

Erythrodermic psoriasis: pathophysiology and current treatment perspectives

Rasnik K Singh,¹ Kristina M Lee,²
Derya Ucmak,² Merrick Brodsky,³
Zaza Atanelov,⁴ Benjamin Farahnik,⁵
Michael Abrouk,³ Mio Nakamura,²
Tian Hao Zhu,⁶ Wilson Liao²

¹Department of Medicine, University of California – Los Angeles, David Geffen School of Medicine, Los Angeles, ²Department of Dermatology, University of California – San Francisco, San Francisco, ³Department of Medicine, University of California – Irvine, School of Medicine, Irvine, CA, ⁴Department of Medicine, New York Medical College, Valhalla, NY, ⁵Department of Medicine, University of Vermont College of Medicine, Burlington, VT, ⁶Department of Medicine, University of Southern California Keck School of Medicine, Los Angeles, CA, USA

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Correspondence: Rasnik K Singh
Department of Dermatology, University of California – San Francisco, 2340 Sutter Street, Room N431, Box 0808, San Francisco, CA 94115, USA
Tel +1 415 476 8364
Fax +1 415 476 8837
Email Rasnik.s@gmail.com

Abstract: Erythrodermic psoriasis (EP) is a rare and severe variant of psoriasis vulgaris, with an estimated prevalence of 1%–2.25% among psoriatic patients. The condition presents with distinct histopathologic and clinical findings, which include a generalized inflammatory erythema involving at least 75% of the body surface area. The pathogenesis of EP is not well understood; however, several studies suggest that the disease is associated with a predominantly T helper 2 (Th2) phenotype. Given the morbidity and potential mortality associated with the condition, there is a need for a better understanding of its pathophysiology. The management of EP begins with a comprehensive assessment of the patient's presentation and often requires multidisciplinary supportive measures. In 2010, the medical board of the US National Psoriasis Foundation published consensus guidelines advocating the use of cyclosporine or infliximab as first-line therapy in unstable cases, with acitretin and methotrexate reserved for more stable cases. Since the time of that publication, additional information regarding the efficacy of newer agents has emerged. We review the latest data with regard to the treatment of EP, which includes biologic therapies such as ustekinumab and ixekizumab.

Keywords: erythrodermic psoriasis, EP, pathogenesis, pathophysiology, treatment, biologics

Introduction

Psoriasis is a chronic inflammatory skin condition affecting roughly 2% of the population.¹ Erythrodermic psoriasis (EP) is a rare and severe variant of the disease, with an estimated prevalence among psoriatic patients ranging from 1%–2.25%.² Furthermore, psoriatic erythroderma is the most common cause of erythroderma, responsible for ~25% of all cases.^{2,3} Although the class I antigens HLA-Cw6, HLA-B57, HLA-B13, and HLA-B17 have been associated with psoriasis vulgaris (PV) and *IL36RN* mutations have been associated with pustular psoriasis, very little is known about the genetic basis of EP.^{4,5} A recent retrospective epidemiological study in 60 patients with EP revealed a 3:1 male-to-female ratio, an average age of 53.7 years, a positive history of psoriasis in 78% of cases, an identifiable trigger factor in 53% of cases, a need for systemic therapy in 55% of cases, clinical improvement in 69.4% of cases, disease recurrence in 15% of cases, and finally three cases of septicemia and one case of stroke.⁶ The average age of onset and male-to-female ratio reported in this study corroborated those of an older epidemiological study reporting on 50 patients with EP.²

Clinical features and presentation

EP presents with generalized cutaneous findings such as erythema, edema, pruritus, ill-defined psoriatic plaques, scaling, hair loss, and occasionally exudative lesions and

palmoplantar or diffuse desquamation.⁷⁻⁹ Nail changes are very common to EP and can range from mild pitting to severe onychodystrophy, more commonly involving the fingernails than the toenails.^{2,8,10} In addition, patients can have systemic symptoms of fever, tachycardia, fatigue, malaise, chills, dehydration, lymphadenopathy, arthralgia, myalgia, insomnia, sweats, diarrhea, constipation, weight changes, allodynia, and rarely high output heart failure (due to excessive water loss and edema) and cachexia.^{8,11,12} Laboratory results may show massive protein and fluid loss, leukocytosis, anemia, elevated C-reactive protein and erythrocyte sedimentation rate, electrolyte abnormalities, temperature irregularities (hypothermia or hyperthermia), and rarely abnormal liver function tests.^{2,13,14}

To clinically diagnose EP, many authors suggest that there must be generalized inflammatory erythema, with or without exfoliation, involving at least 75% of the body surface area. Other authors argue that at least 90% of the body surface area must be affected.^{7,8,11} If clinical suspicion is high, the diagnosis can be confirmed with histologic analysis of EP, which demonstrates an epidermal perivascular infiltrate of lymphocytes and eosinophils, dilated capillaries, and hyperkeratosis. Additional histological features of EP include some features of classical psoriasis, including parakeratosis, acanthosis, spongiosis, Munro micro-abscesses, and occasional apoptotic keratinocytes.^{13,15,16} However, due to exfoliation and loss of the epidermal stratum corneum in EP, Munro micro-abscesses and parakeratosis may not be prominent histologically.¹³ Furthermore, in order to confirm a diagnosis of EP, clinicians must rule out other plausible causes of erythroderma such as atopic dermatitis, pityriasis rubra pilaris, drug eruptions, contact dermatitis, seborrheic dermatitis, immunobullous disorders, connective tissue disorders, and Sezary syndrome and other malignancies.^{8,13,17}

Although the aforementioned parameters are sufficient to make a diagnosis of EP, it is important to note that the disease can be categorized further into two general clinical subtypes. The first is characterized by the presence of psoriatic plaques with gradual additional development of a generalized erythroderma in which the psoriatic plaques remain differentiable from the erythroderma. The disease course is relatively stable and prognosis is favorable in this form of EP. The second subtype, which is more commonly seen in the setting of psoriatic arthritis, is often characterized by rapid whole body erythema and lack of demarcated psoriatic plaques. The disease course is relatively unstable and is more likely to be associated with abnormal vital signs and laboratory values. Accordingly, prognosis is not as favorable

and there is appreciable mortality. The first clinical subtype is often associated with a more chronic and prolonged course, while the second subtype is more likely to be acute, rapidly progressive, and relapsing.^{11,18}

Other rare types of EP include congenital EP and EP secondary to an environmental trigger (Table 1).¹⁹⁻²¹ Documented environmental triggers include sunburn, skin trauma, emotional stress, alcoholism, systemic illness, drug exposure, chemical exposure (such as to computed tomography contrast material or topical tar), and rapid withdrawal from medications known as the rebound phenomenon.^{11,13,14} Common antipsoriatic medications that may lead to the rebound phenomenon include topical and oral steroids, efalizumab, and methotrexate.^{11,22,23} Systemic illnesses that have been known to trigger EP include human immunodeficiency virus, leukemia, T-cell lymphoma, and gout.^{11,24,25} Finally, pharmaceutical drugs that have been reported in the literature to trigger EP include acitretin, etretinate, infliximab, lithium, antimalarials, and trimethoprim/sulfamethoxazole.^{10,26,27}

Because there is such a large list of possible EP triggers, it is sometimes difficult to differentiate the trigger from post-EP-related comorbidities. Therefore, it is important to be aware that EP patients commonly acquire superinfections of the skin and blood with *Staphylococcus aureus* and Group A Streptococcus that may lead an unaware clinician to conclude that the infection was a trigger to the EP.^{8,12} Due to a defective skin barrier, EP patients can present with severe cellulitis, erysipelas, and sepsis.^{12,13} Other complications include pneumonia, endocarditis, and osteomyelitis.^{8,14}

Pathogenesis

The pathogenesis of EP is yet to be fully understood compared to classic PV (Table 2).¹¹ The pathogenesis of PV is known to derive from abnormal interactions between T-lymphocytes, dendritic cells, keratinocytes, neutrophils, and proinflammatory cytokines, leading to activation of the Th17 and Th1 immune axes.²⁸ In contrast, the paucity of information regarding EP has led us to rely on hints of information derived from smaller studies such as case reports, case series, and a small number of studies comparing EP patients to PV patients and healthy controls. In 2005, scientists demonstrated a statistically significant increase in serum immunoglobulin E in EP compared to PV patients. This disparity was attributed to a Th1/Th2 imbalance in favor of Th2 differentiation.²⁹ A more recent study involving 16 EP patients furthered the notion that EP is characterized by a bias toward the Th2 program. This study uncovered three important discoveries regarding the pathogenesis of EP: first, that the ratio of Th1/Th2 was

Table 1 Summary of erythrodermic psoriasis triggers

Type of trigger	Examples	References
Environmental	Sunburn, skin injury/trauma, emotional stress, alcoholism, infection ^b	5, 15, 75
Chemical reaction	Bupropion use in smokers ^a , CT contrast ^c , topical tar	65 ^a , 66 ^a , 75
Systemic illness	HIV, leukemia, T-cell lymphoma, paraneoplastic presentation, gout ^a	5, 22, 45 ^a
Pharmaceutical drugs	Lithium, antimalarials, TMP/SMX, infliximab, acitretin	38, 46, 51
Rebound phenomenon	Topical and oral steroids, efalizumab, methotrexate	5, 30, 32

Notes: ^aStrictly case reports discuss this trigger. ^bWith Group A Streptococcus or *Staphylococcus aureus*.

Abbreviations: CT, computed tomography; HIV, human immunodeficiency virus; TMP/SMX, trimethoprim/sulfamethoxazole.

Table 2 Key studies examining biomarkers in erythrodermic psoriasis

Study	Patient demographics	Biomarkers examined	Key results	Implications
Zhang et al ³⁰	16 patients with EP; 20 patients with PV; 15 healthy controls	Levels of IFN- γ , IL-2, IL-4 and IL-10 (serum); expression levels of T-bet/GATA-3 (skin lesion and PBMCs); Th1 and Th2 levels (blood)	Levels of IL-4 and IL-10 in EP patients were significantly higher than those in PV patients and healthy controls ($P<0.05$); Th1/Th2 ratio was dramatically lower than in PV patients ($P<0.01$); ratio of IFN- γ /IL-4 and T-bet/GATA-3 in EP patients were both <1.0	EP patients may have an increased Th2 response, which could be an important mechanism in EP pathogenesis
Deeva et al ³¹	30 patients with severe forms of psoriasis; ten healthy controls	IL-4, IL-6, IL-10, IL-13, MCP-1, VEGF, and PDGFbb (plasma)	Increased plasma IL-4, IL-6, MCP-1, PDGFbb, VEGF in psoriasis patients compared to healthy controls; EP patients showed a significant increase in IL-13 and MIP1-beta compared to healthy controls	Increased Th2 response and grossly dysregulated angiogenic factors are common to the pathogenesis of psoriasis and EP
Kano et al ³³	One patient with EP	IFN- γ producing CD8+ T-cells (blood); IL-4 and IL-13 producing CD4+ and CD8+ T-cells (blood)	Increased frequency of IFN- γ producing CD8+ T-cells during the EP stage; IL-4 and IL-13 producing CD4+ and CD8+ T-cells were remarkably high during resolution of EP	Shift toward Th2 cytokine predominance contributes to resolution of severe psoriasis
Li et al ²⁹	16 patients with EP; 48 patients with PV as controls	IgE (serum)	Serum IgE elevated in EP group compared to controls ($P<0.001$)	EP may be a Th2 dominant disorder; role of serum IgE needs to be investigated further
Groves et al ³⁸	14 patients with erythroderma; 17 healthy controls	ICAM-1, VCAM-1, and E-selectin levels (plasma)	In erythroderma, median ICAM-1, VCAM-1, and E-selectin levels were significantly elevated	Plasma intercellular adhesion molecules may contribute to the immunosuppressive state in EP due to abnormal cell adhesion mechanisms

Abbreviations: EP, erythrodermic psoriasis; PV, psoriasis vulgaris; IFN, interferon; IL, interleukin; T-bet/GATA-3, T-box expressed in T-cells/GATA-binding protein-3; PBMC, peripheral blood mononuclear cells; Th, T helper cells; psoriasis; MCP-1, monocyte chemoattractant protein-1; VEGF, vascular endothelial growth factor; PDGFbb, platelet derived growth factor-bb; psoriasis; MIP1-beta, macrophage inflammatory protein 1 beta; IgE, immunoglobulin E; AD, atopic dermatitis; TNF- α , tumor necrosis factor-alpha; HBD-3, human beta defensin-3; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; E-selectin, endothelium-specific inducible adhesion molecule.

dramatically lower in EP compared to PV patients; second, levels of interleukin (IL)-4 and IL-10 were significantly higher in EP patients than both PV and healthy patients; and finally, ratios of interferon (IFN)- γ /IL-4 and T-box expressed in T-cells/GATA-binding protein-3 (GATA-3) in EP patients were both <1.0 , representing a reversal when compared with the other two groups. Higher levels of transcription factor GATA-3 – a key regulator of Th2 development from naïve Th cells – and IL-4 – a signature Th2 cytokine – were indicative of Th2 predominance in EP patients. The authors also noted that compared to healthy controls, EP patients had higher serum levels of the Th1 cytokines IFN- γ and IL-2 as well as the Th2 cytokines IL-4 and IL-10.³⁰ Another study showed that the cytokine, chemokine, and angiogenic growth factor profile

for severe psoriatic disease, including very severe plaque psoriasis, psoriatic arthritis, and EP, was characterized by a significant increase in plasma levels of IL-4, IL-6, monocyte chemoattractant protein-1, platelet-derived growth factor-bb, and vascular endothelial growth factor, whereas only EP patients had significantly increased IL-13 and macrophage inflammatory protein-1-beta compared to healthy controls.³¹ These findings suggest that an increased Th2 response and grossly dysregulated angiogenic factors are features of EP.

Interestingly, a previous study had shown that IL-4, the signature Th2-inducing cytokine, was safe and effective in the treatment of plaque-type psoriasis. The authors attributed its efficacy to the induction of the Th2 pathway in skin-infiltrating lymphocytes.³² The study was followed

by investigations demonstrating high levels of CD8+ T-cells during the erythrodermic stage versus high levels of IL-4 and IL-13 producing CD4+ and CD8+ T-cells during the resolution stage of EP, suggesting a shift toward Th2 cytokine predominance contributing to the resolution of severe psoriasis such as EP.³³ Accordingly, many psoriasis therapeutics are either directed against T-cells, tumor necrosis factor- α (TNF- α), the IL-12/IL-23 axis, or redirect cellular immune responses into a protective IL-4-dominated Th2 phenotype.³⁴ Considering all studies together, it remains to be clarified whether the Th2 phenotype seen in EP is associated with disease promotion or with a feedback response resulting in resolution of the disease.

Given their established importance in PV, the contribution of Th17 cells to EP pathogenesis has also recently been investigated. Th17 cells secrete IL-17, IL-22, and IFN- γ , inducing production of inflammatory chemokines by T-cells, dendritic cells, and neutrophils.³⁵ Using immunohistochemical analysis, Moy et al found Th17 to be the most predominant T-cell subset after Th2 in EP lesions. The authors also observed significant immunologic overlap of Th17 cells in EP and erythrodermic atopic dermatitis.³⁶

At a molecular level, TNF- α has been shown to be overexpressed in plaque psoriatic lesions. It has been suggested that rapid systemic release of TNF- α in EP may be responsible for disease onset and severity.³⁷ It is also suspected that the presence of circulating adhesion molecules, such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin, may contribute to the immunosuppressed state in EP due to interference with normal cellular adhesion mechanisms required for immune responses.³⁸ EP has additionally been associated with a dermatogenic enteropathy leading to hypocalcemia and hypophosphatemia, both of which may be exacerbated by excess calcium and phosphate excretion through the skin during EP flares.³⁹

Management of EP

General considerations

Initial management of EP must include correction of any fluid, protein, and electrolyte abnormalities; a nutritional assessment; prophylaxis against hypothermia; and treatment of any secondary infections. Sepsis caused by skin pathogens, most commonly *Staphylococcus aureus*, is a particularly severe and potentially fatal complication that has been reported.^{2,6,40}

In 2010, the medical board of the US National Psoriasis Foundation published consensus guidelines regarding the appropriate management of EP once initial stabilizing

measures have been undertaken. They advocate the use of cyclosporine or infliximab as first-line therapy in acute and unstable cases. For more stable cases, on the other hand, acitretin and methotrexate are the preferred agents. Second-line options include etanercept and combination therapy.⁸ However, since the time of that publication, additional information regarding the efficacy of newer agents has emerged. Later, we review the latest data with regard to the treatment of EP.

Topical therapy

With the development of more potent and targeted therapies, the use of topicals in EP has become less common. Nevertheless, they may be helpful for nontoxic patients or as adjunct therapy for recalcitrant lesions in more severe disease.^{13,34} In these cases, use of medium potency topical steroids under occlusive dressing, colloidal oatmeal baths, topical emollients, topical vitamin D analogs, and various combinations of the aforementioned has been reported in the literature. Of note, coal tar is generally not recommended during the acute phase of EP given its ability to cause substantial skin irritation that may result in Koebner's phenomenon.⁴¹

Topical steroids

A case series of two patients treated with twice-daily topical betamethasone dipropionate ointment, colloidal oatmeal baths, and total body occlusion reported significant skin clearing within three to four hospital days. Both patients had >80% body surface area involvement with unstable vitals and laboratory abnormalities on admission.⁴² Steroids are often used as a temporizing or adjunctive measure while an alternative treatment is introduced.¹³ For instance, clobetasol 0.05% for body and desonide 0.05% for face have been used successfully in combination with methotrexate in a severe patient requiring intensive care unit hospitalization.⁴³

Topical vitamin D analogs

The vitamin D analogs comprise a rising first-line therapy for mild-to-moderate plaque psoriasis given their ability to abrogate skin cell proliferation, enhance skin cell differentiation, and modulate immunologic factors that are involved in disease etiology.^{44,45} Calcipotriol and calcitriol generally should not be used for situations in which patients have a high risk of systemic absorption, such as in severe EP.⁴¹ Nevertheless, two groups effectively incorporated a vitamin D analog as one arm of a combination therapy to treat erythrodermic manifestations. van der Vleuten et al performed a left/right comparison study in a patient who presented with recalcitrant

EP that had failed treatment with methotrexate, topical steroids, and acitretin. Calcipotriol application was begun only after a minor improvement had been achieved with 5 mg/kg/d of cyclosporine. The authors noted a rapid and significant improvement on the side of the patient's body treated with the vitamin D analog. The whole body was then treated with 100 g/wk of calcipotriol in conjunction with low-dose ultraviolet B, leading to marked improvement in 4 weeks.⁴⁶ As an alternative combination therapy, the literature also supports the use of calcipotriene with adalimumab.⁴⁷

Phototherapy

Phototherapy is an effective, first-line treatment for moderate-to-severe plaque psoriasis that works by inhibiting keratinocyte proliferation, promoting keratinocyte apoptosis, and dampening the inflammatory Th1 and Th17 pathways.⁴⁸ The use of phototherapy in acute, fulminant EP is discouraged given the risk of koebernization.¹³ However, phototherapy can play a role in long-term management of EP once the disease course becomes more stable.⁸ One case report supports the use of low-dose ultraviolet B in combination with local calcipotriol for long-term maintenance therapy of EP.⁴⁶ It has also been suggested that phototherapy can be a helpful adjunct in instances where EP is refractory to acitretin monotherapy.⁴⁹

Systemic agents

Second-generation retinoids

Etretinate and its active metabolite, acitretin, are effective systemic treatments for moderate-to-severe psoriasis and other hyperkeratotic disorders (Table 3). They function to normalize keratinocyte proliferation and differentiation, regulate sebaceous gland activity, and modulate local inflammatory responses.⁵⁰ Side effects are dose-dependent and include skin desquamation, cheilitis, xerosis, pruritus, and hair loss.²⁷ Retinoids are also known to be potent teratogens; therefore, the use of these agents in women of childbearing potential is heavily regulated.⁵¹

According to expert consensus, acitretin is considered a high-priority agent for stable cases of EP as it has a relatively

slower onset of action.⁸ Koo⁵² describes a sequential therapy for EP in which patients are started on 25 mg/d of acitretin, which can then be increased by 10–25 mg every 2–4 weeks until the maximally tolerated dose is reached.

A meta-analysis of 12 patients receiving 25–35 mg/d of acitretin noted clinical remission or significant improvement of EP in 83.3% of cases.⁵³ Polat and Serefican found 50 mg/d of acitretin to be similarly effective in one patient with concomitant EP and elephantiasis nostras verrucosa. After 1 month of treatment, the patient had near-complete resolution of his lesions and remained clear at 2-month follow-up.⁵⁴ However, a 4-month trial of acitretin at the same dose in another patient failed to produce any clinical improvement. It is important to note, though, that this patient was significantly overweight and may have been underdosed.⁵⁵

The second-generation retinoids have also been used in combination with other systemic agents, such as cyclosporine and infliximab. Three patients treated with 0.5–0.8 mg/kg/d of etretinate and 3–4 mg/kg/d of cyclosporine experienced significant disease resolution within a few weeks.⁵⁶ The acitretin/cyclosporine combination was ineffective in four other patients, although in one of the cases, the maximum daily dose of acitretin was only 20 mg.^{46,57} In addition, a case series examining acitretin/infliximab reported >90% improvement of erythrodermic manifestations in four patients.⁵⁸

Interestingly, there are also case reports describing acitretin- and etretinate-induced EP, which ultimately resolved after the drug was discontinued and replaced with cyclosporine.^{27,59,60} It is unclear why the retinoids provoked erythroderma in these cases. Systemic retinoids have also exhibited reduced efficacy in the context of low serum albumin levels as it is thought that transport proteins such as albumin are necessary for the migration of acitretin into peripheral tissues.⁶¹

Methotrexate

Methotrexate is an immunosuppressive drug that inhibits the enzyme dihydrofolate reductase. Oral systemic therapy with methotrexate is a first-line option for patients with plaque

Table 3 Studies examining conventional systemic agents as monotherapy in erythrodermic psoriasis

Conventional agent	Total patients	Dosing range	Outcome	Responders n (%) ^a
Acitretin ^{52–54}	14	25–50 mg/d	Complete remission	11 (78.6)
Methotrexate ^{10,20,62–66}	60	5–40 mg/wk	Complete remission or good-to-excellent response	50 (83.3)
Cyclosporine ^{13,25,27,28,76,77}	42	1.5–4.2 mg/kg/d starting dose	Complete remission or significant improvement	36 (85.7)

Note: ^aPartial or complete response.

Abbreviations: d, day; wk, week.

psoriasis who have inadequate control on topicals alone. Like acitretin, methotrexate also has a slower onset of action and is considered a high-priority agent for more stable cases of EP. It is either taken orally or administered as a once-weekly injection, commonly 5–7.5 mg or 15–20 mg, and can be supplemented with 1 mg daily folic acid. Long-term use of methotrexate may increase the risk of hepatotoxicity, hepatic fibrosis, and bone marrow suppression.⁶²

A retrospective analysis of 21 patients with severe psoriasis or EP treated with an initial dose of 5–7.5 mg/wk reported complete remission in 62% of cases and partial remission in 28.5% of cases. Mean remission period lasted 14 months.⁶³ Several case reports also describe EP resolution within 3 weeks to 3 months using the same dosing range. One of these patients was even continued on maintenance therapy for 2 years with lasting remission.^{10,19,64}

Three retrospective studies totaling 53 patients investigating 15–40 mg/wk of methotrexate reported good-to-excellent responses in 43 patients (81%), moderate responses in seven patients (13%), and poor responses in three patients (6%).^{65–67} Two case reports also support the use of 15 mg/wk in patients presenting with diffuse EP. Both patients began to experience significant skin clearing within a few weeks. Notably, one patient was also receiving concomitant compound glycyrrhizin, an agent that is thought to block production of IL-8.^{43,68} Methotrexate has been combined with several other agents for the treatment of EP, including with infliximab^{55,69–71}; with etretinate reporting satisfactory results⁷²; and with cyclosporine or etanercept reporting excellent results.^{64,73}

Cyclosporine

Cyclosporine is an immunosuppressive agent that blocks IL-2 transcription, thereby impairing the growth and activity of T-cells. Cyclosporine is approved by the US Food and Drug Administration for the treatment of severe plaque psoriasis in immunocompetent adults.⁷⁴ Given its rapid onset of action, cyclosporine is considered a critical first-line drug for the control of unstable cases of EP. More severe disease often requires a starting dose of 5 mg/kg/d. Case series and reports advocate the use of cyclosporine in the treatment of EP at doses of 1.5–5 mg/kg/d for 2 weeks to 4 months.^{12,24,26,27,75,76} The largest case series (n=33) described complete disease remission in 67% of patients after 3 months and an overall response rate of 94%.²⁴ Cyclosporine can also be used in combination with topical or systemic agents, such as acitretin and etretinate, in order to reduce the dose, duration, and adverse effects of each individual agent.^{46,56,57} At the time of EP remission (total resolution of skin lesions), cyclosporine can slowly be tapered by 0.5 mg/kg every 2 weeks until

total discontinuation or reappearance of signs of disease.^{12,24} Nephrotoxicity is the most significant potential side effect of cyclosporine; therefore, a >30% elevation of serum creatinine must prompt a reduction in dose or cessation of therapy.

Mycophenolate mofetil

Mycophenolate mofetil is another immune suppressant that selectively inhibits activated lymphocytes. It has efficacy as a monotherapy for moderate-to-severe psoriasis in several case reports, small clinical studies, and a randomized controlled trial.^{77–80} Use of mycophenolate mofetil in two patients with severe EP has also been reported in the literature. Over a 6-week period, both patients experienced 70% skin improvement with no notable side effects or disease relapse after drug cessation.⁷⁸ Of note, mycophenolate mofetil is teratogenic and should not be used during pregnancy.

Biologics

Biologic therapy encompasses an emerging category of drugs that target specific cytokines of the immune system. Given their enhanced selectivity, these agents are a promising alternative to the conventional immunosuppressants, such as methotrexate and cyclosporine. Certain categories of biologics have been adopted for the treatment of EP, including the TNF- α inhibitors, IL-12/IL-23 inhibitors, and most recently, the IL-17A inhibitors (Table 4).

Baseline screening prior to beginning treatment with a biologic includes a tuberculin skin test or IFN- γ -release assay for tuberculosis (QuantiFERON Gold), updated immunizations, hepatitis B and C and human immunodeficiency virus tests, and basic blood and chemistry laboratories including liver function tests.⁸¹

TNF- α inhibitors

Etanercept

Etanercept is a soluble TNF-receptor fusion protein that acts as a decoy for endogenous TNF- α . This interaction inhibits the biological inflammatory cascade of TNF- α . Etanercept is administered subcutaneously once to twice weekly (maximum individual dose of 50 mg). A case series following ten patients with EP reported that eight of ten patients (80%) attained PASI50 (50% or greater reduction of the psoriasis area and severity index) and five patients (50%) reached PASI75 at 12 weeks. At the end of the 24 weeks, six of the total ten patients (60%) had achieved and maintained PASI75.⁸² A multicenter retrospective study provided six further cases of EP treated with etanercept, with four of six (67%) achieving PASI75 between weeks 12 and 14. Clearance, defined as PASI90, was obtained in two of six (33.3%)

Table 4 Studies examining biologic monotherapy in erythrodermic psoriasis

Biologic agent	Total patients	Reaching PASI50 n (%) ^a	# Reaching PASI75 (%) ^b	Earliest clinical response
Etanercept ^{7,81–83}	18	14 (77.8)	12 (66.7)	12 weeks
Adalimumab ^{7,9,46}	11	6 (54.5)	6 (54.5)	12 weeks
Infliximab ^{7,57,89–95}	55	30 (54.5)	30 (54.5)	48 hours
Golimumab ³⁶	1	1 (100)	1 (100)	4 weeks
Ustekinumab ^{7,18,24,54,85–87,99}	40	34 (85)	31 (77.5)	4 weeks
Ixekizumab ¹⁰¹	8	8 (100)	8 (100)	12 weeks

Notes: ^aPASI50, 50% reduction in psoriasis area and severity index; ^bPASI75, 75% reduction in psoriasis area and severity index.

cases with a mean delay of 16 weeks.⁷ Two individual case reports additionally support long-term management of EP using etanercept monotherapy with excellent responses.^{83,84}

Etanercept has also been used concomitantly with methotrexate in a pediatric patient presenting with recalcitrant EP. Her erythrodermic manifestations gradually subsided over a 3-month period and were not noted to reappear throughout 2-year follow-up.⁶⁴

Adalimumab

Adalimumab is a fully human monoclonal antibody against TNF- α . It is administered subcutaneously at an initial dose of 80 mg at week 0, followed by 40 mg every other week starting at week 1.⁸⁵ Two case reports, as well as one multicenter, retrospective study, support the use of adalimumab in EP. The multicenter study reported that 50% of the subjects had a 75% reduction in PASI score from baseline by 12–14 weeks after treatment onset.⁷ Mumoli et al⁴⁷ similarly observed significant disease remission in a patient who was treated with adalimumab for 12 weeks. Lastly, a complicated EP patient with concomitant hepatitis C virus infection and hemophilia remarkably achieved remission at week 3 of treatment with adalimumab.⁹ Interestingly, several patients who were treatment resistant to adalimumab and other anti-TNF- α agents had eventual success with ustekinumab.^{17,55,86–88}

Infliximab

Infliximab is a chimeric anti-TNF- α monoclonal antibody that interacts with both soluble and membrane-bound TNF- α . This interaction results in decreased epidermal T-cell infiltration. For the treatment of severe plaque psoriasis, 5 mg/kg is administered intravenously at weeks 0, 2, and 6, with maintenance dosing every 8 weeks thereafter.⁸⁹ Given its route of administration, infliximab has a relatively quick onset of action that is comparable to that of cyclosporine. Therefore, expert consensus considers the drug an additional first-line option for unstable cases of EP. Several case reports and series, as well as one multicenter clinical trial, support the use of infliximab as a monotherapy in EP. Together, these studies describe 52

patients, with 34 (65%) exhibiting significant improvement as defined by at least a 50% reduction in PASI score from baseline^{7,58,90,91} or by a physician's global assessment of "clear" or "almost clear".^{92–96} Infliximab has also successfully been combined with other systemic agents, such as methotrexate and acitretin, with excellent clinical results.^{58,69,70,97}

However, a couple of case reports suggest that infliximab may lose efficacy after successive infusions. In these patients, no further reduction in PASI was appreciated after 14 weeks and 30 weeks of treatment.^{84,87} It is thought that this phenomenon may occur due to development of anti-infliximab antibodies. Interestingly, it has also been suggested that development of antinuclear antibodies and anti-double-stranded DNA antibodies on anti-TNF- α treatment may signal forthcoming treatment failure.⁸⁸ Larger and longer term clinical trials may help decide whether surveillance for these antibodies is warranted.

Golimumab

Golimumab is a fully human monoclonal antibody against TNF- α and is available for the treatment of psoriatic arthritis.⁹⁸ One case report regarding the use of golimumab in EP has been published. The patient was given 50 mg subcutaneously per month and by the third injection had an 82% reduction in PASI score. He was continued on therapy for >11 months and maintained his achieved results. No significant adverse events were reported throughout the duration of therapy.³⁷

IL-12/23 inhibitors

Ustekinumab

Ustekinumab is a fully human monoclonal antibody that binds the p40 subunit of both IL-12 and IL-23. These two cytokines are involved in the pathogenesis of psoriasis by stimulating the Th1 and Th17 inflammatory pathways, respectively. Ustekinumab is approved for the treatment of moderate-to-severe plaque psoriasis and psoriatic arthritis and is administered subcutaneously. Appropriate dosing is 45 mg for individuals weighing <100 kg and 90 mg for individuals weighing \geq 100 kg. The injections are administered at weeks 0 and 4 and then every 12 weeks thereafter.⁹⁹ The

published literature regarding the efficacy of ustekinumab in EP includes two multicenter retrospective studies,^{7,17} three case series,^{23,86,88} and three case reports.^{55,87,100} Together, the studies comprise a total of 40 patients, with 32 (80%) experiencing clinical improvement, as defined by a 75% reduction in PASI score from baseline. The earliest clinical improvements in these studies were seen after just 4 weeks of treatment (45% of cases). As mentioned in the section on adalimumab, several patients with recalcitrant EP that had failed treatment with other agents, including numerous forms of anti-TNF- α therapy, had eventual success with ustekinumab.^{17,55,86–88}

IL-17 inhibitors

Ixekizumab

Ixekizumab is a humanized IgG4 monoclonal antibody that inhibits IL-17A, an inflammatory cytokine of the Th17 pathway that has been implicated in the pathogenesis of psoriasis.¹⁰¹ Ixekizumab has been tested in Phase II and III clinical trials of moderate-to-severe plaque psoriasis, demonstrating efficacy comparable to that of other biologics. The drug has also more recently been tested in a Phase III, multicenter, single-arm, open-label study of eight EP patients. All subjects received a 160 mg subcutaneous injection at week 0, 80 mg every 2 weeks through week 12, and 80 mg every 4 weeks through week 24. The authors reported that at week 12, eight patients (100.0%) achieved PASI75, five patients (62.5%) achieved PASI90, and two patients (25%) achieved PASI100.¹⁰²

Other biologics

Panitumumab

Panitumumab is a human monoclonal antibody targeting the epidermal growth factor receptor (EGFR). A patient with recalcitrant EP who failed treatment with calcipotriol ointment, topical steroids, etretinate, and psoralen plus ultraviolet A showed dramatic improvement within 10 days of treatment with panitumumab. His achieved results lasted at least 6 months after the initiation of therapy.¹⁰³ This case report suggests that EGFR signaling may contribute to the development of psoriatic skin lesions, and its role in the pathogenesis of EP could be further explored.

Alefacept and efalizumab

Alefacept and efalizumab are two biologics previously approved by the Food and Drug Administration for psoriasis that are no longer available. A case series following two patients has been published regarding the use of alefacept in

EP. Both patients had recalcitrant psoriasis that responded completely to a full course of alefacept. One of the patients achieved this response by 14 weeks, yet flared back to baseline 2 weeks after discontinuing treatment. The second patient was on a concomitant 13-week cyclosporine taper during which he maintained good results.¹⁰⁴ Two patients treated with efalizumab as their first- and third-line biologic therapy, respectively, had no clinical benefit.⁷ On the other hand, one study in which efalizumab was administered at an initial subcutaneous weekly dose of 0.7 mg/kg followed by 1 mg/kg for 6 months reported PASI75 achievement in an EP patient after 18 weeks of treatment.¹⁰⁵

Discussion

EP is a rare and severe disorder that is distinct from PV. Although the exact pathogenesis of EP is not fully understood, it is thought to involve a complex interplay of the Th1, Th2, and Th17 inflammatory pathways. Evidence suggests that in contrast to PV, the Th1/Th2 imbalance of EP tends to favor Th2 differentiation and its related cytokines. IL-4 and IL-13, in particular, have been shown to be elevated in EP relative to both PV patients and healthy controls. Functional studies involving these cytokines may help clarify their roles in the pathogenesis of EP. TNF- α is also an important player in the pathogenesis of EP especially given the documented efficacy of anti-TNF- α agents in disease treatment. Given the morbidity and potential mortality associated with the condition, there is a need for a better understanding of EP pathophysiology.

The management of EP begins with a comprehensive assessment of the patient's presentation. Often patients require supportive measures that address electrolyte abnormalities, nutritional status, impaired thermoregulation, and underlying infection, among other things. Furthermore, potential septic and thromboembolic complications justify close surveillance of patients and often also hospitalization. Severe and unstable cases of EP benefit from rapidly acting agents, such as cyclosporine and infliximab. Despite a comparably rapid onset of action, use of systemic steroids should be avoided given high risk of rebound after withdrawal. Although the most recent expert consensus only recommends acitretin and methotrexate as first-line therapies for stable cases, review of the literature suggests that ustekinumab may also be used in this role. Evidence supporting the efficacy of ustekinumab comes from 40 documented instances of EP in which the biologic was used as a monotherapy. Of these patients, 80% had a significant clinical response to treatment, while 45% began to exhibit improvement in as early as 4 weeks. Furthermore, 75% of responders had recalcitrant EP who previously failed therapy with other

agents, including the TNF- α inhibitors that were also reviewed in this article. Given its response profile, ustekinumab may represent a viable option for the long-term control of EP. The anti-TNF- α agents studied in EP include etanercept, adalimumab, infliximab, and golimumab. Infliximab is already accepted as a first-line systemic therapy for EP and has demonstrated its clinical efficacy in a large volume of patients; 65% of patients on infliximab had at least a 50% reduction in PASI score from baseline. Etanercept, adalimumab, and golimumab have all been employed in relatively fewer instances of EP but have also shown good clinical efficacy. In this regard, 67% of patients in the largest case series investigating etanercept in EP, 50% of patients in the largest clinical study investigating adalimumab in EP, and one EP patient who received golimumab were noted to have at least a 75% reduction in PASI score from baseline.

The other biologics reviewed in this article have been tested in far fewer EP patients. Ixekizumab has been investigated in eight subjects. Although results suggest that ixekizumab shows great therapeutic promise, further large-scale and long-term trials are needed to establish safety and efficacy. Other anti-IL-17 agents such as secukinumab and brodalumab may therefore also represent experimental therapeutic options for EP. Panitumumab, efalizumab, and alefacept were efficacious in 100% (one of one patient), 33.3% (one of three patients), and 100% (two of two patients) of cases, respectively. The efficacy of panitumumab, an EGFR antagonist, alludes to a potential role that the EGFR may play in the pathogenesis of psoriasis. Further studies may be warranted to explore a possible pathophysiologic relationship. Regarding the remaining therapies reviewed in this article, topical steroids can be helpful adjuncts in both acute and later stages of EP, whereas phototherapy may be useful in later stages once the disease course stabilizes.

Conclusion

The treatment options for EP have greatly expanded in the last several years. However, additional controlled trials with extended follow-ups are needed to better understand the pathophysiology of EP, determine the exact role, safety, and efficacy of the new biologics in EP, and reinform treatment guidelines.

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