

Real-Life Analysis of Therapeutic Management and Its Correlation with the Dermatology Life Quality Index Score in 108 Patients with Pustular Psoriasis: An Italian Monocenter Study

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ABSTRACT Introduction: Pustular psoriasis (PP) is a rare life-threatening skin disease with negatively impact on quality of life (QoL). Clinically, it may be systemic (generalized pustular psoriasis [GPP]) or localized on palms and soles (palmoplantar pustulosis [PPP]). It is not rare to observe plaque psoriasis associated with GPP.

Objectives: We explored the therapies used for PP and their correlation with patient QoL scores, through a cross-sectional study using retrospective data from a monocentric database in the period 2017-2021.

Methods: Patient characteristics were summarized using descriptive statistics and treatment predictors of QoL were identified by multiple regression analysis. Among 108 patients with PP, 57.4% had GPP + PSO whereas 42.6% had PPP. The therapeutic management is based on systemic conventional treatments and biological therapies in both GPP and PPP.

Results: GPP + PSO patients with an impaired QoL (DLQI \geq 10) were associated with biological therapy including certolizumab (odds ratio [OR]=2.38), etanercept (OR=2.25), secukinumab (OR=2.03) or ustekinumab (OR=2.79) whereas, PPP patients were positively associated with secukinumab (OR=2.85) or apremilast (OR 4.28, 95%-CI 0.56-9.62).

Conclusions: Currently, systemic conventional therapy remains the therapeutic fulcrum of PP management. A great effect on QoL, especially for GPP+PSO, was assessed regardless the ongoing treatment and only newer biologic options were able to somehow positively impact.

Introduction

Pustular psoriasis (PP) is a rare, life-threatening skin disease characterized by eruptions of neutrophil-filled pustules [1]. The condition imposes a substantial emotional burden on patients impacting on quality of life (QoL) and their daily activities [2]. PP has 2 subtypes: generalized pustular psoriasis (GPP) and localized on palms and soles, called palmoplantar pustulosis (PPP). It is not rare to observe plaque psoriasis associated with generalized pustular forms of psoriasis (GPP + PSO). The involvement of the fingers, toes, and nails is defined as a separate localized variant, acrodermatitis continua of Hallopeau, and is now thought to be a subset of PPP [3]. Immunologically, PP seems to be characterized by an intense inflammatory response resulting from innate immunity hyperactivation, with prominent involvement of the IL-36 axis [4]. However, recent progresses in the identification of genetic mutations have promoted a better understanding of PP pathogenesis highlighting that GPP and PPP are genetically and pathologically distinct conditions [5].

Briefly, IL36RN mutations are the most frequent genetic abnormality in GPP [3,6], CARD14 mutations are primarily present in GPP + PSO and rarely in GPP alone [7,8] and these genetic abnormalities account for only a minority of PPP cases. Nevertheless, IL36 γ gene, which encodes the inflammatory cytokine IL-36 γ , is upregulated in patients with PPP, indicating that a dysregulation of the IL-36 pathway exists in the development of these skin conditions [9]. However, because of the rarity and heterogeneity of PP forms, data on prognosis and therapeutic management are limited. To date, the management is based on existing anti-psoriatic therapies including systemic conventional treatments (eg acitretin, cyclosporine and methotrexate) and biological therapies (eg anti-TNF α , anti-IL12/23, anti-IL23, and anti-IL17) which often show weak evidence of efficacy in both GPP and PPP [9]. Recently, an IL-36 receptor inhibitor, called spesolimab, has been approved in USA and Japan for the treatment of GPP in adults [10]. Clinical trials have shown that this humanized, selective antibody can be a safe and effective maintenance treatment that prevents GPP flare-ups and controls its associated symptoms [11]. Currently,

a phase 2 clinical study is evaluating the effectiveness and safety of another IL-36 receptor inhibitor, imsidolimab, in both GPP and PPP patients [12]. So far, a phase 1 study suggested a favorable side effect profile for this new therapeutic candidate [13].

Objectives

In light of the evidence, we aimed to explore the current real-life therapeutic management of PP and its correlation with patient QoL scores.

Methods

Patients

This noninterventional, cross-sectional study was performed using a database in which adult patients with pustular psoriasis were included. Inclusion criteria were represented by patients with a confirmed diagnosis of PP having performed visits from 2017 to 2021 and at least a follow-up during 2021.

The study protocol was performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Each participant gave written informed consent before the onset of the study.

Data

A spreadsheet was created from available past data of patients' medical files. The analysis was performed in March 2022. We collected data on age, sex, medical history, clinical scores, QoL scores. The severity of the disease was defined as the last clinical score recorded in the database.

For GPP + PSO, when the Generalized Pustular Psoriasis Area Severity Index (GPPASI) was \geq 2.5, the disease was considered moderate-to-severe [14]. For PPP, the guidelines defined a moderate-to-severe PPP by the Palmoplantar Pustulosis Area Severity Index (PPPASI) \geq 2.5 [15]. Finally, a Dermatology Life Quality Index (DLQI) score \geq 10 referred to a significant impact of the disease on QoL [16]. Therapeutic

data concerned systemic treatments commercially available in Italy, including conventional and biological therapies.

Statistical Analysis

Collected variables were described with number and percentage for categorical variables, and mean, range and standard deviation for continuous data. We focused on comparing the current therapies associated with QoL scores in GPP + PSO and PPP patients. Therefore, we adjusted and controlled for DLQI categories (<10 and ≥10) by calculating odds ratios (ORs) and 95% confidence intervals (CIs) for each current treatment. Variables with ORs <1 were interpreted as negative factors, ORs=1 as non-associated factors whereas ORs >1 as positive factors. To calculate statistical differences, we performed χ^2 test or the Fisher exact test, as appropriate. Two-sided P values below 0.05 were considered significant.

Results

Patient Characteristics

A total of 108 patients were included, comprising 62 GPP + PSO and 46 PPP patients. For GPP + PSO, the localization of plaque psoriasis was assessed on nails (29.5%, N = 18), upper extremities (27.4%, N = 17), scalp (22.6%, N = 14), trunk (14.5%, N = 9), and lower extremities (12.9%, N = 8). Other lesions were located on genitals (6.4%, N = 4), face (4.8%, N = 3) or intertriginous regions (4.8%, N = 3) (data not shown). Women represented the majority of GPP + PSO, inversely to PPP. Data regarding sex, age, body mass index (BMI), comorbidities, previous and current therapies are summarized in Table 1.

Therapeutic Management

Systemic non-biological therapy resulted to be the first-line treatment for both groups despite the availability of the newest biological treatment options (Table 2). In particular, acitretin was favored in both PPP and GPP + PSO groups (21.7% versus 35.4%) followed by cyclosporine (8.7% versus 6.4%), methotrexate (8.7% versus 14.5%) and apremilast (4.3% versus 3.2%). Among the biological therapies, secukinumab and adalimumab were the only 2 options for PPP (13% and 8.7%, respectively), whereas adalimumab (11.3%), brodalumab (4.8%), ixekizumab (4.8%), certolizumab (3.2%), etanercept (3.2%), secukinumab (3.2%), tildrakizumab (3.2%), ustekinumab (3.2%), guselkumab (1.6%) and risankizumab (1.6%) were the therapeutical options for GPP + PSO. It is of note that only 1 patient with GPP + PSO (0.9%) was on concomitant therapy with adalimumab + methotrexate, whereas the remaining PPP patients (N = 16, 14.8%) were being treated with topical therapy.

Table 1. Clinical and Epidemiological Data of GPP + PSO and PPP

	GPP + PSO N=62	PPP N=46
Population		
Female	44 (71%)	20 (43%)
Male	18 (29%)	26 (57%)
Mean age, years ± SD	62.9 ± 5,7	60.8 ± 6,4
Mean age onset disease	51.2 ± 4,8	48,8 ± 3,5
Mean BMI ± SD	26.3 ± 4,1	24.1 ± 3,6
DLQI <10	34 (55%)	35 (76%)
DLQI ≥10	28 (45%)	11 (24%)
Comorbidities		
Hypertension	43 (69%)	21 (45%)
Dyslipidemia	11 (18%)	6 (13%)
Psoriatic arthritis	10 (16%)	5 (11%)
Cardiomyopathy	9 (14%)	2 (4%)
Diabetes mellitus	6 (10%)	2 (4%)
Hypothyroidism	3 (5%)	1 (2%)
Ulcerative colitis	2 (3%)	1 (2%)
Previous Therapies		
Systemic nonbiological	48 (77%)	24 (52%)
Systemic biological	10 (16%)	4 (9%)
Phototherapy	7 (11%)	3 (6%)
Topical Therapy	8 (13%)	4 (9%)
Current Therapies		
Systemic nonbiological	37 (60%)	20 (43%)
Systemic biological	25 (40%)	10 (22%)
Topical therapy	0 (0%)	16 (35%)

BMI: body mass index; DLQI: Dermatology Life Quality Index; GPP + PSO: plaque psoriasis associated with generalized pustular forms of psoriasis; SD: standard deviation.

Disease Burden and Quality Life of Patients

GPP + PSO imposed a substantial burden on patient QoL. Indeed, life quality impairment (DLQI ≥10) was reported mostly in GPP + PSO patients than in PPP (45% versus 24%, P < 0.01). However, no significant difference in terms of disease severity examined through the adapted scores for PPP and GPP + PSO was shown in both groups of patients. Major details are summarized in Figure 1.

Therapies Associated with DLQI Categories (<10 and ≥10) in Patients with Pustular Psoriasis

Our multiple logistic regression analysis revealed that GPP + PSO patients with a DLQI score <10 had a significant inverse correlation with certain biologics, eg anti-TNF α , anti-IL-12/23, and anti-IL-17 therapies (certolizumab [OR 0.47; 95% CI 0.08-3.02; P = 0.041], etanercept [OR 0.54;

Table 2. Comparison of Current Systemic Therapies in PPP (n=46) and GPP + PSO (N = 62).

Current Therapy	PPP, N (%)	GPP +PSO, N (%)	P Value	Sign
Systemic non-biological therapy	20 (43)	37 (60)		
• Acitretin	10 (21.7)	22 (35.4)	0.011	
• Cyclosporine	4 (8.7)	4 (6.4)	NS	
• Methotrexate	4 (8.7)	9 (14.5)	0.036	
• Apremilast	2 (4.3)	2 (3.2)	NS	
Systemic biological therapy	10 (22)	25 (40)		
• Adalimumab	4 (8.7)	7 (11.3)	0.048	
• Brodalumab	0 (0)	3 (4.8)	NS	
• Certolizumab	0 (0)	2 (3.2)	NS	
• Etanercept	0 (0)	2 (3.2)	NS	
• Guselkumab	0 (0)	1 (1.6)	NS	
• Ixekizumab	0 (0)	3 (4.8)	0.014	
• Risankizumab	0 (0)	1 (1.6)	NS	
• Secukinumab	6 (13)	2 (3.2)	0.009	
• Tildrakizumab	0 (0)	2 (3.2)	NS	
• Ustekinumab	0 (0)	2 (3.2)	NS	

GPP + PSO: plaque psoriasis associated with generalized pustular forms of psoriasis; NS: not significant; PPP: palmoplantar pustulosis.

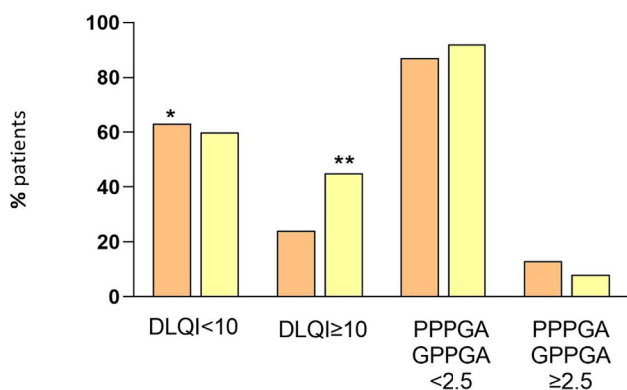


Figure 1. Comparison of gravity indexes score between PPP (n=46, orange bar) and GPP + PSO (N = 62, yellow bar). DLQI = Dermatology Life Quality Index; GPP = generalized pustular psoriasis; PSO = psoriasis.

95% CI 0.067-4.01; P = 0.029], secukinumab [OR 0.38; 95% CI 0.02-5.01; P = 0.037], and ustekinumab [OR 0.29; 95% CI 0.01-4.02; P = 0.035]). Indeed, all these biological treatments were positively associated with DLQI \geq 10 (certolizumab [OR 2.38, 95%-CI 0.67-6.85, P = 0.025], etanercept [OR 2.25, 95%-CI 0.33-4.78, P = 0.041], secukinumab [OR 2.03, 95%-CI 0.07-6.55, P = 0.034], or ustekinumab [OR 2.79, 95%-CI 0.54-5.68; P = 0.013]). A significant inverse correlation with DLQI \geq 10 was found mainly for inhibitors of IL-23/17 axis (guselkumab [OR 0.497, 95%-CI 0.03-4.02, P = 0.030], ixekizumab [OR 0.31, 95%-CI 0.09-2.71, P = 0.025], and risankizumab [OR 0.49, 95%-CI 0.03-4.02, P = 0.03]) (Figure 2). In PPP patients, the use of

acitretin correlated significantly with a DLQI <10 (OR 1.80, 95%-CI 0.64-4.81, P = 0.046) and it was negatively associated with QoL impairment (DLQI \geq 10) (OR 0.42, 95%-CI 0.03-3.26, P = 0.04). In contrast, IL17A and PDE4 inhibitors were favored in PPP with DLQI \geq 10 [(secukinumab [OR 2.85, 95%-CI 0.73-12.66, P = 0.024] and apremilast [(OR 4.28, 95%-CI 0.56-9.62, P = 0.008)] (Figure 3).

In order to explore eventual effects of treatment time, we determined mean duration of ongoing therapies that resulted to significant alter QoL in our sample. GPP + PSO patients were administered with certolizumab, etanercept, secukinumab and ustekinumab respectively for 37.5, 74.3, 23.8 and 50.1 months. PPP patients were administered with acitretin and secukinumab respectively for 68.9 and 25.6 months.

Discussion

The current therapeutic management of PP contemplates different treatment options, but very few with approved indication up to now [4]. We have performed an analysis of PP patient characteristics, drugs and impact on QoL at our Unit including data referred to a period of 5 years to explore which is the current therapeutic approach in real life trying to reveal which factors can influence the treatment options. It is now established that PP affects more frequently the middle-aged adult population with a predilection for female gender [17]. Comorbidities most often encountered in these patients concern an increase in BMI and diseases of the cardiovascular

GPP + PSO

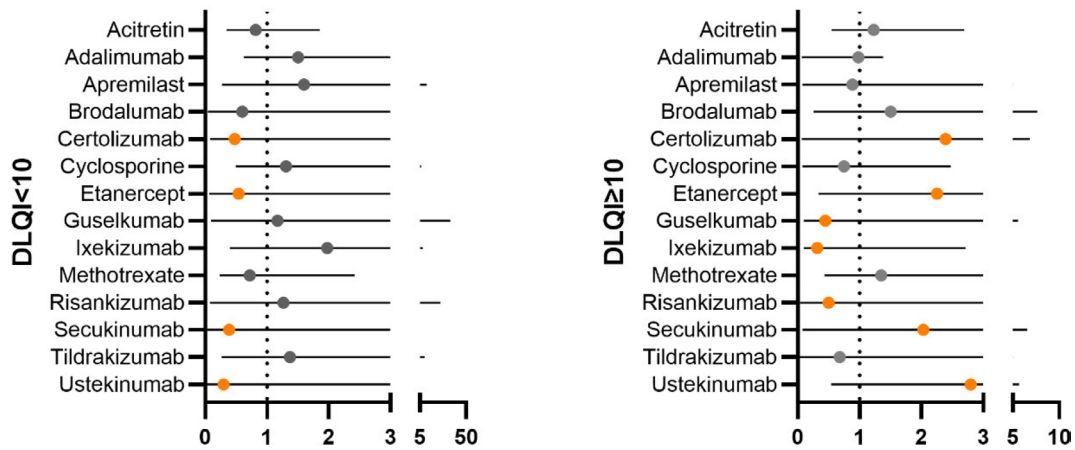


Figure 2. Systemic therapies associated with Dermatology Life Quality Index (DLQI) categories (<10 and ≥10) in patients with generalized pustular psoriasis and plaque psoriasis (GPP + PSO). Odds ratios (OR) and 95% confidence intervals (CI) are depicted. Orange plots indicate a statistically significant association.

PPP

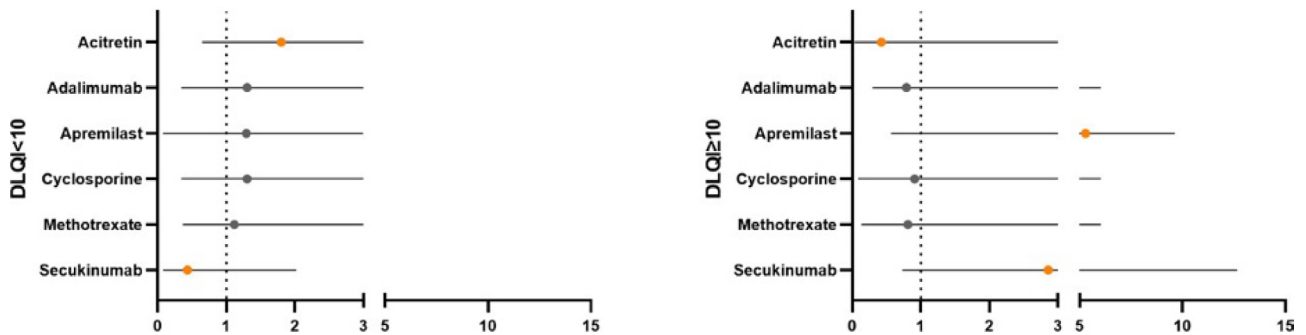


Figure 3. Systemic therapies associated with Dermatology Life Quality Index (DLQI) categories (<10 and ≥10) in patients with palmoplantar pustulosis (PPP). Odds ratios (OR) and 95% confidence intervals (CI) are depicted. Orange plots indicate a statistically significant association.

and metabolic system (primarily arterial hypertension, followed by dyslipidemia and diabetes mellitus). Moreover, as described by Pfohler et al [18], psoriatic arthritis (PsA) and inflammatory bowel disease (IBD) are found with a lower incidence in association with PP patients, unlike plaque psoriasis. This is in line with our population characteristics, even though among analyzed subjects, we included PP both in the absolute palmoplantar subtype (PPP) and in the generalized form associated with psoriasis (GPP + PSO). The prevalence of these 2 conditions is not homogeneous: some authors [17] report a greater prevalence of GPP, other ones [3] a greater frequency of the PPP subtype. In our analysis, we included patients with both subtypes regardless the severity.

Our patients showed mild disease globally (both PPP and GPP + PSO) in terms of PPPASI and GPPASI, respectively, but it has to be taken into account that all patients were on

treatment. There were 6 PPP subjects (13%) and 5 GPP + PSO subjects (8%) with a moderate disease by PPPGA and GPPGA, respectively, since the score was ≥2.5. No significant difference in disease severity for PPP and GPP + PSO was observed. Despite no severe forms of the diseases, we found a great impact on QoL. Indeed, 11 PPP (24%) and 28 GPP + PSO (45%) subjects showed a DLQI ≥10. Analyzing current systemic treatments of our population, we can assess that non-biological systemic therapy represents the first choice both for PPP and GPP + PSO despite the progress made by biologics. Almost half (43%) of PPP patients (20 out of 46) and 60% of GPP + PSO patients (37 out of 62) were treated with nonbiological systemic drugs. Our findings fit with a quite recent analysis performed by Menter et al [9]. In particular, it has been reported that among current systemic nonbiological therapy, acitretin remains the

most used drug in both subtypes of PP, while methotrexate appears to be more prerogative of the generalized form associated with psoriasis [19]. On the other hand, in accordance with what emerges from the review of Wang et al [20], among systemic biological drugs, there is still little experience with the PPP form, except for the use of secukinumab [21]. Indeed, in the GPP subtype, there is evidence [22] of favorable outcomes of some biologics, including adalimumab and ixekizumab, when compared to treatment with traditional drugs.

In line with our results, Schwartz et al [23] confirm the evidence that acitretin first and then methotrexate were the most used drugs, with a significantly higher representation in GPP. Regarding biologics, we have PPP patients treated only with adalimumab or secukinumab, whereas for GPP + PSO patients all biologics are used, even if there is a significantly higher representation for adalimumab and ixekizumab.

In this study, we documented the association of QoL with the current systemic treatments in PPP and GPP + PSO in order to identify factors that may influence the therapeutic decision. PPP patients were more likely to achieve a DLQI <10 with acitretin treatment, whereas they were less likely to achieve such a goal when in treatment with secukinumab. To reinforce this data, mean treatment duration was higher for acitretin respect to secukinumab. Regarding GPP + PSO patients, they were less associated with DLQI ≥10 when treated with guselkumab, ixekizumab and risankizumab, whereas they were significantly associated with DLQI ≥10 when in treatment with certolizumab, etanercept, secukinumab and ustekinumab. The good outcome related to acitretin is already known [24]; nonetheless, the negative association between secukinumab and DLQI <10 was quite surprising, especially in light of the efficacy reported [25].

It has to be taken into account that at the time of the analysis, secukinumab mean duration of treatment was 23.8 months and it has been reported a partial loss of efficacy for this drug around this interval time [26]. An interesting result was that acitretin failed to show neither a positive association with DLQI <10 nor a negative one with DLQI ≥10 as in PPP. This means that acitretin was not able to impact on QoL in GPP + PSO patients as it did in those with the PPP subtype. In contrast, newer biologic options, like guselkumab, ixekizumab and risankizumab, were able to show such negative association with DLQI ≥10 highlighting their effect on QoL. This is in accordance with recent works [22,27] reporting that biologic treatments show favorable outcomes compared to other treatments.

Limitations

This study has some limitations. In particular, it involves a single center and it is a cross-sectional study. Consequently,

it must be taken into account that the general findings are very limited.

Conclusions

Currently, systemic non-biological therapy and, in particular, conventional therapy remain the therapeutic fulcrum of PP management. Our study shows that there are substantial differences between PPP and GPP+PSO. Even if systemic conventional treatment was the most represented in both conditions, it was associated with a good impact on QoL only in PPP. Almost the half of our GPP+PSO patients reported a great impact on QoL regardless of the ongoing treatment, and only newer biologic options, like guselkumab, ixekizumab and risankizumab were able to somehow positively impact on QoL. Outcomes coming from QoL are often signals of unsatisfied needs, and in this study there arises the need of specific approved therapies for the management of PP.

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