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Experience using etanercept off-label in toxic epidermal necrolysis in a tertiary care hospital

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Abstract

Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and SJS/TEN overlap syndrome are rare, severe cutaneous adverse reactions usually triggered by medications. In addition to supportive care, various systemic therapies have been used including glucocorticoids, Intravenous Immunoglobulins (IVIGs), cyclosporin, N-acetylcysteine, thalidomide, infliximab, etanercept, and plasmapheresis. Based on three clinical cases, we wanted to find out the efficacy of etanercept in the treatment of severe skin reactions.

Keywords: Etanercept; TEN; Adverse effect; Nikolsky.

Introduction

Toxic Epidermal Necrolysis (TEN) is a very severe and proco frequent mucocutaneous reaction that can be triggered as an Adverse Effect (AE) to different drugs. It is considered the most severe secondary drug reaction within the spectrum of mucocutaneous reactions [1]. It is a rare disease, with an incidence of 2 to 13 cases per million population. The main drugs associated with NET are aromatic antiepileptics (carbamazepine, phenytoin, phenobarbital), some antibiotics (sulfamethoxazole, -lactams, quinolones), allopurinol and antiretrovirals (abacavir, nevirapine) [2]. It is characterized by separation of the dermal-epidermal junctions, necrosis and detachment of the epidermis in more than 30% of the body surface and mucosal involvement. It has a high mortality (around 25-30%), with sepsis being the main cause of death in these patients [2]. The parameters to assess the severity of NET are the Toxic Epidermal Toxic Necrolysis Mortality Scale (SCORTEN) and the percentage of body surface area affected. The SCORTEN scale consists of a scoring system developed to calculate the probability of death in patients affected by NET by analyzing 7 independent risk factors: age >40 years, heart rate greater than 120/min, presence of solid or hematologic neoplasm, body surface area desquamated >10%, plasma urea >60mg/dL, plasma bicarbonate <20 mEq/L and glycemia >255 mg/dL [3]. The management of the disease is mainly based on the suspension of the suspected drug, as well as a multidisciplinary approach both on the hospital ward and in the ICU (Intensive Care Unit). As for pharmacological treatment, the systemic treatments used base their mechanism of action on suppressing and limiting the inflammatory response and include: glucocorticoids, cyclosporine, Intravenous Human Immunoglobulin (IVIG) and monoclonal antibodies against Tumor Necrosis Factor (TNF) alpha (etanercept) [4,5]. In the following, we describe 3 cases (Table 1) of patients with NET admitted to a tertiary hospital treated with etanercept.

Material and methods

All requests for drugs as off-label use from January 2017 and May 2022 assessed in the Pharmacy Service of a tertiary hospital were collected. All of them were requested on an urgent basis. Data were collected from the electronic medical record: demographic variables (age, sex), medical history, usual medication, drug causing the reaction, affected body surface area (%), SCORTEN, Nikolsky index, days of evolution after etanercept administration, affected body area (face, extremities, trunk and/or back), affected mucosa (buccopharyngeal, anal, ocular and/or genital), ICU stay (number of days) and previous treatment with corticosteroids and/or IVIG.

Results

Case 1: 82-year-old male with a history of Arterial Hypertension (AHT), benign prostatic hyperplasia, bronchial hyperresponsiveness syndrome, baseline pneumonia in 2008, polyarthritis, metabolic syndrome, atrial fibrillation and sensory-motor polyneuropathy with axonal and sensory predominance. As usual medication at home she takes tramadol/paracetamol. She came to the emergency department for 2 days of liquid stools without pathological products (>10 times a day) accompanied by nausea and vomiting (>5 times a day). He was admitted to the ward and started on metronidazole and ceftriaxone. A colonoscopy was performed showing edema, erythema, with continuously eroded mucosa, friability and bleeding on instrumental rubbing along the entire length of the explored colon, including the rectum. No areas of necrosis were observed. Infectious pancolitis was established as the main diagnosis. After 5 days with antibiotic treatment, erythematous macules of truncal predominance with some sparse eroded areas, oral and labial mucosa involvement and painful palmo-plantar skin detachment in block without erythema or underlying lesions appeared on the skin. No apparent ocular involvement. Likewise, in the last 48 hours he presented frank worsening of renal function and marked worsening of hepatic function.

In this context, the patient was admitted to the ICU with suspected NET, presenting mucosal, cutaneous and oral lesions compatible with Stevens-Johnson type toxicoderma. Dermatology was consulted and suspended all medication that was not strictly necessary and started a regimen of methylprednisolone 80 mg/24 h. Prednisone equivalents of 0.75-1 mg/kg. In view of the progression of the lesions and the progressive increase in skin peeling, treatment with intravenous immunoglobulins (Ig IV) at a dose of 3 g/kg in a single dose was requested to the Pharmacy Service as an off-label use. Twenty-four hours after administration, due to the persistence of the lesions and rapid progression, etanercept 50 mg as a single dose was also requested for off-label use, which was administered 7 days after the onset of symptoms. The patient evolved favorably with complete re-epithelialization of the skin lesions and good tolerance to etanercept, and was discharged from the ICU after 5 days. He is currently still admitted to the ward with a diagnosis of pancolitis after 6 months since NET.

Case 2: A 64-year-old man with a medical history of hypertension, dyslipidemia, COVID pneumonia in 2020 with post-COVID Pulmonary Thromboemolism (PTE), coxarthrosis, osteonecrosis of the right femoral head and surgery for upper lip mucocele in 2021. As usual medication at home she takes rosuvastatin, omeprazole, amlodipine, calcium/cholecalcifediol, alendronic acid and tramadol/paracetamol. She came to the emergency department for 5 days of edema and genital erosion, skin and lingual erythematous lesions. As the only associated factor, 9 days ago she had started treatment with trimeptoprim/sulfamethoxazole for MRSA (Methicillin-Resistant Staphylococcus Aureus). On examination she presented with numerous erythematous macular lesions on the anterior trunk, back, face and proximal extremities and mouth with extensive erosions of the tongue and a sensation of dysphagia, affecting 20% of the body surface. They had denudation on scraping (positive Nikolsky) and a SCORTEN index of 2%.

The patient was diagnosed with NET and treatment was started with methylprednisolone 100 mg/24 h. Six days after the onset of symptoms, a single dose of etanercept 50 mg was requested to the Pharmacy Service for off-label use. After administration, a favorable evolution was observed after administration, with a reepithelialization of the lesions. The patient presented good tolerance to the treatment and was finally discharged 14 days after etanercept administration.

Case 3: A 60-year-old male with a medical history of hypertension and bronchial asthma. Beclomethasone dipropionate + inhaled formoterol fumarate is administered as usual medication at home. She came to the emergency department with a painful pruritic skin rash of two days' evolution. She reported taking paracetamol and tetracyclines 3 days before the appearance of the lesions. The physical examination revealed mucosal, genital and cutaneous involvement, with erythematous, edematous, eroded and painful lesions on the back, trunk, abdominal flanks, inner thighs, extremities, hands and feet, as well as ocular involvement and detachment of the glans penis. The patient had an affected area of 4%, SCORTEN index of 1% and positive Nikolsky. With the diagnostic suspicion of NET due to paracetamol or tetracyclines, both drugs were suspended and treatment was requested as off-label with etanercept 50 mg in single dose in combination with corticosteroids and topical antibiotics. After treatment, a favorable evolution with good tolerance was observed, and the patient was discharged after 11 days. All cases were reported as suspected adverse reactions to the Spanish Pharmacovigilance System.

Discussion and conclusion

NET usually presents as a symmetrical, confluent, erythematous exanthem, beginning on the face and trunk, with rapid extension to the rest of the trunk and proximal parts of the extremities. There is also lamellar epidermal detachment and/or blistering, with a significant area of de-epithelialized skin. Typical blistering lesions are flaccid and spread with superficial pressure (positive Nikolsky's sign) [1].

The diagnosis of NET is primarily clinical. Skin biopsies are performed, although they are not specific. For treatment, the main thing is the suspension of suspected causative drugs. As for systemic pharmacological treatment, there is no well-established algorithm since the scientific evidence for curative treatment of NET is scarce [6,7].

In the three patients described, etanercept 50 mg in single dose was requested as an off-label use, approved in all of them by the Pharmacy Committee. The other alternatives considered were: IVIG (administered in case 1), corticosteroids (which were administered in all three patients as first line) and cyclosporine (which finally is not selected due to its potential adverse effects, such as AHT and/or renal failure in predisposed patients [8]. Cures with corticosteroid creams and antibiotics were performed simultaneously in all patients. Only one patient developed NET during hospital admission, being the only one who required ICU stay.

Although treatment with etanercept lacks the support of a randomized controlled trial, like the other treatments currently used for NET, the cases reported highlight a benefit in disease progression and improvement in reepithelialization time [5]. In

Table 1: Summary of NET cases on etanercept treatment.

	Case 1	Case 2	Case 3
Age (years old)	82	64	60
Drug	Metronidazol/ ceftriaxona	Sulfametoxazol/ trimetoprim	Paracetamol/ tetraciclinas
Affected body surface (%)	No data	20%	4%
SCORTEN index	No data	2%	1%
Nikolsky	Negative	Positive	Positive
Evolution after etanercept (days)	Hospitalized for pancolitis	14	11
Face	Yes	Yes	No
Extremities	Yes	Yes	Yes
Body trunk	No	Yes	Yes
Back of the body	No	Yes	Yes
Oropharyngeal mucosa	Yes	Yes	Yes
Anal mucosa	No	No	No
Ocular mucosa	No	No	Yes
Genital Mucosa	No	Yes	Yes
ICU stay (days)	5	No	No
Previous corticotherapy	Yes	Yes	Yes (combined)
Previous IgIV	Yes	No	No

our experience, treatment of NET with etanercept was safe and effective. In the three cases presented, reepithelialization of the lesions and healing of the lesions was observed.

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