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REVIEW

# Biologics for the Management of Erythrodermic Psoriasis: An Updated Review

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**Abstract:** Erythrodermic psoriasis (EP) is a severe and rare variant of psoriasis (less than 3% of cases), characterized by generalized scaling and erythema affecting more than 90% of body surface area. Several systemic symptoms can be present in patients with EP such as lymphadenopathy, arthralgia, fever, fatigue, dehydration, serum electrolyte disturbances, and tachycardia making this condition a possible life-threatening disease, particularly if appropriate treatments are not performed. In this scenario, effective and safe therapies are required. Unfortunately, the rarity of EP makes head-to-head Phase III trials challenging, leading to the lack of established guidelines for its management. Globally, conventional systemic drugs such as cyclosporine, methotrexate, and retinoids often have contraindications linked to patients' comorbidities and have not shown a high profile of efficacy and safety. Recently, the development of biologic drugs including anti-tumor necrosis factor-α and anti-interleukin 12–23, 23, and 17 has revealed favorable results for the management of plaque psoriasis, making them also a possible therapeutic option for EP disease. However, their use in EP is still off-label. The aim of our study was to review current literature on the use of biologic drugs for the treatment of EPs in order to offer a wide perspective on their possible application in EP management.

**Keywords:** erythrodermic psoriasis, treatment, biologic drugs

## Introduction

Psoriasis is a chronic inflammatory skin disease, with a prevalence of 2–3% among the worldwide population.[1–3] Although chronic plaque psoriasis is the most common clinical presentation, accounting for more than 80% of cases, several clinical phenotypes can be distinguished.[1–3] Among these, erythrodermic psoriasis (EP) is a severe and rare variant (less than 3% of cases of psoriasis), characterized by generalized scaling and erythema affecting more than 90% of body surface area (BSA).[4] Usually, EP develops in subjects with poorly controlled psoriatic disease. However, numerous factors such as drugs (eg lithium and interferon), systemic infection, and abrupt withdrawal of systemic medications (mainly corticosteroids) may trigger EP.[5] Moreover, several systemic symptoms can be present in patients with EP such as lymphadenopathy, arthralgia, fever, fatigue, dehydration, and tachycardia, making this condition a possible life-threatening disease, particularly if appropriate treatments are not performed.[5] Moreover, high incidence rates of serum electrolyte disturbances (hypokalemia, hypocalcemia, hyposodemia, and hypophosphatemia) have been related to EP, complicating the clinical picture.[6] Unfortunately, the rarity of EP makes head-to-head phase III trials challenging, leading to the lack of established guidelines for EP management. Indeed, the latest guidelines on EP were published in 2010 by the National Psoriasis Foundation Consensus, before the development of most biologic agents currently approved to treat psoriasis.[7] Globally, conventional systemic drugs such as cyclosporine, methotrexate, and retinoids often show contraindications linked to patients' comorbidities.[8–10] Recently, the development of biologic drugs including anti-tumor necrosis factor (TNF) α and anti-interleukin (IL) 12–23, 23, and 17 have shown favourable results for the management of plaque psoriasis,[11,12] making them also a possible therapeutic option for EP disease.[13–15] However, their

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use in EP is still off-label. The aim of our study was to review current literature on the use of biologic drugs for the treatment of EP in order to offer a wide perspective on their possible application in EP management.

## Materials and Methods

Literature research using the following databases was performed (until April 30, 2023): PubMed, Embase, Cochrane Skin, clinicaltrials.gov, and Google Scholar. The following terms were considered: "psoriasis", "erythrodermic psoriasis", "biologics", "biologic drugs", "effectiveness", "efficacy", "safety", "adalimumab", "etanercept", "certolizumab", "bimekizumab", "infliximab", "secukinumab", "ixekizumab", "brodalumab", "ustekinumab", "risankizumab", "tildrakizumab", "guselkumab". Relevant data from the screened and analyzed manuscripts were pointed out following the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines. Reviews, meta-analyses, clinical studies, real-life experiences, case reports, and series were examined in our review, selecting the most relevant manuscripts. Only English language articles were collected. Moreover, the abstracts and the texts of designated articles were reviewed to refine the research as well as references were also considered to avoid that some manuscripts could be missed. This manuscript is based on previously performed studies and does not contain any studies with human or animal participants carried out by any of the authors.

## Results

Detailed data on clinical studies, case series, and case reports on patients affected by EP treated with currently available biologic drugs are reported in Table 1.

## Adalimumab

Adalimumab is a human monoclonal antibody blocking TNF-α.[70,71] Currently, there are only three case reports regarding EP treated with adalimumab.[16–18] Among these, Richetta et al reported the case of a patient with a history of HCV infection who developed EP after treatment with interferon alpha for HCV,[16] and Wu et al who reported cases of patients affected by EP and niacin deficiency successfully treated with and anti-inflammatory, adalimumab, tripterygium glycoside, and sodium thiosulfate.[17] Finally, Mumoli et al described the case of a patient who developed EP following treatment withdrawal with intravenous corticosteroids for chronic obstructive pulmonary disease treated with adalimumab.[18] Globally, one patient showed remission at week 3,[16] while the remaining two at week 12.[17,18] Unfortunately, none of these cases reported PASI scores.[16–18]

Of interest, six cases of EP have been reported during treatment with adalimumab for psoriatic arthritis,[72] hidradenitis suppurativa,[73] Crohn's disease, rheumatoid arthritis,[74] pityriasis rubra pilaris, and psoriasis.[75,76] Finally, there are two cases of patients affected by EP not responding to adalimumab except for injection sites, which were spared. In both cases, the authors suggested that the lipophilic nature of adalimumab may allow it to achieve higher concentrations in subcutaneous fat at the sites of administration, leading to the differential responses seen in injected and non-injected sites resulting in sparing of injected sites despite an erythrodermic flare elsewhere.[36,77] Patients were successfully switched to secukinumab and to adalimumab plus methotrexate, respectively.[36,77]

## Etanercept

Etanercept is a TNFα inhibitor approved for psoriasis.[78] Its effectiveness in EP management has been reported in a real-life study enrolling 10 patients (male: 80.0%; mean age: 56.4±11.7 years) affected by EP [mean Psoriasis Area Severity Index (PASI) at baseline: 39.1 ± 16.2].[19] After 12 weeks of treatment, 5 (50.0%) patients achieved PASI75 response, as well as 6 (60.0%) subjects reached PASI75 response at week 24.[19] ALthough two adverse events (AEs) were reported (urinary tract infection and pruritus), none of these led to treatment discontinuation.[19] Moreover, a case of EP successfully treated with etanercept has been reported in a patient receiving concomitant therapy for HCV infection,[20] and in a pediatric subject (7 years old) who showed a clinical improvement after 3 months of treatment, without AEs.[21]

**Table 1** Detailed Data on Clinical Studies, Case Series, and Case Reports on Patients Affected by Erythrodermic Psoriasis Treated with Currently Available Biologic Drugs

| Drug | Study | Authors | Patients | Age/Sex | Baseline Score | Efficacy | Safety |
|---|---|---|---|---|---|---|---|
| **Anti-TNFα** | | | | | | | |
| **Adalimumab** | Case Report | Richetta et al[16] | 1 | 48/M | Not reported | Not reported | Not reported |
| | | Wu et al[17] | 1 | Not reported/M | Not reported | Not reported | Not reported |
| | | Mumoli et al[18] | 1 | 62/M | Not reported | Not reported | Not reported |
| **Etanercept** | Real-Life Study | Esposito et al[19] | 10 | Age: 56.4 ± 11.7<br>M: 8 (80.0%)<br>F: 2 (20.0%) | PASI: 39.1 ± 16.2 | 5 (50.0%) PASI75 at W12<br>6 (60.0%) PASI75 at W24 | 2 (20.0%) AEs<br>1 (10.0%) urinary tract infection<br>1 (10.0%) pruritus |
| | Case Report | Talat et al[20] | 1 | 28/M | Not reported | Not reported | Not reported |
| | | Fraga et al[21] | 1 | 7/M | Not reported | Not reported | Not reported |
| **Certolizumab** | Phase III Trial | Okubo et al[22] | Total: 15<br>- Group A: 8 patients, 400mg Q2W<br>- Group B: 7 patients, 400mg W0/2/4 and 200mg Q2W thereafter | Age:<br>- Group A: 47.8 ± 11.3<br>- Group B: 56.0 ± 8.5<br>M: 13 (86.7%)<br>F: 2 (13.3%) | Group A:<br>- PASI: 43.7 ± 17.9<br>- BSA: 87.1 ± 6.8<br>Group B:<br>- PASI: 34.3 ± 9.2<br>- BSA: 86.6 ± 3.6 | Group A:<br>- W16: PASI75/90: 5(62.5%)/5(62.5%)<br>Group B:<br>- W16: PASI75/90: 4(57.1%)/4(57.1%) | 14 (93.3%) patients reported at least 1AE, nasopharyngitis was the commonest (7, 46.7%).<br>1 serious AE (erythema multiforme)<br>3 AE (erythema multiforme, psoriasis, latent tuberculosis) led to treatment discontinuation. |
| **Infliximab** | Case Series | Takahashi et al[23] | 7 | Pt 1: 39/M<br>Pt 2: 46/F<br>Pt 3: 46/M<br>Pt 4: 33/M<br>Pt 5: 40/F<br>Pt 6: 49/M<br>Pt: 56/M | Not reported | PASI90 at W6 | None |
| | | Heikkilä et al[24] | 4 | Pt 1: 16/M<br>Pt 2: 27/M<br>Pt 3: 54M<br>Pt 4: 29/M | Not reported | Not reported | Not reported |
| | Case Report | Kurokawa et al[25] | 1 | 45/M | PASI: 43<br>BSA: >80 | PASI: 5.6 at W13 | None |
| | | Trídico et al[26] | 1 | 55/M | Not reported | Infliximab effectiveness maintained over time (11 years) | None |

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**Table 1** (Continued).

| Drug | Study | Authors | Patients | Age/Sex | Baseline Score | Efficacy | Safety |
|---|---|---|---|---|---|---|---|
| **Anti-IL17** | | | | | | | |
| **Secukinumab** | Case Series | Damiani et al[27] | 13 | Age: 40 (range 28–52)<br>M: 9 (69.2%)<br>F: 4 (30.8%) | PASI: not reported | W16: PASI90/100: 5(38.5%)/4(30.8%)<br>W52: PASI90/100: 5(38.5%)/5(38.5%) | AEs: 5 (48.5%), with injection-site pain as the commonest (3, 60.0%) |
| | | Weng et al[28] | 10 | Age: 42.6 ± 11<br>M: 8 (80.0%)<br>F: 2 (20.0%) | PASI: 32.4 ± 5.7<br>BSA: 89.0 ± 7.1 | W8: PASI75/90/100: 5(50.0%)/2(20.0%)/1(10.0%)<br>W12: PASI75/90/100: 7(70.0%)/4(40.0%)1(10.0%)<br>W16: PASI75/90/100: 7(70.0%)/4(40.0%)2(20.0%)<br>W24: PASI75/90/100: 6(60.0%)/4(30.0%)1(10.0%) | None |
| | | Mateu-Puchades et al[29] | 6 | Pt 1: 54/M<br>Pt 2: 59/M<br>Pt 3: 45/M<br>Pt 4: 36/M<br>Pt 5: 44/M | BSA >85% | W16: PASI90/100: 5(100%)/4(80.0%) | None |
| | | Panda et al[30] | 6 | Pt 1: 40/F<br>Pt 2: 23/M<br>Pt 3: 35/M<br>Pt 4: 40/M<br>Pt 5: 43/F<br>Pt 6: 43/M | Pt 1: PASI: 28<br>Pt 2: PASI: 32.4<br>Pt 3: PASI: 24.6<br>Pt 4: PASI: 28<br>Pt 5: PASI: 22<br>Pt 6: PASI: 20.8 | Pt 1: PASI100 at W28<br>Pt 2: PASI100 at W28<br>Pt 3: PASI100 at W28<br>Pt 4: PASI100 at W28<br>Pt 5: PASI100 at W28<br>Pt 6: PASI100 at W28 | None |
| | | Mugheddu et al[31] | 2 | Pt 1: 28/M<br>Pt 2: 61/M | Pt 1: PASI:45<br>Pt 2: PASI:41 | Pt 1: PASI100 at W8<br>Pt 2: PASI100 at W8 | None |
| | | Liu et al[32] | 2 | Pt 1: 50/F<br>Pt 2: 46/M | Pt 1: PASI:40 BSA:100<br>Pt 2: PASI: 28 BSA: 80 | Pt 1: PASI90 at W12<br>Pt 2: PASI90 at W12 | None |
| | Case Report | Carriero et al[33] | 1 | 72/M | PASI: 60 | PASI100 at W16 | None |
| | | Lu et al[34] | 1 | 70/F | BSA:90 | PASI100 at W12 | None |
| | | Pizzati et al[35] | 1 | 44/M | PASI: 31.5<br>BSA: 95 | PASI100 at W8 | None |
| | | Ozcan et al[36] | 1 | 31/M | PASI: 38<br>BSA: 80 | PASI75 at W12 | None |
| | | Zhao et al[37] | 1 | 7/M | PASI: 37.5 | PASI100 at W18 | None |
| | | Dogra et al[38] | 1 | 13/M | PASI: 50 | PASI100 at W8 | None |
| | | Galluzzo et al[35] | 1 | 55/M | PASI: 42 | PASI90 at W12 | None |

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|---|---|---|---|---|---|---|---|
| **Ixekizumab** | Phase III Trial | Saeki et al[39,40] | 8 | Age: 50.2 ± 12.9<br>M: 7 (87.5%)<br>F: 1 (12.5%) | PASI: 42.8 ± 11.6 | W12: PASI75/90/100: 8(100%)/5(62.5%)/2(25.0%)<br>W24: PASI75/90/100: 8(100%)/7(87.5%)/1(12.5%)<br>W24: PASI75/90/100: 8(100%)/6(75.0%)/1(12.5%) | 7 (87.5%) patients experienced at least 1 AE, with infections as the main one (6, 75.0%). |
| | | Morita et al[41] | 5 (4 completed the study) | Age: 42.2 ± 14.4<br>M: 3 (60.0%)<br>F: 2 (40.0%) | PASI: 41.1<br>BSA: 87.4 ± 8.0 | W12: PASI75/90: 2(50.0%)/1(25.0%)<br>W20: PASI75/90: 3(75.0%)/1(25.0%) | 4/5 (80.0%) patients experienced at least 1 AE, leading to treatment discontinuation in 1 case (seizure) |
| | Case Series | Lo et al[42] | 9<br>POST secuk important | Age: 45.9 ± 13.4<br>M: 7 (77.8%)<br>F: 2 (22.2%) | PASI: 28.1 ± 8.9<br>BSA: 65.1 ± 22.1 | W4: PASI75/90: 2(22.2%)/2(22.2%)<br>W8: PASI75/90: 2(22.2%)/3(33.3%)<br>W12: PASI75/90: 4(44.4%)/1(11.1%) | 1(11.1%) injection site reaction |
| | | Trovato et al[43] | 2 | Pt 1: 67/M<br>Pt 2: 55/F | Pt 1: PASI: 41.5 BSA: >80<br>Pt 2: PASI: 32 BSA: >75 | Pt 1: PASI90 at W8 and PASI100 at W104<br>Pt 2: PASI90 at W6 and PASI100 at W36 | None |
| | Case Report | Megna et al[44] | 1 | 66/F | PASI: 58<br>BSA: 95 | PASI75 at W2 and PASI100 at W6 | None |
| | | Vinaixa Aranzazu et al[45] | 1 | 55/M | PASI: 30.6<br>BSA: 68 | PASI100 at W12 | None |
| | | Pinto-Pulido et al[46] | 1 | 55/M | PASI: 35<br>BSA: 75 | PASI100 at W8 | None |
| **Secukinumab/ Ixekizumab** | Head-to-head | Avallone et al[47] | Secu: 12<br>Ixe: 3 | Secu: 10M (83.3%)<br>Ixe: 0M (0%) | Secu: 21.9 ± 6.2<br>Ixe: 25 ± 5 | Secu:<br>W12: PASI90/PASI100: 7(46.7%)/5(33.3%)<br>W48: PASI90/PASI100: 9(60.0%)/6(40.0%)<br>Ixe:<br>W12: PASI90/PASI100: no cases<br>W48: PASI90/PASI100: no cases | None |
| | Case Series | Bernardini et al[48] | Secu: 2 (pt1-<br>Ixe: 3 (pt2-3) | Pt 1: 52/M<br>Pt 2: 30/M<br>Pt 3: 26/M<br>Pt 4: 37/M<br>Pt 5: 54/M | Pt 1: 42<br>Pt 2: 30<br>Pt 3: 32<br>Pt 4: 39<br>Pt 5: 28 | Pt 1: PASI 6 at W52<br>Pt 2: PASI 5 at W52<br>Pt 3: PASI 6 at W12<br>Pt 4: PASI 4 at W4<br>Pt 5: PASI 4 at W5 | None |
| | | Pangilinan et al[49] | Secu: 1<br>Ixe: 1 | Secu: 31/M<br>Ixe: 60/M | Secu: 24<br>Ixe: 36 | Secu: PASI100 at W4<br>Ixe: PASI75 at W5 | |

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**Table 1** (Continued).

| Drug | Study | Authors | Patients | Age/Sex | Baseline Score | Efficacy | Safety |
|---|---|---|---|---|---|---|---|
| **Brodalumab** | Case Series | Mota et al[50] | 3 | Pt 1: 40/M<br>Pt 2: 59/M<br>Pt 3: 43/M | Pt 1: PASI:48 BSA:100<br>Pt 2: PASI:43 BSA:90<br>Pt 3: PASI:31 BSA:90 | Pt 1: PASI100 at W14<br>Pt 2: PASI100 at W8<br>Pt 3: PASI100 at W8 | None |
| | | Megna et al[51] | 2 | Pt 1: 72/M<br>Pt 2: 42/M | Pt 1: BSA: >90<br>Pt 2: BSA: >90 | Pt 1: PASI100 at W12<br>Pt 2: PASI90 at W12 | None |
| | Case Report | Bernardini et al[52] | 1 | 52/M | PASI: 42<br>BSA: 90 | PASI: 22 at W4 and remaining reduced for 16W | None |
| **Bimekizumab** | Case Report | Megna et al[53] | 1 | 40/M | PASI: 55<br>BSA: 90 | PASI100 at W4 | None |
| **Anti-IL12/23** | | | | | | | |
| **Ustekinumab** | Multicenter Study | Pescitelli et al[54] | 22 | Age: not reported<br>M: 14 (63.6%)<br>F: 8 (36.4%) | PASI: 45.0 ± 7.1 | W28: PASI75/90: 19(86.4%)/15(68.2) | None |
| | Case Series | Wang et al[55] | 8 | Age: 41.6 ± 10.5<br>M: 7 (87.5%)<br>F: 1 (12.5%) | PASI: 34.7 ± 5.3 | W12: PASI75/90: 4(50.0%)/1(12.5%)<br>W28: PASI75/90: 4(50.0%)/3(37.5%) | None |
| | | Stinco et al[56] | 3 | Pt 1: 66/M<br>Pt 2: 51/M<br>Pt 3: 65/M | Pt 1: PASI:48.8<br>Pt 2: PASI:57.2<br>Pt 3: PASI:63 | Pt 1: PASI100 at W19<br>Pt 2: PASI100 at W28<br>Pt 3: PASI100 at W21 | None |
| | | Santos-Juanes et al[57] | 2 | Pt 1: 32/F<br>Pt 2: 41/F | Pt 1: PASI:37<br>Pt 2: PASI:50 | Pt 1: PASI90 at W12<br>Pt 2: PASI90 at W12 | None |
| | | Saraceno et al[58] | 2 | Pt 1: 59/M<br>Pt 2: 53/F | Pt 1: PASI:59 BSA:100<br>Pt 2: PASI:40 | Pt 1: PASI75 at W12<br>Pt 2: PASI100 at W12 | None |
| | | Kim et al[59] | 2 | Pt 1: 42/M<br>Pt 2: 26/M | Pt 1: PASI:64.8<br>Pt 2: PASI:50.9 | Pt 1: PASI:9.6 at W28<br>Pt 2: PASI75 at W16 | None |
| | Case Report | Castiñeiras et al[60] | 1 | 47/M | PASI: 45 | PASI: 7.4 at W28 | None |
| | | Koutsoukou et al[61] | 1 | 60/F | PASI: 69.6 | PASI: 2.1. at W52 | None |
| **Anti-IL23** | | | | | | | |
| **Tildrakizumab** | Case Report | Trevisan et al[62] | 1 | 56/M | PASI: 40<br>BSA: 80 | PASI100 at W16 | None |
| | | Megna et al[63] | 1 | 61/M | PASI: 38<br>BSA: 90 | PASI100 at W16 | None |


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|---|---|---|---|---|---|---|---|
| **Guselkumab** | Phase III Trial | Santo et al[64] | 11 | Age: 54.6 ± 16.7<br>M: 10 (90.9%)<br>F: 1 (9.1%) | PASI: 40.9 ± 10.2<br>BSA: 86.0 ± 5.4 | W16: 5 (45.5%), 3 (27.3%) and 2 (18.2%) patients reached a CGI score of "very much improved", "much improved", and "minimally improved", respectively.<br>W52: PASI: 3.9 ± 4.3<br>W52: BSA: 7.0 ± 6.8 | All of the patients experienced at least 1 AE, with nasopharyngitis as the commonest (4, 36.4%). |
| | Retrospective Study | Chiang et al[65] | 13 | Age: 50.5 ± 15.3<br>M: 12 (92.3%)<br>F; 1 (7.7%) | PASI: 23.8 ± 9.7 | W4: PASI75: 2(15.4%)<br>W12: PASI75/90: 5(38.5%)/1(7.7%)<br>W20: PASI75/90: 7(53.8%)/3(23.1%)<br>W28: PASI75/90/100: 6(46.2%)/4(30.8%)/2 (15.4%) | None |
| | Case Report | Megna et al[66] | 1 | 38/M | PASI: 48<br>BSA: 92 | PASI100 at W20 | None |
| **Risankizumab** | Phase III Trial | Yamanaka et al[67] | 9 | Age: 40.2 ± 18.8<br>M: 8 (88.9%)<br>F: 1 (11.1%) | PASI: 52.1 ± 13.6<br>BSA: 92.4 ± 6.2 | W16: 9 (100%) patients reached CGI score of "slightly improved"<br>W16: PASI90: 7 (77.8%)<br>W52: PASI90: 8 (88.9%)<br>W160: PASI90: 7 (77.8%) | Any AE: 7 (77.8%)<br>Serious AE: 2 (22.2%) |
| | Case Report | Alajlan et al[68] | 1 | 48/M | BSA: 90 | PASI100 at W16 | None |
| **Other studies** | Retrospective Study | Viguier et al[69] | 28 (42 flares)<br>Infliximab: 24<br>Adalimumab: 7<br>Etanercept: 6<br>Ustekinumab: 3<br>Efalizumab: 2 | Age: not reported<br>M: 20 (71.4%)<br>F: 8 (28.6%) | BSA > 90 | PASI75 at W24:<br>Infliximab: 20%<br>Adalimumab: 60%<br>Etanercept: 50%<br>Ustekinumab: 0%<br>Efalizumab: 0% | Any AE: 14<br>Serious AE: 12, with bacterial infection as the main one (7, 58.3%).<br>Treatment discontinuation for safety concerns was collected in 19% of cases |

**Abbreviations**: M, Male; F, Female; PASI, Psoriasis Area Severity Index; W, Week; AE, Adverse event; BSA, Body Surface Area; Pt, Patient.



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## Certolizumab

Certolizumab pegol is currently the only PEGylated anti-TNFα biologic drug approved for psoriasis management.[79] Its use in EP has been investigated in a 52 week, multicenter, phase III study.[22] A total of 15 patients were randomized to receive certolizumab 400 mg every 2 weeks (n = 8) or 200 mg every 2 weeks following a loading dose of 400 mg at week 0/2/4 (n = 7) for 16 weeks, therefore increasing the dosage to 400 mg or withdrawing the study if patients did not respond to treatment.[22] The main outcome was the proportion of patients achieving a Clinical Global Improvement (CGI) of "remission" or "improved." Secondary endpoints included PASI 75/90 response.[22] At week 2, 9/15 (60.0%) patients achieved a CGI response, while all of the subjects reached CGI response at week 16 and 52. PASI75 and PASI90 response were achieved by 9/14 (64.3%) and 9/14 (64.3%) patients at week 16 and by 10/12 (83.3%) and 9/12 (75.0%) subjects at week 52, respectively.[22] Moreover, two patients increased their dose during the maintenance period.[22] As regards the safety, 14 (93.3%) patients experienced at least one AE, with nasopharyngitis the most common (7, 46.7%).[22] Finally, 3 (20.0%) patients with EP discontinued certolizumab for AE: one patient for erythema multiforme, one patient for latent tuberculosis, and one for psoriasis.[22]

## Infliximab

Infliximab is an anti-TNFα approved for psoriasis management.[80] As regards EP, few cases of this form of psoriasis successfully treated with infliximab have been described.[23–26] Among these, Takahashi et al reported the largest case series on seven patients successfully treated with infliximab.[23] All of the patients achieved PASI90 following the third infusion (week 6).[23] Finally, a case of paradoxical EP induced by treatment with infliximab has been described.[81]

## Brodalumab

Brodalumab is a human monoclonal antibody blocking the interleukin-17 receptor.[82] Its effectiveness in EP management has been reported in six cases.[50–52] Among these, Mota et al reported the largest case series involving three patients (mean age: 47.3 ± 10.2 years) affected by EP (mean PASI at baseline: 40.7 ± 8.7) who reached PASI100 response at week 8 (2, 66.7%) and week 14 (1, 33.3%).[50]

## Secukinumab

Secukinumab is a selective IL-17A inhibitor.[83] Its use in the management of EP has been reported in several case series[27–32] and case reports.[33–38,84] However, there are no clinical trials available. The largest case series has been reported by Damiani et al who reported the results of a multi-center, international, retrospective, pilot study enrolling 13 EP patients receiving secukinumab for 52 weeks.[27] At week 16, PASI90/100 response was achieved by 5 (38.5%) and 4 (30.8%) patients, respectively, while at week 52 these results were reached by 5 (38.5%) and 5 (38.5%) subjects, respectively.[27] Of note, 3 (23.1%) non-responders were collected and switched to ustekinumab 90 mg, obtaining PASI100 response after 24 weeks of treatment.[27] As regards safety, AEs were collected in 5 (38.5%) patients, with injection-site pain as the commonest (3, 60.0%).[27]

Similarly, Weng et al reported the results of a real-life study enrolling 10 patients with a mean PASI of 32.4 ± 5.7 and a mean BSA of 89.0 ± 7.1.[28] At week 8, 75/90/100 responses were achieved by 5(50.0%)/2(20.0%)/1(10.0%) patients, respectively, while 6(60.0%)/4(30.0%)/1(10.0%) subjects reached these scores at week 24.[28] No AEs were reported.[28] Of interest, two cases of pediatric EP successfully treated with secukinumab have been described.[37,38]

## Ixekizumab

Ixekizumab is an anti-IL17 biologic drug.[85] Its use in EP management has been reported by clinical trials[39–41] and real-life experiences.[42–46]

Saeki et al reported the results of a 24-week, multicenter, phase III study enrolling eight patients (seven male, 87.5%; mean age 50.2 ± 12.9) with EP undergoing treatment with ixekizumab (160 mg at baseline followed by 80 mg every 2 weeks up to week 12 and 80 mg every 4 weeks thereafter).[39] At baseline, mean PASI was 42.8 ± 11.6. A statistically significant improvement was observed, with 8 (100%), 5 (62.5%), and 2 (25.0%) patients achieving PASI75, PASI90, and PASI100 response at week 12, respectively, as well as 8 (100%), 7 (87.5%), and 1 (12.5%) subjects reached these results

at week 24.[39] As regards the safety, 7 (87.5%) patients experienced at least 1 AE, with infections as the main one (6, 75.0%).[39] Of note, none of the AEs led to treatment discontinuation. The authors also published the results of a 52-weeks extension of this study, reporting a PASI75, PASI90 and PASI100 response in 8 (100%), 6 (75.0%) and 1 (12.5%) patients, respectively.[40] The effectiveness and safety of ixekizumab in EP management has also been reported in a 20-week, phase III study enrolling five patients (three male, 60.0%; mean age: 42.2 ± 14.4 years) receiving ixekizumab at a dosage of 160 mg at baseline followed by 80 mg every 2 weeks up to week 12 (induction phase), then every 4 weeks up to week 20 (maintenance phase).[41] Globally, 5 (100%) patients completed the induction period and 4 (80.0%) the maintenance phase.[41] At week 12 and week 24, PASI75 response was reached by 2 (50.0%) and 3 (75.0%) patients, respectively.[41] Moreover, 1 (25.0%) subject reached PASI 90 response at week 12 and week 24.[41] As regards safety, no notable AEs were reported, except for a case of convulsive seizure, which led to treatment discontinuation at week 12.[41]

These results are in line with several case series and case reports.[42–46] Of note, Lo et al[42] reported the results of a case series enrolling nine patients (seven male, 77.8%; mean age: 45.9 ± 13.4 years) with EP previously treated with secukinumab. Globally, PASI75 and PASI90 were reached by 4 (44.4%) and 1 (11.1%) subjects at week 12, respectively.[42] Finally, cases of EP developed following the discontinuation of ixekizumab have been reported.[86]

## Secukinumab Vs Ixekizumab

Although clinical trials investigating the use of these biologics in EP are absent, Avallone et al conducted a real-life head-to-head study between ixekizumab and secukinumab for the management of EP.[47] A total of 15 patients were enrolled. Of these, 12 (80.0%) and 3 (20.0%) were treated with secukinumab and ixekizumab, respectively.[47] Mean PASI at baseline was 21.9 ± 6.2 in secukinumab cohort and 25 ± 5 in the ixekizumab one. At W12, 7(46.7%) and 5(33.3%) patients receiving secukinumab achieved PASI90 and PASI100 response as well as 9 (60.0%) and 6 (40.0%) subjects of this cohort reached these responses at week 48.[47] However, no patients receiving ixekizumab achieved these scores at these timepoints, even if clinical improvement was observed.[47] These results were also confirmed by a recent case series on five patients receiving ixekizumab (n = 3) and secukinumab (n = 2).[48]

Finally, two patients with HIV infection and EP successfully treated with ixekizumab and secukinumab, respectively, were reported.[49]

## Bimekizumab

Bimekizumab is the latest biologic approved for psoriasis management, acting on both IL17A and IL17F.[87,88] Since its approval, one case of EP successfully treated with bimekizumab has been reported.[53] Of interest, also a case of sub-EP has been described.[89]

## Ustekinumab

Ustekinumab is a biologic drug targeting IL12/23 p40 subunit.[90] Its effectiveness in EP management has been reported by a multicenter study enrolling 22 patients receiving ustekinumab at week 0, 4 and every 12 weeks thereafter.[54] Of note, 16 (72.7%) patients (weighting >100 kg) received ustekinumab 90 mg, while the remaining received a dosage of 45 mg.[54] Mean PASI at baseline was 45.0 ± 7.1.[54] At week 28, PASI75 and PASI90 response were reached by 19 (86.4%) and 15 (68.2%) patients, respectively, without AEs collected.[54] There are also several case series[55–59] and case reports[60,61] on the role of ustekinumab in EP reporting promising results in terms of efficacy (at least 50% of patients reaching PASI75 response at week 12) with a high safety profile (no AEs collected) in all of the patients (n = 19).

## Tildrakizumab

Tildrakizumab is a humanized IgG1 monoclonal antibody acting on IL23 p19 approved for the management of moderate-to-severe forms of psoriasis.[91,92] Although its use in plaque psoriasis has been widely described,[93,94] data on its effectiveness on EP are scant. Indeed, there are only two case reports describing EP successfully treated with tildrakizumab scheduled at labelled dosage (100 mg at weeks 0, 4, followed by every 12 weeks thereafter).[62,63]

## Guselkumab

Guselkumab is an anti-IL23 monoclonal antibody approved for the management of moderate-to-severe psoriasis.[95,96] Its promising results in terms of effectiveness and safety shown for the management of plaque psoriasis[97–99] have also been confirmed in EP. Indeed, a 52-week, phase III trial with the aim of evaluating the efficacy and safety of guselkumab in Japanese patients affected by EP has been conducted.[64] The main outcome was the achievement of a CGI score of "very much improved", "much improved", or "minimally improved" at week 16.[64] Secondary outcomes included the reduction of PASI and BSA at week 52.[64] A total of 11 (10 males, 90.9%; mean age: 54.6 ± 16.7 years) patients were enrolled.[64] Of these, 1 (9.1%) did not complete the study for consent withdrawn.[64] Guselkumab was scheduled at a dosage of 50 mg at weeks 0 and 4 and every 8 weeks thereafter.[64] At baseline, mean PASI and BSA were 40.9 ± 10.2 and 86.0 ± 5.4, respectively.[64] After 16 weeks of treatment, 5 (45.5%), 3 (27.3%) and 2 (18.2%) patients reached a CGI score of "very much improved", "much improved", and "minimally improved", respectively.[64] Similarly, PASI and BSA decreased by up to week 52 (PASI: 3.9 ± 4.3; BSA: 7.0 ± 6.8).[64] As regards safety, all of the patients experienced at least 1 AE, with nasopharyngitis as the commonest (4, 36.4%).[64] No treatment discontinuations for AEs were collected.[64] These results were confirmed by a retrospective study enrolling 13 patients (12 males, 92.3%; mean age: 50.5 ± 15.3 years) with EP receiving guselkumab 100 mg at baseline, week 4 and every 8 weeks thereafter.[65] At baseline, mean PASI was 23.8 ± 9.7. At week 4, 2 (15.4%) patients reached PASI75 response.[65] At week 28, PASI75/90/100 were achieved by 6 (46.2%), 4 (30.8%) and 2 (15.4%) subjects, respectively. No AEs were collected.[65]

The effectiveness of guselkumab in EP management has also been shown by one case report.[66] Of note, guselkumab was scheduled at a labelled dosage (100 mg week 0 and week 4, followed by a maintenance dose every 8 weeks).[66]

## Risankizumab

Risankizumab is a humanized immunoglobulin G1 monoclonal antibody that acts on the p19 subunit of IL23.[100,101] Several studies have reported its effectiveness and safety in psoriasis management.[100,101] As regards EP, the use of risankizumab was investigated in a primary analysis and 180-week follow-up results from the Phase 3, multicenter IMMspire study.[67] A total of 9 patients with EP were enrolled and randomized to receive risankizumab 150 mg (n = 4) or 75 mg (n = 5) at week 0 and week 4 and every 12 weeks thereafter through week 160.[67] At baseline, mean PASI and BSA was 46.7 ± 16.1 and 91.0 ± 7.7 in the risankizumab 75 mg cohort and 58.7 ± 6.8 and 94.3 ± 3.8 in the risankizumab 150 group, respectively.[67] The primary end point was the proportion of patients achieving a clinical response of at least "minimally improved" in the CGI scale.[67] Secondary outcomes included the proportion of patients reaching PASI90 at week 16, week 52, and through week 180 (the last follow-up visit).[67] All of the patients achieved the main endpoint, regardless of risankizumab dosage.[67] Moreover, PASI90 response was reached by 3 (60.0%) and 4 (100%) patients receiving risankizumab 75 mg and 150 mg at week 16, respectively, while 4 (80.0%) and 4 (100%) subjects in these groups reached PASI90 at week 52.[67] Finally, 3 (60.0%) and 4 (100%) subjects receiving risankizumab 75 mg and 150 mg reached PASI90 at week 160, respectively. As regards the safety, 3 (60.0%) and 4 (100%) patients in risankizumab 75 mg or 150 mg cohort experienced at least one AE. Of these, one for each group was considered serious but not treatment-related: a case of ischemic heart failure in the 75 mg group and urinary calculus in the 150 mg cohort.[67] A case report evaluate the effectiveness of risankizumab 150 mg for EP management in a real-life setting.[68] Finally, the pharmacokinetic properties of risankizumab in patients with EP have been investigated.[102]

## Other Studies

Currently, there are few studies comparing the effectiveness and safety of biologics in EP management. Viguier et al reported the results of a multicentre national retrospective study enrolling 28 patients affected by EP, representing 42 flares of erythrodermic psoriasis treated with infliximab (n = 24), adalimumab (n = 7), etanercept (n = 6), ustekinumab (n = 3), or efalizumab (n = 2).[69] At week 24, PASI75 response was reached by 20%, 60%, and 50% of patients receiving infliximab, adalimumab, and etanercept, respectively, whereas these results were not reported in the other treatment groups.[69] As regards safety, 12 serious AEs were collected, with bacterial infection as the main one (7, 58.3%).[69]

Treatment discontinuation for safety concerns was collected in 19% of cases.[69] There is also another head-to-head study, comparing ixekizumab and secukinumab, which has been previously discussed.[47]

## Discussion

EP is considered an emergency in dermatology, due to extensive skin involvement, and several complications (fever, pruritus, dehydration, asthenia, arthralgia, lymphadenopathy, electrolytic imbalances, etc.) linked to this condition.[103] Although the exact pathogenesis of EP is still not fully understood, many factors have been identified as possible triggers for EP onset, such as the abrupt withdrawal of systemic therapy with corticosteroids, infection, physical or emotional stress, and so on.[103] Near these trigger factors, several biomarkers have been hypnotized to be linked to the onset of EP, including an increased Th2 response, an elevation of IgE serum levels, and higher IL4- and IL-13 levels,[104,105] supposing an overlap with the immune phenotype of atopic dermatitis.[106–108] However, a recent study revealed a possible role of tumor necrosis factor-related weak inducer of apoptosis, which may play a role in both EP and psoriasis vulgaris.[109] Due to the rarity of EPto date, updated official guidelines and/or recommendations about EP management are still lacking. Recently, biologic agents deeply changed the management strategy of moderate-to-severe forms of psoriasis,[110] resulting in a change of therapeutic goals, from PASI 50 to PASI 100, and leading patients to reach incredible clinical outcomes in a relatively short treatment period.[110,111] Their safety and efficacy was confirmed also during Covid-19 pandemic period.[112–115] Of note, even if the use of EP in biologics approved for plaque psoriasis is off label, they appear as efficacious treatments for EP due to their rapidity of action as well as efficacy profile.[116] In this scenario, we performed a review of the current literature with the aim of assessing the effectiveness of biologic drugs for the management of EP to a wide clinical perspective on their possible application in this form of psoriasis.

Globally, clinical trials investigating the effectiveness and safety of biologic drugs for EP are scant and limited to certolizumab, ixekizumab, guselkumab, and risankizumab.[22,39–41,64,67] Even if all these trials are phase III studies, the number of enrolled patients is limited, with the largest cohort (15 patients) reported in the trial investigating the use of certolizumab. Moreover, all the trials have been conducted in Japanese population, highly limiting the generalizability of the results. However, excellent efficacy data were shown with these trials reporting up to 100% and 62.5% of patients reaching PASI75 and PASI90 at week 12, respectively.[21,39,66,84,85,97] Perhaps, long-term follow-up data are scant except for a phase III trial on risankizumab, which showed that 77.8% of subjects reached PASI90 at week 160.[66] As regards case reports and case series, most of these regarded patients receiving secukinumab for EP. Globally, there are 27 cases of EP treated with anti-TNFα (adalimumab: 2; etanercept: 12; infliximab: 13), 67 with anti-IL17 (secukinumab: 46; ixekizumab: 14; brodalumab: 6; bimekizumab: 1); 41 with ustekinumab, and 17 with anti-IL23 (tildrakizumab: 2; guselkumab: 14; risankizumab: 1).

Furthermore, head-to-head studies regarding different biologics are scant except for a comparison between secukinumab and ixekizumab, which showed comparable results in terms of effectiveness and safety for both drugs,[47] and a retrospective study investigating the use of infliximab, adalimumab, etanercept, ustekinumab, and efalizumab, which showed a PASI75 response after 24 weeks of treatment in 20%, 60%, and 50% of patients receiving infliximab, adalimumab, and etanercept, respectively, without similar results in ustekinumab and efalizumab cohort.[69]

Finally, seven cases of paradoxical EP during the use of biologic for psoriasis or other diseases have been reported. Of note, they were only referred to use of anti-TNFα (adalimumab: 6; infliximab: 1).

To sum up, several gaps on the EP knowledge still remain. Indeed, EP pathogenesis is not fully understood as well as data on the use of biologics for EP are scant, making more trials necessary to allow a comparison among them in order to establish new guidelines and treatment algorithm.

Globally, biologic drugs are usually given as first-line therapies for EP, showing impressive clinical improvements, with a safe profile. Our review highlighted that, despite limited, currently available data are promising, suggesting biologics as a useful weapon in EP management. In this scenario, the recent introduction of anti-IL17 and anti-IL23 may open a new era in EP management, guaranteeing fast results and excellent durability over time combined with a favourable safety profile. However, head-to-head studies are required in order to point out which biologic should be used for the right patient at the right moment.

## Conclusion

EP is a severe and potential life-threatening form of psoriasis, which requires and is an effective and rapid approach. Our review highlights the currently available data on biologics for EP. Although clinical trials are scant (certolizumab, ixekizumab, guselkumab, and risankizumab), with a reduced number of patients and limited to Japanese population, data from daily clinical practice are increasing, particularly for anti-IL17 and anti-IL23. Certainly, the rarity of the disease is the main challenge for the definition of targeted guidelines. Thus, more studies are required in order to better define the most adequate EP treatment algorithm.

## Disclosure

The authors report no conflicts of interest in this work.

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