Rituximab Treatment and Improvement of Health-Related Quality of Life in Patients With Pemphigus

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PRACTICE **POINTS**

- Pemphigus is an autoimmune blistering disease that can negatively affect patients' lives.
- Assessing the impact of treatment from a patient's perspective using outcome assessment measures is important and relevant in trials of new pemphigus treatments including rituximab.
- Rituximab administration in pemphigus patients led to rapid and notable improvement in health-related quality of life and patient-assessed measures.

Pemphigus is an autoimmune blistering disease that can negatively affect patients' lives. Assessing the impact of treatment from a patient's perspective using outcome assessment measures is important and relevant in trials of new pemphigus treatments including rituximab (RTX). We sought to evaluate the effect of RTX on health-related quality of life (HRQOL) in pemphigus patients and peruse the clinical relevance of the patient-reported outcomes. A retrospective cross-sectional study was designed with 96 pemphigus patients given RTX either 3 months earlier or in the last 2 weeks. The treatment was evaluated by patients using HRQOL assessment tools: 36-Item Short Form Survey (SF-36) and Dermatology Life Quality Index (DLQI). Another patient-reported assessment was the patient global assessment (PGA). We found that RTX administration in pemphigus patients led to rapid and notable improvement in HRQOL and patient-assessed measures.

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Pemphigus is a group of autoimmune blistering diseases characterized by the development of painful and flaccid blisters on the skin and/or mucous membranes. Pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are 2 major subtypes and can be distinguished by the location of blister formation or the specificity of autoantibodies directed against different desmogleins.[1,2] Although rare, pemphigus is considered a serious and life-threatening condition with a great impact on quality of life (QOL) due to disease symptoms (eg, painful lesions, physical appearance of skin lesions) as well as treatment complications (eg, adverse drug effects, cost of treatment).[3-6] Moreover, the physical and psychological effects can lead to marked functional morbidity and work-related disability during patients' productive years.[7] Therefore, affected individuals usually have a remarkably compromised health-related quality of life (HRQOL).[8] Effective treatments may considerably improve the QOL of patients with pemphigus.[6]

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The authors report no conflict of interest.

The eTables are available in the Appendix online at www.mdedge.com/dermatology.

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Despite the available treatment options, finding the best regimen for pemphigus remains a challenge. Corticosteroids are assumed to be the main treatment, though they have considerable side effects.[9,10] Adjuvant therapies are used to suppress or modulate immune responses, leading to remission with the least possible need for corticosteroids. Finding an optimal steroid-sparing agent has been the aim of research, and biologic agents seem to be the best option.[8] Rituximab (RTX), an anti-CD20 monoclonal antibody, has shown great promise in several studies of its clinical efficacy and has become a first-line treatment in new guidelines.[11-14] Rituximab treatment has been associated with notable improvement in physician-assessed outcome measures with a favorable safety profile in patients with pemphigus.[11-15] However, it is important to assess response to treatment from a patient's perspective through the use of outcome-assessment measures that encompass patient-reported outcomes to reflect the complete patient experience and establish the overall impact of RTX as well as its likelihood of acceptance by patients with pemphigus.

In our study, we compared clinical outcomes and HRQOL through the use of disease-specific measures as well as comprehensive generic health status measures among patients with PV and PF who received RTX treatment 3 months earlier and those who received RTX in the last 2 weeks. The clinical relevance of the patient-reported outcomes is discussed.

MATERIALS AND METHODS

Study Design

We conducted a single-center cross-sectional study of 96 patients with pemphigus aged 18 to 65 years of either sex who were willing to participate in this study. Patients with a confirmed diagnosis of PV or PF who received RTX 3 months earlier or in the last 2 weeks were enrolled in the study. Patients were identified using Dermatry.ir, an archiving software that contains patients' medical data. Exclusion criteria included lack of sufficient knowledge of the concepts of the questionnaires as well as age younger than 16 years. The study was conducted from October 2019 to April 2020 by the Autoimmune Bullous Disease Research Center at Razi Hospital in Tehran, Iran, which is the main dermatology-specific center and teaching hospital of Iran. The study protocol was approved by the relevant ethics committee.

Patients were categorized into 2 groups: (1) those who received RTX 3 months earlier (3M group); and (2) those who received RTX in the last 2 weeks (R group).

After an explanation of the study to participants, informed written consent was signed by each patient, and their personal data (eg, age, sex, education, marital status, smoking status), as well as clinical data (eg, type of pemphigus, duration of disease, site of onset, prednisolone dosage, presence of Nikolsky sign, anti-DSG1 and anti-DSG3 values, Pemphigus Disease Area Index [PDAI] score, RTX treatment protocol); any known comorbidities such as hypertension, diabetes mellitus, or morbid obesity; and any chronic pulmonary, cardiac, endocrinologic, renal, or hepatic condition, were collected and recorded in a predefined Case Record.

Patient-Reported Outcome Measures

The effect of RTX on QOL in patients with pemphigus was assessed using 2 HRQOL instruments: (1) a general health status indicator, the 36-Item Short Form Survey (SF-36), and (2) a validated, Persian version of a dermatology-specific questionnaire, Dermatology Life Quality Index (DLQI). The questionnaires were completed by each patient or by an assistant if needed.

The SF-36 is a widely used 36-item questionnaire measuring functional health and well-being across 8 domains—mental health, pain, physical function, role emotional, role physical, social functioning, vitality, and general health perception—with scores for each ranging from 0 to 100. The physical component scores (PCSs) and mental component scores (MCSs) were derived from these 8 subscales, each ranging from 0 to 400, with higher scores indicating better health status.[6]

The DLQI, one of the most frequently used QOL measures in dermatology, contains 10 questions, each referring to the prior week and classified in the following 6 subscales: symptoms and feelings, daily activities, leisure, personal relationships, work and school, and treatment.[16] The total score ranges from 0 (no impact) to 30 (very high impact), with a higher score indicating a lower QOL (eTable 1). The minimal clinically important difference (MCD) for the DLQI was considered to be 2- to 5-point changes in prior studies.[17,18] In this study, we used an MCD of a 5-point change or more between study groups.

Moreover, the patient general assessment (PGA) of disease severity was identified using a 3-point scale (1=mild, 2=moderate, 3=severe).

Statistical Analysis

Data were analyzed using SPSS Statistics version 23. $P \leq .05$ was considered significant. Mean and SD were calculated for descriptive data. The *t* test, Fisher exact test, analysis of variance, multiple regression analysis, and logistic regression analysis were used to identify the relationship between variables.

RESULTS

Patient Characteristics

A total of 96 patients were enrolled in this study. The mean (SD) age of participants was 41.42 (15.1) years (range, 18–58 years). Of 96 patients whose data were included, 55 (57.29%) patients had received RTX 3 months earlier (3M group) and 41 (42.71%) received RTX in the last 2 weeks (R group). A summary of study patient characteristics in each group is provided in eTable 2. There was no significant difference between the 2 groups in terms of age, sex, type of pemphigus,

marital status, education, positive Nikolsky sign, smoking status, existence of comorbidities, site of lesions, and RTX treatment protocol. However, a significant difference was found for duration of disease (P=.0124) and mean prednisolone dosage (P=.001) as well as severity of disease measured by PDAI score (P=.003) and anti-DSG1 (P=.003) and anti-DSG3 (P=.021) values.

Patient-Reported Outcomes

Physical and mental component scores are summarized in eTable 3. Generally, SF-36 scores were improved with RTX treatment in all dimensions except for mental health, though these differences were not statistically significant, with the greatest mean improvement in the role physical index (75.45 in the 3M group vs 53.04 in the R group; P=.009). Mean SF-36 PCS and MCS scores were higher in the 3M group vs the R group, though the difference in MCS score did not reach the level of significance (eTable 3).

Mean DLQI scores in the R and 3M groups were 12.31 and 6.96, respectively, indicating a considerable burden on HRQOL in both groups. However, a statistically significant difference between these values was seen that also was clinically meaningful, indicating a significant improvement of QOL in patients receiving RTX 3 months earlier (P=.005)(eTable 3).

The PGA scores indicated that patients in the 3M group were significantly more likely to report less severe disease vs the R group (P=.008)(eTable 3).

Multivariate Analysis—Effect of the patient characteristics and some disease features on indices of QOL was evaluated using the multiple linear regression model. eTable 4 shows the P values of those analyses.

COMMENT

Pemphigus is a chronic disabling disease with notable QOL impairment due to disease burden as well as the need for long-term use of immunosuppressive agents during the disease course. To study the effect of RTX on QOL of patients with pemphigus, we compared 2 sets of patients. Prior studies have shown that clinically significant effects of RTX take 4 to 12 weeks to appear.[19,20] Therefore, we selected patients who received RTX 3 months earlier to measure their HRQOL indices and compare them with patients who had received RTX in the last 2 weeks as a control group to investigate the effect of RTX intrinsically, as this was the focus of this study.

In our study, one of the research tools was the DLQI. Healthy patients typically have an average score of 0.5.[21] The mean DLQI score of the patients in R group was 12.31, which was similar to prior analysis[8] and reflects a substantial burden of disease comparable to atopic dermatitis and psoriasis.[21,22] In patients in the 3M group, the mean DLQI score was lower than the R group (6.96 vs 12.31), indicating a significant (P=.005) and clinically meaningful improvement in QOL of patients due to the dramatic therapeutic effect of RTX. However, this score indicated a moderate effect on HRQOL, even in the context of clinical improvement due to RTX treatment, which may reflect that the short duration of treatment in the 3M group was a limitation of this study. Although the 12-week treatment duration was comparable with other studies[19,20] and major differences in objective measures of treatment efficacy were found in PDAI as well as anti-DSG1 and anti-DSG3 values, longer treatment duration may be needed for a more comprehensive assessment of the benefit of RTX on HRQOL indices in patients with pemphigus.

Based on results of the SF-36 questionnaire, PCS and MCS scores were not substantially impaired in the R group considering the fact that a mean score of 50 has been articulated as a normative value for all scales.[23] These data demonstrated the importance of using a dermatologic-specific instrument such as the DLQI instead of a general questionnaire to assess QOL in patients with pemphigus. However, better indices were reported with RTX treatment in the 3 SF-36 domains—role physical (P=.009), role emotional (P=.03), and general health perception (P=.03)—with the role physical showing the greatest magnitude of mean change (75.45 in the 3M group vs 53.04 in the R group). Notably, PCS was impaired to a greater extent than MCS in patients in the R group and showed a greater magnitude of improvement after 3 months of treatment. These results could be explained by the fact that MCS can be largely changed in diseases with a direct effect on the central nervous system.[23]

Our results also revealed that the dose of corticosteroid correlated to HRQOL of patients with pemphigus who recently received RTX therapy. Indeed, it is more likely that patients on lower-dose prednisolone have a higher QOL, especially on physical function and social function dimensions of SF-36. This finding is highly expectable by less severe disease due to RTX treatment and also lower potential dose-dependent adverse effects of long-term steroid therapy.

One of the most striking findings of this study was the correlation of location of lesions to QOL indices. We found that the mucocutaneous phenotype was significantly correlated to greater improvement in role emotional, role physical, and social functioning scores due to RTX treatment compared with cutaneous or mucosal types (P=.02, P=.025, and P=.017, respectively). Although mucosal involvement of the disease can be the most burdensome feature because of its large impact on essential activities such as eating and speaking, cutaneous lesions with unpleasant appearance and undesirable symptoms may have a similar impact on QOL. Therefore, having both mucosal and cutaneous lesions causes a worsened QOL and decreased treatment efficacy vs having only one area involved. This may explain the greater improvement in some QOL indices with RTX treatment.

Limitations—Given the cross-sectional design of this study in which patients were observed at a single time point during their treatment course, it is not possible to

establish a clear cause-effect relationship between variables. Moreover, we did not evaluate the impact of RTX or prednisolone adverse effects on QOL. Therefore, further prospective studies with longer treatment durations may help to validate our findings. In addition, MCDs for DLQI and SF-36 in pemphigus need to be determined and validated in future studies.

CONCLUSION

The results of our study demonstrated that patients with pemphigus may benefit from taking RTX, not only in terms of clinical improvement of their disease measured by objective indices such as PDAI and anti-DSG1 and anti-DSG3 values but also in several domains that are important to patients, including physical and mental health status (SF-36), HRQOL (DLQI), and overall disease severity (PGA). Rituximab administration in patients with pemphigus can lead to rapid and significant improvement in HRQOL as well as patient- and physician-assessed measures. Its favorable safety profile along with its impact on patients' daily lives and mental health makes RTX a suitable treatment option for patients with pemphigus. Moreover, we recommend taking QOL indices into account while evaluating the efficacy of new medications to improve our insight into the patient experience and provide better patient adherence to treatment, which is an important issue for optimal control of chronic disorders.

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APPENDIX

eTABLE 1. Classification of Patients Based on DLQI Questionnaire

Score	Disease impact on QOL
0–1	No impact
2–5	Little impact
6–10	Medium impact
11–20	High impact
21–30	Very high impact

Abbreviations: DLQI, Dermatology Life Quality Index; QOL, quality of life.

eTABLE 2. Summary of Patient Demographic and Clinical Data (N=96)

Category	R group	3M group	*P* value
No. of patients	41	55	
Mean age, y	43.18	40.77	.576
Sex, n			
Male	18	24	.979
Female	23	31	
Type of disease, n			
PV	37	47	.485
PF	4	8	
Marital status, n			.738
Single	19	24	
Married	22	31	
Education, n			.555
High school	17	25	
Master's degree	15	21	
Beyond master's degree	9	9	
Nikolsky sign, n			
Positive	14	11	.125
Negative	27	44	
Smoking status, n			
Positive	13	17	.432
Negative	28	38	
Duration of disease, mo			
<3	23	0	.0124
3–6	13	30	
6–12	4	16	
>12	1	9	
Comorbidities, n			
Positive	12	19	.66
Negative	29	36	
Site of lesions, n			
Cutaneous	11	11	.719
Mucosal	6	11	
Mucocutaneous	24	33	
RTX treatment protocol, n			
Rheumatoid arthritis protocol	6	7	.537
Lymphoma protocol	35	48	
Mean prednisolone dosage, mg	33.67	21.45	.001
Mean PDAI score	28.97	15.6	.003
Mean anti-DSG1, IU/mL	54.6	35.44	.003
Mean anti-DSG3, IU/mL	64.2	36.27	.021

Abbreviations: 3M group, received RTX 3 months earlier; DSG, desmoglein; PDAI, Pemphigus Disease Area Index; PF, pemphigus foliaceus; PV, pemphigus vulgaris; R group, received RTX in last 2 weeks; RTX, rituximab.

eTABLE 3. Patient-Reported Outcomes

Characteristic	R group	3M group	*P* value
Mean SF-36 score[a]			
Physical function	54.39	61.6	.965
Role physical	53.04	75.45	.009
Role emotional	43.06	61.14	.03
Vitality (energy or fatigue)	51.95	55.90	.296
Mental health	60.09	55.12	.367
Social functioning	50.67	55.90	.253
Pain	68.81	70.77	.733
General health perception	54.6	68.45	.03
PCS[b]	57.71	69.07	.04
MCS[b]	51.44	57.02	.112
Mean DLQI score[c]	12.31	6.96	.005
PGA score			
Mild	9	23	.008
Moderate	16	23	
Severe	16	9	

Abbreviations: 3M group, received RTX 3 months earlier; DLQI, Dermatology Life Quality Index; MCS, mental component score; PCS, physical component score; PGA, patient global assessment; R group, received RTX in last 2 weeks; SF-36, 36-Item Short Form Survey.

[a]Scores range from 0 to 100.

[b]Scores range from 0 to 400, with higher scores indicating better health status.

[c]Scores range from 0 (no impact) to 30 (very high impact).

eTABLE 4. Comparison of QOL Indices Between 2 Study Groups (R and 3M) for Study Variants[a]

	P value of study variant[a]												
QOL indices	Sex	Age	Marital status	Education	Smoking	Disease duration	Comorbidity	Location	Nikolsky sign	Prednisolone dosage	DSG1	DSG3	PDAI
SF-36													
Physical function	.092	.061	.606	.35	.064	.346	.147	.45	.126	.036 (−0.7)	.034 (−.132)	.035 (−0.03)	.012 (−0.79)
Role physical	.885	.237	.371	.75	.144	.627	.147	.025 (−0.12)	.088	.132	.024 (−0.075)	.013 (−0.09)	.033 (−0.74)
Role emotional	.675	.247	.214	.451	.143	.512	.527	.02 (−1.9)	.143	.213	.002 (−0.235)	.357	.178
Vitality	.338	.596	.278	.451	.543	.243	.187	.710	.262	.312	.022 (−0.335)	.657	.043 (−0.5)
Mental health	.401	.367	.234	.412	.348	.234	.247	.235	.621	.118	.064	.127	.245
Social functioning	.419	.239	.112	.126	.442	.184	.057	.017 (4.4)	.423	.034 (−0.8)	.044 (−0.265)	.015 (−0.04)	.123
Pain	.64	.494	.156	.45	.39	.19	.097	.134	.341	.241	.662	.757	.029 (−0.21)
General health perception	.239	.859	.162	.358	.198	.494	.797	.241	.18	.023 (−0.31)	.462	.857	.245
DLQI	.5	.42	.21	.071	.41	.34	.058	.32	.026 (3.15)	.43	.041 (0.89)	.032 (1)	.046 (1.08)

Abbreviations: 3M group, received RTX 3 months earlier; DLQI, Dermatology Life Quality Index; DSG, desmoglein; PDAI, Pemphigus Disease Area Index; R group, received RTX in last 2 weeks; SF-36, 36-Item Short Form Survey.

[a]Odds ratio (for DLQI) or estimate (for SF-36 dimensions) presented in cases of statistically significant differences (shown in parentheses).