Psoriasis: Targets and Therapy

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REVIEW

Updates on the Treatment of Erythrodermic Psoriasis

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Abstract: Erythrodermic psoriasis (EP) is a rare variant of psoriasis, which is potentially life threatening and often resistant to conventional therapy. Biologics have revolutionized the treatment of plaque-type psoriasis, and shown promise in EP. However, due to the lack of head-to-head studies and the rarity of EP, no high level evidence-based treatment guidelines for EP have been established, and the evidence of treatment of EP is limited to case reports or small case series. Here, we present a narrative review focusing on the up-to-date information for the treatment of EP.

Keywords: erythrodermic psoriasis, treatment

Erythrodermic psoriasis (EP), a rare variant of psoriasis vulgaris, accounts for 1–2% patients with psoriasis.[1,2] A higher prevalence of EP in Asians was found in China and Taiwan study.[3,4] EP is clinically defined as prominent erythema and scaling affecting at least 75–90% of the body surface area (BSA).[1,5] Due to the extensive cutaneous involvement, EP patients can present with systemic symptoms, such as pruritus, fever, chills, dehydration, arthralgia, asthenia and lymphadenopathy.[1,5] Several triggers for causing EP can be identified, including infection, administration of systemic corticosteroids, withdrawal of medication, severe emotional stress and preceding illness.[2,6] Many biomarkers are possibly related to the pathogenesis of EP, including higher IL-4 and IL-10 levels,[7] elevation of serum IgE,[8] increased Th2 response,[7,9] and the presence of circulating adhesion molecules.[10] There may be overlap between the EP and atopic dermatitis immune phenotypes.[11] Recently, a study from China revealed the possible role of the cytokine tumor necrosis factor-related weak inducer of apoptosis (TWEAK) in the pathogenesis of EP and psoriasis vulgaris (PV).[12] Furthermore, according to a recent study from China, a higher prevalence of thyroid dysfunction was found in EP patients.[13] Several human leukocyte antigens (HLA), such as HLA-Cw6 and HLA-DR7 have been linked with psoriasis vulgaris,[14,15] and the same genetic constitution was also related to guttate psoriasis.[16] In Chinese patients with erythrodermic psoriasis, HLA-C*01:02 was reported to be the most frequent HLA-C allele (34.4%) compared to plaque psoriasis (21.9%) and healthy controls (21.2%).[6] Recently, one case reported mutations of the CARD14 gene with EP related to requiring higher doses of ustekinumab.[17] Due to the lack of head-to-head studies and the rarity of EP, no high-level evidence-based treatment guidelines for EP have been established.[1] This review article aims to provide up-to-date information for the treatment of EP (Tables 1–5).

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Table 1 Studies of Conventional Oral Immunosuppressive Agents in EP Patients

Treatment	Author (Year)	Number of Subjects	Study Design	Results	Adverse Events
MTX	Collins et al[18] 1991	7	R	4 (57.1%) Patients with excellent response, 2 (28.6%) patients with good response, 1 patient failed.	NR
MTX	Kumar et al[21] (1994)	5	R	2 (40%) Patients achieved disease-free interval for 14 weeks. All patients relapse within 14 weeks.	Nausea, vomiting
CsA	Giannotti et al[26] (1993)	33	Case series	22 (67%) Patients achieved complete remission in a median time of 2–4 months after 6 months of treatment.	Hypertension, cerebrovascular disorder
CsA	Bruzzese et al[27] (2009)	1	Case report	Under CsA 3 mg/kg, complete remission was seen within 3 months.	NR
CsA + etretinate	Kokelj et al[33] (1998)	3	Case series	After treatment for 11–18 days, remission was seen.	Xerosis, chelitis, GI upset
CsA + UVB	Franchi et al[35] (2004)	7	Case series	After 9 weeks, PASI score Reduction by 57.6, compared with placebo. points	None
Acitretin CsA	Charbit et al[36] (2016)	2 2	R	After 3 months of treatment, 2 patients treated with acitretin failed to achieve greater than 50% clearance. 1 patient treated with CsA had "good" response (>75%).	NR
Etretinate	Kim et al[39] (1991)	12	Case series	Averaged 19.9 days for complete disappearance of scales. After 2–11 months of treatment, 10 (83.3%) patients had satisfactory results.	Cheilitis, elevated lipid profiles level
Etretinate	Rosińska et al[40] (1988)	5	Case series	2 (40%) Patients with clinical improvement.	Focal osteoporosis
MMF	Geilen et al[47] (1998)	2	Case series	After treatment for 6 weeks, both patients reported with 70% skin improvement.	None

Abbreviations: CsA, cyclosporine; EP, erythrodermic psoriasis; GI, gastrointestinal; MTX, methotrexate; MMF, mycophenolate mofetil; NR, not reported; PASI, Psoriasis Area and Severity Index; R, retrospective; UVB, ultraviolet B.

Methods

The electronic databases of PubMed, Embase and Google Scholar were searched for relevant studies from 1985 to March 1, 2021, using the index words, "erythrodermic psoriasis" and the co-indexing terms "treatment", "management", "biologic", " methotrexate", "cyclosporine", "acitretin", " etanercept", "infliximab", "adalimumab", "ustekinumab", "secukinumab", "ixekizumab", "brodalumab", "guselkumab", " tildrakizumab", "risankizumab" and "apremilast".

Conventional Oral Immunosuppressive Agents

Methotrexate

Methotrexate (MTX) is one of the most commonly used immunosuppressive drugs for EP.[18–24] The treatment dosing is variable for the initial dose; the administration of 7.5 to 15mg per week for maintenance was reported based on previous retrospective studies.[18–21,23] Dosing of 7.5 to 40mg weekly for the treatment of EP has been reported.[1] Most of the patients in previous studies reported good response to MTX,[18–20] and Haustein et al reported the treatment response to MTX was observed within 1 to 4 weeks,[20] and 28 (77.8%) patients had good outcomes.[20] Inconsistent results were seen for child patients based on one retrospective study; among three child patients with EP under MTX, one patient did not achieve a disease-free status, but the others had approximately 14 weeks of disease-free interval.[21] Aydin et al reported good responses for two patients treated with a combination of cyclosporine and MTX,[22] and MTX was administered with 10mg intramuscular injection weekly and combined with cyclosporine 3.5mg/kg/day in divided doses. However, the time to

Table 2 Studies of Tumor Necrosis Factor Antagonist in EP Patients

Biologic Agent	**Characteristics**				
Etanercept	Fully humanized, soluble, recombinant fusion protein				
Infliximab	Mouse–human chimeric monoclonal antibody, IgG1				
Adalimumab	Fully humanized, monoclonal antibody, IgG1				
Golimumab	Fully humanized, monoclonal antibody, IgG1κ				
Treatment	**Author (Year0**	**Number of Subjects**	**Study design**	**Results**	**Adverse Events**
Infliximab + acitretin	Takahashi et al[43] (2007)	7	Case series	After third infusion of infliximab, all patients reported 90% improvement.	None
Etanercept	Esposito et al[48] (2006)	10	Case series	At week 12, 5/10 (50%) patients achieved PASI 75. At week 24, 6/10 (60%) patients achieved or maintained PASI 75, 2/10 patients (20%) maintained improvement between PASI 50 and PASI 75.	UTI pruritus
Etanercept	Piqué-Duran et al[49] (2007)	1	Case report	Achieved PASI 100 at week 9	NR
Infliximab Etanercept	Romero-Maté et al[50] (2010)	1	Case report	At week 20, achieved PASI 100 with infliximab. Maintained etanercept therapy for 34 months	NR
Infliximab (n=24) Adalimumab (n=7) Etanercept (n=6) Ustekinumab (n=3) Efalizumab (n=2)	Viguier et al[51] (2011)	28	R	At week 12–14, 48% achieved PASI 75 with infliximab, 50% with adalimumab, 40% with etanercept.	Bacterial infection in 7/12 serious adverse event. Adalimumab: lymphoma. Ustekinumab: sudden death. Infliximab: immunoallergic reaction, suicide attempt.
Etanercept Infliximab	Sahel et al[52] 2016	2	Case report	At week 12, one case with etanercept from PASI 32.8 to 7. The other one improved to PASI 4.8 with infliximab	NR
Etanercept + MTX	Fraga et al[53] (2011)	1	Case report	After 3 months of treatment, erythroderma resolved.	None
Infliximab	Poulalhon et al[54] (2006)	5	Case series	After 14 weeks, 2 (40%) patients achieved PASI 90, and 3 patients achieved PASI 75.	Arthralgia, delayed infusion reaction, pneumonia.
Infliximab + MTX	Lisby et al[55] (2004)	3	Case series	All patients with total clearance after first dose of infliximab.	None
Infliximab + MTX	Heikkila et al[56] (2005)	4	Case series	All patients reported rapidly improvement after 2 or 3 infusions of infliximab.	None

(*Continued*)

Table 2 (Continued).

Biologic Agent	Characteristics				
Infliximab	Torii et al[59] (2011)	8	UCT	At week 50, 4 (50%) with reduction of >5 in DLQI.	Nasopharyngitis
Golimumab	Lee et al[70] (2015)	1	Case report	82% Reduction in PASI score after the third injection.	None

Abbreviations: CsA, cyclosporine; DLQI, Dermatology Life Quality Index; EP, erythrodermic psoriasis; MTX, methotrexate; NR, not reported; PASI, Psoriasis Area and Severity Index; R, retrospective; TNF, tumor necrosis factor; UCT, uncontrolled clinical trial; UTI, urinary tract infection.

Table 3 Studies of IL-12/23, IL-23 Antagonist in EP Patients

Biologic Agent	Targets	Characteristics			
Ustekinumab	p40 Subunit of IL-12 and −23	Fully humanized, monoclonal antibody, IgG1κ			
Guselkumab	p40 Subunit of IL −23	Fully humanized, monoclonal antibody, IgG1			
Risankizumab	p40 Subunit of IL −23	Fully humanized, monoclonal antibody, IgG1			
Treatment	**Author (Year)**	**Number of Subjects**	**Study Design**	**Results**	**Adverse Events**
Ustekinumab	Pescitelli et al[74] (2015)	22	R	At week 16, 70% of patients achieved PASI 75. More than 80% at week 28.	None
Ustekinumab	Santos-Juanes et al[75] (2010)	2	Case series	At week 4, PASI score improvement: 81% and 94%, respectively. At week 12, PASI score improvement: 94% and 97%, respectively.	NR
Ustekinumab	Wang et al[76] (2011)	8	Case series	At week 12 and 28, 50% of patients achieved PASI75. 12.5% achieved PASI 90 at 12 weeks, and 37.5% achieved PASI 90 at 28 weeks.	NR
Ustekinumab	Saraceno et al[80] (2013)	2	Case series	Both of patients achieved PASI at week 12. One case maintained PASI 75 for 12 months. One case maintained PASI 90 for 64 weeks.	NR
Guselkumab	Sano et al[86] (2018)	11	Case series	At week 16, 10 (90.9%) with treatment success.	4 (36.4%) Patients with nasopharyngitis.
Guselkumab	Megna et al[87] (2020)	1	Case report	After 20 weeks of treatment, patient achieved PASI 100, and maintaining to week 48.	NR
Guselkumab	Chiang et al[88] (2021)	13	Case series	PASI 75 rate: At weeks 4, 12, 20, and 28 was 15.4%, 38.5%, 53.9%, and 46.2%.	None
Risankizumab	Suleiman et al[89] (2020)	4	Phase 3 open-label clinical trial	At week 16, all patients achieved PASI 90.	NR

Abbreviations: EP, erythrodermic psoriasis; IL, interleukin; NR, not reported; PASI, Psoriasis Area and Severity Index.

Table 4 Studies of IL-17 Antagonist in EP Patients

Biologic Agent	**Targets**	**Characteristics**			
Secukinumab	Anti-IL-17A	Fully humanized, monoclonal antibody, IgG1κ			
Ixekizumab	Anti-IL-17A	Humanized, monoclonal antibody, IgG4			
Brodalumab	Anti-IL-17R	Fully humanized, monoclonal antibody, IgG2			
Treatment	**Author (Year)**	**Number of Subjects**	**Study Design**	**Results**	**Adverse Events**
Secukinumab	Weng et al[90] (2018)	10	Case series	At week 16, 4 (40%) achieved PASI 90, (70%) of patients achieved PASI 75. At week 24, 30% achieved PASI 90 and 60% achieved PASI 75.	None
Secukinumab	Mugheddu et al[91] (2017)	2	Case series	2 (100%) Patients achieved PASI 75 at week 4. Maintained efficacy were seen at 12–24 week follow-up.	None
Secukinumab	Mateu-Puchades et al[92] (2018)	5	Case series	3 (60%) Patients achieved PASI 75 at week 4. All patients achieved PASI 90 at week 16 and 80% had PASI 100.	NR
Secukinumab	Galluzzo et al[93] (2018)	1	Case report	At week 12, the patients achieved PASI 75.	None
Secukinumab	Rongioletti et al[94] (2018)	1	Case report	At week 12, the patients achieved PASI 100.	None
Secukinumab	Pizzatti et al[99] (2020)	1	Case report	7 days after injection, PASI score improved from 31.5 to 17.6.	None
Ixekizumab	Saeki et al[101] (2017)	8	Case series	At week 52, 8 (100%) patients achieved PASI75, 6 (75%) achieved PASI90, and 1 patient achieved PASI 100.	Allergic reaction, infection, injection site reaction, hepatic disorder
Ixekizumab	Megna et al[103] (2019)	1	Case report	After 6 weeks, patient achieved PASI 100, and maintaining to week 24.	None
Ixekizumab + acitretin, Secukinumab	Pangilinan et al[105] (2020)	1 1	Case series	After two weeks of ixekizumab injection, PASI score improved from 36 to 5. The other one achieved PASI 100 after 4 doses of secukinumab.	None
Ixekizumab	Lo et al[106] (2019)	9	Case series	4 (44%) Patients achieved PASI 75 at week 12.	4 (44.4%) Patients with injection site reaction.
Ixekizumab	Lo et al[107] (2021)	14	Case series	After 52 weeks, three (21.4%) patients achieved PASI 75.	5 (35.7%) Patients with injection site reaction. 1 patient with vulvovaginal candidiasis.
Brodalumab	Yamasaki et al[108] (2017)	18	Case series	After week 12, 14 (77.8%) patients achieved PASI 75, 9 (50%) patients achieved PASI 90, and 3 (16.7%) patients achieved PASI 100. At week 52, 88.9%, 88.9%, and 61.1% achieved PASI 75, PASI 90, and PASI 100.	Nasopharyngitis

(*Continued*)

Table 4 (Continued).

Biologic Agent	Targets	Characteristics			
Brodalumab	Bernardini et al[109] (2020)	1	Case report	At week 4, PASI score decreased from 42 to 22.	None
Brodalumab	Megna et al[110] (2020)	2	Case series	One case achieved PASI 90 at week 3. One case achieved PASI 90 at week 12.	None

Abbreviations: EP, erythrodermic psoriasis; IL, interleukin; IL-17R, interleukin-17 receptor; NR, not reported; PASI, Psoriasis Area and Severity Index.

Table 5 Other Treatment in EP Patients

Treatment	Author (Year)	Number of Subjects	Study Design	Results	Adverse Events
Apremilast	Papadavid et al[111] (2017)	1	Case report	Achieved PASI 100 at 20 days. Relapse after week 12.	None
Apremilast	Krishnamoorthy et al[112] (2019)	1	Case report	Achieved PASI 100 at week 10. Remained free of psoriasis for 1 year.	None
Apremilast	Arcilla et al[113] (2016)	1	Case report	NR	Atrial fibrilliation
Apremilast	Mugheddu et al[114] (2020)	1	Case report	NR	None
Naltrexone	Beltran Monasterio et al[115] (2019)	1	Case report	Achieved complete remission after 3 months of treatment.	None
Panitumumab	Nishizawa et al[116] (2012)	1	Case report	Erythrodermic status improved after 10 days of treatment.	None
Coenzyme Q10 + vitamin E +selenium	Kharaeva et al[117] (2009)	7 7 (placebo group)	RCT	After treatment for 30 days, PASI scores for the supplement group were 19 ± 4 compared to 30 ± 5 in the placebo group ($p<0.05$)	None

Abbreviations: EP, erythrodermic psoriasis; NR, not reported; PASI, Psoriasis Area and Severity Index; RCT, randomized controlled trial.

response was also not documented. Patients with EP usually tolerated MTX well,[18,20–22,24] and nausea and vomiting were the most commonly reported adverse events; however, hepatotoxicity, hematologic and metabolic complications should be monitored.[24,25]

Cyclosporine

Cyclosporine is an immunosuppressive medication that blocks IL-2 transcription and results to inhibiting the growth of T-cell and proliferation.[26] Several case reports and studies revealed the efficacy of cyclosporine for EP.[22,27–37] The reported dosing of cyclosporine ranged from 1.5 to 5mg/kg/day.[27–29,34] The largest study is one open-label, single-center study from Italy which had 22 (66.7%) patients in complete remission, with the initial mean dose of 4.2mg/kg/day, and tapered by 0.5mg/kg every 2 weeks.[27] Ninety-four percent of the patients responded to the treatment according to the study,[27] and approximately 2–4 months were needed to achieve the treatment outcome. A faster treatment response seen within 1 month was reported for a combination treatment of cyclosporine and etretinate.[33–35] Combination therapies with other treatment modalities were also reported, including MTX,[22] alefacept,[32] etretinate[33–35] and phototherapy.[36] One case series reported three cases with

rapid response under cyclosporine and etretinate, achieving complete remission after combination treatment for 11–18 days, and with no signs of relapse during 1 year of follow-up.[34] However, one case series reported failure to control in three patients with acitretin and cyclosporine.[38] Cyclosporine is usually well-tolerated, though side effects including gastrointestinal upset,[37] hypertension[37] and acute kidney injury were reported.[39] Clinicians should avoid using cyclosporine in elderly patients with hypertension or impaired renal function.[1] Cyclosporine is considered a first-line therapy for acute and unstable cases according to the published consensus of the US National Psoriasis Foundation in 2010.[1]

Acitretin/Etretinate

Both etretinate and its active metabolite acitretin are often used for the treatment of EP,[33–35,37,40–45,47] but the results have been inconsistent. Kim et al reported satisfactory outcomes for 12 patients with a monotherapy of acitretin,[40] 10 (83.3%) patients reported remission under the initial dose of 20–60 mg daily. The average time to complete clearing of erythematous scales was 19.9 days, and the duration of clearing of erythema ranged from 2 to 11 months. However, Charbit et al reported two patients who failed to achieve greater than 50% clearance after 3 months of treatment,[37] and in the report by Rosińska et al, only two of five children showed favorable results after treatment of one to 4 months of etretinate.[41] Combination therapies with other immunosuppressive medication were common, including cyclosporine,[37] acitretin with azathioprine,[43] or infliximab,[44] and etretinate with cyclosporine[33–35] or MTX.[42] One patient with EP coexisting with bullous pemphigoid was treated successfully with acitretin and azathioprine.[43] Acitretin and MTX are considered more suitable for stable cases, compared to infliximab and cyclosporine,[1] but due to the possible hepatotoxicity, this combination should be used cautiously. However, a case of EP caused by acitretin was reported.[45] The use of a lower initial dose of acitretin reduced the risk of worsening erythrodermic status compared to higher dose.[46] Cheilitis is the most common side effect under acitretin or etretinate.[34,40] Gastrointestinal upset and elevated lipid profile levels[42] should also be monitored. In addition, bone density should be checked as focal osteoporosis has been reported.[41]

Mycophenolate Mofetil (MMF)

Limited evidence exists for successfully using MMF for treating EP. Only one case reported two patients treated with MMF,[48] and both of them experienced 70% skin improvement after 6 weeks of treatment. No adverse effects were observed during the treatment course, and the disease did not relapse after drug discontinuation.

Tumor Necrosis Factor (TNF) Antagonist

Etanercept

Etanercept, a recombinant human fusion protein, has demonstrated efficacy in treating EP.[49–54] Esposito et al reported that with 25 mg twice weekly, a treatment response could be observed between week 12–24.[49] At week 12, five of ten (50%) patients achieved PASI 75, and at week 24, six of ten (60%) patients achieved or maintained PASI 75, and two of ten patients (20%) maintained improvement between PASI 50 and PASI 75. Piqué-Duran et al reported one case who achieved PASI 100 as early as week 9.[50] Romero-Marte et al reported one case with stable condition under etanercept for 34 months after suboptimal response to infliximab.[51] In a retrospective study, 50 mg dosing twice weekly for 12 weeks, then 50 mg weekly thereafter, 40% patients achieved PASI 50 at week 24–28.[52] Infection is the most common side effect, with pneumonia, and *Staphylococcus aureus* septicemia and urinary infection being reported.[49,52]

Infliximab

Infliximab, a chimeric monoclonal antibody, is considered to be a first-line biologic for EP due to its rapid onset.[1,44,52,53,55–70] In one multicenter study that included 24 patients,[52] one-third of the patients achieved PASI 75 at week 4 with infliximab treatment. But long-term efficacy is not so promising, as at the same study that only 48% of patients achieved PASI 75 at week 14,[52] and one case reported no further improvement after the sixth infusion of infliximab; the subject's condition was then controlled by administration of etanercept.[51] The occurrence of the anti-infliximab antibody was considered to be the reason.[55] Poulalhon et al reported the prevalence of positive detection of antinuclear antibodies (ANA) increased from 12% to 72% at week 22.[55] Thus, the use of infliximab as long-term controlling medication for EP should be evaluated. Concurrent administration with immunosuppressive medication would induce rapid clearing of erythrodermic status,[44,56,57] and MTX and acitretin are often used.

Lisby et al and Heikkila et al reported rapid treatment responses with a combination treatment with MTX.[56,57] Heikkila et al reported four (100%) patients with excellent responses after the second or third infusion of infliximab combined with MTX,[56] and Lisby et al reported three (100%) patients that almost clearance within a week after the first infusion of infliximab.[57] The dosing of infliximab ranged from 2.7 to 4.4 mg per kg and MTX with 5 to 7.5 mg per week.[57] Infection is the most common side effect, such as staphylococcus aureus septicemia,[52,57] nasopharyngitis,[60] and erysipelas.[52,57] Moreover, delayed infusion reactions,[55] myocardial infarction, suicide attempts and immunoallergic shock have also been reported after administration of infliximab.[52] Furthermore, one case reported CD30+ T-cell lymphoma under the treatment of cyclosporine and infliximab,[58] and the lesion regressed after discontinuation of these agents.

Golimumab

Golimumab, another anti-TNF, is a fully human γ-1 immunoglobulin-κ monoclonal antibody. The evidence of golimumab for treating EP is limited with only one report.[71] After three sessions of golimumab 50 mg injections every 4 weeks, the patient achieved PASI 75 without any side effects.

Adalimumab

Adalimumab is another fully human monoclonal antibody against TNF. There have been only nine patients receiving adalimumab for treatment, including one multicenter, retrospective study with seven patients,[52] and two case reports.[72,73] Most data are from the retrospective study which revealed that 67% of the patients achieved PASI75 at week 10 to 14, and at week 22 to 24, 50% of the patients achieved PASI75 or 75% improvement in BSA, compared to 25% of the patients treated with etanercept and 30% of the patients treated with infliximab in that study.[52] Richetta et al reported one case involving a hepatitis C virus (HCV) flare-up after treatment with pegylated interferon alpha-2a and ribavirin. The symptoms were controlled by adalimumab at week 3, and no adverse effects were observed during the 5 weeks of treatment.[73] One patient was diagnosed with nodal T-cell lymphoma 3 months later after administration of adalimumab.[52] Paradoxically, there are also reports regarding adalimumab as a trigger of EP.[74]

IL-12/23, IL-23 Antagonist

Ustekinumab

Ustekinumab, a monoclonal p40 IL-12/23 antagonist, has been reported for treatment of EP in several articles.[75–85] The largest study was from Italy,[75] which include 22 patients. As early as week 4, most of the patients had improved clinical condition, 15 (68.2%) patients achieved PASI 90 at week 28, and sustained effects were seen at week 60. Additionally, Wang et al reported suboptimal treatment effects: at week 28, only 3 (37.5%) patients achieved PASI 90.[77] Ustekinumab has also been reported as effective for cases of prior failure with anti-TNF agents,[76,82–84] and one case reported sustained maintained PASI 90 at week 114 of treatment.[84] However, Viguier et al reported three cases under the treatment of ustekinumab, in which only one (33.3%) had treatment response,[52] with the other two patients experiencing inadequate response to prior anti-TNF agents. Ustekinumab is also considered as a first-line treatment for acute and severe cases of EP.[70] Although ustekinumab is considered to have a relative low risk of infection compared to anti-TNF agents, a case of latent TB reactivation induced by ustekinumab has been reported.[86] One adverse event of sudden death was reported after 9 months of treatment of ustekinumab.[52] Furunculosis and widespread *Staphylococcus* infection have been observed.[52]

Guselkumab

Guselkumab, an interleukin 23 inhibitor that targets the p19 subunit, was reported as effective for EP in 24 cases. In an open-label, multicenter, Phase 3 study[87] (50mg at weeks 0, 4 and every 8 weeks thereafter until week 52), 10 (90.9%) patients achieved treatment success, while 5 (45.5%) patients achieved "very much improved" under Clinical Global Impression of Improvement (CGI). At week 52, 10 (90.9%) patients achieved a mean absolute PASI of 3.9 (SD = 4.27) with a median improvement of 94.1%. Megna et al reported one patient achieved PASI 100 after 20 weeks of therapy, and the effect remained until week 48.[88] Chiang et al reported 13 patients with follow-up for 28 weeks,[89] in which 8 (61.5%) patients achieved PASI 50 response at week 12, and sustained effects were observed for these PASI 50 responders. The treatment efficacy at week 12 could be seen as one predictor for patient response for guselkumab.[89] The most common adverse event was nasopharyngitis.[87]

Risankizumab

Risankizumab is another IL-23 antagonist that targets the p19 subunit. One phase 3 open-label clinical trial has been completed in Japanese patients with pustular psoriasis or EP,[90] dosing with 75 mg at week 0, week 4, and every 12 weeks. At week 16, the clinical response was 100%, and all of the patients achieved PASI 90.

IL-17 Antagonist

Secukinumab

Secukinumab, a fully human monoclonal IL-17A antibody, is administered at a dose of 300 mg weekly for the first 5 weeks and every 4 weeks thereafter for the treatment of EP.[91–101] The efficacy of secukinumab can be seen as early as week 2 to week 6.[92–94] Mateu-Puchades et al reported 5 (100%) patients achieved PASI 90 at week 16 to week 20.[93] Furthermore, long-term remission was observed for patients with EP under secukinumab.[96,97,100,101] One multicenter, retrospective study reported 10 of 13 (76.9%) patients had a treatment response.[98] At week 52, 5 (38.5%) patients achieved PASI 90 and 5 patients achieved PASI 100, and the median time to clearance was 3 weeks.[98] No recurrences were seen during the 52 weeks follow-up.[98] However, Weng et al reported that only 6/10 patients (60%) achieved PASI 75 response at week 24 possibly because most of the patients had failed with multiple biologics previously.[91] No major events were observed during treatment course.[91–93]

Ixekizumab

Ixekizumab, another IL-17A blocker, demonstrated a sustained effect for EP according to a study from Japan.[102,103] In an open-label, phase 3 study, eight patients were enrolled (dosed 160 mg at week 0, 80 mg every 2 weeks through week 12, and 80 mg every 4 weeks until to week 244).[102,103] Eight (100%) patients achieved PASI 75 after 12 weeks of treatment, all patients maintained PASI 75 at week 24 and week 52, and 6 (75%) patients achieved PASI 90.[102] The results revealed that the effects were sustained to week 244, the mean PASI score was 42.8 at baseline, 3.0 at week 52, and 5.0 at week 244. There are also several case reports regarding the efficacy of ixekizumab for EP,[104–106] including one case with human immunodeficiency virus (HIV) infection.[106] For patients with prior failure with secukinumab, ixekizumab still demonstrated a rapid response as early as week 4.[107] Suboptimal responses were reported in only four (44%) patients, who achieved PASI 75 at week 12 according to a previous study. In addition, the response was even poorer after prolonged use.[108] After week 52, the discontinuation rate increased, only three (21.4%) patients achieved PASI 75, and one (7.1%) patient achieved PASI 90. Infection was a common side effect,[103] including upper respiratory tract infection and gastroenteritis. Injection-site swelling was also observed in about 30% of the cases.[107,108]

Brodalumab

Brodalumab, an anti-IL-17-receptor antibody, also demonstrated efficacy for EP.

There is one open-label study and two case reports discussing the treatment of brodalumab.[109–111] During a 52-week, phase 3, multicenter, open-label study,[109] with brodalumab 140mg twice weekly subcutaneous administration initially (week 0, week 1, week 2), 5 (27.8%) patients were shifted to receive 210 mg based on the investigators' decision. Eighteen (100%) patients showed clinical improvement, under the definition of achieving CGI classified as "improved" or "remission" at week 12 and week 52. Sustainable effects were observed through week 52, PASI 75 and PASI 90 achievement rates were both 88.9%, while the PASI 100 response was 61.1%. Bernardini et al reported one case with EP and polycythemia,[110] and the PASI score improved from 42 to 22 within 4 weeks of treatment with brodalumab. Megna et al reported two cases successfully treated with EP, one achieved PASI 90 at week 3 and reached PASI 100 at week 12, and the other one achieved PASI 90 at week 12.[111] Patients usually tolerated brodalumab well without major adverse events,[110,112] The most common adverse event was nasopharyngitis.[109]

Others

Apremilast

Apremilast, a phosphodiesterase 4 (PDE4) inhibitor, has been used for EP in four case reports.[112–115] Papadavid et al reported one case of a previous failure with MTX, cyclosporine and adalimumab, who achieved PASI 100 after apremilast 30 mg twice daily for 20 days.[112] Krishnamoorthy et al reported one case with the total resolution of the lesions after 10 weeks of treatment without relapse for 1 year.[113] Another case was infected with coronavirus 2019 (COVID-19) and was treated successfully with apremilast for EP.[115] Apremilast may also be effective for elderly EP patient, according to one retrospective study.[116] Papadavid et al reported gradual deterioration of the absolute PASI score after 4 months of treatment.[112] Infection is still one of the common side

effects as one case experienced two episodes of upper respiratory infection during the treatment with apremilast.[113] Furthermore, one major adverse event was atrial fibrillation induced by apremilast.[114]

Naltrexone

Naltrexone, which affects the opioid growth factor-opioid growth factor receptor, also plays a role in the immune system. Beltran Monasterio et al reported after oral low-dose naltrexone with a daily dose of 4.5 mg for 3 months, the patient remained complete remission after 6 months of treatment.[117]

Panitumumab

Panitumumab is a human monoclonal antibody against EGFR, and was reported to have some clinical effect for psoriasis in one patient with rectal cancer.[118] The patient had improved clinical condition within 10 days of treatment with panitumumab, although no PASI score was reported.

Antioxidants

In one randomized controlled trial, coenzyme Q10, vitamin E, and selenium supplementation were beneficial for EP.[119] Clinical conditions improved with supplementation of antioxidants. After treatment for 30 days, PASI score was 19 ± 4 for the supplement group and 30 ± 5 for the placebo group ($p < 0.05$). Due to a lack of further studies, the evidence for using antioxidants for EP has been called into question.

Systemic Steroid

Systemic steroid is not recommended according to the published consensus of the US National Psoriasis Foundation in 2010.[1] However, the use of systemic steroid for treatment of psoriasis may be more common than expected in real world but is highly controversial. Exacerbation of erythrodermic status after withdrawal or reduction of systemic corticosteroid has been well documented,[2] but it may be uncommon as reported in some recent studies.[120,121] Anecdotal reports showed improvement of EP following systemic steroid.[86,122] Short course systemic steroid, combined with conventional immunosuppressive agents, can be considered for acute cases[122] who are not accessible or contraindicated to biologics or cyclosporine.

Phototherapy

Phototherapy is not suggested for acute EP, due to the photosensitization can increase the risk of Koebnerization.[1,2] But phototherapy can still be considered as one of the treatment options for long-term, stable EP cases.[1] Some case reported phototherapy as adjunctive therapy for EP.[123,124] Pang et al reported one case with phototherapy as adjunctive therapy who was refractory to acitretin.[123]

Discussion

EP is a variant of psoriasis that is more resistant to conventional treatment. Biologics have revolutionized the treatment of plaque-type psoriasis, and shown promise in EP.[70,125,126] Anti-TNF agents, such as infliximab and etanercept can be combined with traditional immunosuppressive agents for better efficacy,[125] while anti-IL12/23 agents and anti-IL17 agents are usually given as monotherapy for EP due to their superior efficacy, and are therefore used as first-line treatments for EP, including ustekinumab, secukinumab, ixekizumab, guselkumab and brodalumab.[70,125,126] In particular, anti-IL17 agents can control the symptoms of EP within weeks,[92–94,107,109–111,] which may be considered in patients who need rapid control. Furthermore, an ongoing trial for risankizumab revealed promising results for 16 weeks,[90] but the longer-duration efficacy remains to be published.

However, there is evidence supporting the efficacy of biologics for treating EP in case reports and case-series, albeit they often lack long-term follow up data. In pivotal trials of biologics for psoriasis, current or even prior EP have been excluded for the study.[127] Even in countries that issue indications for use of biologics for EP, such as Japan, the number of patients in the trials have been severely limited, 8 for infliximab,[60] 8 for ixekizumab,[102] 11 for guselkumab,[87] and 18 for brodalumab.[109] Moreover, none of the trials were randomized active or placebo controlled trials. Among the biologics, fewer major adverse events were reported for anti-IL12/23 agents and anti-IL17 agents than anti-TNF agents, and infection remains the most common side effect which should be monitored. Interestingly, according to a previous study,[128] in biologic-naïve patients with psoriasis or psoriatic arthritis, anti-IL12/23 agents were associated with a reduced risk of infection compared to anti-TNF and anti-IL-17 agents. However, there is no difference in infection risk in either of these agents in patients with prior biologic use. Whether the result can be applied to EP patients awaits further studies. In addition, it is also important to consider the comorbidities during the treatment of EP.[2] Several articles reported EP triggered by infection, such as HCV and HIV infection.[47,73,106] Although biologics are considered safer

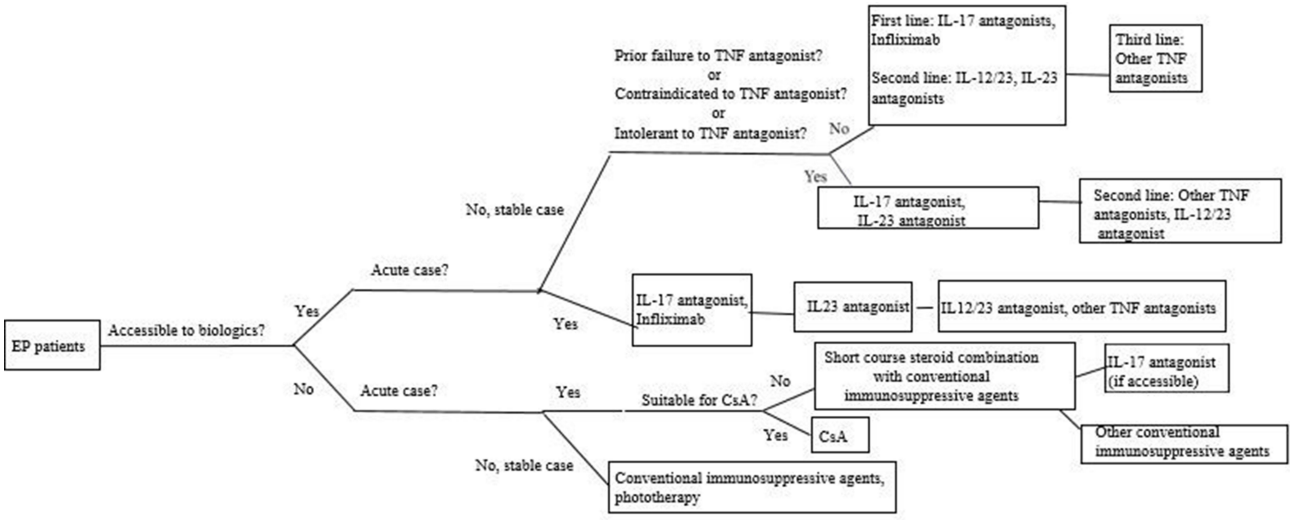

Figure 1 Treatment algorithm of EP, suggested by the author.
Abbreviations: CsA, cyclosporine; EP, erythrodermic psoriasis; IL, interleukin; TNF, tumor necrosis factor.

agents compared to conventional oral agents, their use in patients with viral hepatitis and HIV remains limited.

Drug survival is impaired in EP compared to plaque-type psoriasis in post-marketing studies. Thus, patients with EP treated with biologics tend to have multiple experiences of prior biologics failure, which will also compromise subsequent treatment efficacy.[129] In general, patients achieved better efficacy after switching to IL-23 and IL-17 antagonists after previous poor response to anti-TNF agents and ustekinumab.[130] However, in patients with prior inadequate response to secukinumab,[107,108] the results were poorer than the open-label, phase 3 study after the switch to ixekizumab.[103] Interestingly, although the efficacy of small oral molecules is less satisfactory compared to biologics in the treatment of psoriasis, two promising results of using apremilast were reported in EP[112,113]; however, the case numbers were small. Likewise, tofacitinib has been reported to be effective in patients with moderate to severe psoriasis who had inadequate responses to prior biologics.[131] However, its role in EP remains unknown. Further head-to head controlled studies are needed for more evidence-based treatment guidelines.

For patients who have no access to biologics, conventional immunosuppressive agents are suggested. Cyclosporine is suggested for acute cases, and others for stable cases.[1] Short course systemic corticosteroid should be reserved for EP patients during severe acute flare who do not has access to biologics and are contraindicated to cyclosporine due to uncontrolled hypertension or renal insufficiency or malignancy. Even in these patients, adequate hydration and aggressive control of hypertension should be attempted to enable the use of cyclosporine. However, the optimal dose and duration of systemic corticosteroid use is unknown. Transition and/or overlap to a non-systemic corticosteroid regimen should be initiated once the acute flare is controlled. Preferably, a fast onset biologic such as IL-17 inhibitor should be given to prevent the rebound/flare of psoriasis after corticosteroid withdrawal. However, gradual corticosteroid taper may be needed if conventional oral agents or phototherapy are used. We propose the algorithm for treatment of EP after literature review (Figure 1).

Conclusion

Despite the rapid progress in the development of biologics for psoriasis, data supporting the efficacy in EP remain limited. Also, the remission duration and risk of rebound upon discontinuation are poorly studied. In addition, it is important to understand the drug survival time, optimal dosing, and pharmacokinetics of biologics for EP.

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