Treatment of Toxic Epidermal Necrolysis with Etanercept in a Pediatric Patient

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Toxic epidermal necrolysis is a rare, life-threatening skin disease with no consensus on adjunctive treatment, particularly in pediatric patients. We present the case of a 13-year-old previously healthy patient with drug-associated toxic epidermal necrolysis who experienced significantly shortened length of hospital stay and duration of symptoms compared with published literature when treated with 2 doses of etanercept 50 mg during 5 days.

ABBREVIATIONS IV, intravenous; SJS, Stevens-Johnson syndrome; SMX/TMP, sulfamethoxazole-trimethoprim; TEN, toxic epidermal necrolysis; TNF- α , tumor necrosis factor- α

KEYWORDS adverse drug effect; case report; etanercept; pediatrics; Stevens-Johnson syndrome; toxic epidermal necrolysis

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Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, life-threatening dermatologic conditions for which there is no consensus on adjunctive treatment, particularly in pediatric patients. The diseases are characterized by desquamation of the epidermis involving less than 10% of body surface area for SJS and more than 30% of body surface area for TEN, typically occurring within days or weeks of an offending medication or illness.^{1,2} Antibiotics like sulfamethoxazole-trimethoprim (SMX/TMP) are often associated with the disease.¹ The pathophysiology behind SJS/TEN is thought to be due to apoptosis of keratinocytes, eventually resulting in full-thickness necrosis of the epidermis. Tumor necrosis factor- α (TNF- α) is believed to be involved in the pathology cascade.^{3,4} Etanercept, a TNF- α antagonist, is theorized to be effective in the treatment of SJS/TEN because of its mediating effects on this pathology cascade. On average patients with SJS/TEN spend 20 days in the hospital. Current, and generally accepted, management of SJS/TEN is discontinuation of the offending medication, followed by supportive care at a specialized burn unit.¹ We present the case of a 13-year-old previously healthy patient with TEN who showed significantly shortened length of hospital stay and duration of symptoms when treated with etanercept.

Case Report

A previously healthy, 51.6-kg, 13-year-old male presented to the emergency department with a 2-day history of fever and a painful rash that started on his neck and spread quickly to the rest of his body, involving his palms but sparing his lower legs and soles. Fifteen days

prior to onset of symptoms, the patient received his first lifetime exposure to sulfamethoxazole-trimethoprim (SMX/TMP) for epididymitis. He completed the original 10-day course but had lingering pain for 2 days after finishing the course. The patient was restarted on a second course of SMX/TMP 3 days prior to presentation of the rash. Physical examination revealed a generalized warm, painful, poorly demarcated, erythematous to dusky macular eruption, and fluid vesicles on the patient's left forehead and left neck. He also had fissured lips, a rough white plaque on his dorsal tongue, and painless injection of the conjunctiva and sclera bilaterally. Initial vital signs were remarkable for a fever up to 39.4°C and tachycardia, both of which improved with 500 mg of acetaminophen. Laboratory studies were within normal limits, with the exception of an elevated C-reactive protein concentration of 29.2 mg/L, neutropenia with a white blood cell count of 4.19 K/mm³, and elevated aspartate aminotransferase and alanine aminotransferase values of 130 U/L and 99 U/L, respectively. No viral pathogens were detected in the respiratory virus polymerase chain reaction panel. In addition, no bacterial growth was noted in the blood culture, and the antistreptolysin titer test was negative. Other complaints were significant for a sore throat and a 3-day history of dry cough, but these symptoms resolved quickly, with no concern for respiratory involvement throughout the course of the illness.

The patient's lesions progressed rapidly in the first 24 hours to Nikolsky positive, flaccid bullae of his neck, chest, shoulders, and arms. He also had a mucosal erosion of the hard palate (Image 1). A full-thickness punch biopsy of the affected skin was performed on admission

Image 1. Desquamation of mucosal upper and lower lip with erosion of hard palate; large fluid-filled bulla of right neck and fluid-filled bulla of left neck.

Image 2. Subepidermal vesiculation and split with confluent necrosis of epidermis with necrotic keratinocytes in all levels of epidermis, minimal inflammatory infiltrate, and sparse perivascular infiltrate.

by the dermatology consult team and was noted to be consistent with SJS/TEN the following day (Image 2).

Because of the patient's swift progression overnight, the dermatology consult team recommended initiation of a 5 mg/kg IV loading dose of methylprednisolone on

hospital day 2 and continued maintenance therapy of 2.5 mg/kg IV every 8 hours thereafter until the morning of hospital day 5. They also recommended covering the lesions with triamcinolone 0.1% cream 3 times daily throughout the duration of his hospital stay and suggested the patient receive 2 doses of etanercept 50 mg subcutaneously, the first on hospital day 2 and the second on hospital day 5.

On hospital day 5, the patient was transferred to a burn unit at an outside facility because of his extensive desquamation, which peaked at nearly 90% of body surface area (Image 3). Once he was transferred, he was started on a methylprednisolone 15-day taper, and IV immunoglobulin 1 g/kg every 24 hours for 4 days. He required continued supportive care, including peripherally inserted central catheter placement, nasogastric tube feeds, and enoxaparin for deep vein thrombosis prophylaxis. His wounds began improving, and by hospital day 9 he was transferred from the burn care unit to the general floor. The Patient's Naranjo Adverse Reaction Probability Score of 8 suggests that the adverse reaction is probably due to etanercept (Supplemental Table). The patient was discharged home on hospital day 13. He continues to be followed as an outpatient by dermatology. The patient did not endorse any side effects from the medications and has had no major complications since discharge.

Discussion

To the authors' knowledge this is only the second published case on the use of etanercept for the treatment of SJS/TEN in a pediatric patient. Most of the literature on the treatment of SJS/TEN, in both pediatrics and adults, is focused on supportive care measures.² Recommendations from guidelines and review articles advocate for high-quality supportive care in these patients, but little evidence exists to suggest any adjunctive medication.⁵⁻⁷ There is some emerging evidence for the use of TNF- α inhibitors, like etanercept; however, the evidence is limited to the adult population.⁸⁻¹¹ The patient in our case received high-quality supportive care, and early initiation of adjunctive therapy was initiated because of the severity of symptoms. The decision to initiate etanercept by the dermatology consult team was guided by a recent randomized trial in adult patients and the one other published pediatric case report.

Wang et al⁸ recently conducted a randomized controlled trial comparing etanercept and corticosteroids for the treatment of SJS/TEN in adult patients with a mean age of 56 years. The inclusion criteria for the trial included patients ages 4 years and older; however, the authors did not report how many children were included in the study population of 93 patients. Based on the mean $\pm$ SD of 56.1 $\pm$ 20.8 years, most, if not all, of the study population were adults. Although the authors of the study did not find a mortality benefit, etanercept did demonstrate a shorter time to re-epithelialization com-

Image 3. Fluid-filled Nikolsky-positive bulla of arms and trunk. Full-thickness necrotic desquamation of upper and lower back.

pared with corticosteroids alone. Dosing of etanercept for the intervention group was 25 mg subcutaneously twice weekly for patients weighing ≤ 65 kg, or 50 mg twice weekly for patients weighing >65 kg. This is similar to the typical adult dose of etanercept of 25 to 50 mg subcutaneously once or twice weekly for the indications of ankylosing spondylitis, psoriatic and rheumatoid arthritis, and chronic graft-versus-host disease. Patients in both groups received therapy until their skin lesions healed. Given the rapid advancement of SJS/TEN and severity in our patient, the larger 50-mg dose was chosen, despite his weight being less than 65 kg. Median time to re-epithelialization for the etanercept group in the trial was 14 days, but the authors did not comment on the length of hospital stay. These findings would be consistent with our patient being discharged home on hospital day 13. The overall incidence of adverse events reported in the trial was low, with about 18% of patients reporting an event, the most common being hypertension, hyperglycemia, and grade 2 gastrointestinal hemorrhage. However, the rate of gastrointestinal bleeding in the corticosteroid group was much higher than that in the etanercept group, 18.2% versus 2.6% respectively. Like most of the patients in the trial, our patient did not report any adverse drug events.

The previously published case report by Gavigan and colleagues¹² details an 11-year-old female with a past medical history significant for Prader-Willi syndrome. This patient received IV methylprednisolone 30 mg/kg every 24 hours on hospital days 1 to 5 and received cyclosporine 5 mg/kg IV every 24 hours on hospital days 2 to 4; etanercept 25 mg subcutaneously was initiated on hospital day 4 because of an inadequate response

to therapy and was administered for 2 consecutive days. The patient developed seizures following cyclosporine treatment and it was consequently discontinued after 3 doses. This patient received the 2 doses of etanercept on consecutive days and disease progression was halted on hospital day 5. The total length of stay in the hospital and time to re-epithelialization were not reported.

Our case is limited to the disease course and treatment of a single patient; however, given the paucity of primary literature on the subject, the experiences of individual patients need to be taken into account. Additionally, the patient was transferred after 5 days to another facility to receive specialized wound care in a burn center. This transition of care to providers at another institution with different practices and use of alternative adjunctive therapies, like IV immunoglobulin or additional corticosteroids, could have impacted the disease course of our patient; however, with his disease course peaking at day 5, on the day of the transfer of care, the authors feel the rapid improvement can be attributed to the use of etanercept. The patient in this case report received 2 doses of etanercept and experienced a length of stay in the hospital of 13 days; this is 7 days shorter than the average length of time for patients that present with a similar disease course. The ideal adjunctive medication therapy of SJS/TEN is unknown. Although we present the successful treatment of a patient with etanercept, additional clinical and mechanistic studies in this area are needed to inform decisions on the care of these patients.

Article Information

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Ethical Approval and Informed Consent. Given the nature of this study, the institution review board/ethics committee review was not required and the project was exempt from informed consent.

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References

1. Cartotto R. Burn center care of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. *Clin Plast Surg.* 2017;44(3):583–595.
2. Schneider J, Cohen P. Stevens-Johnson syndrome and toxic epidermal necrolysis: a concise review with a comprehensive summary of therapeutic interventions emphasizing supportive measures. *Adv Ther.* 2017;34(6):1235–1244.
3. Woolridge K, Boler P, Lee B. Tumor necrosis factor alpha inhibitors in the treatment of toxic epidermal necrolysis. *Cutis.* 2018;101(1):15–21.
4. Bellodi-Schmidt F, Shah K. Beyond psoriasis: novel uses for biologic response modifiers in pediatric dermatology. *Pediatr Dermatol.* 2015;33(1):18–27.
5. Fromowitz J, Ramos-Caro F, Flowers F. Practical guidelines for the management of toxic epidermal necrolysis and Stevens-Johnson syndrome. *Int J Dermatol.* 2007;46(10):1092–1094.
6. Creamer D, Walsh SA, Dziejwski P, et al. UK guidelines for the management of Stevens–Johnson syndrome/ toxic epidermal necrolysis in adults 2016. *J Plast Reconstr Aesthet Surg.* 2016;69(6):e119–e153.
7. Lucia L, Silvia C, Paolo B, et al. Clinical features, outcomes and treatment in children with drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis. *Acta Biomed.* 2019;90(3):52–60.
8. Wang CW, Yang LY, Chen CB, et al. Randomized, controlled trial of TNF- α antagonist in CTL-mediated severe cutaneous adverse reactions. *J Clin Invest.* 2018;128(3):985–996.
9. Gubinelli E, Canzona F, Tonanzi T, et al. Toxic epidermal necrolysis successfully treated with etanercept. *J Dermatol.* 2009;36(3):150–153.
10. Paradisi A, Abeni D, Bergamo F, et al. Etanercept therapy for toxic epidermal necrolysis. *J Am Acad Dermatol.* 2014;71(2):278–283.
11. Famularo G, Di Dona B, Canzona F, et al. Etanercept for toxic epidermal necrolysis. *Ann Pharmacother.* 2007;41(6):1083–1084.
12. Gavigan G, Kanigsberg N, Ramien M. Pediatric Stevens-Johnson syndrome/toxic epidermal necrolysis halted by etanercept. *J Cutan Med Surg.* 2018;22(5):514–515.