The Role of Systemic Corticosteroid Therapy in Erythema Multiforme Major and Stevens-Johnson Syndrome

A Review of Past and Current Opinions

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Introduction

Systemic corticosteroid use in the treatment of erythema multiforme major (EMM) and Stevens-Johnson syndrome (SJS) has been debated in the medical literature for many decades. Prior to the 1970s, systemic corticosteroids were used as standard therapy for patients with EMM and SJS. In 1976, Rasmussen et al presented data challenging the role of systemic corticosteroids in treating EMM and SJS, pointing to longer hospital stays and higher complication rates in pediatric patients treated with systemic corticosteroids.[1] Since the time of this article, arguments both for and against systemic corticosteroid use have been widely published—leaving the practicing clinician with little hope of a definitive answer to this question. The problem lies within the type of study that can be reasonably accomplished. The current studies are mostly retrospective and based on anecdotal evidence. Additionally, each seems to have a debatable variable in the study. There is no literature to date based on a large, prospective, randomized, or double-blind study evaluating use of systemic corticosteroids in EMM/SJS. Given the necessity for a large amount of patients and control of several variables to evaluate the benefit of any given treatment, and ethical considerations which would obviate the use of a placebo study arm, such a trial is not likely to ever occur. The scope of this article will therefore present the currently available opinions on this issue.

What are erythema multiforme major and minor?

Erythema multiforme (EM) was once thought to be the early presentation of a continuum of diseases related to SJS, with toxic epidermal necrolysis (TEN) believed to be a distinct entity.[2] It is now generally accepted that a separation exists between EM and SJS. Currently, two different classifications exist: first, an erythema multiforme spectrum (minor and major) and second, an SJS and TEN spectrum (now considered variants of a single disease spectrum).[2–5]

Although EM was first clinically recognized in the early 19th century and referred to by a variety of names, it was not until 1860 that Ferdinand von Hebra termed the disease "erythema multiforme."[3] He described EM as an "acute, mild, self-limited skin disease characterized by evolving skin lesions located primarily on the extremities with a tendency for recurrent episodes to occur."[3] Later, the term EM minor was proposed to differentiate the more mild cutaneous disease (as described by von Hebra) from a more severe form that may involve mucous membranes and systemic symptoms, which at that time was referred to as EM major.[2]

The most common etiologic association with erythema multiforme is herpes simplex virus (HSV) infection, which is frequently concomitant with the EM flare.[5] Other causes include *Mycoplasma* infections, vaccines, and some medications.[5] Overall, infections represent more than 90 percent of the precipitating factors in EM.[5] Both EM minor and major are considered to be delayed-type hypersensitivity reactions that result from a T-cell mediated immune reaction to the causative agent. This reaction leads to a

cytotoxic immunological attack on keratinocytes.[5] For example, in herpes-associated EM, HSV-DNA fragments in the skin or mucosa precipitate the disease and T cells accumulate in response to HSV antigens.[5] In drug-induced EM, it is believed to be reactive drug metabolites that induces the disease.[5] Keratinocyte apoptosis is then induced by tumor necrosis factor (TNF-α) released from keratinocytes, macrophages, and monocytes.[5]

What are important characteristics of Stevens-Johnson syndrome and toxic epidermal necrolysis?

SJS and its more severe progression, TEN, are both rare mucocutaneous diseases that can be life-threatening and almost always caused by drugs.[5] SJS was first described in 1922 by two physicians, Stevens and Johnson, who described a skin eruption similar to EM that also included purulent conjunctivitis, stomatitis, and fever.[3] To date, more than 100 medications have been associated with SJS/TEN. The most common groups of offending drugs include sulfonamides, anticonvulsants, and nonsteroidal anti-inflammatory drugs (NSAIDS).[5] SJS is clinically defined as having skin detachment of less than 10 percent of the total body surface area (BSA); whereas, TEN affects a much greater surface area while also having a much higher tendency to be life threatening.[4] In both conditions, mucosal erosions are present in more than 90 percent of patients, and systemic involvement invariably coexists.[5]

The pathogenesis of SJS/TEN is not entirely understood. Tissue damage in SJS/TEN is thought to be caused by keratinocyte cell death from massive, accelerated apoptosis.[5] Several pathways can induce apoptosis. Cytotoxic T cells that express the skin-homing receptor, cutaneous lymphocyte-associated antigen (CLA), are seen early in the development of cutaneous lesions.[5] Cytotoxic T cells and macrophages seem to play an important role in the extensive epithelial necrosis and subepithelial detachment.[7] Various cytokines (TNF-α, interferon-γ, IL-6 and 18 and the Fas ligand) may also contribute to epidermal cell death as well as to some of the constitutional symptoms.[7] Some believe that apoptosis is principally mediated by the Fas/FasL apoptotic pathway, while others suggest the role of other cytokines as primary mediators (TNF-α, perforin, granzyme B, and interferon gamma).[5–7]

SJS differs from EM major through the absence of the typical "target" lesions, flatter lesions, and more severe mucosal involvement.[4,5] In addition, medications are usually the implicating factor in SJS, whereas in EM, HSV is the common predisposing factor. In distinguishing EM and SJS histologically, EM has a high density of T lymphocyte infiltrates, and SJS/TEN are characterized by a cell-poor infiltrate.[2]

What is the mechanism of action of systemic corticosteroids in EMM and SJS?

Mechanistically, the anti-inflammatory effects of glucocorticosteroids are a result of their profound effect on peripheral leukocytes and their suppressive effects on multiple inflammatory cytokines and chemokines.[8] Glucocorticoids inhibit the function of antigen-presenting cells and macrophages while also influencing the inflammatory response by reducing synthesis of prostaglandins, leukotrienes, and platelet-activating factor, which result from activation of phospholipase A_2.[8] Corticosteroids help to maintain vascular integrity, promote synthesis of lipocortins, and decrease the expression of leukocyte adhesion molecules, resulting in a beneficial, but depressed, inflammatory reaction when treating EM.[9] In SJS, corticosteroids suppress the immunological functions of the damaging effects of cytotoxic T lymphocytes and the macrophages.[10]

What are the arguments against the use of systemic corticosteroid therapy for EMM and SJS?

The role of systemic corticosteroids in EMM and SJS is controversial. It was not until 1976 that Rasmussen published a retrospective study suggesting that the "treatment of SJS with corticosteroids may be associated with significant side effects and prolonged recovery."[1] Specifically, the study indicated that patients receiving systemic corticosteroids (compared to supportive care) had a longer hospital stay and more complications than those who were not treated with corticosteroids.[1]

Subsequent articles supported the concerns reported by Rasmussen et al. Ginsburg published a retrospective study that found that both rates of infection and complications were greater in patients with SJS when treated with corticosteroids.[11] Nethercott and Choi found that the length of a patient's hospital stay was longer with the EM patients receiving

systemic corticosteroids, while a retrospective study by Prendville et al reported a zero mortality rate in their patient cohort when not using systemic corticosteroid therapy.[12,13] Ting and Adams found no better response in EM patients treated supportively than with systemic corticosteroids, except for a shorter duration of fever.[14]

Arguments against systemic corticosteroid use in EM suggest caution particularly when an infectious etiology is suspected. In fact, it has been suggested that the use of systemic corticosteroids in patients "with herpes-associated erythema multiforme may lower the patient's resistance to HSV and promote recurrent HSV infection, and therefore, recurrent erythema multiforme."[4]

In summary, proponents against systemic corticosteroids suggest that their use for the treatment of EM/SJS does not equate to a faster recovery, a shorter hospital stay, or fewer complications. In fact, they argue that the opposite is more likely to occur.[11–14]

What are the arguments for the use of systemic corticosteroid therapy for EMM and SJS?

Advocates for systemic corticosteroid use for EMM and SJS suggest that early administration in the course of the disease is essential. Yeung notes that if systemic corticosteroids are given later in the course of the disease, they "might not be found helpful and could contribute to an increased risk of infection, which could account for the complications reported in the Rasmussen study."[9] A review by Kakuorou et al also agreed that the "higher rate of these effects may be related to delayed initiation of and prolonged administration of corticosteroids."[15] Kardaun and Jonkman concur that the "general negative opinion of corticosteroids is probably because they are often given too late, in too low a dose, and for too long a period" and admit that during "the healing phase corticosteroids may indeed impair wound healing and promote sepsis."[7]

Patterson et al prospectively evaluated 67 patients, finding that systemic corticosteroid use in SJS demonstrated an improved outcome with no increase in complications and found SJS to be a corticosteroid-responsive condition with a hastened recovery through its use.[16] The article concludes "that managing physicians believed corticosteroids were not only essential for management, but possibly essential for survival in many cases."

Kardaun and Jonkman also challenged the general opinion that systemic corticosteroids are detrimental in SJS and TEN and felt that "short courses of high-dose corticosteroids in early SJS/TEN have a good rationale, as immune mechanisms are directly responsible for the cascade of events leading to apoptosis."[7] Kakourou et al concluded that an early and short course of systemic corticosteroid therapy provides a favorable influence on the outcome of erythema multiforme.[15] Schneck et al note that systemic corticosteroids deserve more attention and that only for "corticosteroids is there a trend for a possible benefit, which is of further clinical interest."[17]

The dosing and route of administration that provides the most benefit for EMM and SJS patients is in question. Early therapy with systemic prednisone (0.5 to 1.0mg/kg/day) or pulse methylprednisolone (1mg/kg/day for 3 days) has been shown to be effective.[6] One author suggests tapering the oral prednisolone over 7 to 10 days, while Patterson et al suggests a high dose of corticosteroids for EMM patients followed by a four-week tapering course.[8,18] Still another suggests a bolus infusion for 3 to 7 days of coricosteroids, which showed no relapses after treatment was discontinued.[15] Intravenous (IV) pulsed dose methylprednisolone (3 consecutive daily infusions of 20–30mg/kg to a maximum of 500mg given over 2 to 3 hours) has also been reported, with the suggestion that this approach is superior to oral prednisone because the greatest benefit is seen when treatment is administered as early as possible in the progression of the cutaneous insult.[19]

Kardaun and Jonkman recently proposed dexamethasone pulse therapy (1.5mg/kg IV over 30 to 60 minutes on 3 consecutive days) to avoid long-term use of systemic corticosteroids.[7] The authors described the pleomorphic effects of dexamethasone on the immune system, including inhibition of epidermal apoptosis by several mechanisms. These mechanisms include suppression of various cytokines, such as TNF-alpha; inhibition of interferon-gamma-induced apoptosis; and inhibition of Fas-mediated keratinocyte apoptosis."[9]

Regardless of the dosage or route of administration, it is clear that advocates of systemic corticosteroid use argue for early administration in the course of the disease. They promote use of high doses given over a short period of time (number of days) and with proper tapering of the medication.[6,8,15,18,19]

Can a consensus be reached on the use of systemic corticosteroids for EMM and SJS?

Despite the above "pro and con" arguments related primarily to SJS, there seems to be some published consistencies of opinion when treating the extreme ends of both disease spectrums, EM minor and TEN. In EM minor, symptomatic treatment usually suffices.[6] For severe recurrent oral EM minor, the condition responds promptly to prednisone in doses up to 1mg/kg daily tapered over 2 to 3 weeks.[20] When treating TEN, it is generally agreed that after widespread sloughing occurs, any risk of infection outweighs the potential benefits of systemic corticosteroid therapy.[20]

Schneck et al suggest that a prospective randomized trial is needed before any absolute guidelines can be issued regarding the various measures to treat SJS, but if such a trial should be arranged, the potential benefit of systemic corticosteroids should be tested first.[17] This statement appears to implicitly speak to the future possibility of the important role systemic corticosteroids may play in the standard of care for early EMM and SJS. The potential for systemic corticosteroid use in EMM and SJS can only be verified by future trials that would "require many patients to evaluate a benefit of any treatment, and that leads to the question of feasibility."[17] Patterson et al state it "is apparent that the specific guidance on the use of systemic corticosteroids is variable and will remain variable in the absence of a controlled trial," which he fears cannot be accomplished ethically.[16] Until the day comes when a proper prospective, randomized, blinded, controlled trial is performed, the role of systemic corticosteroids in EMM and SJS will remain controversial. This leaves the practicing clinician without decisive guidance in their treatment measures for EMM and SJS. On the other hand, the practicing clinician should be eased in knowing that overall, whether they choose to use systemic corticosteroid therapy or not, literature support can be found for either decision.

References

1. Rasmussen JE. Erythema multiforme in children. Response to treatment with systemic steroids. *Br J Dermatol*. 1976;95:181–186.
2. Ogundele O. Erythema multiforme. eMedicine (June 2006).
3. Forman R, Koren G, Shear NH. Erythema mutliforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a review of 10 years' experience. *Drug Saf.* 2002;25(13):965–972.
4. Lamoreux MR, Sternbach MR, Hsu WT. Erythema multiforme. *Am Fam Physician*. 2006;74:1883–1888.
5. French L, Prins C. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis. In: Bolognia JL, Jorizzo JL, Rapini RP, eds. *Dermatology.* 2nd ed. Philadelphia PA: Elsevier; 2008:287–300.
6. Scully C, Bagan J. Oral mucosal diseases: erythema multiforme. *Br J Oral Maxillofac Surg*. 2008;46:90–95.
7. Kardaun S, Jonkman M. Dexamethasone Pulse Therapy for Stevens-Johnson syndrome/toxic epidermal necrolysis. *Acta Derm Venereol*. 2007;87:144–148.
8. Chrousos GP. Adrenocorticosteroids and adrenocortical antagonists. In: Katzung BG, ed. *Basic & Clinical Pharmacology*. 9th ed. New York, NY: Lange Medical Books/McGraw-Hill; 2004:641–660.
9. Yeung AK, Goldman RD. Use of steroids for erythema multiforme in children. *Can Fam Physician*. 2005;51(11):1481–1483.
10. Tripathi A, Ditto AM, Grammer LC, et al. Corticosteroid therapy in an aadditional 13 cases of Stevens-Johnson syndrome: a total series of 67 cases. *Allergy and Asthma Proc*. 2000;21:101–105.
11. Ginsburg CM. Stevens-Johnson syndrome in children. *Pediatr Infect Dis J*. 1982;1(3):155–158.
12. Nethercott JR, Choi BC. Erythema multiforme (Stevens-Johnson syndrome)—chart review of 123 hospitalized patients. *Dermatologica*. 1985;171(6):383–396.
13. Prendiville JS, Hebert AA, Greenwald MJ, Esterly NB. Management of Stevens-Johnson syndrome and toxic epidermal necrolysis in children. *J Pediatr*. 1989;115(6):881–887.
14. Ting HC, Adam BA. Erythema multiforme: response to corticosteroid. *Dermatologica*. 1984;169 (4):175–184.
15. Kakourou T, Klontza D, Soteropoulou F, Kattamis C. Corticosteroid treatment of erythema multiforme major (Stevens-Johnson syndrome) in children. *Eur J Pediatr*. 1997;156:90–93.
16. Patterson R, Dykewicz MS, Gonzalzles A, et al. Erythema multiforme and Stevens-Johnson syndrome. Descriptive and therapeutic controversy. *Chest*. 1990;98:331–336.
17. Schneck J, Stat D, Fagot JP, et al.

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;58:33–40.
18. Patterson R, Miller M, Kaplan M, et al. Effectiveness of early therapy with corticosteroids in Stevens-Johnson syndrome: experience with 41 cases and a hypothesis regarding pathogenesis. *Ann Allergy*. 1994;73:27–34.
19. Martinez AE, Atherton DJ. High-dose systemic corticosteroids can arrest recurrences of severe mucocutaneous erythema multiforme. *Pediatr Dermatol*. 2000;17(2):87–90.
20. Wolverton SE. Systemic corticosteroids. In: Wolverton SE, ed. *Comprehensive Dermatologic Drug Therapy*. 2nd ed. Philadelphia, PA: Saunders Elsevier;2007:127–161.

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