BioDrugs (2015) 29:91–101
DOI 10.1007/s40259-015-0119-4

CURRENT OPINION

Erythrodermic Psoriasis: Current and Future Role of Biologicals

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Published online: 10 March 2015

Abstract Erythrodermic psoriasis (EP) is a severe form of psoriasis that may be associated with serious and sometimes fatal complications. The treatment of EP is often a challenge, since several factors, including treatment failure or possible complications, may limit favorable outcomes with traditional drugs. Recent evidence suggests that biological drugs, including both anti-tumor necrosis factor alpha agents and ustekinumab, may be useful in improving the management of EP. Unfortunately, since subjects with EP are usually excluded from pivotal trials involving biological agents, this evidence is currently dispersed in small case series and single case reports. In this paper, we briefly analyze conventional therapies for EP, before going on to critically evaluate the existing clinical evidence for the role of current biological drugs, namely infliximab, etanercept, adalimumab, and ustekinumab. Finally, we discuss the potential benefits that newer/developmental biological agents could bring to the management of EP.

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Key Points

The most recent (2010) recommendations for the treatment of erythrodermic psoriasis (EP) from the National Psoriasis Foundation Medical Board of the USA advise that oral conventional drugs, including acitretin, methotrexate, and cyclosporine, as well as infliximab, should be considered as first-line options, with the last two preferred in severe, acute, and unstable cases. Second-line treatment includes etanercept and combination therapy.

Based on the updated clinical evidence, we believe there is no significant reason to support the use of infliximab in EP over the other biological agents (ustekinumab, etanercept, and adalimumab) as they show efficacy and safety that is either the same as or greater than that of infliximab. The only exception concerns acute, severe, and unstable cases of EP in which infliximab (as well as cyclosporine) may provide a faster onset of action than the other biological agents. Based on a relatively low suspension rate for ustekinumab and a long-term retention of the achieved clinical results in all ustekinumab responders (mean follow-up period 11.6 months, range 3–29), this biological drug seems to be a promising candidate for the long-term control of EP; however, further studies are needed to assess such speculation.

The higher response rate to ustekinumab than to the other biological agents, and its efficacy in many recalcitrant cases, support the important role of interleukin (IL)-12/Th1 and IL-23/Th17 inflammatory pathways in the pathogenesis of EP. Thus, it is possible to speculate that newer/developmental anti-psoriatic biological agents targeting the IL-23/Th17 pathway might play a possible role in the therapy of EP. Such speculation is supported by a recent phase III, multicenter, single-arm, open-label study evaluating clinical response and safety of ixekizumab (an anti-IL-17A monoclonal antibody) in 78 patients with moderate-to-severe plaque psoriasis, five with generalized pustular psoriasis and eight with EP. By week 12, all patients with EP achieved a 75 % reduction in their Psoriasis Area and Severity Index (PASI) score, and the safety profile was good, as no serious adverse events, deaths, or cases of tuberculosis or invasive fungal infections were observed.

1 Introduction

Erythrodermic psoriasis (EP) is a severe form of psoriasis clinically characterized by diffuse erythema involving most of the body surface area (>90 % according to some authors [1] and >75 % according to others [2]). Skin scaling may also be present, but it is quite different from chronic plaque-type psoriasis (psoriasis vulgaris) since there is a superficial exfoliation rather than thick, adherent, white scales [2, 3]. The erythematous-desquamative changes may be accompanied by classical psoriatic nail alterations; itch; palmoplantar keratoderma; widespread or lower extremity edema; mucosal involvement; hair loss; and arthritis and systemic manifestations, including fever, chills, lymphadenopathy, malaise and fatigue [1, 3, 4].

EP is considered a rare skin condition, with an estimated prevalence among psoriatic patients ranging from 1 to 2.25 % [2]. However, it is important to highlight that psoriasis is the most common cause of erythroderma, since it is responsible for about 25 % of all cases [2, 4]. EP is more common in men (male-to-female sex ratio of 1.2–3.3:1) during adulthood (mean age of onset ranging from 41 to 55 years), although it has been described at all ages, including rare congenital instances [1, 5–7]. Although EP may be the first manifestation of psoriasis (de novo onset) in some subjects, it generally occurs in patients who already have chronic plaque-type psoriasis. Based on the results of studies of EP, the average time interval between the onset of psoriasis and the first erythrodermic episode ranges from 11 to 18 years (3 weeks–42 years) [1, 6, 7].

The reason that EP appears is not understood, but several factors are recognized as possible triggers, including systemic illness (e.g., HIV infection), emotional stress, ultraviolet (UV) burns, topical tar, alcoholism, and abrupt withdrawal of anti-psoriatic drugs (rebound phenomenon) such as oral and potent topical steroids, methotrexate, and efalizumab [4, 7–10]. Interestingly, rebound after efalizumab discontinuation has been reported mainly in patients who have not had a satisfactory clinical response [10]. The cause of rebound phenomenon in psoriatic patients is unknown, but it may be linked to down-regulation of cellular receptors and/or development of tachyphylaxis, defined as a rapidly decreasing response to a physiologically active agent after administration of a few doses [11].

The pathogenic mechanisms underlying EP are still unclear. Some authors state that, although both T helper (Th)-1 and -2 lymphocytes are involved in the pathogenesis of EP, such forms of psoriasis would be characterized by a Th1/Th2 imbalance with a relatively weak expression of Th1 and greater Th2 advantage [12]. A similar assumption

could justify the high level of immunoglobulin E (IgE) found in some EP patients [12, 13]. The importance of Th2 response in EP is supported by evidence observed in a recent study in 16 EP patients: (1) Th1/Th2 ratio in peripheral blood significantly lower in EP patients than in those affected by psoriasis vulgaris; (2) higher serum levels of interleukin (IL)-4 and -10, two important Th2 cytokines, in subjects with EP compared with patients with psoriasis vulgaris and a healthy control group; (3) inverted ratios (<1.0) of both interferon (IFN)-γ/IL-4 (serum levels) and T-bet/GATA-3 (levels in both skin lesions and peripheral blood mononuclear cells) in EP patients [12]. However, contrary to such findings, based on analysis of cytokine synthesis capability in peripheral blood T cells in an EP patient, some authors have speculated that a remarkable increase of Th1 cytokines such as IL-2 and IFN-γ might be responsible for the development of erythroderma in psoriatic subjects, while a shift towards type 2 cytokine predominance would contribute to its resolution [14, 15], as previously hypothesized for the improvement of plaque-type psoriasis [16]. Interaction between lymphocyte adhesion molecules and their ligands is another important aspect in the pathogenesis of EP. Indeed, increased concentration of circulating levels of soluble adhesion molecules (intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin) have been reported in EP patients compared with controls [17].

EP may also be classified in two clinical subtypes. In the first form, chronic plaques gradually evolve into a generalized erythrodermic phase; the psoriatic characteristics are retained (typical psoriatic plaques are frequently seen), the disease is generally stable, and the prognosis is good. In the second form, more common in arthropathic psoriasis, the characteristics of the disease are often lost (typically, an extensive erythema is observed, with or without scaling and no recognizable psoriatic plaque), the disease is generally unstable, the patient may be febrile and ill, and there is an appreciable mortality; in contrast to the previous form, itching is often severe [18]. The course of EP may vary from prolonged and chronic (more common for the first clinical subtype) to acute and rapid progressive (more typical of the second clinical subtypes); sometimes, EP may follow a relapsing–remitting pattern, with classic plaques of psoriasis vulgaris during remitting phases [1, 4, 7, 8].

Various severe and sometimes fatal complications have been reported in association with EP, including sepsis from skin pathogens (especially *Staphylococcus aureus*), shock and acute renal failure due to skin fluid loss, acute respiratory distress syndrome, hydroelectrolytic abnormalities, severe anemia, impaired thermoregulation causing hypothermia, severe protein loss, and high-output congestive heart failure due to derangements in the distribution of blood [1, 3, 4, 8].

To date, high-quality evidence to support specific recommendations for one medication over another in the treatment of EP is lacking. Consensus guidelines published in 2010 by the National Psoriasis Foundation Medical Board of the USA support the use of all oral conventional drugs, including acitretin, methotrexate, cyclosporine, and infliximab as first-line options, with the last two preferred in severe, acute, and unstable cases. Second-line treatments include etanercept and combination therapy. Systemic corticosteroids and UV light are generally not advised due to the possible flare upon withdrawal and significant photosensitivity of EP patients, respectively [2].

Acitretin, cyclosporine, and methotrexate have shown efficacy in patients with EP; however, the treatment of such forms of psoriasis is often a challenge since several factors, including failure or possible complications, may limit favorable outcomes with these traditional drugs (mortality rate of 9 %) [7, 19, 20]. Recent evidence suggests that biological agents, including both anti-tumor necrosis factor (TNF)-α agents and ustekinumab, may be more useful in the management of EP [2, 8, 12, 20]. Unfortunately, subjects with EP are usually excluded from all pivotal trials involving biological agents, and this evidence is currently dispersed in small case series and single case reports. In this paper we briefly analyze conventional therapies for EP, before going on to critically evaluate the existing clinical evidence for the role of current biological drugs, namely infliximab, etanercept, adalimumab, and ustekinumab, based on a comprehensive search of the literature using the PubMed electronic database. The search terms were the name of each biological agent and 'erythrodermic psoriasis' and, considering only literature reporting primary data, a total of 21 articles were retrieved (Table 1). Finally, we discuss the potential benefits that newer/developmental biological agents could bring to the management of EP.

2 Conventional Therapies

Table 2 provides a summary of the efficacy of conventional anti-psoriatic drugs (including acitretin, cyclosporine, and methotrexate) used as monotherapy in the treatment of EP. The table is based on the main studies reported in the literature. These studies are discussed below, together with the instances of EP treated with combination regimens (co-administration of a conventional drug with another conventional drug and/or a biological agent).

We have intentionally excluded from our brief analysis systemic corticosteroids and UV light since, according to the most recent guidelines [2], they are generally not advised in the treatment of EP.

Acitretin is generally used in EP with a low starting dose (25 mg/day), which is gradually increased until optimal

Table 1 List of publications reporting primary data on the treatment of erythrodermic psoriasis with infliximab, etanercept, adalimumab, and ustekinumab

References	Publication type	Biological agent/s	Patients (*n*)
Viguier et al. [20]	UCT	INF, ETA, ADA, UST	40[a] (24 INF, 6 ETA, 7 ADA, 3 UST)
Takahashi et al. [23]	CS	INF ± ACT or MTX	7 (2 INF, 4 INF + ACT, 1 INF + MTX)
Heikkila et al. [37]	CS	INF + MTX	4
Lisby and Gniadecki [38]	CR	INF + MTX	1
Fiehn and Andrassy [40]	CR	INF	1
O'Quinn and Miller [41]	CR	INF	1
Rongioletti et al. [42]	CR	INF	1
Torii and Nakagawa [43]	UCT	INF	8
Poulalhon et al. [44]	UCT	INF[b]	5
Romero-Maté et al. [45]	CR	INF	1
Esposito et al. [19]	UCT	ETA	10
Fraga et al. [36]	CR	ETA + MTX	1
Piqué-Duran and Pérez-Cejudo [47]	CR	ETA	1
Richetta et al. [49]	CR	ADA	1
Santos-Juanes et al. [51]	CS	UST	2
Wang and Tsai [52]	CS	UST	8
Castiñeiras et al. [53]	CR	UST	1
Saraceno et al. [54]	CS	UST	2
Stinco et al. [55]	CS	UST	3
Errichetti et al. [56]	CR	UST	1
Koutsoukou et al. [57]	CR	UST	1

ADA adalimumab, *CR* case report, *CS* case series, *ETA* etanercept, *INF* infliximab, *MTX* methotrexate, *UCT* uncontrolled clinical trial, *UST* ustekinumab

[a] This indicates the number of flares and does not take into account two cases treated with efalizumab

[b] Eventual other concomitant therapies were not specified

Table 2 Summary of the efficacy of acitretin, cyclosporine, and methotrexate used as monotherapy in the treatment of erythrodermic psoriasis based on the main studies reported in the literature

Conventional drug	Patients (*n*)	Dosage	Outcome	Total responders (%)	Time to reach outcome
Acitretin	12	25–35 mg/day	Remission or "marked improvement" of erythroderma	83.3	NR[b]
Cyclosporine	33	4.2 mg/kg/day (average starting dose)	CR or a significant improvement (reduction of >70 % vs. baseline)	94	2–4 months
Methotrexate	63[a]	7.5–40 mg/weekly	"Excellent/good" response	84.1	NR[c]

CR complete remission, *NR* not reported

[a] This number includes the patients reported by four retrospective studies

[b] Some authors report that about 4 weeks are usually required to see the first significant clinical effects in the treatment of a case of EP (slower than cyclosporine and methotrexate)

[c] Although the precise time to reach the outcome was not specified, first significant clinical results were generally seen within 1–4 weeks (faster than acitretin but slower than cyclosporine)

response is achieved. The use of a low starting dose helps to minimize the possible initial worsening of erythroderma related to the administration of relatively high doses of acitretin [1, 21]. Usually, about 4 weeks are required to see the first significant clinical effects [1]. The efficacy of acitretin as monotherapy in EP is mainly based on a meta-analysis involving 12 patients (daily dose 25–35 mg), which reported a remission or marked improvement of

erythroderma in 83.3 % of cases [22]. Acitretin has also been used simultaneously with other systemic drugs in the treatment of EP, namely infliximab and cyclosporine. Combination infliximab–acitretin has been found effective (improvement of more than 90 % of basal clinical picture) and well tolerated in four patients [23], while the simultaneous use of acitretin and cyclosporine failed to control erythrodermic manifestations in three patients in a case series [24]. Serious side effects directly related to acitretin therapy in EP would seem uncommon given that only a case of severe myopathy of all four limbs (arose after 2 weeks of treatment) has been reported [25]. However, the remarkable ability of acitretin to cause cutaneous fragility on erythrodermic skin, with consequent increased risk of *S. aureus* colonization [1], should be taken into account in EP patients since they are notorious for having an intrinsic increased susceptibility to developing sepsis due to such microorganisms [1, 8, 12].

Cyclosporine is commonly considered the classic first-line therapy for severe unstable cases of EP because of its rapid onset of action. The recommended starting dose for this form of psoriasis is 5 mg/kg/day (slowly tapered after remission) [8]. The efficacy of cyclosporine in EP is mainly sustained by an open-label, multicenter Italian study in 33 patients (average starting dose 4.2 mg/kg/day), which reported complete remission or significant improvement (reduction of more than 70 % in comparison with baseline) in 67 and 27 % of cases, respectively, after 2–4 months of treatment. The rate of relapse at 12 months was 12 % [26]. Except for the combination cyclosporine–acitretin (as outlined above) [24], the co-administration of cyclosporine with other drugs, including alefacept (one case) [27], methotrexate (two cases) [28] and etretinate (six cases) [29–31], has been reported to be effective for the treatment of EP. In terms of possible serious side effects of cyclosporine in EP patients, particular attention should be paid to renal damage, infections, and electrolyte abnormalities since the erythrodermic state itself may also induce such complications [1, 8].

Methotrexate is a valid therapeutic option for the treatment of EP, with dosages ranging from 7.5 to 40 mg/weekly [2]. The first significant clinical results are generally seen quite quickly, namely within 1–4 weeks (faster than acitretin but slower than cyclosporine) [1, 2, 32]. Its efficacy in EP has been evaluated by four main retrospective reviews totaling 63 patients [1, 32–34]. An excellent/good response was reported in 53 patients, while failure or moderate response were described for ten subjects [1, 32–34]. Combinations of methotrexate with other drugs, including etretinate (one case) [35], cyclosporine (two cases, as outlined above) [28], etanercept (one case) [36], and infliximab (six cases) [23, 37, 38], have been used in EP with excellent results in all patients except one treated with infliximab and methotrexate who developed staphylococcal sepsis and erythrodermic flare during therapy [37]. Although methotrexate is reported as quite well tolerated in the treatment of EP [1, 32–34], caution is required in its use because of the significant susceptibility of EP patients to pneumonitis and hematologic/metabolic complications [1, 3, 4, 8], all potential side effects of this drug [8].

3 Biological Drugs

3.1 Infliximab

Infliximab is a mouse–human chimeric anti-TNFα monoclonal antibody that can bind with high affinity to both soluble and membrane-bound TNFα, thus interrupting the inflammatory cascade. Complementary to its anti-inflammatory effect that is mediated through the neutralization of TNFα, infliximab normalizes keratinocyte differentiation and induces apoptosis of lesional keratinocytes through a caspase-independent mechanism. For treatment of severe plaque-type psoriasis, 5 mg/kg is administered via intravenous infusion at weeks 0, 2, and 6 followed by maintenance dosing every 8 weeks [39].

Infliximab is the most frequently used biological agent in the treatment of EP, with a total of 53 reported instances [20, 23, 37, 38, 40–45]. It was administered as a second-line biological therapy in only three cases (after the failure of etanercept in one patient [42] and of an unknown agent in the other two subjects [20]), while the remaining patients were naive to biological drugs.

The efficacy of infliximab as a monotherapy in EP is sustained by several case series/single case reports [23, 40–43, 45] and one open-label, uncontrolled, multicenter clinical trial [20]. These studies comprised a total of 38 patients, with 24 subjects (63 %) showing “improvement”, defined as reduction of Psoriasis Area and Severity Index (PASI) score from baseline of 50 % (PASI 50) or 75 % (PASI 75) (13/27 patients for both indexes; 48 %) [20, 23, 45], or achievement of physician’s global assessment of “clear” or “almost clear”/subjective report of the investigator (11/11 patients; 100 %) [40–43]. Clinical improvement has been achieved very quickly in most subjects, with 16 (67 %) and 24 (100 %) patients reaching the outcome at week 6 and 12, respectively [20, 23, 40–43, 45]. Significant adverse events observed during follow-up included *S. aureus* septicemia, myocardial infarction, erysipelas, anaphylactic shock, and a suicide attempt occurring at 6 weeks, 2 years, 6 weeks, 2 weeks, and 22 weeks after starting infliximab, respectively [20]. The follow-up duration ranged from 4 weeks to 24 months [20, 23, 40–43]. Although infliximab was administered during the whole

follow-up period in several patients (with retention of achieved clinical results) [23, 40–43], it is important to note that the above-mentioned clinical trial (involving 24 EP cases treated with infliximab) revealed a drug survival rate at week 48 of only 36 %. Primary/secondary lack of efficacy and side effects were the most common causes of drug suspension (data referred to all cases involved in the study, including a further 18 cases treated with other biological agents) [20]. Furthermore, in one patient described in another case report, infliximab lost efficacy after the sixth infusion, with subsequent development of a psoriatic flare (not erythrodermic) controlled with etanercept administration [45]. Such findings highlight the need to assess the real long-term efficacy of infliximab through further large long-term studies, especially in view of the well-known possibility of developing tachyphylaxis over a period of months to years, likely due to anti-infliximab antibodies [8].

Beside the above-reported instances, another five cases of EP treated with infliximab have been described in an open-label, uncontrolled, clinical trial including a further 23 subjects with other forms of severe recalcitrant psoriasis for a total of 28 cases. After 14 weeks of therapy, PASI 90, PASI 75, and PASI 50 were reached in 40 % (two cases), 60 % (three cases), and 60 % (three cases) of erythrodermic patients, respectively. Data about follow-up period, major side effects, previous biological therapies, and eventual concomitant classic anti-psoriatic medications in the EP patient group were not specified [44].

Infliximab has also been administered in combination with other classical medications, including acitretin and methotrexate in four and six instances [23, 37, 38], respectively, with excellent results and no significant side effects in all patients except one (see discussion on conventional therapies).

3.2 Etanercept

Etanercept is a fully humanized, soluble, recombinant fusion protein that exerts its effect by competitively binding to TNF, thereby preventing it from interacting with its natural receptors and precluding its inflammatory cascade. Adult dosing for psoriasis is 50 mg administered subcutaneously twice weekly for 3 months followed by 50 mg/week [46].

The largest body of evidence regarding the use of etanercept in EP is a 24-week, open-label, uncontrolled clinical study in ten patients; in all cases, etanercept was administered as the first-line biological medication. At week 12, PASI 50 and PASI 75 were reached in eight (80 %) and five (50 %) patients, respectively. After 24 weeks of therapy, six of the eight responders (subjects reaching at least PASI 50) achieved or maintained PASI 75, while the remaining two patients maintained between PASI 50 and PASI 75. During the entire study period, etanercept was generally well tolerated, with no severe side effects requiring treatment discontinuation, and patients were compliant and satisfied [19]. Other authors have reported a further six instances of EP treated with etanercept as monotherapy, with four cases (67 %) reaching PASI 75 within weeks 12–14 [20]. In all cases, etanercept was used as the first-line biological therapy, except for one patient who had previously been unsuccessfully treated with another unknown biologic drug. Serious adverse events were reported in two cases, namely *S. aureus* septicemia (in a HIV-positive patient) and pneumonia that occurred 6 and 9 months after starting etanercept, respectively [20]. The follow-up period of these six instances was not specified. The drug survival rate at week 48 was 33 %, with the specific causes of suspension not mentioned. Anyhow, considering all the cases involved in the study (namely a further 36 cases treated with other biological agents), the main reasons for suspension were primary/secondary lack of efficacy and side effects [20]. In addition to the two above-reported case series, an additional case of EP treated with etanercept as monotherapy for 6 months has been described. The PASI score decreased from 72 to 33 after 3 weeks of therapy, and reached a value of 17 and 0 at weeks 6 and 9, respectively; achieved clinical results were retained and no adverse effects were observed during the treatment period [47]. As mentioned in the discussion on conventional anti-psoriatic drugs, etanercept (at the dose of 25 mg/weekly) has also been used simultaneously with methotrexate (7.5 mg/weekly) in a case (a 7-year-old child) of resistant (cyclosporine and methotrexate) EP, with 'gradual' resolution of the manifestation after 3 months. The achieved result was retained during the 2-year follow-up and no significant side effect was recorded [36].

3.3 Adalimumab

Adalimumab is a fully human IgG1 monoclonal antibody that binds with high specificity and affinity to soluble and membrane-bound TNFα, thereby neutralizing the biological activities of the cytokine. In the treatment of plaque psoriasis, it is administered (subcutaneous injection) with an 80 mg starting dose, followed by 40 mg every other week starting 1 week after the initial dose [48].

The efficacy of adalimumab in EP is mainly based on a French retrospective, multicenter study on biologics, including seven erythrodermic flares (number of patients was not specified) treated with adalimumab [20]. After 12–14 weeks of therapy, 67 % of flares achieved PASI 75, while the remaining cases were not responsive (subjects not reaching PASI 50). Adalimumab was administered as second-line biological therapy in four cases, whereas it was

the first biologic drug used in the other three flares. The only major side effect consisted of a case of unclassified nodal T-cell lymphoma (occurring 3 months after starting the medication). Considering all subjects involved in the study, the median follow-up duration was 24 months (range 4–84), but specific data on patients treated with adalimumab were not reported [20]. The drug survival rate at week 48 was 40 %, with the main causes of suspension being primary/secondary lack of efficacy and side effects (data referred to all cases involved in the study, including a further 35 cases treated with other biological agents) [20].

Beside the instances described in the above study, only one other case of EP treated with adalimumab as a monotherapy has been reported in the literature. A 48-year-old man with psoriasis, hemophilia, and hepatitis C virus (HCV) infection developed a steroid-resistant erythrodermic flare after anti-HCV therapy with pegylated interferon alpha-2a and ribavirin. Adalimumab was efficacious (with induction of remission at week 3), and no side effects were reported during the 5 weeks of therapy [49].

3.4 Ustekinumab

Ustekinumab is a fully human monoclonal antibody that binds the p40 subunit of IL-12 and -23, two important cytokines involved in the pathogenesis of psoriasis that stimulate differentiation and proliferation of Th1 and Th17 cells, respectively. It has been licensed for the treatment of moderate to severe plaque psoriasis as subcutaneous injections of 45 mg for individuals weighing <100 kg and of 90 mg for individuals weighing ≥100 kg. Approved dosing intervals are at weeks 0 and 4, and then every 12 weeks thereafter [50].

The use of ustekinumab in the treatment of EP is supported by several small case series and single case reports for a total of 21 patients, with 18 (85.7 %) and 15 (71.4 %) cases reaching PASI 50 and PASI 75, respectively [20, 51–57]. Importantly, two of the three non-responders were multi-resistant cases that had previously been unsuccessfully treated with three anti-TNFα agents [20]. Significant clinical improvement is generally seen quite quickly, with 50 % and 87.5 % of responders (patients reaching at least PASI 50) achieving PASI 50 at weeks 4 and 12, respectively (findings based on cases where such data were described; $n = 16$) [20, 51, 52, 54–56]. The average follow-up duration was 11.6 months (range 3–29); in most patients, the achieved clinical results were retained during the whole period [51–55, 57], and the drug was withdrawn in only two cases due to the onset of severe side effects (see below) [20, 56]. Such findings would support a possible role of ustekinumab as a valuable therapeutic option for long-lasting control of EP [55]. Moreover, it has also shown efficacy in more resistant cases, since 13 and 10 responsive patients had previously failed one and two other biological agents, respectively [55].

Ustekinumab is reported to be well tolerated in the treatment of EP [55], and the only two significant adverse events were a case of widespread cutaneous staphylococcal colonization (occurring 9 months after the first administration of the drug) [20] and development of pulmonary miliary tuberculosis (1 week after the second dose of ustekinumab) in a patient with latent tuberculosis infection, despite isoniazid chemoprophylaxis [56]. Regarding the latter event, it is important to keep in mind that the patient had undergone previous and concomitant systemic steroid therapy, which might have made the subject more vulnerable to the development of active tuberculosis. Moreover, it is not possible to exclude that a possible isoniazid resistance, a well-known issue in tuberculosis management, could also have facilitated the tubercular reactivation [56]. Anyway, compared with the anti-TNFα agents [58], ustekinumab may still be considered a drug with a relatively very low risk of developing active tuberculosis since only two instances have been reported to date [56, 59].

3.5 Role of Current Biologicals in Erythrodermic Psoriasis: Synthesis of Clinical Evidence and Consequent Considerations

A summary of the described instances of EP treated with biological agents as a monotherapy is reported in the Table 3 (we have intentionally excluded cases in which biological agents have been administered in combination with other classic medications in order to assess the efficacy and safety of each biological drug more objectively). Unfortunately, in most cases of EP treated with biological therapies reported in literature, the course of the disease (acute or chronic) was not specified, so we could not divide the data according to this important clinical variable.

A total of 38, 17, 8, and 21 reported cases have been treated with infliximab, etanercept, adalimumab, and ustekinumab, respectively. Considering only the patients in which clinical improvement was assessed by PASI score, the responders (subjects achieving at least PASI 50) were 48 % (of 27), 76 % (of 17), 67 % (of 7), and 86 % (of 21) for infliximab, etanercept, adalimumab, and ustekinumab, respectively. However, if we consider all subjects (including those in whom the outcome was defined as achievement of at least PASI 50 or improvement defined by physician's global assessment of "clear" or "almost clear" and/or subjective report of the investigator), the response rate of infliximab and adalimumab increases to 63 and 71 %, respectively. Regarding the rapidity of action, infliximab was generally quicker than ustekinumab (67 and 100 vs. 50 and 88 % of responders reaching the outcome within weeks 4–6 and 12–14, respectively); data on

Table 3 Summary of erythrodermic psoriasis treated with biological agents as a monotherapy

Biological agent	Total pts	Pts achieving PASI 50[a]	Pts achieving PASI 75[a]	Total responders[b] (%)	Responders[b] reaching the outcome within weeks 4–6 (%)	Responders[b] reaching the outcome within weeks 12–14 (%)	Biological failure pts[c] (%)	Significant AEs during tx (%)
Infliximab	38[d]	48 % of 27	48 % of 27	63	67	100	8	13
Etanercept	17	76 % of 17	65 % of 17	76	[e]	100	6	12
Adalimumab	8	67 % of 7	67 % of 7	71	[e]	100	50	13
Ustekinumab	21	86 % of 21	71 % of 21	86	50	88	71	10

AE adverse event, *PASI* psoriasis area and severity index, *pts* patients, *tx* treatment

[a] Considered only the pts in whom clinical improvement was assessed by PASI score

[b] Includes pts reaching at least PASI 50 or improvement defined by physician's global assessment of "clear" or "almost clear" and/or subjective report of the investigator

[c] Pts unsuccessfully treated with at least one previous biological agent

[d] The number does not include five pts in whom the regimen of administration (monotherapy or combination with other classic medications) was not specified

[e] Data not presented as they were available for only one pt treated with adalimumab and one pt treated with etanercept

etanercept and adalimumab were not available at weeks 4–6 (except for two patients: one treated with etanercept and one under therapy with adalimumab), but all responders achieved the outcome within weeks 12–14. Interestingly, in many cases, ustekinumab and adalimumab were used after the failure of at least one previous biological drug (71 and 50 % of total patients, respectively), while infliximab and etanercept were administered as second-line biological therapy in only 8 and 6 % of all patients, respectively. Significant adverse events have been described with a similar frequency for the various biological agents (from 10 to 13 % of all patients); no deaths directly attributable to EP or biological therapies have been reported.

According to the most recent (dating back to 2010) recommendations about the treatment of EP, infliximab is the unique biological agent included in the first-line options (besides acitretin, methotrexate, and cyclosporine) [2]. Based on the updated above-reported clinical evidence, we believe there is no significant reason to support the use of one such biological over the others (ustekinumab, etanercept, and adalimumab) as they show the same or greater efficacy and safety as infliximab. The only exception concerns acute, severe, and unstable cases that need a quick intervention; in such instances, infliximab (as well as cyclosporine) may provide a faster onset of action than the other biological agents (probably because it is administered as an intravenous infusion) [2]. In view of the possible chronicity of EP, it is important to consider the long-term efficacy and safety of biological drugs, particularly for infliximab. Indeed, it is well known that over a period of months to years many initial infliximab responders may develop tachyphylaxis [8]; this concern is warranted by its low drug survival rate in EP patients (suspension within 48 weeks of therapy in 42 % of cases, mainly for primary/secondary lack of efficacy and side effects). A significant suspension rate (for the same reasons) has also been reported for adalimumab (38 % of cases), while etanercept and ustekinumab have been withdrawn in only 24 and 10 % of cases. Importantly, these results have to be considered with some caution, since the data reported in the literature so far are often fragmentary, and the follow-up period in the various studies is highly variable. However, based on the foregoing and according to the evidence that in all ustekinumab responders the achieved clinical result was retained during a mean follow-up period of 11.6 months (range 3–29), this biological drug seems to be a promising candidate for the long-term control of EP. A final interesting finding resulting from the instances of EP treated with biological agents is the significant percentage of responders (particularly subjects treated with ustekinumab but also those treated with adalimumab) who had previously been unsuccessfully treated with at least one other biological agent, thus supporting the possibility of using another biological agent in case of failure or intolerance. Overall, large randomized controlled trials with long-term follow-up are needed to clarify such open questions, generate appropriate guidelines for the treatment of EP, determine the precise role of each biological drug in its management, and assess the safety of these agents in the treatment of such forms of psoriasis. Lastly, it is important to highlight that, although less commonly compared with the other variants of psoriasis, the anti-TNFα agents have been rarely reported to trigger EP [60, 61]. The mechanisms underlying such a paradoxical effect remain elusive, although some authors have speculated that TNF inhibition would lead to increased production of IFNα by plasmacytoid dendritic cells and local expression of type I IFN-induced genes in the skin of predisposed individuals, including chemokines CXCL9 and CXCL10, and overexpression of C-X-C motif receptor 3 and Tia-1 (involved in

skin homing and cytotoxic activity, respectively) in T cells [60, 62].

3.6 Future Perspectives

Although the exact pathogenesis of EP is not yet fully understood, the efficacy of anti-TNFα agents and ustekinumab supports the importance of TNFα and both IL-12/Th1 and IL-23/Th17 inflammatory pathways, respectively. The key role of these last two pathways is emphasized by both the higher response rate to ustekinumab compared with the other biological agents and its efficacy in recalcitrant cases since 13 (62 %) and ten (48 %) responsive patients had previously failed one and two other biological agents, respectively. It is difficult to establish which pathway between IL-12/Th1 and IL-23/Th17 is mainly involved in the pathogenesis of EP, as ustekinumab exerts its effect by binding to the p40 subunit shared by both IL-12 and IL-23, thus reducing both Th1 and Th17 responses [50, 63]. However, according to experimental evidence from mouse models of inflammation demonstrating that deficiency of IL-12 does not protect from the development of autoimmune diseases and often these mice have a more severe clinical picture than their wild-type counterparts [63, 64], it is possible to speculate a more important role for IL-23. This hypothesis is also supported by another study showing that the messenger RNA (mRNA) levels of the subunit p19 (unique to IL-23) were elevated in psoriasis lesional skin compared with non-lesional skin, whereas the levels for p35 (a subunit distinct to IL-12) showed no differences [65]. IL-23 is an essential cytokine for differentiation of Th17 lymphocytes, which are implicated in the pathogenesis of psoriasis via production of pro-inflammatory cytokines such as IL-17A, IL-17F, and IL-22 [66]. In particular, IL-17A is considered a key 'driver' of pro-inflammatory cytokines in psoriasis pathogenesis since it can activate keratinocytes, leading to hyper-proliferation and further production of antimicrobial peptides, cytokines, and chemokines, which, in turn, recruit and activate other immune cells, leading to amplification of psoriasis inflammation [66].

On the basis of the foregoing discussion, it is possible to hypothesize that newer/developmental anti-psoriatic biological agents targeting the IL-23/Th17 pathway might play a positive role in the therapy of EP, including anti-IL-23p19 antibodies (tildrakizumab and guselkumab), anti-IL17A antibodies (secukinumab and ixekizumab) and brodalumab (an anti-IL-17-receptor antibody) [66]. This speculation is supported by a recent phase III, multicenter, single-arm, open-label study evaluating clinical response and safety of ixekizumab in 78 patients with moderate-to-severe plaque psoriasis, five with generalized pustular psoriasis and eight with EP. All patients received subcutaneous ixekizumab 160 mg at week 0, then 80 mg every 2 weeks through week 12, and 80 mg every 4 weeks through week 24. In EP patients, PASI 75, PASI 90, and PASI 100 response rates were 100.0 % (8/8), 62.5 % (5/8), and 25.0 % (2/8) at week 12, respectively. Similar response rates were observed at week 24, as 100.0 % of patients maintained PASI 75, a total of 87.5 % (7/8) achieved PASI 90, and 12.5 % (1/8) achieved PASI 100. No serious adverse events, deaths, or cases of tuberculosis or invasive fungal infections were observed. This study presented several limitations, mainly the absence of a control group and the small sample sizes [67]. Therefore, future studies are needed to confirm the possible role of such agents and the precise implication of the IL-23/Th17 pathway in EP. In this regard, a phase III, multicenter, open-label study evaluating the efficacy and safety of guselkumab in the treatment of subjects with generalized pustular psoriasis or EP should start shortly (estimated total number of patients: 20). Participants will receive subcutaneous guselkumab 50 mg at weeks 0, 4, and 12. At week 16 up to week 52, participants defined as "Very much improved" or "Much improved" in the Clinical Global Impression scale will continue to receive guselkumab 50 mg every 8 weeks from week 20 to the study end (week 52). At each visit timing from week 20, participants defined as "No change" or "Worsened" will receive guselkumab 100 mg and continue at 100 mg every 8 weeks dosing until week 52. Participants who are "Minimally improved" will also receive guselkumab 100 mg only if the investigator considers it necessary. Participants will primarily be assessed for treatment success. Participants' safety will be monitored throughout the study [68].

Acknowledgments The authors have no financial disclosures or conflicts of interest.

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