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Letter to the Editor

Erythrodermic psoriasis treated with ustekinumab: An Italian multicenter retrospective analysis

Keywords:
Psoriasis; Erythrodermic psoriasis; Biologics; Ustekinumab; Safety; Efficacy

Dear Editor,

Erythrodermic psoriasis (EP) is one of the most severe cutaneous conditions which may lead to serious morbidity and even mortality. This condition is often difficult to manage and, due to its rarity (estimated prevalence 1–2.25% of psoriatic patients) there is a lack of high-quality medical literature examining treatment options [1].

Data on the use of biologics in EP are very sparse because erythroderma represented exclusion criteria in all the main studies investigating biologics efficacy and safety in psoriasis [1,2].

Until now only two retrospective studies have tried to assess the efficacy and safety of anti-TNF-α in EP with promising results [3,4].

Here we report the results from a multicenter, retrospective analysis of patients with EP treated with ustekinumab in 9 Italian Dermatology Hospital Departments.

Data of 22 patients with EP (defined as a generalized, inflammatory erythematous dermatosis, with or without associated exfoliation lasting for at least 3 months involving at least 75% of the body surface area, with the characteristic clinical and/or histological features of psoriasis and the exclusion of the other main differential diagnoses for erythroderma) [1], treated with ustekinumab between February 2010 and July 2014, were included. Each patient has been evaluated with the Psoriasis Area and Severity Index (PASI), before and after 4, 16 and 28 weeks of treatment.

Baseline characteristics of the study population are summarized in Table 1.

19 patients have a positive personal history of plaque type psoriasis while 3 experienced erythroderma since the beginning of the disease. In the latter cases diagnosis of EP was made excluding other possible causes of erythroderma.

Patients received ustekinumab at weeks 0, 4 and then every 12 weeks. 16 patients (weighting ≤100 kg) received ustekinumab 45 mg while 6 (weighting >100 kg) 90 mg.

Table 1
Baseline characteristics of the 22 studied patients.

Patients	Sex	Age Pso	Age EP	Previous treatment Pso	Previous treatment EP	Baseline PASI	Ustekinumab dose (mg)
1	M	25	46	Cs, PUVA, ETA	–	41.6	45
2	M	40	59	MTX, Cs, EFA, ETA	CCS	59	45
3	F	13	53	Cs, MTX, EFA, ETA, INF	CCS	40	45
4	M	23	45	Cs, MTX	Ret, CCS	45	90
5	M	46	46	–	Cs, Ret, CCS	49	90
6	M	49	67	UVB, MTX	MTX, Cs, UVB	41	45
7	F	35	67	–	Cs, MTX, Ret, ADA	48	90
8	M	46	63	Cs	Cs, CCS, ADA	48.8	45
9	M	57	62	Ret, MTX, Cs	Ret, Cs, ADA, ETA	63	45
10	M	29	46	Ret, MTX, Cs	Ret, Cs, ETA	57.2	45
11	M	29	36	Cs	Cs, CCS	37.8	45
12	F	49	54	Cs, Ret, ADA	Cs, ETA, INF, CCS	45.2	45
13	F	15	15	–	MTX, Cs, Ret, CCS	35	45
14	F	9	26	PUVA, MTX, Cs, EFA	ADA, ETA	42	90
15	F	28	34	–	MTX, Cs, INF	50	90
16	F	12	42	Cs, PUVA	–	42.3	45
17	M	23	43	Ret, PUVA	–	41.4	45
18	M	9	54	Cs, PUVA	–	42.3	90
19	M	29	34	Cs, Ret, ADA, ETA	CCS	38	45
20	M	38	61	UVB, Cs, MTX, Ret	INF, ADA, ETA	42	45
21	M	56	66	UVB, MTX, Ret	Cs, CCS	41	45
22	F	59	59	Cs, PUVA, Ret	–	40.8	45

CCS: systemic corticosteroids; Cs: ciclosporin; Ret: oral retinoids; MTX: methotrexate; PUVA: psoralen plus ultraviolet A; UVB: ultraviolet B; ADA: adalimumab; EFA: efalizumab; ETA: etanercept; INF: infliximab. Topical therapies not included.

Five patients received ustekinumab as first treatment at the onset of EP.

The remaining 17 patients received as first treatment for EP, prior to ustekinumab, systemic steroids, conventional systemic treatments (acitretin, methotrexate, cyclosporine) phototherapy, other biologic therapies.

The efficacy of ustekinumab was assessed by the proportion of patients reaching a 50, 75 and 90% improvement in PASI (PASI 50, PASI 75, PASI 90) at different time points (Fig. 1).

After 4 weeks of ustekinumab treatment more than half of patients showed a clinical improvement of at least 50% compared with baseline PASI score while after 16 weeks about two third of patients reached PASI75. After 28 weeks of treatment 68.2% of patients reached PASI 90, 86.3% PASI 75 and 90.9% PASI 50.

At the time of data collection, the median follow-up duration was 60 weeks (mean 66.5, range 24–120 weeks) after the onset of ustekinumab treatment.

16 patients were still receiving ustekinumab with a median PASI of 2.3 (mean 2, range 0–8) at the end of the follow-up period. Causes of treatment withdrawal were failure in PASI 50 achievement after 28 weeks (2 patients) and clinical remission (4 patients).

EP is one of the clinical subtypes of psoriasis associated with poor prognosis and direct mortality [1].

EP most commonly arises from a pre-existing long-standing chronic psoriasis vulgaris or, more rarely, it can occur abruptly as the initial presentation of psoriasis.

Current evidence supporting the use of biologics in EP is limited to case reports and case series [1].

To the best of our knowledge this is the largest retrospective study investigating the efficacy and safety of ustekinumab in patients with EP.

Successful use of ustekinumab in EP was reported in various case reports [5–10] underlining its efficacy even after failure of various anti-TNF agents.

The larger evaluation of ustekinumab in EP currently available is an Asian case series of 8 patients with 75%, 50% and 37.5% of patients reaching respectively PASI50, PASI75 and PASI90 at week 28 [10]. In this study ustekinumab 45 mg was given only at baseline and after 4 weeks; this could explain their disappointing results. Moreover, it seems that biologics treatment for psoriasis may have a less impressive response in Asian races, as stated also by the same authors. In a recent French multicenter retrospective study on the safety and efficacy of different biologic treatments in EP, 3 patients were treated with ustekinumab with only limited efficacy reported [3]. However the authors underscored that in the reported cases ustekinumab treatment was prescribed as a fourth-line biological treatment in all cases, and these were the most recalcitrant ones.

Our case series highlight the efficacy of ustekinumab in EP with a percentage of patients reaching PASI 75 close to 70% at week 16 weeks. This percentage increases more than 80% at week 28. In terms of time related clinical improvement (PASI reduction) our results are equal to or greater than those obtained with others biologics [2,3]. The four patients who have withdrawal ustekinumab after reaching clinical remission have maintained this condition throughout the end of the follow-up period.

Ustekinumab was generally well tolerated and patients were compliant and satisfied.

No severe infection, injection site reaction, or drug-related laboratory abnormalities have been reported among the subjects enrolled in this study.

We didn't find any relation among any clinical factors (BMI, previous treatments, duration of EP, smoking habit) and quality of response (efficacy, quick onset of response) to ustekinumab treatment. This may be due to the limited number of patients of our study.

Our retrospective analysis demonstrates that ustekinumab is a highly effective treatment for EP, providing rapid and significant clinical response associated with an excellent safety profile.

The limitation of the current study is that the efficacy of ustekinumab was investigated retrospectively. Another limitation should be the small number of patients included but talking about EP treatment with one biologic this represents the longest series up to now.

Even if there is a clear need for dedicated and prospective comparative clinical trials to assess which are the safest and most efficacious therapies for the management of EP, the rapidity of clearance and the excellent safety profile observed in our case series suggests that ustekinumab can play an important role in its management.

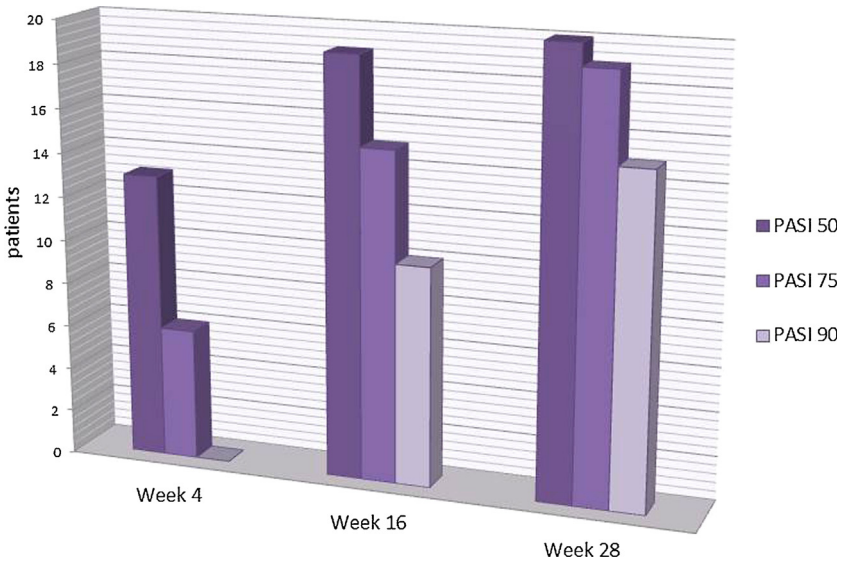

Fig. 1. Improvement of PASI of the 22 studied patients at different timelines.

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Letter to the Editor

Atopic dermatitis-like dermatitis emerges unevenly on different sites in flaky tail mice

Keywords:
Atopic dermatitis; Flaky tail mice

To the Editor,

Flaky tail mice (FTM; *ma/ma*, $Flg^{ft/ft}$) have two pathogenic genetic abnormalities related to cutaneous permeability barrier homeostasis, namely, gene mutations in filaggrin (Flg^{ft}) and matted (*ma*), and are known to exhibit atopic dermatitis (AD)-like dermatitis "spontaneously" and the spontaneous emergence is mainly attributed to the matted mutation [1–4]. Although FTM has been used as one of the murine AD models, whether such spontaneous emergence is consistent with the pathogenesis of human AD, in which genetic abnormalities are not the sole determinant but the combination of genetic abnormalities and environmental factors is the most important characteristic, remains questionable. In the present study, we determined whether site-dependent emergence of skin manifestations, which is one of clinical characteristics of human AD, is seen in FTM.

The severity of dermatitis and age of onset in FTM differ among laboratories [1,2,5,6]. Such inconsistency might be related to the presence or absence of the *matted* mutation and/or to variations in the genetic background of individual strains and in environmental factors [2,7]. In our laboratory, young FTM (7–8 weeks old) did not have any clinical or histological symptoms of dermatitis [8]. FTM aged over 40 weeks (old FTM) developed marked dermatitis on the ears, eyelids, cheeks and neck accompanied by elevation of serum IgE levels (Fig. 1, Supplementary Figs. S1–S3). The dermatitis on the

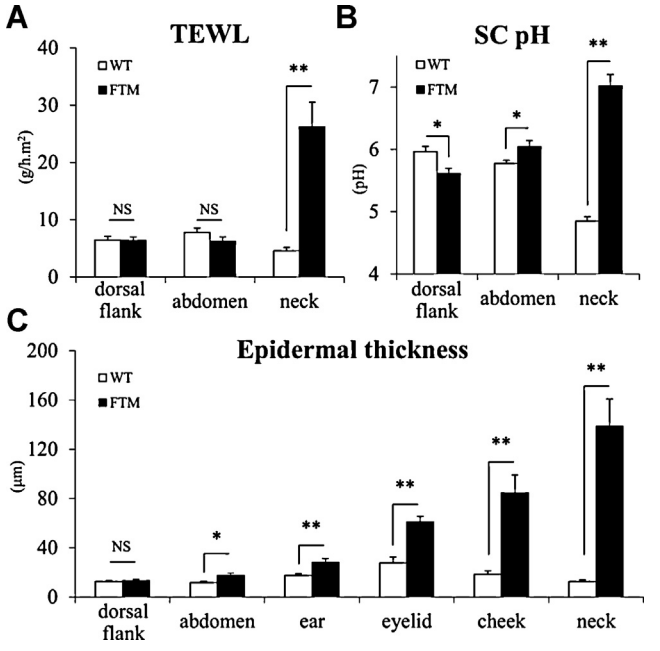

Fig. 1. Physiological and histological findings. Transepidermal water loss (TEWL, A), stratum corneum (SC) pH (B), and epidermal thickness (C) were compared at each site between old C57BL/6 (WT) and flaky tail mice (FTM) (40- to 90-week-old), as described in the supplementary file. $N = 7–9$ in A, $N = 5–8$ in B, and $N = 6–10$ in C. NS, not significant, * $P < 0.05$, ** $P < 0.01$.