Journal of Dermatology Research

ATHENAEUM SCIENTIFIC PUBLISHERS

Research Article

Skin Related Paradoxical Adverse Events (Mainly Psoriasis) During Il-17 Blockage: A Systematic Review

Alexandra Maria Giovanna Brunasso[1*], Martina Montinari[1]

[1]Dermatology, Villa Scassi Hospital ASL3, Genoa, Italy

***Correspondence author:** Alexandra Maria Giovanna Brunasso, Dermatology, Villa Scassi Hospital ASL3, Genoa, Italy;
Email: giovanna.brunasso@asl3.liguria.it; Giovanna.brunasso@gmail.com

Citation: Brunasso AMG, et al. Skin Related Paradoxical Adverse Events (Mainly Psoriasis) During Il-17 Blockage: A Systematic Review. J Dermatol Res. 2023;4(2):1-11.

https://doi.org/10.46889/JDR.2023.4208

Received Date: 02-06-2023

Accepted Date: 23-06-2023

Published Date: 30-06-2023

Abstract

Background: Paradoxical Adverse Events (PAEs) during biological therapy are characterized by the onset of a new inflammatory disease or by the exacerbation of the preexisting condition (with a different morphology or localization) while treating the patient with a class-agent proven efficacious for both conditions. They can be divided in two subgroups: "true PAE" characterized by the previously proven efficacy of the biological agent for the PAE and "borderline PAE" defined by the development of an inflammatory condition where the biological agent has not a proven efficacy.

Methods: systematic search of English databases in order to identify true and borderline-skin PAE under anti IL-17 therapy.

Results: We retrieved 58 patients affected by skin-PAE during anti-IL-17 therapy, 40 cases classified as True-PAE and 18 as Borderline-PAE., with a mean age of onset of 51 years. Secukinumab was the most frequent agent associated to skin-PAE and mean onset of the skin-PAE was 18 weeks.

Conclusion: True-skin-PAE occur during anti Il-17 therapy, the underlaying immunological mechanism is not yet known, but pustular variants of psoriasis seem to be more prevalent; withdrawal of the anti-IL-17 therapy has been mainly performed and other therapies such as anti-IL-23 biologics seem to control both the underlying disease and the true-skin-PAE. Further studies are needed in order to better understand the immunological mechanism involved.

Keywords: Psoriasis; Palmoplantar Psoriasis; Palmoplantar Pustulosis; Plaque Psoriasis; Brodalumab; Ixekizumab; Secukinumab; IL-17

Introduction

Paradoxical Adverse Events (PAEs) during biological therapy are characterized by the onset of a new inflammatory disease or by the exacerbation of the preexisting condition (with a different morphology or localization) while treating the patient with a class-agent proven efficacious for both conditions [1,2]. Toussirot, et al., have proposed a classification of PAE in two subgroups: "true PAE" characterized by the previously proven efficacy of the biological agent for the PAE (for example, new onset of pustular psoriasis and plaque psoriasis during the treatment with a proven efficacious agent for an inflammatory condition that also has well known efficacy in treating psoriasis) and "borderline PAE" defined by the development of an inflammatory condition where the biological agent has not a proven efficacy in phase-3 clinical trials and registration, despite a rationale for its use (for example, Behcets disease, pyoderma gangrenosum, alopecia areata, vitiligo, sarcoidosis, hidradenitis suppurativa) [1-3].

Induction or worsening of psoriasis was initially noted almost 20 years ago in patients with Inflammatory Bowel Disease (IBD), Rheumatoid Arthritis (RA) and Ankylosing Spondylitis (AS) treated with each of the available TNF-α inhibitors, reporting a 5% prevalence that clearly exceeds the 1-2% prevalence expected by chance [3]. In most cases, psoriasis appearing during anti-TNF-

α therapy shows a pustular palmoplantar pattern that has been considered a class effect of TNF-α blocking agents rather than a drug-specific adverse event [3]. The mechanism underlying this paradoxical phenomenon seems to be related to the increased production of Interferon (IFN)-γ after TNF-α blockage, as IFN-γ is a key element in the induction of innate forms of psoriasis, mainly acute psoriasis and erythrodermic, guttate and might play also a role in pustular variants such as palmoplantar pustulosis [3].

IL-17 plays a key role in the pathogenesis of psoriasis and Psoriatic Arthritis (PsA). Protein levels of IL-17A, IL-17C, and IL-17F in lesional psoriatic skin are significantly increased when compared to non-lesional skin [4]. The IL-17 pathway plays a pivotal role in the inflammatory cycle of psoriasis. When an individual with a genetic predisposition gets into contact with trigger factor for psoriasis (mainly infections), the adaptive immune system initiates an immunologic cascade. Myeloid dendritic cells initiate the release of IL-12 and IL-23 (being the role of Il-23 essential in the whole process). IL-23 enhances the survival, differentiation, and activation of Th17 cells, which secrete IL-17 cytokines. IL-17 promotes keratinocyte proliferation and the production of psoriasis-related cytokines, chemokines, and antimicrobial peptides [4].

In the last five years, anti-IL-17 therapies have been routinely prescribed, while increasing their use diverse adverse events not reported during Randomized Clinical Trials (RCT) have emerged [4].

In the literature we can find isolated reports of skin related PAE associated to IL-17 blockage with Secukinumab (a recombinant fully human IgG1κ monoclonal antibody against IL-17A), Ixekizumab (a humanized IgG4 monoclonal antibody against IL-17A) and Brodalumab (a human monoclonal IL-17 receptor antibody (RA) antibody), but well-designed studies are missing and focus on this argument has not been given; for this reason, we decided to conduct the present systematic review of the literature in order to collect all of such cases in order to characterized general features, outcomes and to highlight this new emerging condition.

Materials and Methods

We followed PRISMA criteria and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines. No ethical approval was requested. We performed a systematic search of English databases (PubMed, Embase and Web of Science) from January 2000 until March 2022, using the following keywords and [MESH FORMS]: "palmoplantar pustulosis" and/or "paradoxical" and/or “pustular” and/or “new onset psoriasis” and/or “pyoderma gangrenosum” and/or “Behcet” and/or “alopecia areata” and/or “vitiligo” and/or “hidradenitis suppurativa” and/or “sarcoidosis” and/or "brodalumab" and/or "secukinumab" and/or "ixekizumab" No exclusion criteria were applied. Articles in English, German and Spanish were reviewed.

Data Extraction and Quality Assessment

Two reviewers (ABV and MM) independently screened all the identified studies and any disagreement was discussed and resolved. The following information was collected and analyzed for each case: demographics (age, sex), primary disease diagnosis, previous biological therapy, type of skin-PAE, previous PAE under other biological therapies, trigger molecule (Secukinumab, Ixekizumab or Brodalumab), time to onset of skin-PAE, time to withdrawal of trigger molecule and outcome of skin-PAE.

Definition of Cases Included and Excluded

We included all cases found that fullfeed the definition of “true”- or “borderline”-PAE. We excluded cases of eczematous reactions or atopic dermatitis or photosensitive skin reactions, because anti IL-17 agents have not a proven efficacy in the treatment of such conditions in a considerable way (in a phase-2 RCT, secukinumab failed to obtain improvement in atopic dermatitis) and only sporadic cases report their utility [5]. Recently Cardarola, et al., have reviewed such conditions in depth [6]. According with the literature, some specific adverse events as, lichenoid reactions, cutaneous vasculitis and subacute lupus erythematosus, occurring during biological therapy were not considered as PAE and excluded from the review, because of the possible underlying mechanisms related with immunogenicity, immune complex deposition and autoantibodies formation that are not primarily related to the Th17 pathway and cannot be classified as paradoxical [1].

We also excluded cases of flared psoriasis during anti Il-17 because they did not fulfill the criteria for PAE such as exacerbation

of the preexisting condition with a different morphology or localization, therefore we excluded the cases that represented a secondary failure of therapy or loss of efficacy.

Results

We retrieved 40 publications describing a total of 58 patients affected by skin-PAE during anti-IL-17 therapy (Secukinumab, Ixekizumab and Brodalumab). The articles retrieved are case series, case reports and retrospective observational studies. We identified 220 reports, 65 were assessed for eligibility and only 40 publications fulfilled the requirements for the present systematic review [6-45]. The majority of the articles retrieved are case series, case reports and retrospective observational studies. The overview of the research strategy and a Flow chart of the systematic literature search according to PRISMA guidelines published in 2021 is illustrated on Fig. 1.

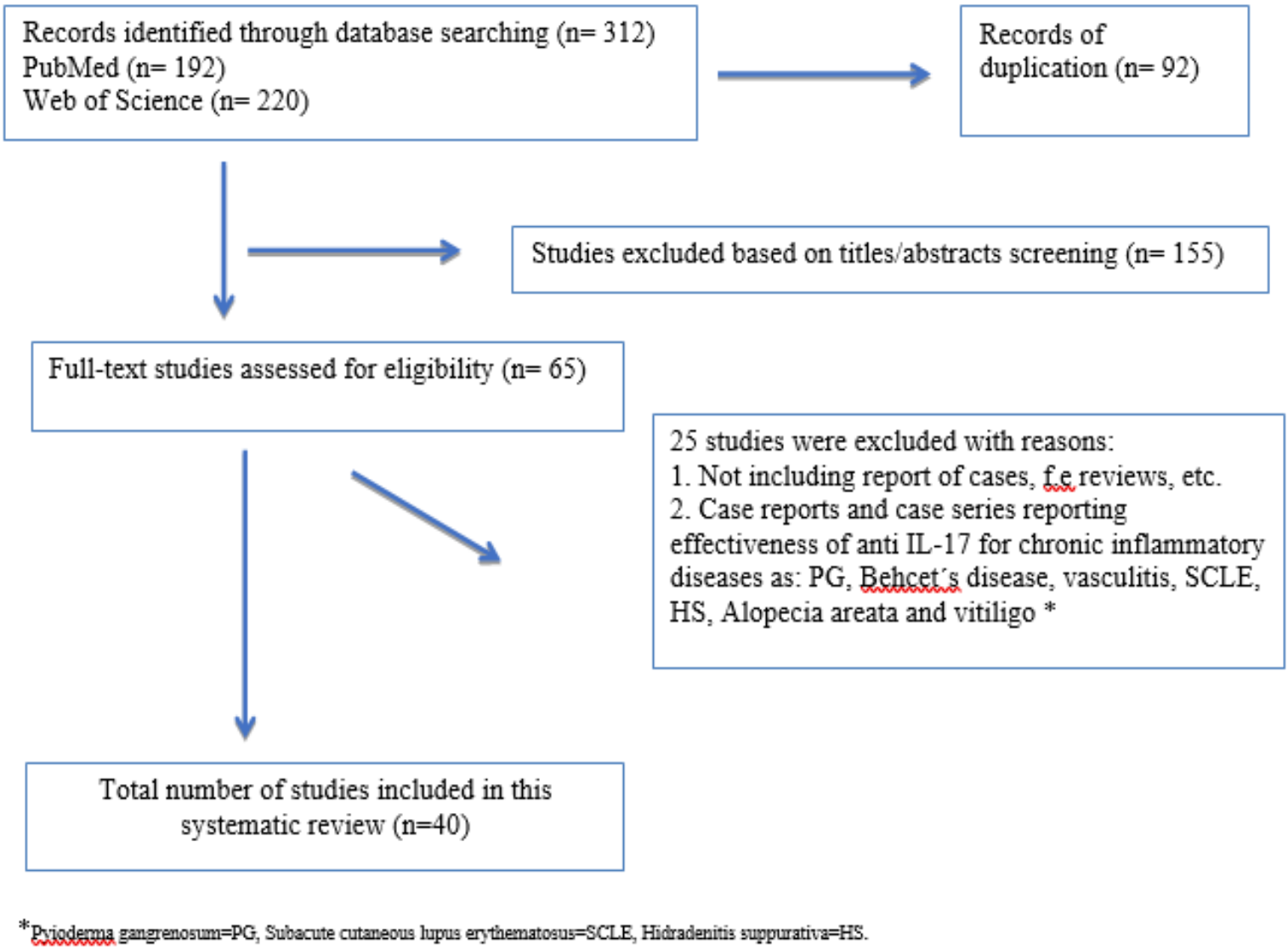

Figure 1: Overview of the research strategy (according the PRISMA 2020 Statement).

The patients identified with skin-PAE were 58 in total, 40 cases classified as True-PAE and 18 as Borderline-PAE. Regarding sex distribution 21 males and 30 females (in seven cases sex was not available) were reported, being males 45% (20/44) and females 55% (24/44) of the whole cohort (Table 1). Mean age of onset of skin-PAE was 51 years.

Author, Year	Age (sex)	Primary Disease	Trigger Molecule	Type of Skin PAE	Time to-onset	Withdrawal Time	Outcome/Withdrawal (Yes/No)	Type of PAE: True/Borderline
Moessner , et al., 2020 [7]	26y (F) 44y (F) 45y (F)	Psoriasis Psoriasis and PsA Psoriasis and PsA	Brodalumab Secukinumab Secukinumab	PPP PPP PPP	8 We 16 Mo 14 We	24 We 20 Mo 14 We	Switch to Ustekinumab with complete improvement/Yes Resolved after withdrawal without therapy/Yes Switch to Ustekinumab with improvement/Yes	True True True
Abbruzzese, et al., 2020 [8]	63y (F)	Psoriasis and PsA	Secukinumab	PPP	N.A	No	Cyclosporine was added with complete remission/No	True
Honma, et al., 2019 [9]	64 y (F)	GPP	Secukinumab	PPP	N.A	No	Good control of GPP and persistence of PPP/No	True
Sadik, et al., 2019 [10]	42y (F)	Psoriasis	Brodalumab	PPP, PG	6 We	6 We	Improvement of PPP, PG and joints after switch to Ustekinumab/Yes	True
Martinez-Domenech, et al., 2019 [11]	53y (M)	Plantar psoriasis	Ixekizumab	Plantar vault psoriasis	N.A.	No	Persistence of lesions/No	True
Pirro, et al., 2019 [12]	48y (M)	Psoriasis	Ixekizumab	PPP, inverse psoriasis, HS, vitiligo	12 We	No	Persistence of lesions/No	True
Nakao, et al., 2018 [13]	66y (M)	Psoriasis	Secukinumab	PPP	2 Mo	N.A	Switch to Brodalumab with improvement of PPP and psoriasis/Yes	True
Takahashi, et al., 2018 [14]	69y (F)	Psoriasis	Brodalumab	PPP	4 Mo	N.A	Switch to cyclosporine with complete improvement of PPP and joints/Yes	True
Noell, et al., 2017 [15]	53y (F)	Psoriasis	Secukinumab	Inverse, palmoplantar psoriasis	1 We	N.A	Switch to infliximab with complete improvement/Yes	True
Brunasso, et al., 2021 [16]	47y (M)	Psoriasis	Brodalumab	PPP	1 We	20 We	Switch to Guselkumab with complete improvement of PPP and psoriasis/Yes	True
Dogra, et al., 2019 [17]	22y (M)	Psoriasis	Secukinumab	GPP	9 Mo	10 Mo	Switch to infliximab with complete improvement/Yes	True
Hosokawa, et al., 2019 [18]	67y (M)	Psoriasis	Brodalumab	Scalp pustular psoriasis	1 Mo	N.A.	Switch to Guselkumab with complete improvement/Yes	True

Durmaz, et al., 2020 [19]	47y (F)	AS	Secukinumab	Plaque psoriasis	N.A	N.A	Improvement with topical therapy/No	True
Sladden, et al., 2017 [20]	61y (F)	Psoriasis	Secukinumab	Nail psoriasis	3 Mo	3 Mo	Switch to Ustekinumab with complete improvement/Yes	True
Hoshina, et al., 2018 [21]	43y (F)	Psoriasis and PsA	Secukinumab	Plaque psoriasis	4 We	4 We	Switch to cyclosporine with improvement/Yes	True
Teraki, et al., 2018 [22]	33y (F) 52y (M) 89y (M)	Psoriasis and PsA Psoriasis Psoriasis/GPP	Secukinumab Secukinumab Ixekizumab	Eye-lid psoriasis Eye-lid psoriasis Eye-lid psoriasis	N.A 4 Mo 4 Mo	N.A No No	Improvement without therapy after withdrawal/Yes Improvement with topical therapy/No Improvement with topical therapy and recurrence/No	True True True
Oiwa, et al., 2019 [23]	76y (M)	Psoriasis	Ixekizumab	Erythrodermic psoriasis	8 We	8 We	Switch to cyclosporine with improvement/Yes	True
Brunasso, et al., 2021 [16]	79y (F)	Psoriasis	Secukinumab	Eye-lid psoriasis	1 Mo	No	Improvement with topical therapy and recurrence/No	True
EL-Komy, et al., 2020 [24]	46y (F)	Psoriasis and PsA	Secukinumab	Psoriasis and GPP	N.A	No	Increase of dose and acitretin improvement/No	True
Currado, et al., 2020 [25]	54 y (F)	Psoriasis	Secukinemab	Inverse psoriasis	10 Mo	N.A	Complete improvement after withdrawal/yes	True
Tadiotto Cicogna et al, 2019 [26]	52y (F)	PsA	Secukinumab	Acrodermatitis of Hallepeau	9 mo	4 We	Improvement after withdrawal/Yes	True
Caldarola, et al., 2020 [6]	53y (M) 34y (M) 52y (M) 48y (M) 42y (F)	Psoriasis Psoriasis Psoriasis Psoriasis Psoriasi	Ixekizumab Ixekizumab Secukinumab Ixekizumab Ixekizumab	Psoriasiform eruption Psoriasiform eruption Psoriasiform eruption Psoriasiform eruption Psoriasiform eruption	20 We 8 We 16 We 12 We 26 We	N.A No N.A No No	N.A/Yes Topical steroids/No N.A./Yes Topical steroids/No Topical steroids/No	True True True True True
Hlaca, et al, 2021 [27]	50y (F)	Psoriasis	Ixekizumab	PPP	3 We	1 Mo	Switch to Guselkumab complete improvement /Yes	True
Caravello, et al., 2021 [28]	46y (N.A)	Psoriasis	Brodalumab	Scalp psoriasis and PPP	4 Mo	2 Mo	Switch to Secukinumab/Yes with partial improvement	True
Penalba-Torres, et	36y (F)	HS	Secukinumab	PPP	16 We	9 Mo	Topical therapy/complete	Borderline

al., 2021 [29]	54y (F)	Spondyloarthropaty	Secukinemab	PPP	4 We	5 We	improvement after withdrawal Topical therapy/complete improvement after withdrawal	True
Tan, et al., 2021 [30]	62y (F)	Psoriasis	Ixekizumab	Psoriasiform alopecia	6 Mo	N.A	Improvement after 2 Mo from withdrawal	True
Bataille, et al, 2022 [31]	5 patients (N.A)	Psoriasis	Secukinumab (97%) and ixekizumab (3%)	Paradoxical reaction, psoriasis?	N.A	N.A	N.A	True all 5 cases
Jin, et al., 2018 [32]	47y (F)	Psoriasis, PsA, PPP	Secukinumab	PG	4 Mo	4 Mo	Switch to cyclosporine with complete improvement/Yes	Borderline
Wollina, et al., 2018 [33]	33y (F)	Psoriasis	Secukinumab	PG	10 Mo	12 Mo	Switch to prednisolone with complete improvement/Yes	Borderline
Petty, et al., 2020 [34]	50y (F)	Psoriasis and PPP	Secukinumab	PG	3 We	3 We	Switch to Cyclosporine, then to systemic steroids and improvement with Ustekinumab/Yes	Borderline
Barrado-Solis et al., 2020 [35]	46y (F) 48y (F)	Psoriasis Psoriasis and PsA	Secukinumab Secukinumab	Behcet´s disease Behcet´s disease	1 We 6 Mo	N.A N.A	Switch to steroid therapy and complete improvement/Yes Switch to steroid therapy and complete improvement/Yes	Borderline Borderline
Dincses, et al., 2019 [36]	34 y (M) 29y (M)	AS AS	Secukinumab Secukinumab	Behcet´s disease Behcet´s disease	4 We 3 We	4 We 3 We	Switch to Certolizumab with complete improvement/Yes Switch to Infliximab with complete improvement/Yes	Borderline Borderline
Calleja-Algarra, et al, 2020 [37]	45y (F)	Psoriasis and PsA	Secukinumab	Behcet´s disease	1 Mo	10 Mo	Switch to apremilast with complete improvement/Yes	Borderline
Navarro-Trivino, et al., 2019 [38]	58y (M)	Psoriasis, PsA	Secukinumab	HS	2 We	N.A	Switch to Ustekinumab with complete improvement/Yes	Borderline
Marasca, et al., 2019 [39]	46y (M)	Psoriasis	Secukinumab	HSS	3 Mo	7 Mo	Switch to adalimumab with good response/Yes	Borderline
Eldirany, et al.,2019 [40]	70y (M)	Psoriasis, PsA	Ixekizumab	Alopecia areata	13 Mo	13 Mo	Complete remission after withdrawal and switch to Guselkumab/Yes	Borderline

Yalici, et al., 2019 [41]	41y (M)	Psoriasis	Secukinumab	Alopecia areata	6 Mo	No	Add.on cyclosporine with response and recurrence/No	Borderline
Yajima, et al., 2019 [42]	62y (F) 40 y (F)	Psoriasis Psoriasis	Secukinumab Brodalumab	Diffuse alopecia Diffuse alopecia	6 Mo 2 Mo	6 Mo 2 Mo	Oral prednisolone with complete improvement/Yes Switch to Ustekinumab with complete improvement/Yes	Borderline Borderline
Nieto-Benito, et al., 2020 [43]	39y (M) 43y (F)	Psoriasis Psoriasis	Secukinumab Secukinumab	Vitiligo Vitiligo	24 Mo 12 Mo	No No	Topical tacrolimus with improvement/No Topical tacrolimus with improvement/No	Borderline Borderline
Mery-Bossard, et al, 2017 [46]	N.A	N.A	Secukinumab	Vitiligo	N.A.	N.A	N.A	Borderline
Marasca, et al., 2021 [47]	53y (M)	Psoriasis	Ixekizumab	Vitiligo	12 We	N.A	N.A	Borderline

Table 1: Skin-PAE during anti IL-17 therapy.

Psoriasis and Psoriatic Arthritis (PsA) were the most common primary disease treated with IL-17 blocking agents, psoriasis 64% (37/58), concomitant psoriasis and PsA 19% (11/58), followed by anchylosing spondylitis (AS) with 7% (4/58), Generalized Pustular Psoriasis (GPP) with 3,5% (2/58), and concomitant PPP in 3,55% (2/58), Spondyloarthropathy 1,7% (1/58), hidradenitis suppurativa 1,7% (1/58) in one case such information was not available (Table 1).

Secukinumab was the most frequent agent associated to skin-PAE (67%, 39/58) followed by Ixekizumab (20%, 12/58) and Brodalumab 7/58(12%).

A total of 64 skin-PAE were recorded, one patient developed simultaneously four different skin-PAEs (PPP, inverse psoriasis, vitiligo and hidradenitis suppurativa) during Brodalumab-therapy and three patients recorded two skin-PAEs during Secukinumab (2 patients) and one case under Brodalumab. All of the cases of multiple skin-PAEs involved the new onset of pustular forms of psoriasis.

True skin-PAE manifested mainly as PPP in 33% (18/58) of patients and as other forms of psoriasis in 67%, 27/40 (plaque, plantar, inverse, palmoplantar plaque, GPP, scalp, nail, eye-lid, erythrodermic, acrodermatitis of Hallopeau, psoriasiform eruption, psoriasiform alopecia) Table 2. Between the 40 cases classified as True-PAE in 45% of patients (18/40) a variant of pustular psoriasis was described, mainly PPP (78%, 14 cases), but also GPP and in one case ACH Table 2. Borderline skin-PAE were recorded in 31% of cases (18/58): new onset of Behcet´s disease, pyoderma gangrenosum, diffuse alopecia/alopecia areata, vitiligo and hidradenitis suppurativa Table 2.

Type pf Paradoxical Event	True Skin-PAE	Borderline Skin-PAE
Number of patients	39	19
Percentage of patients	67%	33%
Percentage of females	61%	56%
Percentage of PPP	33%	5%

Table 2: Type of paradoxical event and patient distribution.

In 7% (4/58) of cases a previous skin-PAE was recorded as follows: palmoplantar plaque psoriasis by adalimumab, dermatomyositis during adalimumab, PPP by adalimumab and alopecia areata during Certolizumab pegol [32,37]. Table 1 mean onset of the skin-PAE was 18 weeks, range: 1 week to 24 months after the first dose of anti-IL-17 therapy. 60% (35/58) of patients discontinued anti IL-17 therapy due to skin-PAE and 28% (16/58) did not interrupt it; in 7 cases (12%) withdrawal or continuation was not reported. Between patients that withdrew anti-IL-17 therapy, 20% were switched with improvement to anti IL-12/23 (Ustekinumab: 7/35) or to anti-IL-23 in 9% (Guselkumab: 3/35), or to an anti-TNF-a in 14% of cases (5/35) and to other anti-IL-17 agent in two cases (6%). In 7 cases cyclosporine was introduced (Table 1).

Discussion

After extensive review of the available literature, we found 58 patients affected by 64 episodes of skin-PAE during anti IL-17 therapy, 40 of those cases can be classified as true-PAE, with an almost equal distribution between genders and a mean age of onset of 51 years. The most frequent agent associated to skin-PAE was Secukinumab, such finding can be explained by its earlier approval for both psoriasis and PsA in comparison with Ixekuzumab and Brodalumab and its broader use worldwide. The mean time to skin-PAE onset was 18 weeks, but with a great variability between one week to 24 months after the first administered dose of anti-IL-17 therapy.

Diverse phenotypes of psoriasis, mainly pustular forms were described as Skin-PAE, in 33% of cases PPP was recorded and in 67% of patients, other form of psoriasis, including acrodermatitis of Hallopeau, GPP, palmoplantar plaque psoriasis, eye-lid psoriasis, nail and scalp psoriasis, inverse and erythrodermic psoriasis were seen. True-skin-PAE were all psoriasis-related, interestingly, we found an increased frequency (45%) of pustular variants of psoriasis, much higher than the prevalence of pustular psoriasis in general population and in accordance to previously reported skin-PAE during anti-TNF-a therapies [2] Borderline (non-psoriatic) skin-PAE were mainly neutrophilic dermatoses as Behcet´s disease and Pyoderma Gangrenosum, accounting for 18% of all skin-PAE.

It is worth to notice that the majority of patients (77%) who experienced a skin-PAE during anti IL-17 therapy were previously treated with other biologicals (not naïve to biological therapy), in first-line patients were treated with TNF-a blockers in 79% of cases and in only 17% (4 cases) a previous skin-PAE was recorded (recurrent skin PAE during two different mechanism of action). In 83% of IL-17 related skin-PAE the previous use of a TNF-a blocker did not trigger such reaction, suggesting a different or specific immunological mechanism related to anti-IL-17 Skin-PAE. We have to consider that patients that were switched from TNF-a blockers to anti-IL-17, experienced a lack of efficacy during the former and we would like to underline that the vast majority of skin-PAE appear while the primary disease is under optimal control, advocating a diverse immunological pathway involved. Such findings make us state that skin-PAE usually appears while the putative biological agent demonstrates efficacy in controlling the primary disease. For the cases with recurrent skin-PAEs we hypothesize a genetic predisposition. Considering the high frequency of pustular psoriasis variants between skin-PAE is probable that the immunological mechanism differs from the one in chronic plaque psoriasis. Probably an immunological imbalance cause by the Th17 downregulation contributes to the up-regulation of IL-36 cytokines that have been recognized as essential to pustular psoriasis pathogenesis under a specific genetic background. In contrast to classical pustular psoriasis, paradoxical pustular psoriasis under anti-TNF-a and anti Il-17 therapy, as demonstrated in this systematic review, tend to complete remission after the withdrawal of the offending agent and are not prone to become recurrent as it would be expected, suggesting a transitory immunological imbalance. Exactly as with pustular variants of psoriasis, paradoxical psoriasis seems to be slightly more frequent in females.

The mean time of onset of skin-PAE during anti Il-17 therapy was 18 weeks, it can be considered as delayed making us think that trigger factors might contribute to such a late onset. In the four cases where recurrent skin-PAE were recorded the mean time of onset was 6 weeks, significantly shorter if compared to the rest, suggesting as previously discussed a genetic predisposition/background. Similar time of onset has been reported for paradoxical psoriasis during anti TNF-a therapies where the onset might range from few days to several months [46-48].

In two-thirds of cases anti-IL-17 withdrawal was performed, with complete improvement without systemic therapy in 3 cases (10%), with effective switch to anti IL-23 therapies in 34%, switch to anti-TNF-a in 17% and introduction of cyclosporine in 24%. Such data suggests that IL-23 blockers might be a safe and efficacious option for patients affected by skin-PAE. Interestingly the

switch to an anti-TNF-a therapy did not trigger another skin-PAE suggesting an alternative mechanism involved in anti-IL-17 and anti-TNF-a induced paradoxical events.

The onset of unexpected and antagonistic reactions associated with these targeted therapies reveals the complexity of the immunogenetic pathways involved in human disease. A paradox provokes fresh thought about a contradictory event.

Conclusion

True-skin-PAE occur not only under anti TNF-a therapy but also during anti Il-17 therapy, the underlaying immunological mechanism is not yet known, but pustular variants of psoriasis seem to be more prevalent than in general population; withdrawal of the anti-IL-17 therapy has been mainly performed and other therapies such as anti-IL-23 biologics seem to control both the underlying disease and the true-skin-PAE. Further studies are needed in order to better understand the immunological mechanism involved and eventually the genetical predisposition to such reactions.

Conflict of Interest

The authors have no conflict of interest to declare.

References

1. Toussirot É, Aubin F. Paradoxical reactions under TNF-α blocking agents and other biological agents given for chronic immune-mediated diseases: an analytical and comprehensive overview. RMD Open. 2016;2(2):e000239.
2. Puig L. Paradoxical Reactions: Anti-tumor necrosis factor alpha agents, ustekinumab, secukinumab, ixekizumab, and others. Curr Probl Dermatol. 2018;53:49-63.
3. Brunasso AM, Laimer M, Massone C. Paradoxical reactions to targeted biological treatments: A way to treat and trigger? Acta Derm Venereol. 2010;90(2):183-5.
4. AbuHilal M, Walsh S, Shear N. The role of IL-17 in the pathogenesis of psoriasis and update on IL-17 inhibitors for the treatment of plaque psoriasis. J Cutan Med Surg. 2016;20(6):509-16.
5. Ungar B, Pavel AB, Li R, Kimmel G, Nia J, Hashim P, et al. Phase 2 randomized, double-blind study of IL-17 targeting with secukinumab in atopic dermatitis. J Allergy Clin Immunol. 2020;S0091-6749(20):30684-9..
6. Caldarola G, Pirro F, Di Stefani A, Talamonti M, Galluzzo M, D'Adamio S, et al. Clinical and histopathological characterization of eczematous eruptions occurring in course of anti IL-17 treatment: a case series and review of the literature. Expert Opin Biol Ther. 2020;20(6):665-72.
7. Mössner R, Pinter A. Paradoxical palmoplantar pustulosis induced by secukinumab and brodalumab: a report of three cases. Eur J Dermatol. 2020.
8. Abbruzzese A, Venerito V, Lopalco G, Fornaro M, Giannotta M, Iannone F. Paradoxical pustular psoriasis in a patient with psoriatic arthritis on secukinumab treatment. J Clin Rheumatol. 2020;26(6):e208-9.
9. Honma M, Nozaki H, Hayashi K, Iinuma S, Ishida-Yamamoto A. Palmoplantar pustulosis emerged on a case of generalized pustular psoriasis successfully treated by secukinumab. J Dermatol. 2019;46(12):e468-e9.
10. Sadik CD, Thieme M, Zillikens D, Terheyden P. First emergence of pyoderma gangraenosum, palmoplantar pustulosis and sacroiliitis in a psoriasis patient associated with switching from secukinumab to brodalumab. J Eur Acad Dermatol Venereol. 2019;33(11):e406-7.
11. Martínez-Doménech Á, García-Legaz-Martínez M, Magdaleno-Tapial J, Giácaman M, Hernández-Bel P, Pérez-Ferriols A. Paradoxical reversed plantar involvement during ixekizumab therapy for psoriasis. Dermatol Online J. 2019;25(4):13030.
12. Pirro F, Caldarola G, De Simone C, Moretta G, Giovanardi G, Peris K. Multiple paradoxical reactions during ixekizumab therapy. Dermatol Ther. 2019;32(3):e12852.
13. Nakao M, Asano Y, Kamata M, Yoshizaki A, Sato S. Successful treatment of palmoplantar pustular psoriasis with brodalumab. Eur J Dermatol. 2018;28(4):538-9.
14. Takahashi H, Sato K, Takagi A, Iizuka H. Brodalumab-induced palmar pustular eruption and joint swelling accompanied by muscle pains in two cases of psoriasis. J Dermatol. 2018;45(11):e325-6.
15. Noell C, McQuade B, Gottlieb A, Rosmarin D. Anti IL-17 flared psoriasis in a patient on secukinumab. Dermatol Ther. 2017;30(4).
16. Brunasso AMG, Massone C. Paradoxical psoriasis during Il-17 blockage: two memorable patients. J Dermatology and

Dermatitis. 2022;6(2).
17. Dogra S, Bishnoi A, Narang T, Handa S. Secukinumab-induced paradoxical pustular psoriasis. Clin Exp Dermatol. 2019;44(1):72-3.
18. Hosokawa Y, Hamada T, Ashida H, Ikeda M. Effective treatment with guselkumab for psoriatic alopecia as paradoxical reaction. J Dermatol. 2019;46(8):e302-3.
19. Durmaz K, Ataseven A, Ozer I. Paradoxical plaque psoriasis due to secukinumab treatment in an ankylosing spondylitis patient. Dermatol Ther. 2020;33(4):e13504.
20. Sladden MJ, Sladden CS, Gulliver WPF. Secukinumab-Induced Psoriasiform Eruption. JAMA Dermatol. 2017;153(11):1194-5.
21. Hoshina D, Haga N, Furuya K, Sakai M. Paradoxical localized exacerbation of psoriatic eruptions triggered by secukinumab. Clin Exp Dermatol. 2018;43(6):718-9.
22. Teraki Y, Takahashi A, Inoue Y, Takamura S. Eyelid dermatitis as a side effect of interleukin-17A inhibitors in psoriasis. Acta Derm Venereol. 2018;98(4):456-7.
23. Oiwa T, Fujita M, Takase S, Nishimura Y, Ota M, Okada K, et al. A case of ixekizumab-induced psoriasiform eruption. Acta Derm Venereol. 2019;99(4):446-7.
24. El-Komy M, Amer M, Mostafa A, ElKalioby M. Secukinumab retreatment associated psoriasis flare with pustules. J Dermatolog Treat. 2020:1-4.
25. Currado D, Margiotta D, Conforti C, Coppola R, Panasiti V, Afeltra A, et al. New onset of psoriasis induced by secukinumab in a patient with ankylosing spondylitis: a case report. Scand J Rheumatol. 2020;49(1):75-6.
26. Tadiotto Cicogna G, Messina F, Nalotto L, Szekely S, Alaibac M. Case Report: Paradoxical acrodermatitis of Hallopeau-like eruption following anti-IL-17 therapy. F1000Res. 2019;8:336.
27. Hlaca N, Zagar T, Kastelan M, Brajac I, Prpic-Massari L. Ixekizumab-induced paradoxical pustular reaction successfully treated with guselkumab. Clin Exp Dermatol. 2021;46(8):1572-3.
28. Caravello S, Moggio E, Soglia S, Zane C. Paradoxical reaction to brodalumab in a patient affected by psoriasis. Ital J Dermatol Venerol. 2021;156(4):511-2.
29. Penalba-Torres M, Rivera-Díaz R. Palmoplantar pustulosis under secukinumab in two patients without psoriasis. J Dtsch Dermatol Ges. 2022;20(1):106-9.
30. Tan TL, Taglia L, Yazdan P. Drug-induced psoriasiform alopecia associated with interleukin-17 inhibitor therapy. J Cutan Pathol. 2021;48(6):771-4.
31. Bataille P, Layese R, Claudepierre P, Paris N, Dubiel J, Amiot A, et al. AP-HP/Universities/Inserm COVID-19 research collaboration and on behalf of the 'Entrepôt de Données de Santé' AP-HP consortium. Paradoxical reactions and biologic agents: a French cohort study of 9303 patients. Br J Dermatol. 2022.
32. Jin K, Matsuzaki Y, Akasaka E, Nakano H, Sawamura D. Pyoderma gangrenosum triggered by switching from adalimumab to secukinumab. J Dermatol. 2019;46(3):e108-9.
33. Wollina U, Schönlebe J, Fürll C. Pyoderma gangrenosum induced by secukinumab-A late paradoxical drug reaction. Dermatol Ther. 2020;33(1):e13161.
34. Petty AJ, Whitley MJ, Balaban A, Ellington K, Marano AL. Pyoderma gangrenosum induced by secukinumab in a patient with psoriasis successfully treated with ustekinumab. JAAD Case Rep. 2020;6(8):731-3.
35. Barrado-Solís N, Rodrigo-Nicolás B, De la Morena-Barrio I, Pérez-Pastor G, Sanchis-Sánchez C, Tomás-Cabedo G, et al. Report of two cases of Behçet's disease developed during treatment with secukinumab. J Eur Acad Dermatol Venereol. 2020.
36. Dincses E, Yurttas B, Esatoglu SN, Melikoglu M, Hamuryudan V, Seyahi E. Secukinumab induced Behçet's syndrome: a report of two cases. Oxf Med Case Reports. 2019;2019(5):omz041.
37. Calleja Algarra A, Aragón Miguel R, Andrés Lencina JJ, Pinilla Martín B, Vico Alonso C, Rodríguez Peralto JL, et al. Behçet's-like disease during secukinumab treatment: new paradoxical reaction? J Dtsch Dermatol Ges. 2020.
38. Navarro-Triviño FJ, Sanchez-Parera R, Ruiz-Villaverde R. Secukinumab-induced paradoxical hidradenitis suppurativa. Dermatol Ther. 2020;33(1):e13150.
39. Marasca C, Megna M, Balato A, Balato N, Napolitano M, Fabbrocini G. Secukinumab and hidradenitis suppurativa: Friends or foes? JAAD Case Rep. 2019;5(2):184-7.
40. Eldirany SA, Myung P, Bunick CG. Ixekizumab-induced alopecia areata. JAAD Case Rep. 2019;6(1):51-3.
41. Yalici Armagan B, Atakan N. New onset alopecia areata during secukinumab therapy. Dermatol Ther. 2019;32(5):e13071.

42. Yajima M, Akeda T, Kondo M, Habe K, Yamanaka K. Alopecia diffusa while using interleukin-17 inhibitors against psoriasis vulgaris. Case Rep Dermatol. 2019;11(1):82-5.
43. Nieto-Benito LM, Baniandrés-Rodríguez O. New-onset vitiligo during treatment with secukinumab: report of two cases and review of the literature. Clin Drug Investig. 2020;40(11):1089-91.
44. Méry-Bossard L, Bagny K, Chaby G, Khemis A, Maccari F, Marotte H, et al. New-onset vitiligo and progression of pre-existing vitiligo during treatment with biological agents in chronic inflammatory diseases. J Eur Acad Dermatol Venereol. 2017;31(1):181-6.
45. Marasca C, Fornaro L, Martora F, Picone V, Fabbrocini G, Megna M. Onset of vitiligo in a psoriasis patient on ixekizumab. Dermatol Ther. 2021;34(5):e15102.
46. Bucalo A, Rega F, Zangrilli A, Silvestri V, Valentini V, Scafetta G, et al. Paradoxical psoriasis induced by anti-TNFα treatment: evaluation of disease-specific clinical and genetic markers. Int J Mol Sci. 2020;21(21):7873.
47. Mylonas A, Conrad C. Psoriasis: classical vs. paradoxical. The yin-yang of TNF and type I interferon. Front Immunol. 2018;9:2746.
48. Stalder R, Brembilla N, Conrad C, Yawalkar N, Navarini A, Boehncke WH, et al. Interleukin-17E, inducible nitric oxide synthase and arginase1 as new biomarkers in the identification of neutrophilic dermatoses. Clin Exp Dermatol. 2022;47(4):675-83.