

Corticosteroid Therapy in an Additional 13 Cases of Stevens–Johnson Syndrome: A Total Series of 67 Cases

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ABSTRACT

Stevens-Johnson syndrome (SJS) is a severe cutaneous eruption that can be a life-threatening emergency. Previously, we have reported our favorable experience in treating 54 patients with SJS with systemic corticosteroids. We continued our prospective analysis of consecutive patients with SJS treated with corticosteroids. Possible etiologic factors and clinical outcomes of the patients are described. All 13 patients improved with initiation of systemic corticosteroid therapy. There was no mortality or permanent sequelae attributable to SJS. Drugs were the offending agents in all 13 cases. There was one death unrelated to SJS. In conclusion, prompt treatment with systemic corticosteroids reduces morbidity and improves outcome of SJS patients. This analysis extends our series to 67 consecutive patients with SJS who were treated with corticosteroids and had a favorable outcome. (Allergy and Asthma Proc 21:101–105, 2000)

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Stevens-Johnson syndrome (SJS) is a severe mucocutaneous eruption that can feature visceral involvement and cause significant morbidity and mortality. Both infectious agents and medications can cause SJS. The immunopathogenesis of SJS is believed to involve keratinocyte apoptosis, a scenario similar to graft versus host disease.^{1,2} Just as graft versus host disease (GVHD) is steroid responsive, so is SJS.

SJS must be distinguished from toxic epidermal necrolysis (TEN), which is a more severe reaction featuring epidermal necrosis covering greater than 30% of the total body surface area.³ TEN also features extensive CD8⁺ T cell mediated keratinocyte necrosis; however, unlike SJS and GVHD, it has not been observed to improve with systemic corticosteroids.⁴

Previously, we have reported our favorable experience in treating 54 patients with SJS with systemic corticosteroids.^{5–8} This report extends our prospective analysis of SJS cases treated with corticosteroids. In all 13 new cases in this report, systemic corticosteroids were efficacious when given in appropriate doses early in the course of the eruption. We do not believe that patients with widespread epidermal necrosis benefit from corticosteroids; therefore, patients with TEN are excluded from this prospective analysis.

MATERIALS AND METHODS

Thirteen consecutive patients with SJS were evaluated by the Allergy-Immunology (A/I) Division during a 3½ year period from December 1994 to June 1998. Patients were seen in consultation at Northwestern Memorial Hospital or the Veterans Affairs Chicago Health Care System, Lakeside Division, Chicago, Illinois. All patients were man-

TABLE I

Characteristics of Cases of Stevens-Johnson Syndrome Treated with Corticosteroids

Patient Sex/Age (yrs)	% Skin Involvement	Bullous Lesions	Mucosal* Lesions	Visceral Involvement	Suspected Drugs	Days Before Onset of Corticosteroids	Initial Corticosteroid Dose/Day†
1 F (51)	80	—	E, O	Liver	Clindamycin	1	M 0.24 g
2 M (70)	75	+	E, O	—	Piperacillin; Ciprofloxacin; Metronidazole; Vancomycin	2	M 0.12 g
3 M (45)	70		E, O	Liver	Trimethoprim sulfamethoxazole (TMP-SMX)	11‡ 14	P 0.03 g M 0.24 g
4 M (44)	50	—	E, O	Liver	Phenytoin; Phenobarbital	2	M 0.24 g
5 F (72)	50	—	O	Liver	Sertraline	7	M 0.24 g
6 M (69)	40	—	E	Liver	Amoxicillin- clavulanate	3	M 0.24 g
7 M (36)	40	—	O	Liver Kidney	Trimethoprim	1	M 0.24 g
8 M (76)	70	+	E, O	—	Amoxicillin- clavulanate; TMP-SMX; Phenobarbital	3	M 0.24 g
9 M (33)	50	—	E, O	Liver	TMP-SMX	3‡ 10	P 0.015 g M 0.24 g
10 F (44)	80	—	E, O	—	Phenytoin; Vancomycin; Cephalexin	7	M 0.24 g
11 F (59)	30	—	O, R	Colon	Vancomycin	7	M 0.24 g
12 M (35)	80	—	E, O, U, R	—	Zidovudine; Nevirapine;	4	M 0.24 g
13 F (32)	50	—	O	Liver	Vancomycin	1	P 0.06 g

*E, eye; O, oral; U, urethral; R, rectal.

†M, methylprednisolone; P, prednisone.

‡On oral prednisone prior to initiation of IV methylprednisolone.

aged by A/I Division physicians until full recovery. The criteria for diagnosis of SJS included an extensive maculopapular cutaneous eruption with involvement of at least two mucosal surfaces or one mucosal surface and visceral involvement.⁹ Visceral involvement implied hepatic, gastrointestinal, or renal impairment. The possible precipitating cause, extent of skin and mucosal involvement, and laboratory findings were evaluated in all patients. The minimum laboratory investigation included a complete blood count with differential, serum electrolytes, liver function tests (LFTs), and urinalysis (U/A). Abnormal values were monitored serially. Skin biopsies were obtained in three of the 13 cases. Ophthalmology consultation was sought in all patients with ocular involvement. Possible etiologic drugs were stopped at presentation. Intravenous methylprednisolone at doses of 160–240 mg per day was initiated at diagnosis. The corticosteroid dose was reduced when examination demonstrated a response to therapy. On discharge

from the hospital, patients were managed in the A/I outpatient clinic until full recovery.

A placebo-controlled study was considered unethical to perform because in our earlier series of SJS patients, premature tapering of systemic corticosteroids had resulted in recrudescence of cutaneous lesions.

RESULTS

Clinical Characteristics

Eight males and five females are reported in this series. Extent of skin involvement ranged from 30 to 80%. Bullous lesions were present in two patients. The oral cavity was affected in 12 of the 13 patients with ulcers and erosions. Nine of the 13 patients also had ocular involvement ranging from mild conjunctival hyperemia to marked injection. No corneal involvement was noted. Nine patients had temperature

TABLE II

Cutaneous Locations and Visceral Involvement of Patients in Previous Four Series⁵⁻⁸

	Number of Patients (n = 54)
Bullous Lesions	27
Mucosal Lesions	
Ocular	42
Oral	39
Nasal	7
Urethral	7
Vaginal	3
Rectal	3
Visceral Involvement	
Liver	25
Kidney	18
Lung	2
Full Recovery	54

elevations from 99° to 103°F. Clinical characteristics of the patients are presented in Table I.

Identification of a single precipitating factor was not possible in five patients because they were on multiple possible offending medications. Nine of the 13 patients were receiving antibiotics which most likely precipitated the cutaneous eruptions. One patient was being treated with both phenytoin and phenobarbital at the time of diagnosis of SJS. Two patients were receiving both antibiotics and an anticonvulsant at presentation, and it is unclear as to which agent was responsible for the SJS.

Table II summarizes the location of the cutaneous lesions and visceral involvement of the 54 patients with SJS previously reported by the A/I Division.⁵⁻⁸

Laboratory Results

Laboratory investigations revealed eight patients with abnormal LFTs and one patient with hematuria. Three patients were noted to have elevated leukocyte count during the initial evaluation ranging from 10 K/mm³ to 22 K/mm³. All findings normalized on recovery.

Patient Outcomes

All patients recovered from SJS with systemic corticosteroid therapy (Table III). None of the patients developed sepsis or any complications from the corticosteroids. There was no mortality or permanent sequelae related to SJS.

Patient 2 had undergone surgery for esophageal perforation. He developed SJS most likely from antibiotics given perioperatively. Treatment with steroids resulted in improvement of his skin lesions over 3 weeks. Forty-two days after surgery, he died from a recurrent hemothorax. The hemothorax was thought to be a complication of his surgical

procedure. His family elected to pursue palliative care instead of surgical options. The death was not attributable to SJS or corticosteroid administration, as the skin lesions had almost completely resolved at the time of his death.

Two patients (3 and 9) were treated initially with 15 and 30 mg prednisone, respectively, without improvement. However, there was dramatic improvement of their symptoms with initiation of higher doses of methylprednisolone at 0.24 g a day. In patient 9, the steroid dose was reduced by the primary care physician on Day 3 of methylprednisolone, which resulted in worsening of the skin eruption. The eruption improved rapidly with reinitiation of higher dose methylprednisolone. There was complete resolution without recurrence of symptoms when the corticosteroids were reduced slowly.

Patient 11 presented with a generalized erythematous eruption, watery diarrhea, and fever to 102°F. She had received vancomycin for the preceding 5 weeks for treatment of osteomyelitis. A flexible sigmoidoscopy revealed erythematous and friable mucosa with submucosal hemorrhages, which was considered consistent with drug related injury. Stool cultures and *Clostridium difficile* toxin were negative. Her diarrhea and skin eruption started improving within 3 days of discontinuing vancomycin and initiating methylprednisolone.

DISCUSSION

SJS can be a life-threatening condition with a mortality rate of about 5%.¹⁰ It features various extent of mucocutaneous involvement with dusky to violaceous maculopapular lesions. Lesions may feature subepidermal separation resulting in the evolution of bullous lesions as seen in two of our patients. Mucosal lesions range from hyperemia to frank erosions and may be very painful. Complications from SJS can include death, secondary bacterial infections, permanent ocular damage, dysphagia, and extensive skin disfigurement. Esophageal, renal, pulmonary, and liver involvement may occur.^{9,11} Although SJS has been associated with infections, drugs are implicated in the majority of cases.^{3,12} SJS typically occurs within the first 1 to 3 weeks of exposure to the offending drug. Onset may be especially precipitous when the patient is reexposed to a known offending agent.⁹ This was seen in Patient 1 of this series, in whom initial exposure to clindamycin had evolved into SJS. Inadvertent reexposure resulted in rapid onset of SJS after only two doses.

SJS is thought to be immunologically mediated through cell mediated responses. Evidence is accumulating that keratinocyte destruction is caused by CD8⁺ T cells, which are the predominant inflammatory cells in the epidermis in bullous drug exanthems, SJS, and TEN.¹³⁻¹⁶ One study has found up-regulation of adhesion molecule expression in the epidermis of erythema multiforme patients.¹⁷ These molecules, such as ICAM 1 on keratinocytes, facilitate recruitment of T cells to the epidermis. Perforin, a cytoplasmic peptide contained in cytotoxic T cells, also has been demonstrated in the dermis of SJS patients.¹ Perforin can damage target cell membranes and allow other granules such as granzymes access to the target

TABLE III

Outcome of Patients in Table I Treated with Corticosteroids

Patient	Outcome	Comment
1	Recovery	History of SJS from clindamycin 3 years previously. On repeat exposure to clindamycin developed fever to 103°F and an eruption within 24 hours.
2	Resolution of skin lesions	Death from surgical complication. Not attributable to SJS or corticosteroid administration.
3	Recovery	HIV+; Reversal of fever in 24 hours. Patient was placed on prednisone 30 mg daily for 3 days before A/I evaluation.
4	Recovery	
5	Recovery	
6	Recovery	Patient received methylprednisolone and amoxicillin-clavulanate for a chronic bronchitis exacerbation. On reduction of the corticosteroid dose, skin eruption started and progressed on discontinuation of corticosteroid. Eruption resolved with restarting methylprednisolone at a higher dose and reducing the dose slowly.
7	Recovery	HIV+; Presented with fever of 102°F and diarrhea. U/A revealed red blood cells. There was dramatic resolution of symptoms with methylprednisolone alone. History of sulfa allergy in childhood.
8	Recovery except for mild hyperpigmentation	Presented with fever and leukocytosis. All cultures were negative. Skin biopsy consistent with SJS. Fever and leukocytosis resolved in 1 day.
9	Recovery	Presented with abdominal pain, hemoptysis, pleuritic chest pain, fever, and malaise. All cultures were negative. Chest x-ray was normal. Gastric lavage revealed minimal blood. Skin biopsy consistent with SJS. He was being treated with prednisone 5 mg TID for 3 days by his internist. He improved with methylprednisolone.
10	Recovery	Fever and leukocytosis reversed within 1 day of corticosteroids.
11	Recovery	Presented with watery diarrhea and fever. Biopsy of rectal mucosa consistent with drug injury. Dramatic reversal of symptoms on discontinuing vancomycin and starting methylprednisolone.
12	Recovery	HIV+; Complained of dysuria and rectal pain without hematuria or diarrhea. All laboratory findings including an U/A were normal. Symptoms began to resolve within 2 days of initiation of corticosteroids and discontinuation of HIV medications.
13	Recovery	

cells. These granules are known to trigger a series of reactions leading to apoptosis.¹⁸ Histopathological specimens from patients with SJS and TEN have shown epidermal apoptosis.^{1,19} Another apoptotic mechanism of keratinocyte destruction may involve Fas-Fas ligand interactions. A recent study has found high concentrations of soluble Fas ligand in the sera of patients with TEN.²⁰ Others have reported that cells of the monocyte-macrophage lineage also have a role in SJS. They may act as antigen presenting cells and can also cause keratinocyte destruction by releasing cytokines such as TNF- α .²¹ Corticosteroids probably suppress the immunological response by inhibiting functions of the cytotoxic T lymphocytes and the macrophages.

SJS and GVHD share almost identical clinical and histological features.² They both appear to be mediated by cytotoxic T cells and mononuclear cells.²² As in SJS, apoptosis in GVHD most likely is mediated through cytotoxic peptides such as perforin as well as Fas-Fas ligand interactions.²² Cytokines released by mononuclear cells also appear to be important in the pathogenesis of GVHD.²³ GVHD is considered an aberrant immune response by engrafted lymphocytes against a foreign host and is clearly responsive to corticosteroid therapy. As both GVHD and SJS appear to share a similar immunologic pathogenesis, and, knowing that GVHD is corticosteroid responsive, we believe it is reasonable to justify the use of corticosteroids in

SJS. The improvement of the SJS patients in this series treated with corticosteroids supports this notion.

Therapy for SJS includes discontinuation of precipitating factors as well as local skin and ocular care with early ophthalmologic consultation when indicated. Hepatic and renal function, and fluid balance must be monitored. In addition, we believe the data from this series support early initiation of systemic corticosteroids. In all patients treated with systemic corticosteroids in this report, improvement was observed. No patients developed sepsis, bacteremia, skin infections, or other complications attributable to corticosteroids. The eruption worsened in two patients in whom the corticosteroids were reduced prematurely. There was dramatic reversal when the corticosteroids were reinitiated at a higher dose. Therefore, we believe that, for SJS, early initiation of systemic corticosteroids reduces morbidity and mortality. The only death occurred in a patient who developed recurrent hemothorax as a complication of esophageal surgery.

Overall, the use of corticosteroids for SJS remains controversial. Some reports in the literature suggest an increase risk of complications with corticosteroid therapy.²⁴⁻²⁸ In particular, they note pneumonia, sepsis, and gastrointestinal hemorrhages. In some of these reports, there was no differentiation made between patients with SJS versus those with TEN. In addition, the complications suggested in these reports may actually be complications of SJS itself. In some of these cases, the corticosteroids may not have been started in a timely manner or in adequate doses. Inadequate dosing may not have sufficient antiinflammatory action as seen in Patients 3 and 9 who were receiving low dose prednisone before evaluation by the A/I division. They had dramatic reversal of their manifestations when higher doses of methylprednisolone were used. The efficacy of corticosteroids was reported recently in a prospective pediatric trial of treatment of SJS with and without corticosteroids.²⁹

In summary, this prospective analysis of 13 patients extends our series to 67 patients with SJS who were treated with systemic corticosteroids. Our observation has been improved outcome with no increase in complications in these patients. We believe that SJS is a steroid responsive condition and systemic corticosteroids benefitted these patients and hastened their recovery.

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INDICATIONS AND USAGE

ALLEGRA is indicated for the relief of symptoms associated with seasonal allergic rhinitis in adults and children 12 years of age and older. Symptoms treated effectively include sneezing, rhinorrhea, itchy nose/palate/throat, itchy/watery/red eyes.

CONTRAINDICATIONS

ALLEGRA is contraindicated in patients with known hypersensitivity to any of its ingredients.

PRECAUTIONS

Drug Interactions

In two separate studies, fexofenadine hydrochloride 120 mg twice daily (twice the recommended dose) was co-administered with erythromycin 500 mg every 8 hours or ketoconazole 400 mg once daily under steady-state conditions to normal, healthy volunteers (n=24, each study). No differences in adverse events or QTc interval were observed when subjects were administered fexofenadine hydrochloride alone or in combination with erythromycin or ketoconazole. The findings of these studies are summarized in the following table:

Effects on Steady-State Fexofenadine Pharmacokinetics After 7 Days of Co-Administration with Fexofenadine Hydrochloride 120 mg Every 12 Hours (twice recommended dose) in Normal Volunteers (n=24)		
Concomitant Drug	C _{max,ss} (Peak plasma concentration)	AUC _{0-12h} (Extent of systemic exposure)
Erythromycin (500 mg every 8 hrs)	+82%	+109%
Ketoconazole (400 mg once daily)	+135%	+164%

The mechanisms of these interactions are unknown, and the potential for interaction with other azole antifungal or macrolide agents has not been studied. These changes in plasma levels were within the range of plasma levels achieved in adequate and well-controlled clinical trials. Fexofenadine had no effect on the pharmacokinetics of erythromycin or ketoconazole.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential and reproductive toxicity of fexofenadine hydrochloride were assessed using terfenadine studies with adequate fexofenadine exposure (based on plasma area-under-the-curve [AUC] values). No evidence of carcinogenicity was observed when mice and rats were given daily oral doses of 50 and 150 mg/kg of terfenadine for 18 and 24 months, respectively; these doses resulted in plasma AUC values of fexofenadine that were up to four times the human therapeutic value (based on a 60-mg twice-daily fexofenadine hydrochloride dose).

In in-vitro (Bacterial Reverse Mutation, CHO/HGPRT Forward Mutation, and Rat Lymphocyte Chromosomal Aberration assays) and in-vivo (Mouse Bone Marrow Micronucleus assay) tests, fexofenadine hydrochloride revealed no evidence of mutagenicity.

In rat fertility studies, dose-related reductions in implants and increases in postimplantation losses were observed at oral doses equal to or greater than 150 mg/kg of terfenadine; these doses produced plasma AUC values of fexofenadine that were equal to or greater than three times the human therapeutic value (based on a 60-mg twice-daily fexofenadine hydrochloride dose).

Pregnancy

Teratogenic Effects: Category C. There was no evidence of teratogenicity in rats or rabbits at oral terfenadine doses up to 300 mg/kg; these doses produced fexofenadine plasma AUC values that were up to 4 and 37 times the human therapeutic value (based on a 60-mg twice-daily fexofenadine hydrochloride dose), respectively.

There are no adequate and well-controlled studies in pregnant women. Fexofenadine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects. Dose-related decreases in pup weight gain and survival were observed in rats exposed to oral doses equal to and greater than 150 mg/kg of terfenadine; at these doses the plasma AUC values of fexofenadine were equal to or greater than 3 times the human therapeutic values (based on a 60-mg twice-daily fexofenadine hydrochloride dose).

Nursing Mothers

There are no adequate and well-controlled studies in women during lactation. Because many drugs are excreted in human milk, caution should be exercised when fexofenadine hydrochloride is administered to a nursing woman.

Pediatric Use

Safety and effectiveness of ALLEGRA in pediatric patients under the age of 12 years have not been established. Across well-controlled clinical trials in patients with seasonal allergic rhinitis, a total of 205 patients between the ages of 12 to 16 years received doses ranging from 20 mg to 240 mg twice daily for up to two weeks. Adverse events were similar in this group compared to patients above the age of 16 years.

Geriatric Use

In placebo-controlled trials, 42 patients, age 60 to 68 years, received doses of 20 mg to 240 mg of fexofenadine twice daily for up to two weeks. Adverse events were similar in this group to patients under age 60 years.

ADVERSE REACTIONS

In placebo-controlled clinical trials, which included 2461 patients receiving fexofenadine hydrochloride at doses of 20 mg to 240 mg twice daily, adverse events were similar in fexofenadine hydrochloride and placebo-treated patients. The incidence of adverse events, including drowsiness, was not dose related and was similar across subgroups defined by age, gender, and race. The percent of patients who withdrew prematurely because of adverse events was 2.2% with fexofenadine hydrochloride vs 3.3% with placebo. All adverse events that were reported by greater than 1% of patients who received the recommended daily dose of fexofenadine hydrochloride (60 mg twice-daily), and that were more common with fexofenadine than placebo, are listed in the following table.

Adverse Experiences Reported in Placebo-Controlled Seasonal Allergic Rhinitis Clinical Trials at Rates of Greater Than 1%

Adverse Experience	Fexofenadine 60 mg Twice Daily (n=679)	Placebo Twice Daily (n=671)
Viral Infection (cold, flu)	2.5%	1.5%
Nausea	1.6%	1.5%
Dysmenorrhea	1.5%	0.3%
Drowsiness	1.3%	0.9%
Dyspepsia	1.3%	0.6%
Fatigue	1.3%	0.9%

Adverse events occurring in greater than 1% of fexofenadine hydrochloride-treated patients (60 mg twice daily), but that were more common in the placebo-treated group, include headache and throat irritation.

The frequency and magnitude of laboratory abnormalities were similar in fexofenadine hydrochloride and placebo-treated patients.

Prescribing Information as of April 1998

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