Measuring perceived benefit and disease-related burden in patients affected with vulvar lichen sclerosus after a standard topical corticosteroid treatment. Results from a cohort study using Pictorial Representation of Illness and Self-Measure and Dermatology Life Quality Index

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Funding sources: None.

Conflict of interest: The authors have no conflicts of interest to disclose.

Ethics approval: This study was approved by the Ethics Committee of University/Hospital of Ferrara, Italy (protocol n 634/2019/Oss/AOUFe).

Consent to participate: Written informed consent was obtained from patients.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dth.14334

Acknowledgments: Honorarium, grant, or other form of payment were not given to any of the authors to produce the manuscript.

Author Contributions: A. Borghi: design of the study, interpretation of data, drafting of the manuscript, critical revision of the manuscript. G. Odorici: drafting of the manuscript, critical revision of the manuscript; V. Scuderi: acquisition of data, critical revision of the manuscript; G. Valpiani: analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript; C. Morotti: analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript; M. Corazza: design of the study, acquisition of data, interpretation of data, critical revision of the manuscript. All authors read and approved the final manuscript.

Abstract

Improvement in suffering after treatment has been poorly investigated in women affected with vulvar lichen sclerosus (VLS). We performed an observational study on a cohort of VLS patients for assessing the effect of a 12-week topical corticosteroid treatment on their VLS-related burden, as measured with Pictorial Representation of Illness and Self-Measure (PRISM) and Dermatology Life Quality Index (DLQI). Demographics and disease-related subjective and objective scores (at baseline, T0, and at the control visit, T1) were recorded. The PRISM and DLQI were administered at T0 and T1. We assessed the variation of PRISM and DLQI at T1 compared to baseline and the relevance of several variables on these changes. Sixty-three patients were included. A significant improvement was found in both PRISM and DLQI after treatment. A higher coefficient of variations was observed for PRISM and DLQI as compared to subjective and objective scores. Improvement of global subjective score after treatment was the sole variable associated with PRISM and DLQI variations. The corticosteroid treatment led to a significant decrease in the impact of VLS on patients' well-being, in terms of suffering and quality of life impairment. PRISM seems a reliable instrument for integrating clinicians' and patients' perspectives for a comprehensive VLS management.

Keywords: vulvar lichen sclerosus, PRISM, DLQI, quality of life, mometasone furoate.

Introduction

Vulvar chronic inflammatory diseases may be very distressing due to their symptoms, chronic course, involvement of intimate parts, sexual dysfunction, possible disfiguring anatomical changes and the response to treatment**,** which is often unsatisfactory[1-5]. A recent study provided practical evidence of the suitability of the Pictorial Representation of Illness and Self-Measure (PRISM) in capturing and quantifying the global burden of suffering in patients affected with these diseases, namely lichen sclerosus, lichen planus and lichen simplex chronicus[6]. This visual, nonverbal instrument appeared to be more suitable in focusing the degree of these patients' suffering than a conventional tool aimed at assessing the patient quality of life impairment, like the Dermatology Quality of Life Index (DLQI). The capability of PRISM to explore patients' self-perceived health status in relation to their diseases from a different perspective as compared to DLQI, may explain this finding[7,8]. In fact, suffering is a multidimensional experience, which encompasses not only physical symptoms and functioning impairment, but also emotional, spiritual and existential distress. It stems from the direct consequences of a certain disease, but also from the personal experience and perception of those affected. In this view, the detrimental impact of diseases which are highly symptomatic and touch intimate spheres of life, like vulvar inflammatory disorders, may be better focused by tools like PRISM, which explore and quantify 'difficult-to-verbalize' issues, than by questionnaire-based tests exploring quality of life items. PRISM seems to be able to quantify abstract feelings, otherwise difficult to measure. Moreover, PRISM has several practical strengths. It is easy to understand and to use, even for elderly subjects or those with low educational levels. It does not take long and provides immediate results. In a few studies, PRISM was also shown to be reliable in measuring the

improvement in the extent of patient's suffering due to therapy[9-12]. By virtue of these aspects, PRISM is particularly suitable in clinical contexts.

In the present study we aimed to assess the improvement in disease-related burden in patients affected with vulvar lichen sclerosus (VLS) and treated with a conventional corticosteroid treatment, using both PRISM and DLQI.

Material and methods

Study design and objectives

The present study was set up as a prospective, cohort study of patients with a histologically proven VLS who attended our Vulva Unit between October 2019 and May 2020. The participants were patients who had already taken part in a previous cross sectional study assessing the degree of suffering and quality of life impairment in subjects affected with chronic vulvar disorders[6]. All the VLS patients included in that previous study were put on a 12-week treatment with a topical corticosteroid. The main objectives of the present study were to assess 1) the improvement in both suffering and quality of life impairment, measured with PRISM and DLQI respectively, achieved with treatment; i.e. we were interested in measuring the effect of a standard treatment on illness-related burden, using these two different tools; 2) the correlation between PRISM and DLQI in measuring the changes in illness burden obtained with treatment; 3) the relevance of some heterogeneous variables, both patient- and disease-related, on the changes in the degree of suffering and in quality of life impairment, at treatment completion with respect to the baseline.

Study patients

In order to address these study objectives, among the subjects previously enrolled, only those affected with VLS were eligible. Baseline inclusion and exclusion criteria are reported elsewhere[6]. We

included the patients who adhered to the therapeutic regimen and presented to the control visit after treatment.

This study was approved by the Ethics Committee of University/Hospital of Ferrara, Italy (protocol n 634/2019/Oss/AOUFe). Written informed consent was obtained from patients.

Study procedures and assessments

At the baseline visit, patients were instructed to apply mometasone furoate (MMF) 0.1% ointment on the affected vulvar surfaces initially once daily for 5 days a week for 4 weeks, then on alternate days for 4 weeks and, for the third month, twice weekly, as previously described[13]. No additional treatments, nor cosmetic products, expected to relieve VLS, were administered. A control visit was scheduled after 12 weeks, at treatment completion.

As reported in detail in Corazza et al[6], the following data were recorded at baseline: 1) age at inclusion; 2) marital status; 3) educational level; 4) employment; 5) disease duration; 6) first diagnosis or disease recurrence at inclusion visit. Assessment and scoring of both subjective symptoms and clinical features were performed in consensus by the same investigators for all patients at baseline (T0) and at the 12-week control visit (T1). In particular, the degree of itching and burning was quantified by interview using a visual analogue scale (VAS, which included a numeric rating scale 0-10). A global subjective score (GSS) was obtained by summing the scores of each symptom parameter (highest GSS = 20). Dyspareunia was assessed separately from the other symptoms as numerous patients reported avoiding sexual activity for reasons other than disease-related discomfort (scoring range 0-10). The following objective parameters were considered and scored for evaluating the clinical features: 1) leukoderma / pallor, 2) sclerosis-scarring, 3) erythema, 4) hyperkeratosis, 5) purpuric lesions and itching-related excoriations. Each sign was scored using the following 4-point

scale: 0 = absence, 1 = mild, 2 = moderate, 3 = severe. A global objective score (GOS) was obtained by summing the scores of each clinical parameter (highest GOS = 15).

Both PRISM and DLQI were administered to all participants by the same investigator at T0 and T1 visits. In the present study we used the original version of PRISM[7] and the Italian translation of DLQI[14]. DLQI is a 10-item questionnaire that measures the disability caused by skin diseases in routine daily practice, by exploring several areas of quality of life, such as symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment[15]. Patients indicate, on a 4-point scale from 0 to 3 for each of the 10 items, how their skin condition influences quality of life at the time of the assessment and the week before. The total score ranges from 0 to 30, with higher scores corresponding to a greater disability. PRISM test is performed by showing the patient an A4-sized (210 x 297 mm) white sheet of paper, which represents her life as it is at the moment, with a printed yellow disc 6 cm in diameter at the bottom right hand corner, that represents the patient herself (Fig. 1)[7,8]. The patient is asked to place a cardboard, 4-cm-diameter, red disc, which represents her vulvar disease, onto the sheet after being asked: 'Where would you locate your vulvar illness (the red disc) in your life (the sheet) at this moment?' The main quantitative measure derived from PRISM is the Self–Illness Separation (SIS) i.e. the distance, in millimeters, between the two disc centers, namely between the illness and the self (SIS range 0-273 mm). Lower SIS scores indicate a greater extent of suffering, and higher scores are supposed to show a lower impact of the disease.

Statistical analysis

Shapiro-Wilk test was used to test for normality of distribution of the continuous variables. In the presence of symmetry of the distributions, the variables were represented with mean and standard

deviation (sd) whereas, in the case of non-normal distribution, with the median value and interquartile range [1Q 3Q]; categorical data were expressed as total numbers and percentages.

Wilcoxon matched-pairs was used for assessing changes in the median scores for GSS, dyspareunia, GOS, DLQI and PRISM between T0 and T1.

Correlation between PRISM and DLQI variations was expressed using the Spearman rank correlation coefficient (ρ).

Coefficient of variation was calculated to compare the magnitudes of variation among GSS, dyspareunia, GOS, DLQI and PRISM after treatment.

Mann Whitney test was used to analyze the differences in GSS, GOS, DLQI, PRISM and dyspareunia variations between the 2 groups.

Univariate linear regression was used to identify factors associated with PRISM and DLQI score variation after treatment; statistically significant variables in the univariate analysis were allowed entry in the multivariate linear regression.

All analyses were performed using Stata 15.1 SE (Stata Corporation, College Station, Texas, USA). P value <0.05 was defined as statistically significant.

Results

Patient characteristics

Among the 87 VLS patients previously enrolled[6], 63 were included in the present study. Nine patients dropped out because they did not attend the control visit and 15 did not adhere to the treatment prescription. In Table 1 the main patient-related demographics are reported.

Treatment outcomes

The median scores of all subjective and objective features, except the one referring to sclerosis-scarring, significantly decreased after treatment (Table 2). A highly significant improvement was noticed for both PRISM and DLQI median scores as well. Higher coefficients of variations were observed for PRISM and DLQI scores as compared to subjective and objective scores (Table 3). By performing Spearman rank correlation coefficient, we found a moderate correlation (ρ = -0.54; $p<0.001$) between the variation of PRISM and DLQI scores from T0 to T1.

Relevance of patient- and disease-related variables in PRISM and DLQI changes with treatment

Multivariate linear regression showed that GSS change after treatment was the sole variable significantly associated with the variations of both PRISM and DLQI as a result of the treatment (Tables 4 and 5). In particular, the greater the global symptoms' scores decrease at treatment completion, the greater was the improvement of both PRISM and DLQI scores at the 12 week-control visit. Decrease in dyspareunia score due to treatment was found to be significantly associated with DLQI improvement (Table 5). No other variables significantly conditioned PRISM or DLQI changes at the end of the treatment.

Discussion

This study specifically addressed an issue still rather scarcely considered and measured among treatment outcomes for vulvar inflammatory diseases, such as the impact of treatment on patient well-being. In clinical trials symptoms and objective features as assessed by the investigators are usually the only measuring stick for treatment effectiveness. On the other hand the extent of patient suffering, and its improvement after treatment, have only rarely been the object of investigation[16-18]. For this purpose, we administered both PRISM and DLQI to women affected with histologically proven VLS

who underwent a 12-week treatment with mometasone furoate 0.1% ointment (MMF) at tapering regimen, as previously described[13,19]. These two tools were administered both at baseline and at the 12-week control visit, contextually to the assessment and scoring of subjective and objective VLS-related features. We chose to use both these tools as each of them investigates similar, but not identical**,** aspects of illness burden.

A first expected result of our study was the great efficacy of a topical potent corticosteroid, like MMF, in improving both symptoms and clinical signs of VLS (Table 2). The median scores of all subjective and objective VLS-related features significantly improved after treatment when compared to baseline. The median score for sclerosis and scarring was the sole exception, in agreement with the poor responsiveness of these features to treatments. A more noteworthy finding was that both PRISM and DLQI scores significantly changed after treatment. In particular, PRISM median score increased from 85 [55-180] to 180 [90-270] at treatment completion (p<0.0001) and DLQI median score decreased from 6 [3-8] to 2 [1-5] (p<0.0001). It was particularly interesting that PRISM and DLQI sores showed greater coefficients of variation when compared with those referred to global symptoms (GSS), objective features (GOS) and dyspareunia (Table 3). This suggests that the treatment led to a greater improvement in the detrimental impact of the disease on the patients' well-being than in the disease itself. In other words, the perceived therapeutic benefits were greater than the objective ones. Coefficient of variation of PRISM scores (1.59) was, albeit slightly, higher than DLQI (1.55). In line with this, we found a moderate correlation between PRISM and DLQI score variation after treatment (ρ = -0.54; p<0.001). This finding indicates that PRISM may be more reliable than DLQI in capturing the changes in disease-related burden after treatment as well as it appeared in quantifying the baseline burden[6].

Linear regression analysis showed that the global subjective score (GSS) decrease after treatment was the sole variable significantly associated with changes of both suffering, expressed by PRISM scores, and quality of life impairment, measured with DLQI (Tables 4 and 5). The improvement of DLQI was also associated with the reduction of the scores referred to dyspareunia. No other variables, either disease or patient-related, were found to significantly impact the improvement of PRISM or DLQI scores. This means that neither improvement in clinical features**,** nor demographics**,** appeared to be statistically relevant for ameliorating the disease-related burden. This suggests two considerations. First, symptom relief, obtained with the therapy, was the main cause of relief of disease burden to the same extent that global symptoms were the main determinant of the level of suffering and quality of life impairment among the patients with vulvar inflammatory diseases[6,2]. Moreover, although the burden of suffering is usually determined and conditioned by personal characteristics as well, these latter did not appear sufficiently relevant to affect the improvement of well-being achieved with therapy. These findings further indicate the VLS-related symptoms as the main target of treatment in order to make patients feel better.

Our study has some limitations, which should be considered when interpreting its findings. The PRISM tool depends on an interviewer and cannot be performed alone. This may inhibit patients in answering and may lead to partial mystifications of their real perception of the disease-related burden. Univocal and validated methods to assess vulvar disease severity are not available in the literature, thus objective and subjective parameters and scores were arbitrary, although already used elsewhere[13,19,20]. A quality life questionnaire specifically focused on vulvar disorders, like the recently introduced Vulval Disease Quality of Life Index (VDQLI)[21], could have been administered to the study patients together with or instead of DLQI. However, when the present study was planned,

VDQLI had not yet been published. Other variables, such as comorbidities, potentially conditioning the patient's perception of her disease, were not considered in the logistic regression analysis. The patients included attended a tertiary clinic, specifically dedicated to genital diseases, so the study population is not representative of the whole population affected with VLS and a selection bias cannot be excluded.

In conclusion, the findings of this study indicate a significant decrease in the impact of VLS on patients' well-being achieved with a standard 12-week corticosteroid treatment, as measured with both PRISM and DLQI. This further encourages an adequate and timely treatment of VLS in order to bring substantial relief in the emotional burden caused by the disease, in terms of both suffering and quality of life impairment. An effective reduction of disease-related symptoms should be the first goal to be reached in this perspective. In our opinion, the burden of suffering should be included in daily clinical practice when assessing VLS patients' management, since it reflects the treatment effectiveness on a range of relevant aspects**,** which otherwise remain unrevealed with clinical assessment alone. This could lead to an integrated assessment of clinicians' and patients' points of view and provide a broader therapeutic benefit. With this specific objective, PRISM appears to be a reliable, feasible and well-accepted instrument.

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Figure Legend

Figure 1. PRISM tool consists of a A4-sized (210 x 297 mm) white sheet of paper representing the "patient's life at the moment," with a printed yellow disc at the bottom right hand corner, which represents the patient's "self." A cardboard red disc, which represents her vulvar disease, is handed to the patient. She is then asked to place this red disc onto the sheet after being asked: 'Where would you locate your vulvar illness (the red disc) in your life (the sheet) at this moment?'. The distance between the two disc centers, called the Self-Illness Separation (SIS), ranging from 0 to 273 mm, reflects the patient's burden of suffering, with higher SIS distances reflecting lesser impairment.

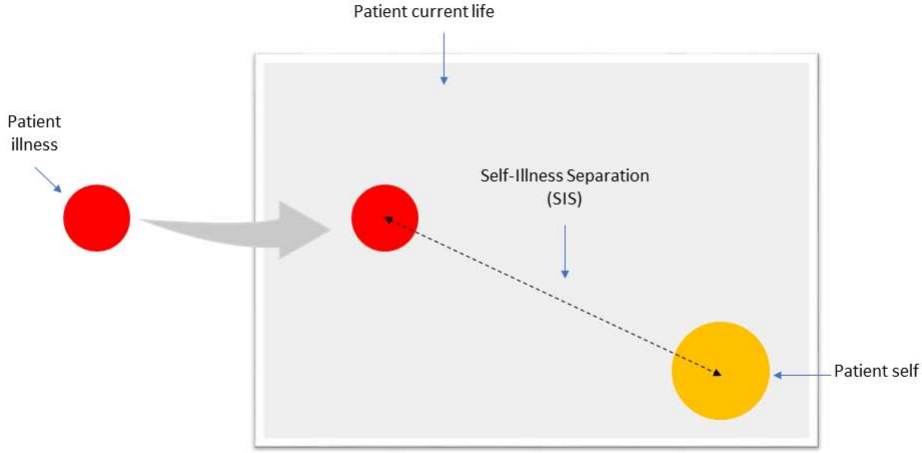

Table 1. Demographic data of the study patients

Variables		Total (n. 63)
Age, mean ± SD, [range]		64.3 ± 13.4 [22-93]
Educational level, n (%)		
	primary-intermediate school	36 (57.1)
	high school-university degree	27 (42.9)
Employment, n (%)		
	employed	32 (50.8)
	unemployed	2 (3.2)
	student	1 (1.6)
	retired	20 (31.7)
	homemaker	8 (12.7)
Marital status, n (%)		
	single - never married	3 (4.8)
	married - domestic partnership	48 (76.1)
	divorced- separated	3 (4.8)
	widowed	9 (14.3)
Study inclusion visit, n (%)		
	first diagnosis	20 (31.8)
	relapse	43 (68.2)
Disease duration (months), median [1Q 3Q]		34.1 [10.7-72.2]

SD, standard deviation; [1Q 3Q] interquartile range

Table 2. The study variables' scores at basal assessment (T0) and at the end of the 12-week therapy (T1).

Variable	T0 (total, n. 63) median [1Q 3Q]	T1 (total, n. 63) median [1Q 3Q]	*P*-value
Global Subjective Score (0-20)	9 [5-14]	2 [0-6]	**<0.0001**
itching (0-10)	5 [3-8]	1 [0-3]	**<0.0001**
burning (0-10)	4 [0-6]	0 [0-3]	**<0.0001**
Dyspareunia* (0-10)	6.5 [0-10]	1.5 [0-7]	**0.0004**
Global Objective Score (0-15)	4 [3-6]	2 [1-4]	**<0.0001**
erythema (0-3)	1 [0 1]	0 [0 1]	**<0.0001**
sclerosis-scarring (0-3)	1 [0 2]	1 [0 1]	0.1446
leukoderma / pallor (0-3)	2 [1 2]	1 [0 1]	**<0.0001**
purpuric lesions and itching-related excoriations (0-3)	0 [0 1]	0 [0 0]	**0.0007**
hyperkeratosis (0-3)	0 [0 1]	0 [0 0]	**0.0038**
DLQI (0-30)	6 [3-8]	2 [1-5]	**<0.0001**
PRISM (SIS 0-273 mm)	85 [55-180]	180 [90-270]	**<0.0001**

SIS, Self–Illness Separation; *dyspareunia was evaluable in 34 patients; [1Q 3Q] interquartile range; in bold: significant values

Table 3. Mean and coefficient of variation of the main scores after treatment (T1) compared with baseline (T0)

	Mean variation	Standard deviation	Coefficient of variation
Global Subjective Score (0-20)	5.4	6.41	1.19
Global Objective Score (0-15)	2.11	2.57	1.22
Dyspareunia score* (0-10)	2.37	3.23	1.37
PRISM score (SIS 0-273 mm)	67.70	107.85	1.59
DLQI score (0-30)	-2.87	4.45	1.55

SIS, Self–Illness Separation; * dyspareunia was evaluable in 34 patients

Table 4. Relevance of demographic and clinical features on PRISM score changes after treatment (T1) compared with baseline (T0)

PRISM variation								
	Univariate Analysis				Multivariate analysis			
Variables	**β**	**95% CI**		***p* value**	**β**	**95% CI**		***p* value**
		Lower	**Upper**			**Lower**	**Upper**	
Age (1 year increment)	-0.47	-2.52	1.57	0.645	-0.66	-3.54	2.22	0.641
Marital status (referred to married)	35.48	-28.19	99.15	0.27				
Educational level	50.69	-3.11	104.5	0.064				
Employment (referred to employed)	6.12	-48.65	60.89	0.824				
First diagnosis *versus* disease recurrence	7.52	-48.08	63.13	0.788				
Disease duration	0.07	-0.07	0.22	0.332				
Global Subjective Score at T0	8.36	3.73	12.99	**0.001**				
Dyspareunia at T0	-5.35	-14.24	3.54	0.229				
Global Objective Score at T0	-2.25	-12.63	8.13	0.666				
Variation of Global Subjective Score from T0 to T1	-8.74	-12.43	-5.06	**<0.001**	-11.49	-19.03	-3.94	**0.004**
Variation of dyspareunia from T0 to T1	-14.12	-23.26	-4.98	**0.004**	-3.39	-15.19	8.41	0.56
Variation of Global Objective Score from T0 to T1	-4.73	-15.39	5.93	0.379				

CI, confidence interval; in bold significant values

Table 5. Relevance of demographic and clinical features on DLQI score changes after treatment (T1) compared with baseline (T0)

DLQI variation								
	Univariate Analysis				Multivariate analysis			
Variables	**β**	**95% CI**		***p* value**	**β**	**95% CI**		***p* value**
		Lower	**Upper**			**Lower**	**Upper**	
Age (1 year increment)	0.66	-0.02	0.15	0.117	0.03	-0.08	0.14	0.617
Marital status (referred to married)	-0.27	-2.93	2.38	0.839				
Educational level	-1.19	-3.46	1.07	0.296				
Employment (referred to employed)	1.78	-0.44	9.99	0.113				
First diagnosis *versus* disease recurrence	-2.70	-4.89	-0.51	**0.016**	-0.16	-3.29	2.96	0.916
Disease duration	0.01	-0.01	0.01	0.131				
Global Subjective Score at T0	-0.38	-0.57	-0.19	**<0.001**				
Dyspareunia at T0	-0.12	-0.52	0.28	0.542				
Global Objective Score at T0	0.15	-0.28	0.58	0.484				
Variation of Global Subjective Score from T0 to T1	0.41	0.26	0.55	**<0.001**	0.52	0.22	0.81	**0.001**
Variation of dyspareunia from T0 to T1	0.49	0.05	0.92	**0.031**	0.59	0.11	1.06	**0.017**
Variation of Global Objective Score from T0 to T1	0.06	-0.38	0.5	0.785				

CI, confidence interval; in bold significant values