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Report

Drug survival of biologics and non-biologics in patients affected by palmoplantar psoriasis: a "real-world", mono-center experience

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Abstract

Background Data on the treatment of palmoplantar psoriasis (PP) are very limited as these patients are often excluded from clinical trials. Moreover, this form of psoriasis is often resistant to treatment, making its clinical management complex.

Methods Primary endpoint was to evaluate the clinical and demographic characteristics and the drug survival of both biological and non-biological drugs in a population affected by PP. Secondary endpoint was to highlight any differences between the hyperkeratotic and pustular variant. We analyzed data from 233 psoriasis patients with palmoplantar involvement, with or without chronic plaque psoriasis. We performed a drug-survival analysis with the aid of Kaplan-Meier survival and a multivariate analysis to highlight the influence of certain variables on treatment persistence using a Cox regression model.

Results The drug-survival analysis revealed that biologic drugs compared to non-biologic drugs are associated with a higher persistence in treatment (59.73 vs. 43.56%); in particular, anti-IL23 drugs were found to be the drugs with the best drug-survival overall (67.94% of patients at 60 months are still on these drugs). Furthermore, our multivariate analysis shows that when compared with biological drugs, non-biological drugs are associated with an increased risk of treatment discontinuation (HR = 1.95 [95% CI: 1.41–2.68], $P = 0.001$).

Conclusions Our study confirms the difficulty of treating PP and shows that biologic drugs are associated with longer persistence in treatment than non-biologics in both PP's variants, not because of their higher effectiveness but because of their better safety profile.

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Introduction

Palmoplantar psoriasis (PP) is an uncommon clinical variant of psoriasis in which cutaneous lesions are typically localized on palms and soles and may represent the only manifestation of the disease (almost 40% of cases) or be associated with typical psoriatic plaques on other body sites.[1,2]

Two main clinical subtypes of PP are described: a hyperkeratotic variant and a pustular variant (or palmoplantar pustulosis). To date, there is much debate whether palmoplantar pustulosis should be considered as a clinical variant of psoriasis or a separate entity.

The hyperkeratotic variant of PP can occur at any age and has a slightly higher prevalence in males than females; conversely, the pustular variant mainly affects female adults (20–60 years).[3]

Although it involves only 5% of the body surface area (BSA), PP has a negative impact on patients' quality of life (QoL), as it affects visible areas of the body with great functional importance.[4]

For this reason, the assessment of disease severity must take into account not only the extension of the disease but also the associated degree of mental distress, physical disability, and social impact.[5]

Similar to plaque psoriasis, an association between hyperkeratotic PP and comorbidities such as diabetes, cardiovascular disease, and mood disorders has been reported in a recent retrospective study.[6]

Data on the specific treatment of PP are scarce because patients with PP are often excluded from clinical trials due to the limited BSA (<10%). In addition, this variant of psoriasis is often resistant to treatments, making its clinical management a challenge for physicians.[7]

According to a systematic review,[8] biologics can be effective in both hyperkeratotic PP and pustular PP.[9] Noteworthy, guselkumab, an anti-IL-23A monoclonal antibody, was recently approved in Japan for the treatment of pustular PP in patients refractory to previous conventional treatments, after an RCT showed its safety and efficacy at 16 weeks, that was maintained up to 52 weeks.[10]

Materials and methods

We performed a single-center, retrospective, observational study analyzing data of patients suffering from PP referred to the outpatient clinic of Dermatology at the Fondazione Policlinico Universitario A. Gemelli IRCCS between April 2015 and March 2022.

The primary endpoint was to evaluate the clinical and demographic characteristics and the drug survival of both biological and non-biological drugs in a population affected by PP.

The secondary endpoint was to highlight any differences between the hyperkeratotic and pustular variants.

Inclusion criteria were: adult patients (≥18 years) with psoriasis and palmoplantar involvement, with or without chronic plaque psoriasis in other body sites, with or without psoriatic arthritis.

Data on patients' characteristics, clinical features of PP, ongoing and previous treatments were collected. In detail, patients' characteristics included sex, age at diagnosis, weight, height, smoking habits, BMI, and comorbidities (hypertension, impaired glucose tolerance/diabetes, dyslipidemia, liver disease, depression/anxiety, psoriatic arthritis, plaque psoriasis). Furthermore, clinical variants of psoriasis (hyperkeratotic or pustular form), extension of acral involvement (palmar involvement, plantar involvement, palmoplantar involvement), and involvement of other skin sites and nails were registered. We considered eligible patients who had moderate-to-severe palmoplantar involvement regardless of the presence or absence of involvement of other skin sites. Palmoplantar pustulosis was considered as a clinical variant of psoriasis.

Finally, data on ongoing and previous therapies were collected; biological drugs were categorized as anti-TNF-alpha, anti-IL-17, and anti-IL-23 rather than as individual drugs. We considered ustekinumab, an anti-IL-12/23 agent, to be part of the anti-IL-23 class. Data on the use of non-biological drugs (methotrexate, acitretin, cyclosporine, apremilast, and dimethyl fumarate), a combination of two or more treatments, and the use of topical drugs as monotherapy as well as of phototherapy were also collected. The date of treatment initiation, any treatment discontinuation, date of end of treatment, and the reason for discontinuation were also taken into account. We included data from patients who were receiving treatment with any of these therapies and counted each treatment course separately. As for those patients who were under combination therapy, we accounted for them as two different treatment courses. We defined treatment course as the undertaking of a new treatment starting from the first and ending with the last administration of the considered drug.

As for descriptive statistical data, continuous variables were reported using mean (SD) after verifying their normal distribution, while categorical variables were reported as absolute and relative frequencies (%). Their statistical significance was assessed by the Student's *t*-test for continuous variables and the Fisher's exact test for categorical variables.

In addition, an analysis of drug survival, i.e., persistence in the treatment of all systemic and biologic therapies considered in this study, was carried out. This analysis was reported descriptively with the help of the Kaplan–Meier survival curves. Three drug-survival-related "events" were considered and analyzed individually: overall discontinuation, discontinuation due to treatment ineffectiveness, discontinuation due to adverse events, or other causes. The latter two were considered as a single parameter due to the low number of events in our population. Patients were censored if lost to follow-up or if their discontinuation was due to remission and then excluded from the drug-survival analysis.

To highlight a possible association between drug survival events and demographic and clinical variables, a multivariate analysis was performed using the Cox regression model. The analyses were also stratified according to the variant of psoriasis and adapted accordingly. The data obtained were reported as the hazard ratio (HR), with confidence intervals set at 95%. Statistical significance has been set at a $P < 0.05$. The statistical analyses described were carried out using the software STATA 13.0 (StataCorp).

Institutional review board approval was not required for this study because all the procedures did not deviate from routine clinical practice. All the patients signed a hospital-based informed consent. The study was performed following the principles of the Declaration of Helsinki.

Results

Baseline characteristics

In total, 233 patients were included. The mean age of patients was 58.6 years (SD: 14.6), and 60.9% were female. The mean BMI was 28.2 kg/m^2 (SD: 4.3). The mean duration of the disease was 15.1 years (SD: 13.6), 41 patients (17.6%) had PsA, and 95 patients (40.8%) had concomitant plaque psoriasis. In total, 172 patients (73.8%) had hyperkeratotic PP, while 61 patients (26.2%) had pustular PP. In our population with pustular PP, patients were mainly females (60.9% $P = 0.009$), while in hyperkeratotic PP there was no difference in prevalence between genders. Compared to the hyperkeratotic variant, involvement of both palms and soles was significantly more frequent in pustular PP (75.4% $P = 0.020$), which was also more frequently the only manifestation of the disease (31.1% $P = 0.024$). There were no significant differences in terms of the mean age, the BMI, and smoking habits between the two forms. Other clinical characteristics are reported in Table 1.

Therapy

A total of 442 treatment courses were recorded during the observation period. In detail, 69.5% of patients received systemic therapy with non-biologics (the majority of them were treated with methotrexate [30.0% of study patients]) and 54.5% a therapy with biologics (the majority with anti-TNF-alpha drugs

Table 1 General characteristics of study patients

Patients characteristics	Total (n = 233)	Hyperkeratotic PP (n = 172)	Pustular PP (n = 61)	P-value
Mean age	58.6 ± 14.6	58.4 ± 15.0	59.0 ± 13.8	0.758
BMI	28.2 ± 4.3	28.6 ± 4.6	27.8 ± 4.1	0.695
Female gender	142 (60.9%)	96 (55.8%)	46 (75.4%)	0.009
Male gender	91 (39.1%)	76 (44.2%)	15 (24.6%)	
Smokers	100 (42.9%)	57 (33.1%)	35 (57.4%)	0.148
Former smokers	27 (11.6%)	33 (19.2%)	0 (0%)	
Never smokers	106 (45.5%)	82 (47.7%)	26 (42.6%)	
Age at diagnosis	43.4 ± 16.0	43.0 ± 16.1	44.8 ± 15.5	0.444
Duration of illness (years)	15.1 ± 13.6	15.4 ± 13.5	14.2 ± 14.0	0.564
Plaque psoriasis	95 (40.8%)	76 (44.2%)	19 (31.1%)	0.051
Palmar involvement	68 (29.2%)	58 (33.7%)	10 (16.4%)	0.02
Plantar involvement	11 (4.7%)	6 (3.5%)	5 (8.2%)	
Palmoplantar involvement	154 (66.1%)	108 (62.8%)	46 (75.4%)	
Other cutaneous sites	103 (44.2%)	84 (48.8%)	19 (31.1%)	0.024
Nail involvement	22 (9.4%)	14 (8.1%)	8 (13.1%)	0.308
Comorbidities				
Hypertension	85 (36.5%)	67 (39.0%)	18 (29.5%)	0.217
Diabetes	31 (13.3%)	21 (12.2%)	10 (16.4%)	0.39
Dyslipidemia	57 (24.5%)	43 (25%)	14 (22.9%)	0.863
Hepatological disorders	16 (6.9%)	10 (5.8%)	6 (9.8%)	0.375
Depression/anxiety	13 (5.6%)	7 (4.1%)	6 (9.8%)	0.109
Psoriatic arthritis	41 (17.6%)	28 (16.3%)	13 (21.3%)	0.434
Plaque psoriasis	95 (40.8%)	76 (44.2%)	19 (31.1%)	0.051

PP, palmoplantar psoriasis; BMI, body mass index.

[20.6% of study patients]). Further information about therapies (topical therapy, phototherapy, non-biological drugs, and biological drugs) is shown in Table 2. Treatment discontinuation was detected in 239 of 442 courses (54.1%), in most cases due to ineffectiveness (19.9% of treatments), occurrence of adverse events (14.5%), disease remission (7%), loss at follow-up (8.6%), and other reasons (4.1%) (Table 3).

The drug survival function shows that 65.60, 59.94, and 54.52% of the study population persisted in therapy after 1, 2, and 5 years of treatment, respectively (Figure 1). A drug survival analysis for overall interruption, discontinuation for ineffectiveness, and discontinuation due to adverse events or other causes was conducted for both biologics and non-biologics (Figure 2a–c). At 60 months, the two survival curves for discontinuation events due to ineffectiveness overlap; on the contrary, the survival curves for discontinuation events due to adverse effects or other causes showed a percentage of 85.42% of patients on biologic drugs versus 59.35% of patients on non-biologic drugs. Furthermore, a drug survival analysis was conducted for overall treatment discontinuation events with methotrexate, acitretin, cyclosporine, anti-TNF-alpha, anti-IL17, and anti-IL23 drugs, and data were compared for PP and for both hyperkeratotic and pustular variants separately (Figure 3a). Among biological drugs, anti-IL23 drugs are associated with a higher persistence in treatment over time (67.94% of patients are still on these drugs at 60 months) regardless of PP variant; cyclosporine is the systemic drug with the highest rate of discontinuation over time (at 60 months, 21.81% of patients are on cyclosporine therapy). With regard to drug survival for overall discontinuation events in the hyperkeratotic variant (Figure 3b), acitretin and anti-IL23 were confirmed as the drugs with the lowest discontinuation rate (54.29% of patients on acitretin therapy, and 67.94% of patients on anti-IL23 therapy at 60 months). Cyclosporine has the highest discontinuation rate in this form (21.81% of patients are on cyclosporine therapy at 60 months). Moreover, when drug survival for overall discontinuation events in the pustular variant is considered (Figure 3c), anti-IL23 biological drugs are again the ones with the lowest discontinuation rate (67.94% of patients are on these drugs at 60 months).

Table 2 Number of treatment courses

Treatment	Total treatment courses (n = 442)	Hyperkeratotic PP (n = 310)	Pustular PP (n = 132)
Topical therapy	139 (31.4%)	108 (34.8%)	31 (23.5%)
Phototherapy	14 (3.2%)	12 (3.9%)	2 (1.5%)
Non-biological drugs	162 (36.7%)	108 (34.8%)	54 (40.9%)
Acitretin	47 (10.6%)	36 (11.6%)	11 (8.3%)
Methotrexate	70 (15.8%)	43 (13.9%)	27 (20.5%)
Cyclosporine	31 (7.0%)	20 (6.5%)	11 (8.3%)
Apremilast	9 (2.0%)	5 (1.6%)	4 (3.0%)
Dymethyl fumarate	5 (1.1%)	4 (1.3%)	1 (0.8%)
Biological drugs	127 (28.7%)	82 (26.5%)	45 (34.1%)
Anti-TNF-alpha drugs	48 (10.9%)	34 (11.0%)	14 (10.6%)
Adalimumab	32 (7.2%)	24 (7.7%)	8 (6.1%)
Etarnecept	9 (2.0%)	5 (1.6%)	4 (3.0%)
Infliximab	3 (0.7%)	3 (1.0%)	0 (0%)
Certolizumab pegol	4 (0.9%)	2 (0.6%)	2 (1.5%)
Anti-IL17 drugs	36 (8.1%)	21 (6.8%)	15 (11.4%)
Ixekinumab	22 (5.0%)	10 (3.2%)	12 (9.1%)
Secukinumab	12 (2.7%)	9 (2.9%)	3 (2.3%)
Brodalumab	2 (0.5%)	2 (0.6%)	0 (0%)
Anti-IL23 drugs	43 (9.7%)	27 (8.7%)	16 (12.1%)
Guselkumab	10 (2.3%)	4 (1.3%)	6 (4.5%)
Risankizumab	9 (2.0%)	6 (1.9%)	3 (2.3%)
Tildrakizumab	2 (0.45%)	2 (0.6%)	0 (0%)
Ustekinumab	22 (5.0%)	15 (4.8%)	7 (5.3%)

PP, palmoplantar psoriasis.

In order to analyze the influence of certain variables on persistence in treatment, a multivariate analysis was conducted. The only variable that significantly correlates with persistence in treatment is the type of therapy; indeed, when compared with biological drugs, therapy with non-biological drugs is associated with an increased risk of treatment discontinuation (HR = 1.95 [95% CI: 1.41–2.68], P-value = 0.001) (Table 4). For the same purpose, a multivariate analysis on persistence to treatment was conducted considering patients with hyperkeratotic PP and those with pustular PP separately. In patients with pustular PP, the presence of another skin site involvement has a statistically significant negative impact on treatment persistence (HR = 2.27 [95% CI: 1.00–5.14], P-value = 0.04). In patients with hyperkeratotic PP, cyclosporine treatment increases the risk of discontinuation more than twofold compared to anti-TNF-alpha drugs (HR = 2.45 [95% CI: 1.15–5.22], P-value = 0.001). Again, in patients with hyperkeratotic PP, acitretin and anti-IL23 are associated with a reduction in the risk of discontinuation by more than half compared to anti-TNF-alpha (HR = 0.38 [95% CI: 0.16–0.91], P-value = 0.030 for acitretin [anti-TNF-alpha reference value]) (HR = 0.39 [95% CI: 0.15–1.02], P-value = 0.05 for anti-IL23). In both variants, the overall risk of discontinuation was higher with non-biologics than with biologics (HR = 1.76 [95% CI: 1.18–2.60], P-value = 0.005, for hyperkeratotic PP) (HR = 2.12 [95% CI: 1.24–3.92], P-value = 0.006, for pustular PP) (Table 5).

Discussion

Palmoplantar involvement is considered a difficult-to-treat site[11] and a negative predictor of response to treatment in patients with psoriasis.[12,13]

Few data on the prevalence of PP in both sexes are also available to date. Based on data collected in a recent systematic review,[3] the prevalence of PP is slightly higher in the male population, and the most frequent subtype of the two variants was hyperkeratotic. On the contrary, it has been estimated that about 90% of

Table 3 Overview of treatment discontinuation, remission, and loss at follow-up were censored in the subsequent drug survival analysis

	Total interruptions	Ineffectiveness	Adverse events	Remission	Other	Lost at follow-up
Total (n = 442)	239 (54.1%)	88 (19.9%)	64 (14.5%)	31 (7.0%)	18 (4.1%)	38 (8.6%)
Topical therapies (n = 139)	42 (30.2%)	24 (17.3%)	4 (2.9%)	3 (2.2%)	4 (2.9%)	7 (5.0%)
Phototherapy (n = 14)	10 (71.4%)	3 (21.4%)	0 (0%)	5 (35.7%)	0 (0%)	2 (14.3%)
Non-biological drugs (n = 162)	121 (74.7%)	29 (17.9%)	46 (28.4%)	16 (9.9%)	7 (4.3%)	23 (14.2%)
Acitretin (n = 47)	40 (85.1%)	4 (8.5%)	10 (21.3%)	9 (19.1%)	4 (8.5%)	13 (27.7%)
Methotrexate (n = 70)	45 (64.3%)	19 (27.1%)	19 (27.1%)	0 (0%)	2 (2.9%)	5 (7.1%)
Cyclosporine (n = 31)	27 (87.1%)	4 (12.9%)	14 (45.2%)	5 (16.1%)	1 (3.2%)	3 (9.7%)
Apremilast (n = 9)	6 (66.7%)	1 (11.1%)	2 (22.2%)	1 (11.1%)	0 (0%)	2 (22.2%)
Dimethyl fumarate (n = 5)	3 (60%)	1 (20%)	1 (20%)	1 (20%)	0 (0%)	0 (0%)
Biological drugs (n = 127)	66 (52.0%)	32 (25.2%)	14 (11.0%)	7 (5.5%)	7 (5.5%)	6 (4.7%)
Anti-TNF-alpha drugs (n = 48)	31 (64.6%)	20 (41.7%)	1 (2.1%)	2 (4.2%)	4 (8.3%)	4 (8.3%)
Anti-IL17 drugs (n = 36)	20 (55.6%)	11 (30.6%)	4 (11.1%)	2 (5.6%)	3 (8.3%)	0 (0%)
Anti-IL23 drugs (n = 43)	15 (34.9%)	1 (2.3%)	9 (20.9%)	3 (7.0%)	0 (0%)	2 (4.7%)

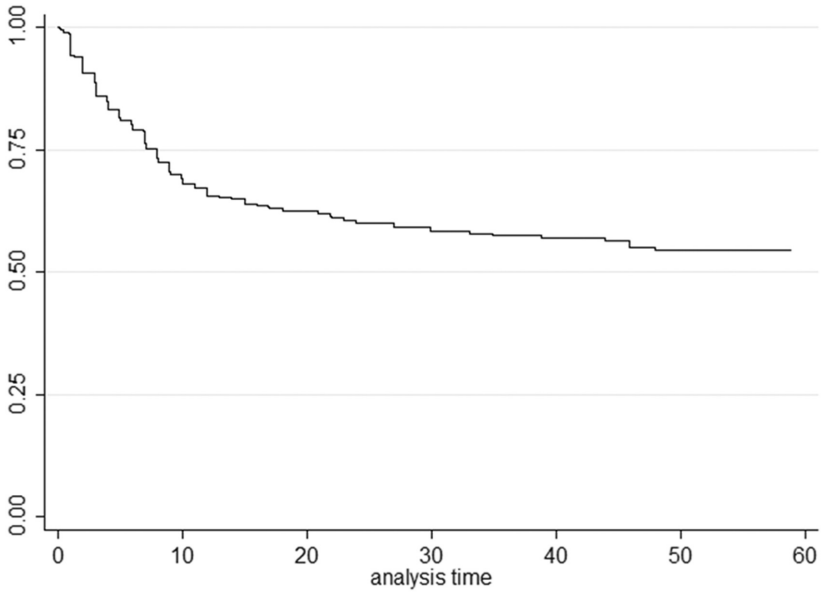

Figure 1 Survival function for overall treatment discontinuation in the whole study population

patients with the pustular variant are women.[14] In our study, pustular PP was significantly more frequent in female patients too, while in the hyperkeratotic variant, the prevalence was equal in both sexes. This data should deserve more attention in the future, as the gender difference in the pustular variant could have negative implications on prognosis and therapy by limiting, for example, the choice of drugs at teratogenic risk in women of childbearing age. In addition, it is known that the female sex is a predictor of treatment discontinuation in patients with psoriasis.[15]

Most of our patients presented with PP in isolated form, and less than half also had plaque psoriasis; the presence of other skin involvement was significantly more frequent in the hyperkeratotic variant than in the pustular one.

It is known that plaque psoriasis is associated with several comorbidities; however, it remains unclear whether or not these comorbidities are also associated with PP, as the data available on this topic are few.[6,16] The spectrum of comorbidities in our population of PP patients was in line with what is reported in the literature about plaque psoriasis, particularly with regard to hypertension,[17] diabetes and/or insulin resistance,[18] dyslipidemia,[19] and psoriatic arthritis.[20]

The drug survival analysis conducted in our study revealed particularly interesting results. First, 54.1% of the treatment courses were discontinued during the observation period of the study, demonstrating the real difficulty in adequately treating this form of psoriasis. The only variable that positively affected

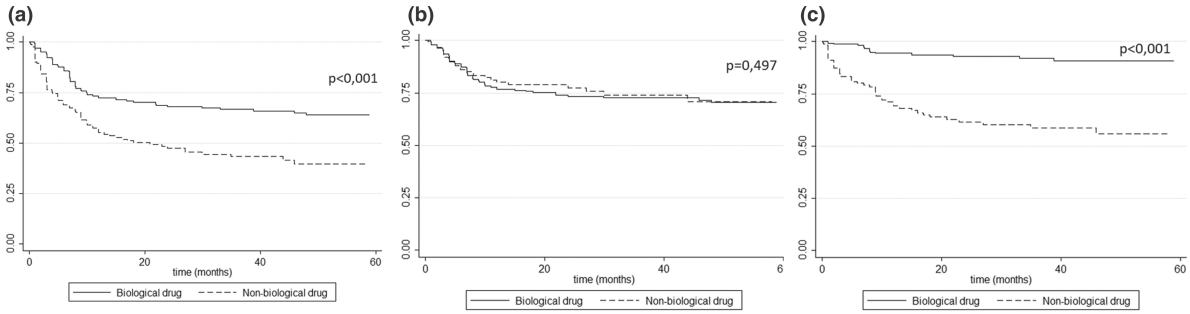

Figure 2 Survival functions for biologics and non-biological drugs: Survival function for overall discontinuation of treatment (a); Survival function for interruption due to ineffectiveness of treatment (b); Survival function for interruption due to adverse events or other causes (c). Remission and loss at follow-up were censored events and not included among other causes of discontinuation

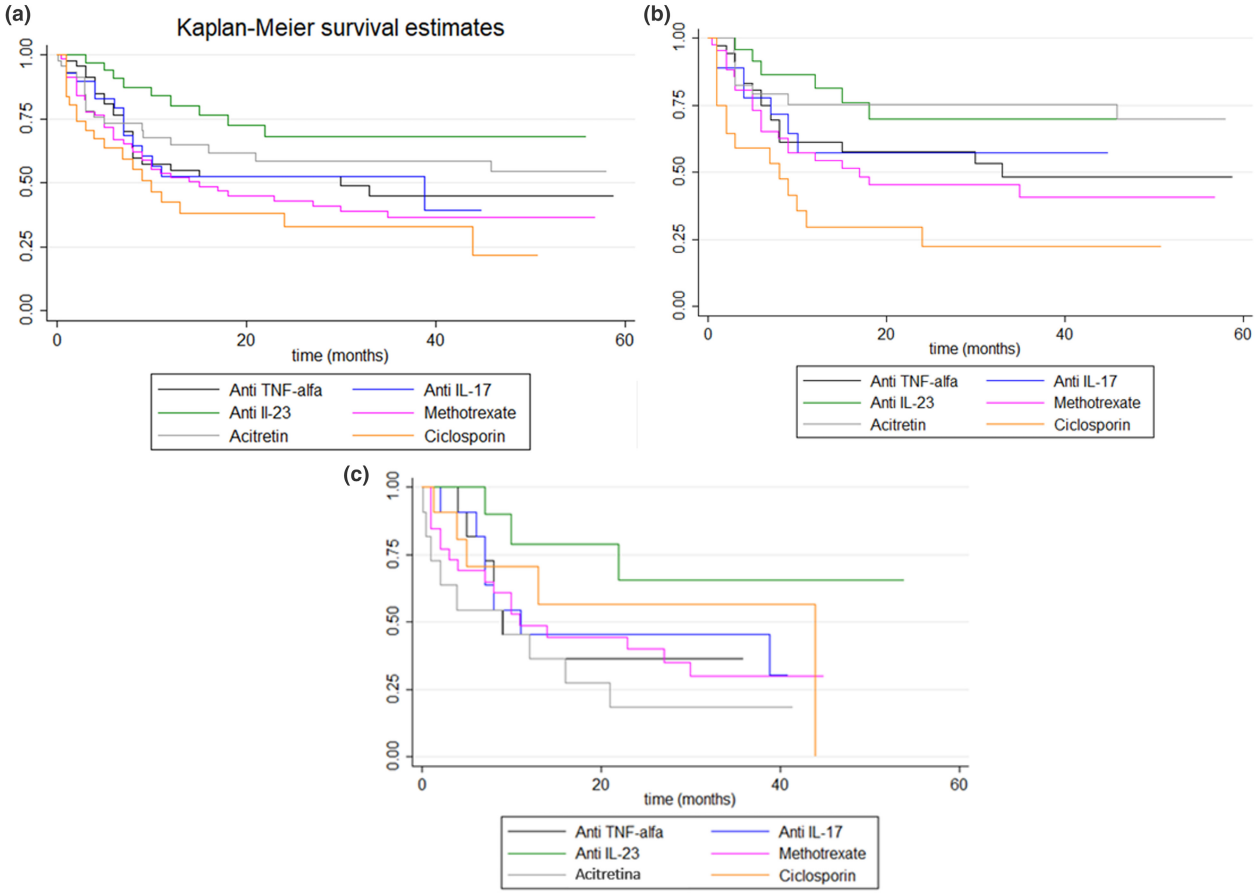

Figure 3 The Kaplan–Meier curves for overall treatment discontinuation with methotrexate, acitretin, cyclosporine, anti-TNF alpha drugs, anti-IL17 drugs, and anti-IL23 drugs in the whole study population (a), in the population with hyperkeratotic PP (b) and the population with pustular PP (c)

the drug survival in patients with PP was ongoing therapy with biological drugs. Consequently, it is possible to conclude that biological drugs, in spite of non-biological ones, are associated with a higher rate of treatment persistence. In our study, the primacy of biological drugs was not due to a higher effectiveness in the treatment of PP but mainly to a better tolerability profile. This datum is of particular interest because, although the higher effectiveness of biological drugs compared to

Table 4 Multivariate analysis of drug survival-related variables for overall treatment discontinuation events

Variables	Hazard ratio (95% CI)	*P*-value
Age	1.00 (0.99–1.01)	0.920
Gender		
Female	Ref	
Male	1.02 (0.71–1.46)	0.903
Psoriatic arthritis		
No	Ref	
Yes	1.33 (0.92–1.94)	0.130
Other skin involvement		
No	Ref	
Yes	1.05 (0.73–1.52)	0.293
Palmoplantar psoriasis		
Hyperkeratotic	Ref	
Pustular	1.31 (0.93–1.84)	0.124
Palms and soles involvement		
Palms	Ref	
Soles	0.63 (0.24–1.62)	0.335
Palmoplantar	1.05 (0.73–1.52)	0.790
Therapy		
Biologics	Ref	
Non-biologics	1.95 (1.41–2.68)	<0.001

non-biologics in the treatment of chronic psoriasis in plaques has been demonstrated by numerous studies, there is a paucity of data regarding their use in palmoplantar psoriasis (PP).

Specifically, anti-IL23 drugs showed the best drug-survival in our study.

In the hyperkeratotic variant, besides anti-IL23 drugs, acitretin also obtained excellent results in terms of drug survival, while cyclosporine was the drug with the highest rate of interruptions.

The persistence of the treatment of our patients did not seem to be significantly influenced by age, sex, disease characteristics, or the co-presence of psoriatic arthritis and/or plaque psoriasis. A retrospective multicenter study of 347 patients with pustular PP compared treatment characteristics, drug survival, and reasons for discontinuation of therapies of this patient cohort with a control cohort of plaque psoriasis patients. Again, the drug survival of biologics was greater than that of non-biologics (the mean duration of treatment with biologics was 12 months versus 6 months for non-biologics). Overall, the main cause of treatment discontinuation was for ineffectiveness, while for what concerns discontinuation for adverse effects, the drugs most frequently involved were non-biologics (in particular, dimethyl fumarate, acitretin, and cyclosporine). In comparison with the control population, the drug survival of patients with pustular PP was lower than that of patients with plaque psoriasis (mean duration of treatment 8 vs. 14 months, respectively); this supports the evidence that PP is more difficult to treat than plaque psoriasis.[21]

The uniqueness of our study lies in having demonstrated a greater persistence in the treatment of patients on biologics in both variants of PP and in having shown that anti-IL23 biologics are associated with greater persistence in treatment, as already demonstrated for plaque psoriasis,[22] due to their safety and tolerability.

Table 5 Multivariate analysis of drug survival-related variables for hyperkeratotic and pustular PP overall treatment discontinuation events

Variables	Hyperkeratotic PP HR (95% CI)	*P*-value	Pustular PP HR (95% CI)	*P*-value
Age	1.02 (1.00–1.03)	**0.02**	1.00 (0.98–1.03)	0.50
Gender				
Female	Ref		Ref	
Male	1.24 (0.75–2.05)	0.38	0.71 (0.30–1.64)	0.42
Psoriatic arthritis				
No	Ref		Ref	
Yes	0.85 (0.46–1.55)	0.59	1.47 (0.72–3.02)	0.28
Psoriasis in other skin sites				
No	Ref		Ref	
Yes	0.95 (0.58–1.56)	0.85	2.27 (1.00–5.14)	**0.04**
Type of drug used				
Biological	Ref		Ref	
Non-biological	1.76 (1.18–2.60)	**0.005**	2.12 (1.24–3.92)	**0.006**
Therapy				
Anti-TNF-alpha	Ref		Ref	
Anti-IL17	0.82 (0.32–2.06)	0.68	1.03 (0.33–3.13)	0.95
Anti-IL23	0.38 (0.14–1.01)	**0.05**	0.30 (0.07–1.25)	0.10
Methotrexate	1.01 (0.52–1.97)	0.96	0.95 (0.37–2.40)	0.91
Acitretin	0.37 (0.15–0.90)	**0.03**	2.31 (0.77–6.91)	0.13
Cyclosporine	2.45 (1.15–5.22)	**0.01**	0.96 (0.27–3.36)	0.95

PP, palmoplantar psoriasis.
Bold indicates significance level at *P*-value < 0.05.

Our study had some limitations: due to its observational nature, data were collected retrospectively without control groups. Furthermore, a critical aspect of the concept of "drug survival" is the intermittent administration of those therapies at risk of cumulative toxicity. This requirement limits the significance of this measure of long-term effectiveness for all treatments whose administration is already planned as intermittent (e.g., phototherapy and cyclosporine). Finally, persistence in treatment is not only influenced by effectiveness, tolerability, and safety but also by a number of factors such as patient preferences, compliance with treatment, and its comorbidities.

In conclusion, our study confirms the difficulty of treating PP and shows that biologic drugs are associated with longer persistence in treatment than non-biologics in PP, not so much because of their higher effectiveness but because of their better safety profile. Our study is, to our knowledge, the first to have evaluated treatment persistence and the factors influencing it by considering the two forms of PP separately. Further studies are definitely needed to better understand the pathogenetic differences between PP and plaque psoriasis and between the different subtypes of PP, and larger-scale studies are needed to optimize the treatment of this difficult-to-treat form of psoriasis.

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