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Quality of Life, Anxiety, and Depression in Patients With Early-Stage Mycosis Fungoides and the Effect of Oral Psoralen Plus UV-A (PUVA) Photochemotherapy on it

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Background: Little is known about psychological discomfort and quality of life (QoL) in early stage mycosis fungoides (MF) and the effect of psoralen plus UV-A (PUVA) on it.

Objective: To evaluate QoL, anxiety, and depression with validated instruments in early stage MF patients and whether PUVA treatment improves it.

Methods: Patients with stage IA to IIA MF were treated with PUVA twice weekly for 12–24 weeks, followed by maintenance treatment or not, in a prospective randomized clinical trial. Patients completed a questionnaire on DLQI as well as the Hospital Anxiety and Depression Scale (HADS) prior to therapy, after their last PUVA exposure, and after the PUVA maintenance or observance phase.

Results: For 24 patients with early stage MF, completed questionnaires were available and analyzed. Prior to treatment, 17% reported strong (DLQI $>$ 10) and 29% moderate impairment (DLQI 6–10) in QoL; 33% of patients reported HADS scores indicating anxiety, and 21% reported scores indicating depression. PUVA significantly improved overall QoL by reducing mean DLQI scores by 58.6% ($p = 0.003$), HADS-A by 30% ($p = 0.045$), and HADS-D by 44% ($p = 0.002$). Improvements in QoL and psychological well-being seemed to be sustained, irrespective of maintenance treatment or not.

Limitations: Small sample size.

Conclusions: PUVA sustainably improves QoL and psychological well-being in patients with early stage MF.

Clinical trial registration: ClinicalTrials.gov identifier: NCT01686594.

Keywords: mycosis fungoides, quality of life, anxiety, depression, PUVA, phototherapy

INTRODUCTION

Studies show that MF leads to impaired quality of life (QoL) (1–3) and a higher risk for depression and anxiety in affected patients (2, 4). This accounts especially for late-stage MF (2, 5), alopecia within MF lesions, and female gender as a recent study suggests by observing a significantly worse health-related QoL in these patients (2). However, Semenov et al. (6) showed that early stage MF must not be trivialized either as patients with MF stage IA–IIB reported poorer QoL than patients with end-stage kidney disease, diabetes mellitus, or an overall cancer cohort, only to be surpassed by patients suffering from stroke or osteoarthritis. In fact, a nationwide American study on the impact of CTCL on QoL reveals that, overall, 72.7% of CTCL patients felt depressed due to their skin condition, and 39% felt ashamed even though the percentage of early stage MF was 80% in the study (1).

The importance for QoL screening and adequate screening tools in patients suffering from cutaneous lymphomas has recently been highlighted (7). Since MF is commonly considered to be incurable with decreased survival rates in advanced stages (8), disease control, life prolongation, and improvement of quality of life and psychological well-being have emerged as major goals in the treatment of the disease (4, 7, 9, 10). While recent work from the Prospective Cutaneous Lymphoma International Prognostic Index (PROCLIPI) study has enlightened the impact of MF on health-related Qol (2), anxiety and depression have been hardly assessed in clinical trials and, if so, most often using questionnaires not specific and not validated for these conditions. Interest in the potential beneficial effect of therapeutic strategies on patients' QoL increases (11–13), but the effect on psychological comfort remains unknown. This accounts especially for early stage MF and treatment with phototherapy. So far, the impairment of QoL in phototherapeutically treated patients has only been investigated in patients treated with photopheresis (14).

Phototherapy belongs to the most frequently used therapeutic approaches in early stage disease (15), of which psoralen plus UVA (PUVA) photochemotherapy is considered to be a very efficient and well-tolerated treatment option despite its potential cancerogenic effects (10, 16). In fact, PUVA increases the risk for non-melanoma skin cancer, mainly squamous cell skin cancer, in a dose-dependent fashion (i.e., at >200 sessions or cumulative dosage of 2,000 J/cm^2) (17). Furthermore, a timely delayed increased risk for melanoma has been observed in patients exposed to more than 200 PUVA irradiations 15 years after the first PUVA treatment (18, 19). However, in terms of efficacy, PUVA with its complete response rate of 70% in this study population (20) beats, by far, other treatment options, such as bexarotene (complete response rates 7–13%) (21, 22) or interferon α-2a plus acitretin (complete response rate 38%) (23). Furthermore, a recent meta-analysis reveals that complete response rates of PUVA being 73.8% in early stage MF (Ia-IIa) were significantly superior to that of UVB with 62.2% (24). Moreover, PUVA is considered to be the most helpful treatment option in early stage MF from the patients' perspective (1) although systemic treatments have recently been questioned to improve QoL (25). We, therefore, aimed to evaluate the effect of PUVA on QoL, anxiety, and depression in patients with early stage MF.

Abbreviations: MF, mycosis fungoides; PUVA, psoralen plus UV-A; DLQI, Dermatology Life Quality Index; HADS, Hospital Anxiety and Depression Scale; QoL, quality of life; EORTC, The European Organisation for Research and Treatment of Cancer.

METHODS

Study Design and Setup

The aims of this analysis were the determination of QoL impairment and the psychological burden in patients suffering from early stage MF and the effect of oral PUVA on them. The objectives of the analysis relate to the secondary endpoints of the Austrian trial on low-dose, low-frequency oral psoralen-UV-A treatment with or without maintenance in early stage MF (20, 26). Please see our previously published work for details about the inclusion and exclusion criteria, previous treatments, phototherapeutic characteristics, clinical treatment response, and adverse events (20). This analysis is in accordance with the ethical approval of the Medical University of Graz and in full compliance with the Austrian Medicinal Products Act and in accordance with the International Conference on Harmonization Good Clinical Practice guideline (27). All participants gave written informed consent according to the principles of the Declaration of Helsinki (28).

Questionnaires

German versions of questionnaires on Dermatology Life Quality Index (DLQI) and Hospital Anxiety and Depression Scale (HADS) were used in this trial. The items of the original study questionnaires are enclosed in the supplements (**Supplemental Methods 1**).

Statistical Analysis

The Wilcoxon signed-rank test was applied to determine statistical significance of improvement comparing overall DLQI and HADS scores and single items of the respective questionnaires that had been collected prior to, during, and after PUVA. Fisher's exact test was performed to test for differences in patient characteristics of complete and partial responders. Spearman analysis was performed for evaluation of the correlation between clinical response (mSWAT reduction) and response of QoL and anxiety and depression (DLQI and HADS). Mann-Whitney *U*-test was done for analysis of individual reductions (at the end of PUVA induction) in overall DLQI, HADS-A, and HADS-D comparing patients with complete and partial remission as well as in individual reductions in patients receiving PUVA maintenance therapy or not. Statistics were performed using SPSS V25.0 (IBM Corp. Armon, NY). Graphics were designed with Microsoft Office 365 (Microsoft Corporation, Redmond, USA) and Adobe Acrobat DC Pro V1.7 (Adobe, San Jose, USA). Statistical significance was set at $p < 0.05$.

TABLE 1 | Patient characteristics.

	Complete responders	Partial responders	*p*-value
Number of patients	18	6	
Age, mean (range)	57.9 (30–80)	62.3 (31–75)	$p = 0.542$
Sex			
Male	12 (67%)	4 (67%)	$p = 1.000$
Female	6 (33%)	2 (33%)	
Lesion type			
Patch	18 (100%)	6 (100%)	$p = 0.15$
Plaque	5 (28%)	4 (67%)	
Stage			
IA	8 (44%)	3 (50%)	$p = 0.276$
IB	10 (56%)	2 (33%)	
IIA	0 (0%)	1 (17%)	
Initial mSWAT score, mean (range)	17.8 (1–66)	20.85 (5–46)	$p = 0.700$
Comorbidities			
Complete responders	Previous history of penis carcinoma 1, previous history of colon carcinoma 1, Huntington's disease 1, coronary heart disease 3, benign prostatic hyperplasia 2, omarthrosis 2, gonarthrosis 1, disc prolapse 2, carpal tunnel syndrome 1, diabetes 1, cholecystolithiasis 2, nephrolithiasis 1, hypertension 4, chronic sinusitis 1		
Partial responders	Previous history of prostate cancer 1, diabetes 1, spinal stenosis 1, obesity 1, gonarthrosis 1, chronic cholecystitis 1, atrial fibrillation 1, hypertension 3, depression 1, hyperlipidemia 1, hypothyreosis 1		
Number of patients having no comorbidities	4/18	1/6	$p = 1{,}000$

RESULTS

Study Participants

Twenty-seven patients were enrolled in the study of whom one was excluded due to therapy-related adverse events (vomiting and recurring nausea) and missing questionnaires at baseline. Questionnaires on DLQI and HADS were completed prior to and after induction therapy by 24 of the remaining 26 patients enrolled at the five study centers across Austria (Graz, Hietzing, Vienna, Salzburg, Innsbruck) in the trial and available for analysis (for excluded patients, see **Supplemental Figure 1**). The mean age of the remaining 24 patients (11 stage IA, 12 stage IB, and 1 stage IIA) was 60 (range 30–80) years (**Table 1**).

DLQI

Prior to treatment, 7 of 24 (29%) patients felt no impairment of QoL at all (DLQI 0-1); 4/24 (17%) reported strong impairment (DLQI >10), 7/24 (29%) moderate impairment (DLQI 6–10), and 6/24 (25%) slight impairment (DLQI 2–5) of QoL by MF (**Supplemental Figure 2**). Specific DLQI results are shown in **Figure 1**. Severity of QoL impairment shows no correlation with the degree of affected body surface (**Supplemental Figure 3**). PUVA led to a significant improvement in severity of QoL affection by reducing overall DLQI scores from a mean of 5.83 $\pm$ 4.92 to 2.41 $\pm$ 2.56 (58.6% reduction, $p = 0.003$) (**Figure 2**) and reducing the scores of the most strongly impaired items [i.e., item 1 regarding "itching, aching, or stinging of the skin" (from mean of 1.21 $\pm$ 0.82 to 0.50 $\pm$ 0.58; $p < 0.001$), item 2 regarding "embarrassment" (from mean of 0.79 $\pm$ 0.96 to 0.33 $\pm$ 0.47; $p = 0.028$), and item 3 regarding "interfering with daily life routine (e.g., shopping, home, gardening)" (from mean of 0.42 $\pm$ 0.64 to 0.04 $\pm$ 0.20; $p = 0.031$)]. Subgroup analysis revealed DLQI improvement in complete responders and partial responders without statistically significant differences (**Supplemental Table 1**). Medical records revealed no significant differences in patient characteristics regarding age and comorbidities of any type between complete and partial responders (**Table 1**). Taken together, the non-significant specific items (items 4–10) of the DLQI questionnaire (and excluding the significant items 1–3), statistically significant improvement was also reached ($p = 0.039$) (**Supplemental Table 2**). As depicted in the supplements (**Supplemental Table 3**), improvement of QoL and anxiety and depression seemed to be sustained at least until the last visit before recurrence, considering the first 9 months after end of induction, irrespective of whether patients were allocated to maintenance or no maintenance treatment (observation arm) (**Supplemental Table 3**).

HADS-Anxiety

Prior to phototherapeutic treatment, 16 of 24 (67%) patients felt no signs of anxiety at all, and 8/24 (33%) of the patients reported scores indicating anxiety, consisting of four patients with a borderline score and four patients with an abnormal HADS-A score (**Supplemental Figure 2**). Severity of anxiety showed no correlation with the degree of affected body surface (**Supplemental Figure 3**). PUVA led to a significant improvement of overall HADS-A values by improving it from a mean of 5.62 $\pm$ 4.56 to a mean of 3.93 $\pm$ 2.83 ($p = 0.045$) (**Figure 2**). After PUVA, four patients showed borderline abnormal HADS-A scores, and normal scores were observed for the remaining patients. Items with the strongest impairments were item 2 "frightened feelings" (15 patients), item 1 "inner tension" (15 patients), and item 6 "restlessness" (16 patients). PUVA led to a significant reduction of patient-reported "inner tension" from a mean of 1.00 $\pm$ 0.93 to 0.42 $\pm$ 0.50 (item 1; $p = 0.011$) (**Supplemental Figure 4**). Subgroup analysis failed to show a significant difference in the reductions of HADS-A, comparing complete and partial responders (**Supplemental Table 1**). Similar as for the DLQI, the improvement of anxiety seems to be sustained (**Supplemental Table 3**).

HADS-Depression

At study enrollment, 19 of 24 (79%) patients felt no signs of depression, and 4/24 (17%) patients had a borderline score, and 1/24 (4%) patient an indicative score for depression as reported in the HADS-D questionnaire (**Supplemental Figure 2**). The results on the specific items of HADS are depicted in **Supplemental Figure 4**. Severity of depression shows no correlation with the degree of affected

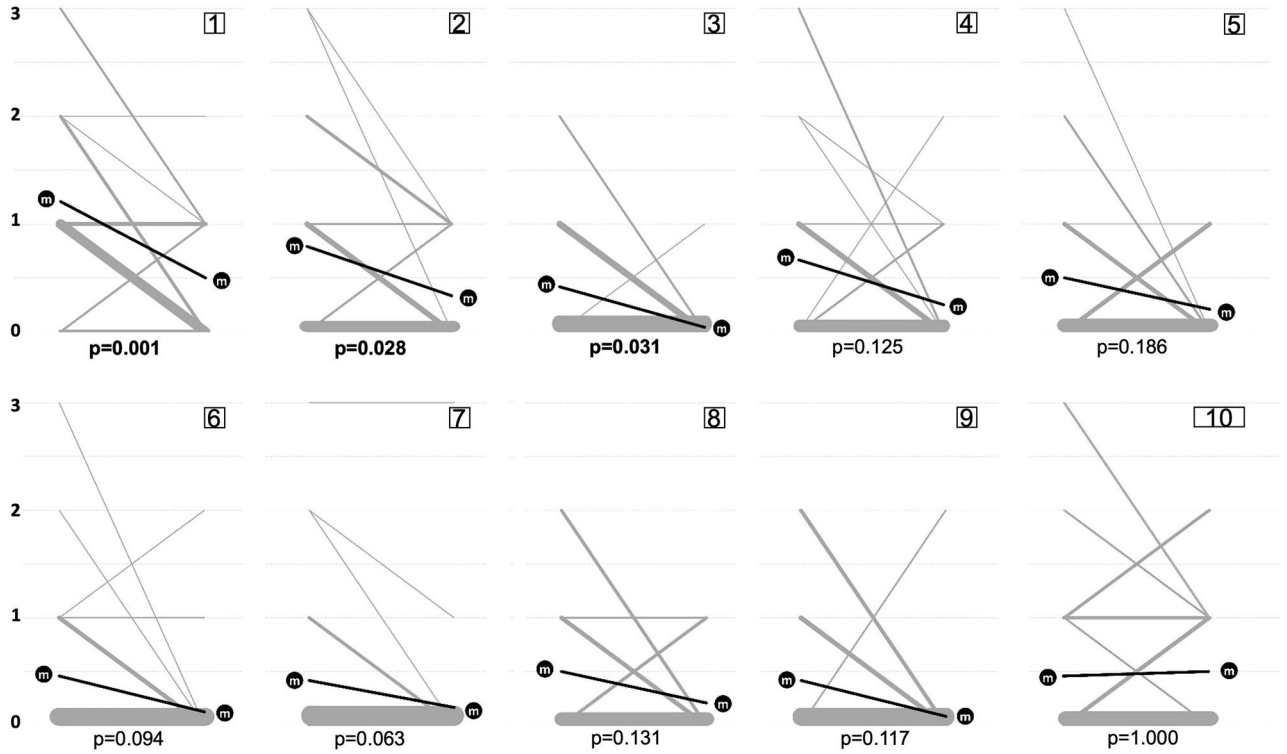

FIGURE 1 | Evolution of DLQI items. Individual values of the 10 Dermatology Life Quality Index (DLQI) items for the time points prior to (left side) and after (right side) Psoralen-UV-A (PUVA) treatment. Numbers in square boxes on top of the panels represent item number of DLQI: item 1 (itching, aching, stinging), item 2 (embarrassment), item 3 (shopping, home), item 4 (affection on clothing), item 5 (social activities), item 6 (sports), item 7 (working, studying), item 8 (interpersonal problems), item 9 (sexual difficulties), and item 10 (treatment difficulties). Each item can be categorized with zero to three points. Items marked as not relevant were awarded with zero points. Thickness of gray lines is proportional to the number of patients and their DLQI evoluting in a certain way. Statistical comparison was performed by Wilcoxon signed-rank test, and respective *p*-values are shown underneath plots. Evolution of mean value (*m*) is shown by the black line and the black circles.

body surface (**Supplemental Figure 3**). PUVA led to a significant improvement of the means in overall HADS-D score from 4.50 ± 3.64 to 2.50 ± 2.65 ($p = 0.002$) (**Figure 2**) as well as in the specific item score "enjoyment of things" from 0.79 ± 0.78 to 0.33 ± 0.48 (item 1; $p = 0.016$) and in the item "looking forward with enjoyment" from 1.00 ± 1.06 to 0.42 ± 0.77 (item 6; $p = 0.014$). After PUVA, two patients showed borderline abnormal HADS-D scores although normal scores were observed for the remaining patients. Similar as for DLQI and HADS-A, the improvement of depression (as measured by HADS-D) seemed to be sustained. Relative differences comparing changes in DLQI and HADS-A in the course of time after the end of induction treatment ranged between 8.3 and 8.5% for DLQI and −4.8 and 5.7% for HADS-A, respectively, in patients treated with maintenance therapy vs. patients in the observance arm (non-significant). There were larger differences in the HADS-D score, but they did not reach significance (**Supplemental Table 3**).

Correlation Analysis

Spearman analysis revealed a statistically significant correlation between DLQI and HADS-A ($r = 0.518$; $p = 0.009$) and HADS-A and HADS-D ($r = 0.643$; $p = 0.001$), analyzing baseline values at start of treatment (**Supplemental Table 4** and **Supplemental Figure 3**). However, no significant correlation between DLQI and HADS-D was observed ($r = 0.342$; $p = 0.102$). Furthermore, overall DLQI improvement after PUVA treatment correlated with HADS-A improvement ($r = 0.541$; $p = 0.006$) but not HADS-D improvement (data not shown). DLQI, HADS-A, and HADS-D did not correlate with mSWAT. Absolute and relative values of improvement after therapy in DLQI, HADS-A, and HADS-D did not correlate with mSWAT either (data not shown).

DISCUSSION

DLQI scores reported in this study prior to photochemotherapy are in the range of overall scores observed for severe psoriasis (29) and atopic dermatitis (30) although the mean overall score in MF appears to be slightly lower. PUVA improved QoL significantly by reducing the overall DLQI score (**Figure 2**) and leading to a significant decrease in "skin sensation" (item 1), "embarrassment" (item 2), and "interfering with daily life activities" (item 3) (**Figure 1**). There have been only a few studies in which the effect of treatment on QoL in

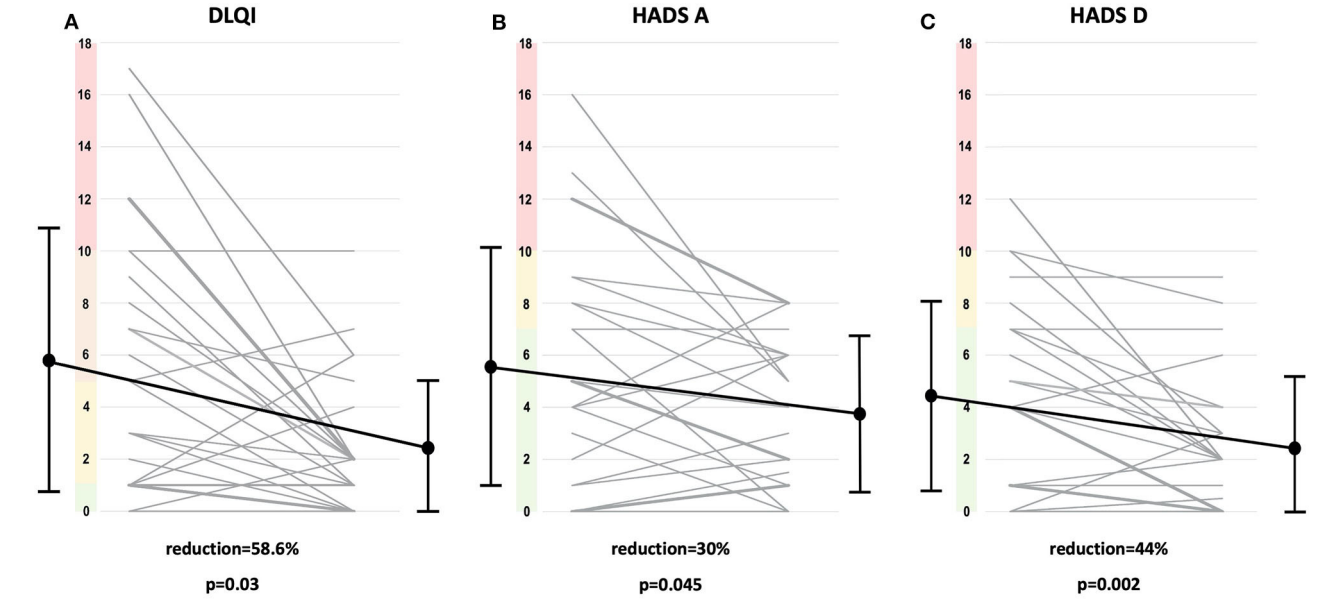

FIGURE 2 | DLQI and HADS scores. Individual overall values of Dermatology Life Quality Index (DLQI) **(A)** and the Hospital Anxiety and Depression scale HADS-A **(B)** and HADS-D **(C)** of the 24 patients prior to (left side) and after psoralen-UV-A (PUVA) induction (right side) and their specific evolution (gray line) are shown. Thickness of gray lines is proportional to the number of patients and their DLQI, HADS-A, or HADS-D evoluting in a certain way. Range of DLQI severity groups are colorized on the *y*-axis of the plot: no impairment (green; 0–1 points); slight (yellow; 2–5), moderate (orange; 6–10), and severe (red; >10 points) impairment. Range of HADS severity groups colorized on the *y*-axis of the plots: no signs of anxiety/depression (green; 0–7 points), borderline abnormal (yellow; 8–10), abnormal values (red; >10 points). Mean values (black dots), standard deviations (black intervals), and evolution of means (black lines) prior to (left side) and after (right side) PUVA treatment are plotted. Percentages of reduction comparing overall scores prior to and after PUVA treatment are depicted. Statistical significance was determined by Wilcoxon signed-rank test and respective *p*-values are plotted.

MF has been investigated, but none address psychological well-being (11–13, 21, 31). Notably, this work addresses for the first time the effect of photochemotherapy on QoL and psychological comfort in early stage MF. A recent study suggests adjusting overall DLQI scores for answers marked as not relevant and coins the term DLQI-R (32). In our study, the percentages of not relevant marked items was relatively low, and although the calculation of a DLQI-R did slightly increase the significance level of *p*-values, overall, it did not change the results (data not shown). Improvement of QoL using oral psoralen and daylight has been described for patients with severe psoriasis experiencing a higher QoL impairment (33) than the MF patients of this study. Of note, in psoriasis and atopic dermatitis, impairment, and improvement of QoL are linked to body surface extension of disease (34–38). Moreover, psoriasis patients with therapy-induced improvement but not complete clearance of skin may still suffer from substantial QoL impairment (34). However, data on the impact of PUVA in other chronic diseases are limited, making it hard to compare the outcome with our results. In a recently published study (36), narrowband UVB phototherapy decreased overall DLQI values by roughly 63% in patients with psoriasis and by 47% in patients with atopic dermatitis—both sets of patients having higher DLQI values at baseline than the MF patients of this study. The QoL improvements were sustained for at least 3 months after phototherapy end although to a higher extent in the atopic dermatitis than psoriasis patients (36).

The screening and surveillance of anxiety and depression using HADS has not been applied in MF previously although it is reported that the early stage of the disease leads to psychological discomfort (1, 3). HADS has emerged as a reliable instrument for detecting states of depression and anxiety since its publication in 1982 (39). It has been used in dermatology for patients with psoriasis, atopic dermatitis, acne, and hidradenitis suppurative (40–44) and has also been widely accepted as a screening and surveillance tool in non-dermatologic diseases (45–49). The expanded use of HADS allows us to compare our results with that in other dermatologic diseases and beyond. HADS-A and HADS-D scores observed for MF in this study are in the range of scores reported for severe psoriasis (29) and are partly higher than in patients with malignant melanoma stage Ia (50). In comparison with non-dermatologic diseases, the HADS results of this study are in the range of values observed in adolescents with severe asthma, coronary arteria disease, or dialysis (51–53). Strikingly, PUVA led to a significant decrease in overall HADS-A and HADS-D (**Figure 2**). Similar to QoL, the improvement of psychological comfort seems to be sustained, irrespective of whether patients received maintenance treatment or not (**Supplemental Table 3**) although (due to small sample size of subgroups) the study was not powered enough to determine statistical significance for this comparison.

Since HADS has not been used in MF before, direct comparison with previous findings remains difficult. However, considering the fact that a higher risk for depression has been reported in MF (3, 4), it is high time for the use of a validated instrument to detect anxiety and depression in such patients. Previous studies use mainly health-related QoL questionnaires to detect psychological discomfort, lacking valid screening of anxiety, and depression (1, 2). Further studies will have to prove if HADS is the adequate instrument for detection of anxiety and depression in early stage MF patients.

We find a statistically significant correlation between DLQI and HADS-A as well as HADS-A and HADS-D, analyzing baseline values at start of treatment (**Supplemental Table 4**). Notably, DLQI, HADS-A, and HADS-D do not correlate with mSWAT. Improvement in DLQI, HADS-A, and HADS-D after induction treatment does not correlate with mSWAT either. This indicates that patients with early stage MF are affected in QoL and psychological well-being irrespective of extent of disease (as measured by mSWAT). Similar findings were recently observed in a larger cohort of patients with early stage MF although with different QoL instruments (5). In fact, for patients with higher stage MF (>IIA) overall a worse QoL was recently reported (2, 5), indicating that disease stage *per se* does affect QoL more than area and extent of body involvement. A previous study reveals (1) that >93% of the surveyed MF patients worried about their disease being serious and >80% worried about dying. When patients were asked about their treatment, 93% reported good communication about their disease and progress, and 85% of them considered their disease after treatment more manageable than before. Furthermore, 84% were satisfied with the explanations about the indolent course of the disease, possibly helping them to handle their disease (better). Moreover, at least theoretically, (P)UVA may have contributed independently to improvement of psychologic well-being by an opioidergic effect, resulting from UV-induced production of endorphins and its (systemic) release, modulating itch and pain in the skin and reducing patient's stress by interaction with the neuroendocrine system (54–57) as low-level UV was recently reported to induce the production and release of endocannabinoids (58).

LIMITATIONS

The major limitations of this study are the small overall sample size and, from a statistical point of view, the overall good response of all patients without any poor responders. The fact, that we were unable to detect a correlation in reduction of absolute mSWAT values with DLQI and HADS may have been at least additionally hampered by the statistical limitations resulting from low scattering with the high rate of complete responders (with mSWAT values of zero) and partial responders (with mSWAT values near to zero).

CONCLUSIONS

Improvement of quality of life as well as reduction of anxiety and depression are in the spotlight of desirable treatment achievements. This study confirms relatively high impairment of QoL and psychological comfort in patients with early stage MF and discloses the effect of photochemotherapy on it. Sustained improvement of QoL and psychological well-being were linked to PUVA treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission der Medizinischen Universität Graz, LKH-Universitätsklinikum—Eingangsgebäude, Auenbruggerplatz 2, 3.OG, A-8036 Graz, ethikkommission@medunigraz.at. The patients/participants provided their written informed consent to participate in this study.

AUTHOR'S NOTE

Parts of this study were presented as poster at the EORTC-CLTF meeting 2019 September 26–28, 2019 in Athens, Greece. We thank Honnavara N. Ananthaswamy, Houston, TX, for critical reading and editing of the manuscript.

AUTHOR CONTRIBUTIONS

TG, PV-G, and PW had full access to all of the data in the study, take responsibility for the integrity of the data, the accuracy of the data analysis, concept, and design. PW: supervision and obtained funding. PV-G, RF-P, SPor, SPöc, RL, SS, P-GS, AH, AG-W, FL, and PW: administrative, technical, or material support. TG, FQ, and PW: statistical analysis. TG and PW: drafting of the manuscript. All authors: critical revision of the manuscript for important intellectual content, acquisition, analysis, or interpretation of data.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2020.00330/full#supplementary-material

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