

STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS: A SYSTEMATIC LITERATURE REVIEW

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Abstract: Introduction: Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are serious conditions, caused by late drug reactions in most cases. In general, the clinical picture includes fever, cough, eye irritation, erythematous or maculopurpuric skin reactions, which may progress to skin detachment, forming blisters. **Goal:** To address management and treatment possibilities for patients with SJS and TEN. **Methodology:** Systematic literature review performed by searching for eligible articles in the PubMed database and the following descriptors combined with Boolean operators: "Stevens-Johnson Syndrome AND toxic epidermal necrolysis AND treatment". **Results:** After reading the selected articles, it was seen that the treatment for TEN and SJS includes treatment of the affected areas, supportive care and pain management. The most important initial step in management is the identification and discontinuation of all possible offending drugs. **Discussion:** In addition to dermatological disorders, SJS and TEN can also cause complications in various organs. In the case of non-pharmacological treatment, supportive care is important, which is the mainstay of treatment for patients with SJS/TEN and includes discontinuation of the causative drug, fluid and electrolyte management, nutritional assessment, supplemental oxygen, and treatment of the wounds. Pharmacological therapy involves corticosteroids, immunoglobulins, cyclosporine, tumor necrosis factor inhibitors, among others. **Conclusion:** Finally, it became clear, in several studies, the importance of supportive care, both in the treatment of the disease and in the management of patients' pain, in addition to the best pharmacological choices. **Keywords:** Drug-Related Side Effects and Adverse Reactions; Stevens-Johnson Syndrome and Skin Diseases.

INTRODUCTION

Not infrequently, drug treatments can cause adverse reactions, which are classified into different types, one of which is hypersensitivity. Among the classification of hypersensitivity, in turn, there are type IV hypersensitivity reactions, also called delayed reactions, which are immune-mediated by T lymphocytes, defined as those that occur more than 6 hours after administration. (1) In addition, Delayed hypersensitivity reactions are divided into 4 subtypes (a, b, c, d), according to the cell type, the immune system mediators involved and the clinical picture, and may also be related to serious conditions of lower incidence and high mortality, such as Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). (two)

Both Stevens-Johnson Syndrome and toxic epidermal necrolysis are involved with reactions to type IVc drugs, which have a mechanism related to cytotoxic mediators that result in apoptosis of keratinocytes. Both are rare - they have an incidence of 1 to 6 cases/million people/year and 0.4 to 2 cases/million people/year, respectively. The use of medication is related to up to 50% of SJS cases and 80% of TEN cases, considering sulfonamide antibiotics, aromatic anticonvulsants, NSAIDs, allopurinol and nevirapine the most frequent. Citing etiology in children specifically, retrospective pediatric studies have identified drugs as the cause of SJS and TEN in 72% to 90% of cases. (3)

These late drug reactions are considered severe pharmacodermias, characterized by detachment of the epidermis, ranging from mild to severe, depending on the affected body surface. Classification into SJS, TEN or SJS-TEN overlap is made according to the extent of skin detachment, where the percentage of affected body surface is less than 10% in SJS, from 10% to 30% in overlap, and greater than 30% on NET. (two)

Still in relation to the clinical picture of these reactions, it can start with fever, eye irritation, cough and odynophagia, symptoms and signs that can be confused with an upper respiratory tract infection. However, after 1 to 3 days, skin reactions occur, including erosive mucositis on at least two surfaces. (4) First, skin lesions appear on the trunk, also progressing to the face, neck, and proximal portion of the upper limbs. Less commonly, these lesions affect the lower limbs, palmar and plantar regions. In addition, erythema and oral, ocular and genital mucosal erythema and erosions are quite common, occurring in more than 90% of cases of these severe pharmacodermias. Specifically in TEN, in about 25% of cases, the respiratory tract epithelium is involved, and gastrointestinal involvement may also occur. (two)

Initially, lesions that occur in SJS, TEN, or SJS-TEN overlap are erythematous or maculopurpuric, irregular in size and shape, and may coalesce. However, atypical lesions may look like targets. Necrosis of these lesions occurs according to the progress of epidermal involvement, and the epidermis begins to detach from the dermis, forming blisters. Generalized peeling results in exposed and inflamed dermis that is very painful for the patient. (5)

Still on the characteristics of TEN, relating them to mortality, the severity and prognosis of the disease can be further outlined using the SCORTEN criteria, which take into account the following risk factors: age over 40 years; presence of malignancy; heart rate above 120 beats per minute; body surface area involved greater than 10%; serum urea above 28 mg/dL; serum glucose above 252 mg/dL, serum bicarbonate below 20mEq/L. Each risk factor corresponds to one point, and the estimated mortality based on the total score varies: 3.2% (0 to 1 point), 12.1% (2 points), 35.3% (3

points), 58, 3% (4 points) or 90% (5 or more points). (6)(2) This classification proved to be as effective for the pediatric population as for the adult population. (5)

Regarding the diagnosis and complementary tests involving SJS and TEN, it is extremely important to carry out a good anamnesis and physical examination, and it is essential to ask the patient about medications in use. The final diagnosis is made by matching the aforementioned clinical features with histopathological findings, such as disseminated epidermal necrosis, subepidermal blisters, apoptotic keratinocytes, and a generally sparse dermal inflammatory infiltrate. (5)

Therefore, in view of all the characteristics presented by SJS, TEN and the overlap of both, the severity of the diseases and the urgent need for adequate management and treatment, taking into account the clinical condition, such as the signs and symptoms presented, and the severity of the frame.

GOAL

This study aims to address the possibilities of treatment and management of people with Stevens-Johnson Syndrome and/or toxic epidermal necrolysis, which are severe forms of late drug reactions.

METHODOLOGY

The article in question is a systematic review of the literature. The PubMed database was used to search for eligible articles, and the search descriptors used, retrieved from the medical subject headings (MeSH), were combined with Boolean operators as follows: "Stevens-Johnson Syndrome AND toxic epidermal necrolysis AND treatment".

The filters applied for the best selection of articles, available on the Pubmed platform, were: systematic reviews, analyzes and meta-analyses, published in the last 5 years, with

free and full availability in the aforementioned database, which were related to the human species and written in English, Portuguese or Spanish.

From this first selection, 63 articles were obtained and, after an exploratory and selective reading, articles that addressed both clinical aspects and possibilities of treatment and management of children and/or adults with Stevens-Johnson Syndrome or toxic epidermal necrolysis; articles that addressed Stevens-Johnson Syndrome or toxic epidermal necrolysis as reactions resulting from drug use. Studies that did not have the main focus on the aforementioned severe late reactions, resulting from drug causes, were excluded.

RESULTS

From the first selection of articles using the descriptors and filters mentioned above, 63 articles were obtained. After a selective reading of these articles, 17 articles were included in the work that addressed, in addition to clinical aspects of the diseases, possible management and treatments.

Among the non-pharmacological treatments, interruption of the causative drug, supportive care, wound treatment and pain management were the most evident.

Of the 17 articles included and analyzed, 10 highlighted the great importance of identifying and stopping the use of the offending drug. In addition, supportive care was advocated in 12 articles, including fluid and electrolyte management, intensive care care, supportive measures in burn units or

Author	Treatment/management for ssj/ net
1- HASEGAWA, Akito; ABE, Riichiro.	<p>Non-pharmacological treatment:</p> <ul style="list-style-type: none"> - Quick withdrawal of the culprit drug. - Support intensive care. - Multidisciplinary assessment and early management in a specialized hospital setting are key to improving mortality. <p>Pharmacological treatment:</p> <ul style="list-style-type: none"> - The use of systemic corticosteroids and intravenous immunoglobulin (IVIG) is controversial. - Recently, there have been an increasing number of studies suggesting the effectiveness of cyclosporine or TNF-α inhibitors. - Antibiotic treatment must be given when there is clinical suspicion of skin infection.
2- FRANTZ, Robert	<p>Non-pharmacological treatment:</p> <ul style="list-style-type: none"> - Fluid and electrolyte management. - Infection control and wound care. - Identification and cessation of the causative drug are the most important components. <p>Pharmacological treatment:</p> <ul style="list-style-type: none"> - Immunosuppressive therapies help in the treatment, involving different combinations of corticosteroids, IVIG, cyclosporine and TNF-alpha inhibitors. - Cyclosporine has shown positive results in several studies.
3- LUCIA, Liotti et al.	<p>Non-pharmacological treatment:</p> <ul style="list-style-type: none"> - Immediately discontinue the causative drug and initiate supportive care. - Wound treatment. - Admission to a specialized burn unit. <p>Pharmacological treatment:</p> <ul style="list-style-type: none"> - Pain management. - When clinical signs of infection occur, systemic antibiotics must be administered. - The therapeutic role of intravenous immunoglobulin (IVIG) is controversial. - The use of corticosteroids is beneficial in some situations, but it also has its risks. - Patients treated with steroids associated with IVIG appear to have a better outcome. - TNF-α inhibitors may be useful. - Cyclosporine reduces mortality.

4- SCHNEIDER, Jeremy A.; COHEN, Philip R.	<p>Non-pharmacological treatment:</p> <ul style="list-style-type: none"> - Supportive care is the most universally accepted intervention. <p>Pharmacological treatment:</p> <ul style="list-style-type: none"> - Adjuvant therapies are used in the most severe cases. - The use of systemic corticosteroids as a single therapy is not supported and is related to significantly higher rates of infection. - More recent studies on cyclosporine and tumor necrosis factor inhibitors are promising but not powered to provide definitive evidence of efficacy. - Thalidomide increases mortality.
5- ZIMMERMANN, Stefanie	<p>Non-pharmacological treatment:</p> <ul style="list-style-type: none"> - Treatment with supportive care. <p>Pharmacological treatment:</p> <ul style="list-style-type: none"> - Glucocorticosteroids and cyclosporine were associated with a promising survival benefit.
6- RAMIEN, Michele; GOLDMAN, Jennifer L.	<p>Non-pharmacological treatment:</p> <ul style="list-style-type: none"> - Quick identification and removal of the causative drug. <p>Pharmacological treatment:</p> <ul style="list-style-type: none"> - Adjuvant therapy: corticosteroids are the most used, followed by IVIG both as monotherapy and in combination with corticosteroids.
7- KLAMA-BARYŁA, Agnieszka et al.	<p>Non-pharmacological treatment:</p> <ul style="list-style-type: none"> - Amniotic membrane transplantation has been shown to be effective both in the treatment of skin lesions and in the therapy of ocular complications.
8- ZHANG, Jingzhan et al.	<p>Pharmacological treatment:</p> <ul style="list-style-type: none"> - No consensus has been established on the use of corticosteroids, but they may inhibit the inflammatory response. - Intravenous immunoglobulin and cyclosporine have shown to be promising treatments.
9- CONNER, Clayton D.; MCKENZIE, Emily; OWEN, Cindy E.	<p>Non-pharmacological treatment:</p> <ul style="list-style-type: none"> - Coverage with biosynthetic skin derivatives on the affected areas. - Burn treatment centers are the most suitable places to treat patients. <p>Pharmacological treatment:</p> <ul style="list-style-type: none"> - Cyclosporine has been proposed as a treatment. - Immunoglobulin G and cyclosporine A are currently used in most treatment centers. - Corticosteroid and cyclophosphamide treatments are currently in disuse.
10- ATO, Izumi et al.	It is not discussed about treatment
11- ABATE, Mallory S. et al.	<p>Non-pharmacological treatment:</p> <ul style="list-style-type: none"> - The most important initial step in management is the identification and discontinuation of all possible offending drugs. - Many patients require immediate transfer to the burn unit. <p>Pharmacological treatment:</p> <ul style="list-style-type: none"> - The most commonly used adjuvant therapies include systemic corticosteroids, intravenous immunoglobulin, cyclosporine, and tumor necrosis factor inhibitors.
12- XU, Lili et al.	It is not discussed about treatment
13- CATALDI, Mauro; MANCO, Federica; TARANTINO, Giovanni.	It is not discussed about treatment
14- SI, Xiaoyan et al.	<p>Non-pharmacological treatment:</p> <ul style="list-style-type: none"> - Drugs causing the reaction must be permanently discontinued. - Patients require hospitalization. - Fluid and electrolyte management as well as intensive care are required. <p>Pharmacological treatment:</p> <ul style="list-style-type: none"> - Intravenous prednisone/methylprednisolone and intravenous immunoglobulin are required. - In severe cases or cases that do not respond to steroids, the addition of other agents such as infliximab, mycophenolate mofetil or cyclosporine may be considered.
15- LEE, Q. U.	It is not discussed about treatment

16- GISONDI, Paolo et al.	It is not discussed about treatment
17- PATEL, Tejas K.; PATEL, Parvati B.; THAKKAR, Sejal.	Non-pharmacological + pharmacological treatment The hierarchy of efficacy in treatments was cyclosporine, steroid + intravenous immunoglobulin, etanercept, steroids, intravenous immunoglobulin, supportive care, and thalidomide.
18- WHITE, Katie D. et al.	It is not discussed about treatment
19- ROUJEAU, Jean-Claude et al.	Non-pharmacological treatment: - Supportive measures in burn units or other specialized departments were the best approach available. Pharmacological treatment: - No etiological treatment is considered effective.
20- COLEMAN, Emily L.; OLAMIJU, Brianna; LEVENTHAL, Jonathan S.	Non-pharmacological treatment: - Supportive care in an intensive care unit. - Suspicious drug discontinuation. Pharmacological treatment: - Oral corticosteroids or intravenous immunoglobulin.
21- KARNES, Jason H. et al.	It is not discussed about treatment
22- GONZALEZ-HERRADA, Carlos et al.	Non-pharmacological treatment: - Immediate withdrawal of the offending drug and the application of supportive measures are the main therapeutic pillars. Pharmacological treatment: - The use of cyclosporine is associated with a significant reduction in mortality during hospitalization compared to other treatments, in particular compared to intravenous immunoglobulin.
23- SCHUNKERT, Elisa Maria; SHAH, Pranali Nitin; DIVITO, Sherrie Jill.	It is not discussed about treatment
24- SUKASEM, Chonlaphat et al.	It is not discussed about treatment
25- NG, Chau Yee et al.	It is not discussed about treatment
26- KARNES, Jason H. et al.	Non-pharmacological treatment: - Interruption of the offending medication. - Aggressive supportive care in a tertiary intensive care center (usually a burn unit). - Early assessment by subspecialists of all organ systems involved in SJS/TE. Pharmacological treatment: - Systemic corticosteroids remain the mainstay of treatment. - This study suggests the promise of TNF-alpha antagonists in treatment. - Highlights the need for comparative data with other drugs such as cyclosporine, which has been shown to have an efficacy benefit in smaller observational studies.
27- ARNOLD, Kathryn A.; GAO, Jingyun; STEIN, Sarah L.	Non-pharmacological treatment: - The first step in management is to discontinue the offending drug and provide intensive multisystem supportive care, usually best performed in a burn or intensive care unit. Pharmacological treatment: - Several small retrospective studies have failed to show benefits of systemic corticosteroids or intravenous immunoglobulin in children with SJS/TEN. - Cyclosporine and tumor necrosis factor inhibitors have shown promise in case reports and preliminary studies in adults.

other specialized departments that perform wound management and infection prevention.

Regarding pharmacological treatment, studies were seen on the use of systemic corticosteroids, intravenous immunoglobulin, TNF- α inhibitors, cyclosporine and thalidomide.

The results regarding the use of systemic corticosteroids in the treatment of Stevens-Johnson Syndrome and toxic epidermal necrolysis were controversial, being beneficial in 8 articles, but ineffective or with inconclusive results in 5 articles.

Regarding intravenous immunoglobulin, 2 articles showed its therapeutic role as controversial, however, 7 articles were favorable to the use of immunoglobulin in therapy, when applicable. Only one article, comparing intravenous immunoglobulin and cyclosporine, highlighted the smaller reduction in mortality resulting from the use of IVIG. The association between steroids and intravenous immunoglobulin was shown to be beneficial by one of the studies.

Regarding cyclosporine, there are positive results in several studies. 13 articles showed favorable results in relation to the use of cyclosporine in the treatment, reducing the hospitalization and mortality rate, being associated with a promising survival benefit.

In addition, in relation to TNF- α inhibitors, 6 articles highlighted that studies related to this treatment are promising, relating it to good results.

Finally, the use of thalidomide in the treatment of SJS and TEN was addressed in 2 articles, which showed little efficacy and even as harmful, increasing patient mortality.

DISCUSSION

Type IV hypersensitivity is a delayed reaction involving multiple effector cells, resulting in maculopapular rash, fixed drug eruptions, drug reaction with eosinophilia

and systemic symptoms, Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), so that clinical manifestations involve the skin, mucosa, or multiple organs. In cases of drug reactions, the diagnosis of hypersensitivity requires a detailed history and knowledge of any underlying disorders, and it is also important to assess the time to onset of symptoms after the use of a particular medication. (7)

In relation to SJS and TEN, initial dermatological findings may include erythematous or dark macules that progress to fluid-filled blisters and/or denuded skin, with the involved skin without blisters usually scaling with direct lateral pressure (Nikolsky's sign). (8) In addition to dermatological involvement, SJS and TEN can also cause complications in various organs, such as the liver, kidneys, and respiratory tract. Thus, multidisciplinary assessment and early management in a specialized hospital setting are essential to improve mortality. (9)

Other complications of SJS/TEN are ocular, especially in pediatric patients, so aggressive initial management, including adjuvant amniotic membrane transplantation, can reduce damage. Even in the absence of severe ocular involvement in acute TEN/SJS, children may develop progressive ocular surface disease and conjunctival inflammation over time. And, late eyelid margin keratinization, vision deterioration, and corneal damage may occur after TEN/SJS, emphasizing the importance of ongoing ophthalmologic follow-up. (10)

SJS and TEN, triggered by the use of a particular drug, reach their peak between 24 to 72 hours after the administration of the drug or allergen and are mediated by the direct cytotoxicity of CD8+ T cells or by the release of cytokines from CD4+ cells, which act through of antigen presenting cells (APC) such as macrophages and dendritic cells (DCs) to stimulate chronic inflammatory

reactions. These conditions, with severe skin manifestations, are rare and can be highly fatal. (7,11)

Taking into account that the pathogenic mechanisms of SJS and TEN are the same, the differentiation between the two is clinical and based on the amount of skin affected. When the involvement is less than 10%, the diagnosis is SJS, and when the cutaneous involvement is greater than 30%, the diagnosis is TEN. In cases of skin involvement between 10% and 30%, there is an overlap between SJS and TEN. (11, 12)

Among the drugs at greatest risk for drug-induced SJS/TEN are nevirapine, lamotrigine, carbamazepine, phenytoin, phenobarbital, co-trimoxazole, other anti-infective sulfonamides, sulfasalazine, allopurinol, and NSAIDs oxycam. Mortality risk can be predicted using the SCORTEN scoring system, first described by Bastuji-Garin, consisting of seven binary parameters calculated on the days of admission. (13) The most important initial step in patient management is the identification and discontinuation of all possible offending drugs, so many patients require immediate transfer to the burn unit. (14)

In the case of non-pharmacological treatment, supportive care is important, which is the mainstay of treatment for patients with SJS/TEN and includes, in addition to stopping the causative drug, fluid and electrolyte management, nutritional assessment, supplemental oxygen and the treatment of wounds. Of these components, identification and cessation of the causative drug is the most important, but optimization of each measure is necessary to achieve the best results. (15, 9) As skin detachment infection is a common complication in patients and is associated with impaired reepithelialization, which can lead to sepsis, daily skin care must be performed. (9)

With regard to nutritional assessment, an

important aspect is the nutritional status of children with SJS/TEN, because the energy needs of pediatric patients with SJS/TEN are increased, and a factor of 30% for resting energy needs must be applied when calculating nutritional support. (15, 10)

Some studies have shown wound care includes debridement of ruptured blisters, removal of necrotic skin, topical antiseptics or antibiotics, dressings, and a warm environment (28°C). Thus, admission to a specialized burn unit when skin involvement is greater than approximately 25 to 30% has been shown to be correlated with decreased morbidity and mortality rates. When clinical signs of infection occur, systemic antibiotics must be administered, always guided by systematic cultures of skin, mucosa, catheters and urine. (16)

Another important point with regard to patients with SJS or TEN is pharmacological treatment. However, due to the rarity of these diseases, there are few prospective studies that have analyzed the effectiveness of specific adjuvant therapies, and therefore there is no established standard of care regarding the use of medications. Due to the immunological nature of the disease, immunosuppressive therapies are believed to help with treatment, including many case reports indicating positive results with treatment regimens involving, for example, different combinations of corticosteroids, intravenous immunoglobulin (IVIg), cyclosporine, and TNF inhibitors-Alpha. (14)

The role of corticosteroids as a monotherapy is still debated in studies, and recently researchers performed a meta-analysis of 11 studies to compare corticosteroid use versus supportive therapy and found a positive treatment effect with the use of this drug, albeit statistically insignificant. (OR, 0.54; 95% CI, 0.29-1.01). (15) In addition, a retrospective European

multicenter study and a recent meta-analysis of observational studies showed the beneficial effects of corticosteroids. Another observational study reported that short-term use of high doses of corticosteroids in the early stages of SJS/TEN reduced mortality without increasing the risk of infection. (9)

When the effectiveness of the use of immunoglobulin, the results of the studies prove to be controversial. The European Study of Severe Cutaneous Adverse Reactions (EuroSCAR) indicated that this drug did not improve mortality compared with supportive care alone. However, recent meta-analyses have shown that high-dose IVIg (<2 g/kg) has a beneficial effect in decreasing SJS/TEN mortality. (9) High-dose application proved to be effective, especially when applied within the first 4 days after the onset of skin lesions. (16)

The best evidence on treatment before the period 2017 to 2018 was from a large systematic review (n = 128 cases), which was published in 2011, and which suggested that patients receiving IVIg and prednisone had better outcomes than those receiving IVIg and prednisone. who received only supportive care. A recent Taiwanese randomized clinical trial of etanercept in TEN included children over 4 years of age and showed that etanercept (25 mg twice weekly < 65 kg and 50 mg if > 65 kg) decreased the predicted mortality rate and reduced the skin healing time compared to corticosteroids (1 to 1.5 mg/kg per day intravenously) in the group as a whole. (10)

Cyclosporine has been shown to be a very promising substance in studies and, after several studies on the treatment of TEN, better survival was shown with cyclosporine compared to supportive care [OR- 0.19 (95% CrI: 0.05, 0.59)] and intravenous immunoglobulin [OR-0.21 (95% CrI: 0.05, 0.76)]. (17)

Cyclosporine, a calcineurin inhibitor, affects T-lymphocyte-mediated cytotoxicity

and inhibits FasL, nuclear factor-kB, and TNF- α , so some case reports and meta-analyses have shown that cyclosporine treatment improved mortality in patients with SSJ/NET. Researchers performed a meta-analysis of 10 studies and reported the standardized mortality ratio (SMR) of cyclosporine compared to supportive care, with the SMR taking into account initial disease severity, allowing for a more accurate description of improvement in mortality compared to death rates (MR). In this study, the authors reported an SMR of 0.320 (95% CI, 0.119-0.522, p=0.002), indicating a survival benefit in patients treated with cyclosporine. (15, 9)

Another search, also a meta-analysis, of 7 studies reported equally positive results with an SMR of 0.42 (95% CI, 0.19–0.95) when cyclosporine was administered. (15, 9) In addition, another study collected data from four patients at the University of Louisville Hospital in Louisville, KY, all over 18 years of age and dermatologist-diagnosed with SJS and TEN, so that three out of four patients re-epithelialized within an average of 3.67 days after starting 3-4 mg/kg/day of cyclosporine for treatment. (13)

Still on cyclosporine, despite being considered one of the promising treatments for SJS/TEN, there are still uncertainties about the real effectiveness. In this regard, a 2017 analysis of a cohort of 44 patients (24 treated with cyclosporine) revealed a statistically insignificant survival benefit compared to supportive care. (6)

In the case of tumor necrosis factor inhibitors, due to skin lesions and vesicular fluid in SJS/TEN containing high levels of TNF- α , TNF- α inhibitors such as etanercept and infliximab have been shown to be effective in stopping the progression of the disease. . In patients with moderate to severe SJS/TEN, in a randomized trial, a TNF- α antagonist

showed some advantages over corticosteroids, including a significantly shorter time to skin healing and a lower incidence of gastrointestinal bleeding. (16) However, further studies are needed to confirm the efficacy of these drugs in treatment. (9)

Another treatment under discussion for SJS/TEN is plasmapheresis (PP), which aims to remove pathogenic factors such as a drug, drug metabolites, and disease-induced cytokines/chemokines from the patient's blood. Although an observational study concluded that the treatment of PP is ineffective, the overall survival in this study was 87.5%. Another study showed that PP was effective in patients with TEN refractory to supportive therapy or systemic corticosteroid therapy and revealed that serum cytokine levels decreased after treatment. (9)

In a study on the hierarchy of treatments based on the "surface under the cumulative classification curves" (SUCRA) value, cyclosporine (0.93), the steroid together with intravenous immunoglobulin (0.76), etanercept (0.59), steroids (0.46), intravenous immunoglobulin (0.40), supportive care (0.34) and thalidomide (0.02). (17) However, on thalidomide, in another study, a harmful effect of the therapy was found. (18)

Finally, with regard to the treatment of SJS/TEN, in addition to wound management and infection prevention, the use of cyclosporine, corticosteroids, intravenous immunoglobulin (IVIg), TNF-alpha inhibitors, plasmapheresis, and others are options. therapies, in which variable results have been described, and there is still no consensus on the drug of choice. (16)

Furthermore, it is important to consider cost-effectiveness when selecting therapies, so that of the drugs described in the treatment of SJS/TEN, the most expensive is infliximab and the least expensive options are cyclosporine and corticosteroids. Ultimately,

more prospective studies are needed to solidify treatment guidelines. (15)

CONCLUSION

In view of the above, it became evident that late drug reactions, which occur in patients all over the world, mainly due to the wide spectrum of drugs that are available for use today, can cause very serious reactions and greater complications to patients. Examples of severe late reactions are Stevens-Johnson Syndrome (SJS) and topical epidermal necrolysis (TEN).

In view of the understanding of the clinical picture and severity of SJS and TEN, there is a need for adequate management and effective treatments for patients with these conditions. Therefore, the articles analyzed, which addressed management and therapy, showed conclusions from studies involving pharmacological and non-pharmacological treatments, highlighting the most promising therapies for the context of SJS and TEN.

First, it is essential to identify and stop the drug causing the reaction. In addition, other non-pharmacological possibilities for disease management were addressed, including supportive care, which encompass fluid and electrolyte management, nutritional assessment, supplemental oxygen, and wound care to prevent sepsis and promote re-epithelization. use of antibiotics if necessary.

Regarding pharmacological treatment, further studies are needed to prove the effectiveness of adjuvant therapies for SJS and TEN, in order to establish a standard of care in relation to drug use. However, in view of the existing studies and addressed in the analyzed articles, it is believed that immunosuppressive therapies help in the treatment, involving corticosteroids, intravenous immunoglobulin, cyclosporine and TNF-alpha inhibitors.

Corticosteroids used as monotherapy, to date, have shown beneficial effects, but not very significant. These drugs are related to reduced mortality, even if less significantly.

Regarding the use of immunoglobulin, the conclusions are controversial, since, while one study indicates its ineffectiveness in the face of supportive treatments, other studies reveal a positive effect in reducing mortality when used in high doses. It was seen that this beneficial effect can be achieved even with the association of immunoglobulin with prednisone. Therefore, the use of immunoglobulin in SJS and TEN, alone or in association, shows promise, but requires further studies.

Regarding cyclosporin, many studies have led to results that include this substance as promising for the treatment of SJS and TEN. Compared with supportive care and immunoglobulins, it has a higher chance of survival. Therefore, it is currently one of the best treatment possibilities for patients who are in the conditions of the aforementioned severe drug reactions.

Regarding tumor necrosis factor inhibitors, they proved to be effective in containing the progression of the disease, helping to accelerate the healing process and collaborating with the treatment of gastrointestinal symptoms. However, this class also requires further studies to prove its effectiveness.

Finally, it is concluded that, to date, cyclosporine, intravenous immunoglobulin and tumor necrosis factor inhibitors are beneficial in the treatment of Stevens-Johnson Syndrome and toxic epidermal necrolysis, in addition to the possibility of individual use. or associated corticosteroid therapy. However, there is a clear need for further studies in relation to these pharmacological options that prove the individualized effectiveness of each one, the possibilities of associations, so that the combination of non-pharmacological and

pharmacological treatments are convenient and sufficient for the treatment of patients in question.

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