients by the Registry of EuroSCAR and RegiSCAR, demonstrated that the long term use of corticosteroids before the reaction onset, can extend its latency and progression, without adversely influencing the severity or mortality [34]. Because of the low frequency of SCARs, small number of clinical studies, and the ethical issues regarding submitting patients with severe reactions to a placebo, it is difficult to draw a definitive conclusion regarding the anti-inflammatory management of patients with SJS-TEN. However, there does seem to be a benefit derived from treatment with methylprednisolone, immunoglobulin and cyclosporine, when comparing the observed mortality with the expected rate using the SCORTEN score [39].
In the case of patients with DRESS reported in this study, 100% received systemic corticosteroids, which was similar to other studies with a high rate of management with these drugs[16, 24, 40, 41]. Corticosteroids have been considered the gold standard for the treatment of DRESS, showing a rapid reduction in fever and exanthema, as well as a rapid hepatic and hematologic response with a decrease of the transaminases and eosinophilia [42]. The systemic therapy with corticosteroids must be initiated using a minimum dose of 1mg/kg/day of prednisone or its equivalent, with a gradual reduction within a period of 6-8 weeks. The prednisone administration must be maintained even if there are signs of clinical improvement or a relapse may occur. Additionally, DRESS patients have a high risk of developing immune reconstitution inflammatory syndrome if corticosteroids are rapidly interrupted[40, 43].

In addition, IVIG has also been used to treat SCARs; however, its use is still controversial. In the present study only 9 (12.8%) of the patients were managed with this drug, all of them having SJS-TEN. Several non-controlled, small clinical studies have found conflicting results with the use of IVIG; one of them showed no differences regarding mortality and progression [35], but other studies have shown favorable results [44-46].

Several studies suggest that tumor necrosis factor (TNF) alpha released from inflammatory cells and activated keratinocytes in the epidermis plays an important role in the immune response by inducing direct cytotoxicity and apoptosis [47]. Therefore, selective TNF blockade with infliximab has proven useful by leading to quick recovery from lesions in patients with TEN, some of them, used infliximab as
monotherapy [48-51], in combination with other systemic therapies[52, 53] or following failure of other systemic agents[50, 54-58]. However, all studies mentioned above are case report, there are no randomized control trials about therapeutical approaches for the management of TEN, therefore the management of this disease continue being controversial [59]. In the present study, infliximab was administered to four patients, two of them with TEN, one with DRESS and final patient with AGEP and associated psoriasis. Patient 1° was a 17-year-old woman who received carbamazepine for epilepsy. Two weeks later, she presented multiple blisters, loss of epidermis in 70% of the patient’s body surface and mucous involvement. TEN was diagnosed (SCORTEN, 3). Culprit drug was withdrawal and support therapy started. She received 2g/kg of IVIG without improvement, so a single dose of 5mg/kg of infliximab was started. After two weeks all lesions disappeared but ocular sequelae (conjunctival synechiae) was reported. Patient 2° was a 5-year-old girl, who received allopurinol for chronic renal failure secondary to Henoch-Schölein purpura. After five weeks, she developed diffuse rash with epidermal sloughing involving 100% of her body surface. A diagnosis of TEN was made (SCORTEN, 2). Given the extent of lesions and no improvement after 1g/kg of IVIG, she received 5 mg/kg of infliximab with great clinical improvement. No sequelae was seen. Patient 3 was a 13-year-old girl who developed DRESS after six weeks of treatment with Carbamazepine for an occipital focal epilepsy. She received systemic corticoids, but multiorganic failure was developed, with cardiac, hepatic and renal involvement. 5mg/kg of infliximab was administered, and her skin lessons, laboratory findings and general condition gradually improved. However, she had renal failure as a sequelae. Chua y colaboradores[60] in 2018 describe a
paediatric case series of DRESS, and the first reported use of infliximab in a 14-year-old girl who developed DRESS due to co-trimoxazole, she was treated with systemic corticoids, azathioprine, cyclosporine A and mycophenolatemofetil without improvement. Monthly IVIG, infliximab, topical corticosteroids, acitretin and phototherapy but clinical efficacy was not observed for this patient. Further research is needed to evaluate the role of anti-TNF alpha in DRESS. Finally, patient 4° was a fifty-year-old woman with associated psoriasis who received terbinafine for an onicomychosis, a week later, she presented acute edematous erythema in folds and face, followed by multiple small non follicular sterile pustules arising. In this patient pustular psoriasis was discarded due to the absence of conventional histological features of psoriasis and the strong association with a culprit drug (terbinafine) with relapse after involuntary reintroduction. Systemic corticoid was administered without improvement, so a single dose of infliximab (5mg/kg) was given and skin lesions had completely disappeared on day 14°.

Regarding AGEP, there is no specific treatment, except to discontinue the treatment with the causative drug and provide clinical support based on the situation. AGEP is a self-limiting clinical entity, with a favorable prognosis, although it can cause a severe infection that may endanger patients with a poor general medical condition [19]. Of the six patients reported with AGEP in this study, four (66%) received systemic corticosteroid, one cyclosporine and the other infliximab as mentioned previously. The use of systemic treatment was higher than
reported by Davidovici, et al. [19] and Guevara, et al. [33], where only 25% of the patients required them.

In this study, complications were seen in 75.7%, of the cases which is above that of previously reported studies [22], possibly related to the higher number (16, 42%) of cases of DRESS-DiHS with liver disease as a complication. This has been reported as the main complication of patients suffering from this syndrome, some as high as 87.5% or even 94.2% [17]. As expected, sepsis was also frequently observed in patients with TEN (41.7%), due to the extended cutaneous involvement. McCullough and collaborators [20] reported 57.5% of their patients had complications with infections, mainly urinary tract infections (15%), pneumonia (25%), and bacteremia (17.5%).

In this study, there were three cases (4.3%) of mortality, all of them exhibiting SJS-TEN, therefore, within this group, the mortality rate was 16.7% which is similar to what has been previously reported [8] but is higher than predict mortality by SCORTEN: the median SCORTEN in our patients with TEN/SJS was 2 for a predict mortality of 12.1%. [61] The SCORTEN scores in these patients were of 3, 5, and 6, respectively.

Sequela occurred in 13 patients (18.6%), mainly cutaneous skin issues (12.8%), followed by eye problems (4.2%). This is similar to the rates reported in other studies [62, 63]. We found no psychiatric or autoimmune conditions, although a follow-up assessment of some patients may be needed in order to evaluate the long term effects and implications.
Limitations

The data reported here cannot be interpreted as a reliable sample of SCARs in Latin America because it does not included all the patients who suffered from SCARs in the five contributing countries. However, there are referral centers in the five countries, so many patients with SCARs are referred to one of the centers participating in this study. The patients were diagnosed based on the clinical picture and the majority of them did not receive a cutaneous biopsy nor subsequent in vivo (patch and intradermal test with late reading) or in vitro tests (lymphocyte transformation test, LTT) to assess the T-cell response to the suspected drug.[64] However, this study is very valuable, since it has been the first study concerning SCARs in Latin America, and it has provided the basis for further research, including identifying genetic markers from the Latin American population that can be related to these severe reactions and help to prevent them.

CONCLUSION

This is the first study carried out concerning SCARs in Latin America. DRESS-DIHS was the most frequent reaction and the anticonvulsant were the main triggers. The majority of the patients received systemic corticosteroids. Complications were frequent and three patients died.
Data have been presented in poster form at EAACI Congress 2019, Lisbon, Portugal.

Financial sources
This investigation did not receive financial sponsorship

Conflict of Interest
Each one of the researchers from the participating institutions declare that they have no conflict of interest.

REFERENCES

1. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med. 1994;331(19):1272-85.
2. Duong TA, Valeyrue-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. Lancet. 2017;390(10106):1996-2011.
3. Kardaun SH, Sekula P, Valeyrue-Allanore L, Liss Y, Chu CY, Creamer D, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol. 2013;169(5):1071-80.
4. Roujeau JC. Stevens-Johnson syndrome and toxic epidermal necrolysis are severity variants of the same disease which differs from erythema multiforme. J Dermatol. 1997;24(11):726-9.
5. Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesviruses and antiviral and antidrug immune responses. Allergol Int. 2006;55(1):1-8.
6. Alvarado SA, Munoz-Mendoza D, Bahna SL. High-risk drug rashes. Ann Allergy Asthma Immunol. 2018;121(5):552-60.
7. Pichler WJ, Naisbitt DJ, Park BK. Immune pathomechanism of drug hypersensitivity reactions. J Allergy Clin Immunol. 2011;127(3 Suppl):S74-81.
8. Schneck J, Fagot JP, Sekula P, Sassolas B, Roujeau JC, Mockenhaupt M. Effects of treatments on the mortality of Stevens-Johnson syndrome and toxic
epidermal necrolysis: A retrospective study on patients included in the prospective EuroSCAR Study. J Am Acad Dermatol. 2008;58(1):33-40.

9. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol. 1993;129(1):92-6.

10. Sidoroff A, Halevy S, Bavincik JN, Vaillant L, Roujeau JC. Acute generalized exanthematous pustulosis (AGEP)--a clinical reaction pattern. J Cutan Pathol. 2001;28(3):113-9.

11. Kardaun SH, Sidoroff A, Valeyrice-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? Br J Dermatol. 2007;156(3):609-11.

12. Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K, et al. ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clin Pharmacol Ther. 2010;88(1):60-8.

13. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239-45.

14. Demoly P, Kropf R, Bircher A, Pichler WJ. Drug hypersensitivity: questionnaire. EAACI interest group on drug hypersensitivity. Allergy. 1999;54(9):999-1003.

15. Mockenhaupt M, Viboud C, Dunant A, Naldi L, Halevy S, Bouwes Bavincck JN, et al. Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risks with emphasis on recently marketed drugs. The EuroSCAR-study. J Invest Dermatol. 2008;128(1):35-44.

16. Sultan SJ, Sameem F, Ashraf M. Drug reaction with eosinophilia and systemic symptoms: manifestations, treatment, and outcome in 17 patients. Int J Dermatol. 2015;54(5):537-42.

17. Hiransuthikul A, Rattananupong T, Klaewsongkram J, Rerknimitr P, Pongprutthipan M, Ruxungham K. Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS): 11 years retrospective study in Thailand. Allergic Int. 2016;65(4):432-8.

18. Sidoroff A, Dunant A, Viboud C, Halevy S, Bavincck JN, Naldi L, et al. Risk factors for acute generalized exanthematous pustulosis (AGEP)-results of a multinational case-control study (EuroSCAR). Br J Dermatol. 2007;157(5):989-96.

19. Davidovici B, Dodiuk-Gad R, Rozenman D, Halevy S, Israeli Regi SN. Profile of acute generalized exanthematous pustulosis in Israel during 2002-2005: results of the RegiSCAR Study. Isr Med Assoc J. 2008;10(6):410-2.

20. McCullough M, Burg M, Lin E, Peng D, Garner W. Steven Johnson Syndrome and Toxic Epidermal Necrolysis in a burn unit: A 15-year experience. Burns. 2017;43(1):200-5.

21. Li LF, Ma C. Epidemiological study of severe cutaneous adverse drug reactions in a city district of China. Clin Exp Dermatol. 2006;31(5):642-7.

22. Su P, Aw CW. Severe cutaneous adverse reactions in a local hospital setting: a 5-year retrospective study. Int J Dermatol. 2014;53(11):1339-45.

23. The RegiSCAR project [Internet]. [cited 2019 Feb 13].
24. Oh HL, Kang DY, Kang HR, Kim S, Koh YI, Kim SH, et al. Severe Cutaneous Adverse Reactions in Korean Pediatric Patients: A Study From the Korea SCAR Registry. Allergy Asthma Immunol Res. 2019;11(2):241-53.

25. Dibek Misirlioglu E, Guvenir H, Bahceci S, Haktanir Abul M, Can D, Usta Guc BE, et al. Severe Cutaneous Adverse Drug Reactions in Pediatric Patients: A Multicenter Study. J Allergy Clin Immunol Pract. 2017;5(3):757-63.

26. Botelho LF, Porro AM, Enokihara MM, Tomimori J. Adverse cutaneous drug reactions in a single quaternary referral hospital. Int J Dermatol. 2016;55(4):e198-203.

27. Yang CY, Dao RL, Lee TJ, Lu CW, Yang CH, Hung SI, et al. Severe cutaneous adverse reactions to antiepileptic drugs in Asians. Neurology. 2011;77(23):2025-33.

28. Blaszczzyk B, Lason W, Czuczwar SJ. Antiepileptic drugs and adverse skin reactions: An update. Pharmacol Rep. 2015;67(3):426-34.

29. Chung WH, Chang WC, Lee YS, Wu YY, Yang CH, Ho HC, et al. Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. JAMA. 2014;312(5):525-34.

30. Zeng T, Long YS, Min FL, Liao WP, Shi YW. Association of HLA-B*1502 allele with lamotrigine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese subjects: a meta-analysis. Int J Dermatol. 2015;54(4):488-93.

31. McCormack M, Alfirevic A, Bourgeois S, Farrell JJ, Kasperaviciute D, Carrington M, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med. 2011;364(12):1134-43.

32. Sahnoun R, El Aidli S, Zaiem A, Lakhoua G, Kastalli S, Daghfous R. [DRESS syndrome induced by ciprofloxacin]. Nephrol Ther. 2015;11(2):111-3.

33. Guevara-Gutierrez E, Uribe-Jimenez E, Diaz-Canchola M, Tlacuilo-Parra A. Acute generalized exanthematous pustulosis: report of 12 cases and literature review. Int J Dermatol. 2009;48(3):253-8.

34. Lee HY, Dunant A, Sekula P, Mockenhaupt M, Wolkenstein P, Valeyrive-Allanore L, et al. The role of prior corticosteroid use on the clinical course of Stevens-Johnson syndrome and toxic epidermal necrolysis: a case-control analysis of patients selected from the multinational EuroSCAR and RegiSCAR studies. Br J Dermatol. 2012;167(3):555-62.

35. Bachot N, Revuz J, Roujeau JC. Intravenous immunoglobulin treatment for Stevens-Johnson syndrome and toxic epidermal necrolysis: a prospective noncomparative study showing no benefit on mortality or progression. Arch Dermatol. 2003;139(1):33-6.

36. Gilbert M, Ann Scherrer L. Efficacy and safety of cyclosporine in Stevens-Johnson syndrome and toxic epidermal necrolysis. Dermatol Ther. 2018:e12758.

37. Paradisi A, Abeni D, Bergamo F, Ricci F, Didona D, Didona B. Etanercept therapy for toxic epidermal necrolysis. J Am Acad Dermatol. 2014;71(2):278-83.

38. Halebian PH, Corder VJ, Madden MR, Finklestein JL, Shires GT. Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. Ann Surg. 1986;204(5):503-12.
39. Carrillo D. ZL, Serrano C. Tratamiento antiinflamatorio en el síndrome de Stevens-Johnson y la necrólisis epidérmica tóxica: revisión sistemática de la literatura científica. Rev Asoc Colomb Dermatol. 2012;20(4):330-6.
40. Chiou CC, Yang LC, Hung SI, ChangYC, Kuo TT, Ho HC, et al. Clinicopathological features and prognosis of drug rash with eosinophilia and systemic symptoms: a study of 30 cases in Taiwan. J Eur Acad Dermatol Venereol. 2008;22(9):1044-9.
41. Chen YC, Chiu HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol. 2010;146(12):1373-9.
42. Natkunarajah J, Goolamali S, Craythorne E, Benton E, Smith C, Morris-Jones R, et al. Ten cases of drug reaction with eosinophilia and systemic symptoms (DRESS) treated with pulsed intravenous methylprednisolone. Eur J Dermatol. 2011;21(3):385-91.
43. Jevtovic DJ, Salemovic D, Ranin J, Pesic I, Zerjav S, Djurkovic-Djakovic O. The prevalence and risk of immune restoration disease in HIV-infected patients treated with highly active antiretroviral therapy. HIV Med. 2005;6(2):140-3.
44. Tristani-Firouzi P, Petersen MJ, Saffle JR, Morris SE, Zone JJ. Treatment of toxic epidermal necrolysis with intravenous immunoglobulin in children. J Am Acad Dermatol. 2002;47(4):548-52.
45. Aires DJ, Fraga G, Korentager R, Richie CP, Aggarwal S, Wick J, et al. Early treatment with nonsucrose intravenous immunoglobulin in a burn unit reduces toxic epidermal necrolysis mortality. J Drugs Dermatol. 2013;12(6):679-84.
46. Trent JT, Kirsner RS, Romanelli P, Kerdel FA. Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: The University of Miami Experience. Arch Dermatol. 2003;139(1):39-43.
47. Torres MJ, Mayorga C, Blanca M. Nonimmediate allergic reactions induced by drugs: pathogenesis and diagnostic tests. J Investig Allergol Clin Immunol. 2009;19(2):80-90.
48. Fischer M, Fiedler E, Marsch WC, Wohlrab J. Antitumour necrosis factor-alpha antibodies (infliximab) in the treatment of a patient with toxic epidermal necrolysis. Br J Dermatol. 2002;146(4):707-9.
49. Hunger RE, Hunziker T, Buettiker U, Braathen LR, Yawalkar N. Rapid resolution of toxic epidermal necrolysis with anti-TNF-alpha treatment. J Allergy Clin Immunol. 2005;116(4):923-4.
50. Zarate-Correa LC, Carrillo-Gomez DC, Ramirez-Escobar AF, Serrano-Reyes C. Toxic epidermal necrolysis successfully treated with infliximab. J Investig Allergol Clin Immunol. 2013;23(1):61-3.
51. Chafranska L, Saunte DM, Behrendt N, Nygaard U, Christensen RJ, Sand C, et al. Pediatric toxic epidermal necrolysis treated successfully with infliximab. Pediatr Dermatol. 2019;36(3):342-5.
52. Gaitanis G, Spyridonos P, Patmanidis K, Koulouras V, Nakos G, Tzaphlidou M, et al. Treatment of toxic epidermal necrolysis with the combination of infliximab and high-dose intravenous immunoglobulin. Dermatology. 2012;224(2):134-9.
53. Patmanidis K, Sidiras A, Dolianitis K, Simelidis D, Solomonidis C, Gaitanis G, et al. Combination of infliximab and high-dose intravenous immunoglobulin for
toxic epidermal necrolysis: successful treatment of an elderly patient. Case Rep Dermatol Med. 2012;2012:915314.
54. Al-Shouli S, Abouchala N, Bogusz MJ, Al Tufail M, Thstrup-Pedersen K. Toxic epidermal necrolysis associated with high intake of sildenafil and its response to infliximab. Acta Derm Venereol. 2005;85(6):534-5.
55. Wojtkiewicz A, Wysocki M, Fortuna J, Chrupek M, Matczuk M, Koltan A. Beneficial and rapid effect of infliximab on the course of toxic epidermal necrolysis. Acta Derm Venereol. 2008;88(4):420-1.
56. Kreft B, Wohlrab J, Bramsiepe I, Eismann R, Winkler M, Marsch WC. Etoricoxib-induced toxic epidermal necrolysis: successful treatment with infliximab. J Dermatol. 2010;37(10):904-6.
57. Worsnop F, Wee J, Natkunarajah J, Moosa Y, Marsden R. Reaction to biological drugs: infliximab for the treatment of toxic epidermal necrolysis subsequently triggering erosive lichen planus. Clin Exp Dermatol. 2012;37(8):879-81.
58. Scott-Lang V, Tidman M, McKay D. Toxic epidermal necrolysis in a child successfully treated with infliximab. Pediatr Dermatol. 2014;31(4):532-4.
59. Ganzetti G, Campanati A, Simonetti O, Giuliani K, Giangiacomi M, Lemme G, et al. Use of infliximab in toxic epidermal necrolysis: a still opened challenge. G Ital Dermatol Venereol. 2015;150(4):467-71.
60. Chua GT, Rosa Duque JS, Chong PCY, Lee PPW, Lau YL, Ho MHK. Paediatric case series of drug reaction with eosinophilia and systemic symptoms (DRESS): 12-year experience at a single referral centre in Hong Kong and the first reported use of infliximab. Eur Ann Allergy Clin Immunol. 2018;50(6):273-6.
61. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. J Invest Dermatol. 2000;115(2):149-53.
62. Olteanu C, Shear NH, Chew HF, Hashimoto R, Alhusayen R, Whyte-Croasdaile S, et al. Severe Physical Complications among Survivors of Stevens-Johnson Syndrome and Toxic Epidermal Necrosis. Drug Saf. 2018;41(3):277-84.
63. Saka B, Akakpo AS, Teclessou JN, Mahamadou G, Mouhari-Toure A, Dzidzinyo K, et al. Ocular and Mucocutaneous Sequelae among Survivors of Stevens-Johnson Syndrome and Toxic Epidermal Necrosis in Togo. Dermatol Res Pract. 2019;2019:4917024.
64. Monge-Ortega OP, Cabanas R, Fiandor A, Dominguez-Ortega J, Gonzalez-Munoz M, Quirce S, et al. Overlap Between DRESS Syndrome and Exanthema Induced by Sulfadiazine in a Patient Treated With Sulfamethoxazole: Utility of the Lymphocyte Transformation Test for Identification of the Culprit Drug. J Investig Allergol Clin Immunol. 2018;28(2):132-4.
## TABLES

### Table 1. Demographic and Clinical Characteristics of Patients with SCARs

|                      | SJS/TEN (n=18) | DRESS-DIHS (n=42) | AGEP (n=6) | Other (n=4) | Total (n=70) |
|----------------------|----------------|-------------------|------------|-------------|--------------|
| **Age**              | 34.3 (21.8)    | 4.2 (2.1)         | 36.3 (14.9)| 45.2 (2.1)  | 38.7 (2)     |
| **Gender**           |                |                   |            |             |              |
| Female               | 11 (61)        | 25 (59.5)         | 3 (50)     | 3 (75)      | 42 (60)      |
| Male                 | 7 (39)         | 17 (40.5)         | 3 (50)     | 1 (25)      | 28 (40)      |
| **Country**          |                |                   |            |             |              |
| Colombia             | 15             | 22                | 3          | 4           | 44 (62.8)    |
| Argentina            | 2              | 8                 | 1          |             | 11 (15.7)    |
| Brazil               | 7              | 2                 |            |             | 9 (12.8)     |
| Paraguay             | 3              |                   |            |             | 3 (4.3)      |
| Peru                 | 1              | 2                 |            |             | 3 (4.3)      |
| **Latency period**   |                |                   |            |             |              |
| <24 hours            | 1              |                   |            |             | 1 (1.4)      |
| 24 hours to 1 week   | 5              | 4                 | 5          | 2           | 16 (22.9)    |
| 1 to 4 weeks         | 10             | 24                | 1          | 2           | 37 (52.9)    |
| 4 to 8 weeks         | 1              | 7                 |            |             | 8 (11.4)     |
| >8 weeks             | 2              | 6                 |            |             | 8 (11.4)     |

The values are presented as average value (Standard Deviation, SD) and number (%). SJS: Stevens-Johnson Syndrome, TEN: Toxic Epidermal Necrolysis, TEN/SJS: the whole spectrum of entities including overlapping TEN and SJS, DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms, DIHS: Drug Induced Hypersensitivity Syndrome, AGEP: Acute generalized exanthematous pustulosis, SCARs: Severe Cutaneous Adverse Reactions induced by Drugs.
Table 2. Drugs involved

| Drug involved                        | Specific syndrome |
|--------------------------------------|-------------------|
|                                      | SJS/TE N (n=18)   | DRESS-DIHS (n=42) | AGEP (n=6) | Other (n=4) | Total (n=70) |
| **NSAIDS**                           |                  |                  |            |             |              |
| Acetylsalicylic acid                 | 1                | 2 (4.8)          | 4 (5.7)    |             |               |
| Diclofenac                           | 1                | 1                | 2          |             |               |
| Ibuprofen                            | 1                | 1                | 1          |             |               |
| Meloxicam                            | 1                | 1                | 1          |             |               |
| **Beta-lactam antibiotics**          |                  |                  |            |             |              |
| Amoxicillin                          | 1                | 1                | 1          | 4           |               |
| Cefazolin                            | 2                | 1                | 1          | 2           |               |
| Ceftriaxone                          | 1                | 1                | 1          | 1           |               |
| Meropenem                            | 1                | 1                | 1          | 1           |               |
| BenzathinePenicillinG               |                  | 1                | 1          | 2           |               |
| Piperacillin-Tazobactam              | 1                | 1                | 1          | 1           |               |
| **Non-beta-lactam antibiotics**      |                  |                  |            |             |              |
| Azithromycin                         | 1                | 1                | 1          |             |               |
| Ciprofloxacin                        | 1                | 1                | 2          |             |               |
| Clindamycin                          | 1                | 1                | 1          |             |               |
| Erythromycin                         | 1                | 1                | 1          |             |               |
| Vancomycin                           | 1                | 1                | 1          |             |               |
| **Anticonvulsants**                  |                  |                  |            |             |              |
| Carbamazepine                        | 3                | 12               | 15         |             |               |
| Phenytoin                            | 1                | 11               | 12         |             |               |
| Lamotrigine                          | 1                | 2                | 4          |             |               |
| **Sulfonamides**                     |                  |                  |            |             |              |
| Sulfamethoxazole-Trimethoprim        | 1                | 1                | 1          |             |               |
| **Antiretroviral therapy**           |                  |                  |            |             |              |
| Efavirenz                            | 1                | 1                | 1          |             |               |
| Nevirapine                           |                  | 1                | 1          |             |               |
| **Hyperuricemia Treatments**         |                  |                  |            |             |              |
| Allopurinol                          | 3                | 2                | 1          | 6           |               |
| **Antineoplastic drugs**             |                  |                  |            |             |              |
| **Other Drugs**                      |                  |                  |            |             |              |
| Acyclovir                            | 1                | 1                | 1          |             |               |
| Albendazole                          | 1                | 1                | 1          |             |               |
| Benzimidazole                        | 1                | 1                | 1          |             |               |
| Escitalopram                         | 1                | 1                | 1          |             |               |
| Glucantime                           | 1                | 1                | 1          |             |               |
| Metronidazole                        | 1                | 1                | 1          |             |               |
| Rosuvastatin                         | 1                | 1                | 1          |             |               |
| Terbinafine                          | 1                | 1                | 1          |             |               |
The values are presented as numbers (%). SJS: Stevens - Johnson syndrome, TEN: Toxic Epidermal Necrolysis, TEN/SJS: the whole spectrum of entities including overlapping TEN and SJS, DRESS: Drug reaction with Eosinophilia and Systemic Symptoms, DIHS: Drug Induced Hypersensitivity Syndrome, AGEP: Acute generalized exanthematouspustulosis, SCARS: Severe Cutaneous Reactions induced by drugs.

| Nº Drugs |   |   |
|----------|---|---|
| 1        |   | 53 (75.7) |
| ≥2       |   | 17 (24.3) |
**Table 3. Treatment**

|                          | SJS/TEN (n=18) | DRESS-DIHS (n=42) | AGEP (n=6) | Other (n=4) | Total (n=70) |
|--------------------------|----------------|-------------------|------------|-------------|--------------|
| Suspected drug withdrawn | 18             | 42                | 6          | 4           | 70           |
| Systemic Corticosteroid |                |                   |            |             |              |
| Corticosteroid + IVIG    | 7              |                   |            |             | 7 (10)       |
| IGIV                     | 9              |                   |            |             | 9 (12.8)     |
| Cyclosporine             | 2              | 4                 | 1          |             | 3 (4.3)      |
| Ciclosporine + corticosteroid | 2     | 1                 | 1          |             | 3 (4.3)      |
| Infliximab               | 2              | 1                 | 1          |             | 4 (5.7)      |
| Other treatment          |                |                   |            |             |              |
| Antihistamine            | 3              | 4                 | 3          |             | 10 (14.3)    |
| Colchicine               |                |                   | 4          | 1           | 5            |
| N-acetylcysteine         | 1              |                   | 1          |             | 1            |
| Without data             | 1              |                   | 2          | 1           | 3            |
| Treatment duration (days)| 7.5            | 21                | 10.5       | 14          | 14 (7-30)    |
|                          | (3.2-12.5)     | (14-30)           | (5-30.5)   | (7-30)      |              |
| Latency to treatment (days)| 3.5          | 7                 | 3          | 6           | 5            |
|                          | (2.2-6)        | (3-10)            | (1.7)      | (2.5-34)    | (2-10)       |

The values presented as number (%) and median (IQR). SJS: Stevens-Johnson Syndrome, TEN: Toxic Epidermal Necrolysis, TEN/SJS: the whole spectrum of entities including overlapping TEN and SJS, DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms, DIHS: Drug Induced Hypersensitivity Syndrome, AGEP: Acute generalized exanthematous pustulosis, SCARS: Severe Cutaneous Reactions Induced by Drugs.
Table 4. Hospitalization and Outcome

|                   | SJS (n=5) | TEN (n=12) | TEN/SJS (n=1) | DRESS-DIHS (n=42) | AGEP (n=6) | Other (n=4) | Total (n=70) |
|-------------------|-----------|------------|---------------|-------------------|------------|-------------|--------------|
| **Hospitalization** |           |            |               |                   |            |             |              |
| Length of hospitalization | 12.5 (7.5-58.5) | 21.5 (8-29) | 8 (6-16)       | 7 (4.5-13)       | 6 (4-8)    | 10 (7-23)   |              |
| ICU               | 3 (3-85)  | 10 (8-20)  | 1 (3)         | 8 (3-8)           | 1 (4-19)   | 23 (7-23)   |              |
| ICU duration      | 10 (3)    | 16.5 (8-20)| 44 (3)        | 7 (4-19)          | 9 (4-19)   | 9 (4-19)    |              |
| **Complications** |           |            |               |                   |            |             |              |
| Sepsis            | 1 (1)     | 5 (1)      | 3 (1)         | 3 (1)             | 9 (1)      | 9 (1)       |              |
| Hydroelectrolytic imbalance | 1 (1) | 8 (1) | 2 (1) | 3 (1) | 3 (1) | 3 (1) |              |
| Kidney Failure    | 1         | 2          | 8 (1)         | 2 (1)             | 3 (1)      | 3 (1)       |              |
| Hepatopathy       | 2 (1)     | 10 (1)     | 16 (1)        | 1 (1)             | 20 (1)     | 20 (1)      |              |
| Multi organ Failure | 1 (1) | 2 (1) | 1 (1) | 5 (1) | 5 (1) | 5 (1) |              |
| Other complications | 2 (1)   | 5 (1)      | 5 (1)         | 7 (1)             | 7 (1)      | 7 (1)       |              |
| **In-hospital death** | 2 (1) | 5 (1) | 4 (1) | 1 (1) | 1 (1) | 3 (1) |              |
| **Sequealae**     |           |            |               |                   |            |             |              |
| Cutaneous alterations | 1 (1) | 3 (1) | 3 (1) | 1 (1) | 1 (1) | 9 (1) |              |
| Mucousal alterations | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |              |
| Eye alterations   | 1 (1)     | 2 (1)      | 1 (1)         | 3 (1)             | 3 (1)      | 3 (1)       |              |
| Depression        | 0 (0)     | 0 (0)      | 0 (0)         | 0 (0)             | 0 (0)      | 0 (0)       |              |
| Other sequelae    | 1 (1)     | 1 (1)      | 1 (1)         | 1 (1)             | 1 (1)      | 1 (1)       |              |

The values are presented as number (%) and median (IQR). SJS: Stevens-Johnson Syndrome, TEN: Toxic Epidermal Necrolysis, TEN/SJS: overlapping TEN and SJS, DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms, DIHS: Drug Induced Hypersensitivity Syndrome, AGEP: Acute generalized exanthematouspustulosis, SCARS: Severe Cutaneous Reactions induced by Drugs, ICU: Intensive Care Unit. Other sequelae: autoimmune thyroiditis, diabetes mellitus, arthritis, renal disease.
FIGURES

Figure 1. Type of reaction

SJS: Stevens-Johnson Syndrome, TEN: Toxic Epidermal Necrolysis, TEN/SJS: the whole spectrum of entities including overlapping TEN and SJS, DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms, DIHS: Drug Induced Hypersensitivity Syndrome, AGEP: Acute generalized exanthematous pustulosis, SCARs: Severe Cutaneous Reactions Induced by Drugs.