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Patient-assigned health utility values for controlled and uncontrolled pemphigus vulgaris and foliaceus

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Abstract

Background The assessment of health-related quality of life (HRQoL) in patients with pemphigus is now of increasing interest due to the availability of highly effective new therapies. Preference-based HRQoL values or health utilities required for medical and financial decision-making are not yet available directly from pemphigus patients.

Objective To obtain health utility values for current health and hypothetical health states from the perspective of pemphigus patients.

Methods A cross-sectional questionnaire survey was carried out with pemphigus patients. Disease severity was rated by Autoimmune Bullous Skin Disorder Intensity Score (ABSIS). Patients were asked to evaluate their current health as well as three common hypothetical pemphigus health states [uncontrolled pemphigus vulgaris (PV), uncontrolled pemphigus foliaceus (PF) and controlled PV/PF] by using composite time trade-off (cTTO). Multiple regression was applied to explore determinants of utility values.

Results Responses of 108 patients (64.8% women, mean age 57.4 years) were analysed. Mean ABSIS score was 11.6. The mean utility values for the hypothetical uncontrolled PV, uncontrolled PF and controlled PV/PF health states were 0.41, 0.52 and 0.66 with cTTO. The mean cTTO scores for current health were higher compared with the hypothetical health states (0.76; $P < 0.001$). Patients with higher ABSIS, worse pain intensity scores and those having a caregiver reported lower utility values for current health ($P < 0.05$).

Conclusions In pemphigus, HRQoL impairment expressed in utility values seems to be considerable, especially in comparison with other chronic dermatological conditions (e.g. psoriasis, atopic eczema, chronic hand eczema). These health utilities inform physicians, policymakers and funders about the overall extent of health loss in pemphigus and provide evidence to guide medical decisions and cost-effectiveness analyses of treatment strategies. Future research is needed to evaluate the caregiver burden in pemphigus.

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Conflicts of interest

None declared.

A. Szegedi and F. Rencz have equally contributed to this work.

Introduction

Pemphigus is a group of rare chronic autoimmune diseases of the skin and mucosa.[1,2] Reported incidence varies between 0.5 and 32 per million across geographic regions.[3] Typical age of onset is 50–60 years, and it is more common in women.[4] There are two major subtypes of disease: pemphigus vulgaris (PV) and pemphigus foliaceus (PF). Clinical manifestation of PV includes the formation of painful flaccid blisters on the skin and/or mucosa, commonly in the oral cavity.[5] PF is characterized by crusted erosions on the skin, while oral lesions are rarely seen in this form of disease.[5] Skin lesions can develop on any body part; however, they generally appear on the scalp, upper chest and back.

Health-related quality of life (HRQoL) in pemphigus is now of increasing interest due to the US Food and Drug Administration (FDA) approval of the first-line application of a biologic agent, rituximab for PV in June 2018.[6] Autoimmune blistering diseases including pemphigus are reported to cause one of the largest HRQoL impairment among chronic skin diseases.[7–9] HRQoL outcomes are increasingly being recognized as an important tool to aid treatment decisions in dermatology.[10–12] A method to quantify the HRQoL loss from disease and the HRQoL benefits of treatments is the assessment of health utility values. So far, many HRQoL studies have been performed with pemphigus patients;[13,14] however, none of these elicited health utility values. Health utilities represent preferences for a given health state measured on a cardinal scale anchored on 0 (=death) and 1 (=full health). In addition to assessing the burden of disease, utilities may be used to calculate quality-adjusted life years (QALYs). The QALY is a single index that combines the impact of health interventions on both mortality (i.e. survival) and morbidity (i.e. utility gain).[15] One year spent in 'full health' equals 1 QALY. For instance, when a treatment results in 10 years of survival and an average utility improvement of 0.2 that yields a total of two QALYs gained. In cost-effectiveness analyses, estimating the cost of a QALY gained is a useful outcome to compare the benefits of two alternative treatment strategies.[16]

Undoubtedly, the rarity of disease represents a major limitation of assessing health utilities in pemphigus. Few patients characterized by severe skin lesions are accessible, as the majority of patients are treated and presenting with milder symptoms in secondary or tertiary care settings. Our main aim was to elicit health utility values directly from pemphigus patients. Thus, patients in this study valued both their current health and three common hypothetical pemphigus health states (uncontrolled PV, uncontrolled PF and controlled PV/PF) based on vignettes describing symptoms and HRQoL impact of disease. The issue of whose preferences to elicit for economic evaluations is widely discussed in the literature.[17,18] In most European countries, utilities obtained from the general public are recommended; never-theless, health valuations typically differ between patients and the general population. The secondary aim was to compare utilities for these three states derived from patients and the general population.[19]

Methods

Study setting and patients

Between December 2014 and June 2017, a cross-sectional questionnaire survey was carried out. Consecutive pemphigus patients (≥18 years of age) regardless of type and severity of pemphigus were recruited to the study at all four university dermatology clinics in Hungary. All patients agreed to take part in the survey and signed in an informed consent. Ethical approval was obtained from the National Scientific and Ethical Committee (reference no. ETT-TUKEB 27416-3/2016/EKU). Outpatients filled in the questionnaires right after clinical examinations at the doctor's office or in the waiting room, while hospitalized patients completed the survey in the ward. Patients answered questions on personal data (e.g. age, gender, education) and pain experienced. The average and worst pemphigus-related pain intensity in the past three months was recorded on a horizontal visual analogue scale (VAS) with the endpoints of 'no pain at all' (=0) and 'pain as bad as it could be' (=10).[20]

Dermatologists provided data on medical history and treatments as well as rated disease severity by Autoimmune Bullous Skin Disorder Intensity Score (ABSIS). The ABSIS is a validated scoring system for disease severity in autoimmune bullous skin diseases, including pemphigus.[21,22] ABSIS scores range between 0 and 206, where higher scores refer to more severe disease. Out of 206, 150 points can be attached to skin involvement, 11 points to oral involvement and 45 points to subjective discomfort.

Dermatology-specific HRQoL was assessed by completing the Dermatology Life Quality Index (DLQI).[23] The DLQI is a self-administered 10-item questionnaire designed to measure the impact of skin disease on patients' life over the past week. Responses range from 'not at all' or 'not relevant' (=0), 'a little' (=1), 'a lot' (=2) to 'very much' (=3). The total score is calculated by adding up the scores of each item, where '0' reflects the best, and '30' reflects the worst HRQoL.

Utility assessment

The study design builds on an earlier study assessing three pemphigus health states by the general population in Hungary.[19] Utilities were obtained via paper-based questionnaires, completed in the presence of a dermatologist who explained the exercises. Patients filled in the questionnaires themselves, but they were encouraged to ask any questions either before or during the task any time having concerns. The detailed methodology of the utility assessment has been published elsewhere,[19] and

we briefly summarize the main points here. An example valuation task is provided in Appendix S1.

Based on results of a systematic literature review[13] on HRQoL in pemphigus, three health state descriptions – an uncontrolled PV, an uncontrolled PF and a controlled PV/PF – were defined reflecting different pemphigus experiences according to skin and mucosal symptoms, possible food avoidance, bathing and/or clothing issues, and effects on work and social life (Appendix S2). According to the European S2 guideline for diagnosis and treatment of pemphigus, control of disease activity was defined by the time at which new lesions cease to form and established lesions begin to heal.[24] In order to determine the clarity of descriptions, the health state vignettes were pilot-tested in four pemphigus patients. The vignettes were presented in a table format, as patients strongly prefer this format over narrative health state descriptions.[25]

Composite time trade-off (cTTO) was used for the health state valuations. The cTTO task combines a conventional TTO to elicit values for states regarded better than dead and a lead-time TTO for states worse than dead.[26] In the conventional TTO for current health, patients were asked to imagine that they were living in their current health status for the next 10 years followed by death. Then, they were asked to find the amount of time in full health, which is considered equal to 10 years in their current health (Appendix S1, Q1). The lead-time TTO was introduced for those patients who chose immediate death over 10 years in their own health. These respondents were given 10 extra years in full health before the 10 years to live in pemphigus (a total of 20 years), while the alternative option offered a shorter life span (i.e. a maximum of 10 years) in full health (Appendix S1, Q2).[26] A similar procedure was followed for the three hypothetical states.

Data analysis

Invalid or logically inconsistent cTTO responses were excluded. A response sheet was considered invalid (i) if the patient did not complete each row of the cTTO sheet, but only indicated a response at a single year; (ii) if the patient indicated a 'cannot decide' answer at each year; and (iii) if an answering pattern was detected [i.e. the patient provided exactly the same response pattern for each cTTO task), with the exception of non-trading behaviour (i.e. rated all health states including current health equal to full health)]. Examples for inconsistent cTTO response sheets are published elsewhere.[27]

cTTO responses were scored by two researchers with experience in using the method conforming to the guidelines described by Gudex et al.[28] Utility values were calculated according to the following formulas, with utilities anchored on 0 (death) and 1 (full health):

$$\text{Better than dead responses: } U = \frac{t}{10}$$

$$\text{Worse than dead responses: } U = \frac{t - 10}{10},$$

where U is the utility value, and t is the number of years required in full health.[26] For example, if a patient is indifferent between 10 years in pemphigus and 6 years in full health, the utility is calculated as $U = 6/10 = 0.6$. For states worse than dead, if a patient considers 10 years in full health followed by 10 years in pemphigus to be equal to 2 years in full health, $U = (2–10)/10 = -0.8$.

Descriptive statistics (mean, median, standard deviation, IQR) of utility values were computed. A Wilcoxon signed-rank test was used to test the difference in cTTO utilities between health states. We assessed the association between cTTO utilities for current health and DLQI and ABSIS scores by Spearman's correlation coefficients. We performed multiple generalized least squares (GLS) regression analyses to explore demographic and clinical predictors of utilities. We adopted a repeated measures approach, whereby observations were grouped within individuals. We used a mixed model assuming fixed effects both for the hypothetical health states and for the observed individual characteristics, complemented by a random intercept for each individual plus an idiosyncratic error term.

For each health state, utility values derived from patients were compared to results of an earlier study eliciting utilities for exactly the same three health states from a convenience sample of the general population in Hungary.[19] Given the differences in demographic and socioeconomic characteristics between patients and the general public, we adjusted utility values for participants' age, gender, education level and employment status. Analysis of covariance (ANCOVA) was applied to compute adjusted mean utility values for hypothetical health states of the two groups. All statistics were two-sided, and a $P < 0.05$ was taken as statistically significant. All analyses were undertaken in IBM SPSS (version 22.0, IBM Corp., Armonk, NY, USA) and R (version 3.5.0, R Core Team, Vienna, Austria).

Results

Characteristics of the patient population

Overall, 108 patients participated in the survey. Demographic and clinical characteristics of the patients are presented in Table 1. Mean ± SD age was 57.4 ± 14.7 years, and 64.8% were women. With respect to disease severity, the majority of patients were in a relatively mild health state (mean ABSIS score 11.6 ± 17.4 on a scale from 0 to 206). Mean DLQI score of patients with pemphigus was 5.5 ± 6.9 (on a scale from 0 to 30).

Utility results

Figure 1 shows that overall five cTTO tasks were left blank from three patients. A further 71 (16.3%) cTTO tasks were excluded

Table 1 Characteristics of the patient population (*n* = 108)

Variables	Mean (SD) or *N* (%)
Age (years)	57.4 (14.7)
Gender	
Female	70 (64.8%)
Male	38 (35.2%)
Education	
Primary school	22 (20.4%)
High school	57 (52.8%)
College/university	29 (26.9%)
Employment status[†]	
Employed	51 (47.2%)
Unemployed	6 (5.6%)
Disability pensioner	14 (13.0%)
Retired	38 (35.2%)
Student	1 (0.9%)
Other	4 (3.7%)
Having a caregiver	28 (25.7%)
Disease duration (years)	3.8 (4.9)
Type of pemphigus	
Pemphigus vulgaris	80 (74.1%)
Pemphigus foliaceus	27 (25.0%)
IgA pemphigus	1 (0.9%)
Outcome measures[‡]	
ABSIS (0–206)	11.6 (17.4)
DLQI (0–30) (missing *n* = 1)	5.5 (6.9)
Average pain intensity VAS[§] (0–10) (missing *n* = 3)	2.14 (3.1)
Worst pain intensity VAS[§] (0–10) (missing *n* = 2)	3.4 (3.8)
Current treatment	
None	3 (2.8%)
Topical therapy (only)	10 (9.3%)
Systemic therapy	95 (88.0%)

†Combinations may occur.
‡For all outcome measures, a higher score represents a worse outcome.
§For the past 3 months.
ABSIS, Autoimmune Bullous Skin Disorder Intensity Score; VAS visual analogue scale.

according to the exclusion criteria. The most common reason for exclusion was indicating the 'cannot decide' response option for each year (8.7%).

The rate of '1' answers (i.e. full health) on the cTTO was 14.0% for uncontrolled PV, 19.3% for uncontrolled PF, 34.1% for controlled PV/PF and 54.6% for current health. There were eight patients (7.4%) who were non-traders (i.e. rated all health states including their current health equal to '1'; Table 2). Overall 11.6%, 9.0% and 3.3% judged the uncontrolled PV, uncontrolled PF and controlled PV/PF health states as bad or worse than being dead (utility ≤ 0). In contrast, there was only one '0' utility, and no negative utilities occurred for current health.

Table 2 shows that mean ± SD utility values for the hypothetical uncontrolled PV, uncontrolled PF and controlled PV/PF health states were 0.41 ± 0.45, 0.52 ± 0.42 and 0.66 ± 0.36. Significant differences were observed between all hypothetical health states ($P < 0.001$). The mean cTTO scores for current health were higher compared with the hypothetical health states (0.76 ± 0.30; $P < 0.001$). There was no significant difference between PV and PF patients (0.75 ± 0.30 vs. 0.78 ± 0.30, $P = 0.771$). cTTO scores for current health demonstrated a weak correlation with DLQI ($r = -0.29$, $P = 0.006$) and a very weak correlation with ABSIS scores ($r = -0.14$, $P = 0.200$).

Predictors of utilities

Table 3 presents the results of multiple regression analyses about predictors of cTTO utilities. The uncontrolled PV and uncontrolled PF health states implied a 0.306 and 0.156 lower mean cTTO values in comparison with the controlled PV/PF health state. Patients' cTTO utilities for hypothetical health states were decreased by 0.0070 with every one-year increase in age. ABSIS had a positive, although diminishing effect on cTTO values, as is implied by the negative coefficient of the quadratic term ($ABSIS^2$).

With respect to current health, patients who assigned one unit higher cTTO rating for the hypothetical controlled PV/PF health state also tended to evaluate their current health 0.555 units higher on average. Every point increase on worst pain as measured with the VAS pain scale decreased the cTTO utility for current health state by 0.017, and furthermore, patients reported to have a caregiver provided on average 0.131 lower cTTO values. We have also found a diminishing negative effect for ABSIS on cTTO utilities.

Comparison of utilities between patients and the general public

Mean differences between the utility values for the three hypothetical health states from patients vs. the general population are presented in Table 2. A convenience sample of the general population was recruited in 2015.[19] They had a mean age of 26.0 ± 9.1 years, 58% were females, 78% had a college/university degree, and 51% was employed. No significant differences were found in cTTO utilities for hypothetical health states, which remained unchanged after adjusting for demographic and socioeconomic characteristics (mean adjusted cTTO utilities for uncontrolled PV, uncontrolled PF and controlled PV/PF were 0.43, 0.55 and 0.68; $P > 0.05$ for all).

Discussion

This study aimed to obtain health utility values for current health and hypothetical health states from the perspective of pemphigus patients. As a practical matter, current health utilities are useful for understanding the HRQoL burden pemphigus poses on HRQoL of patients, while the utilities for hypothetical health states may be applied for estimating QALYs in economic evaluations of pemphigus treatments.
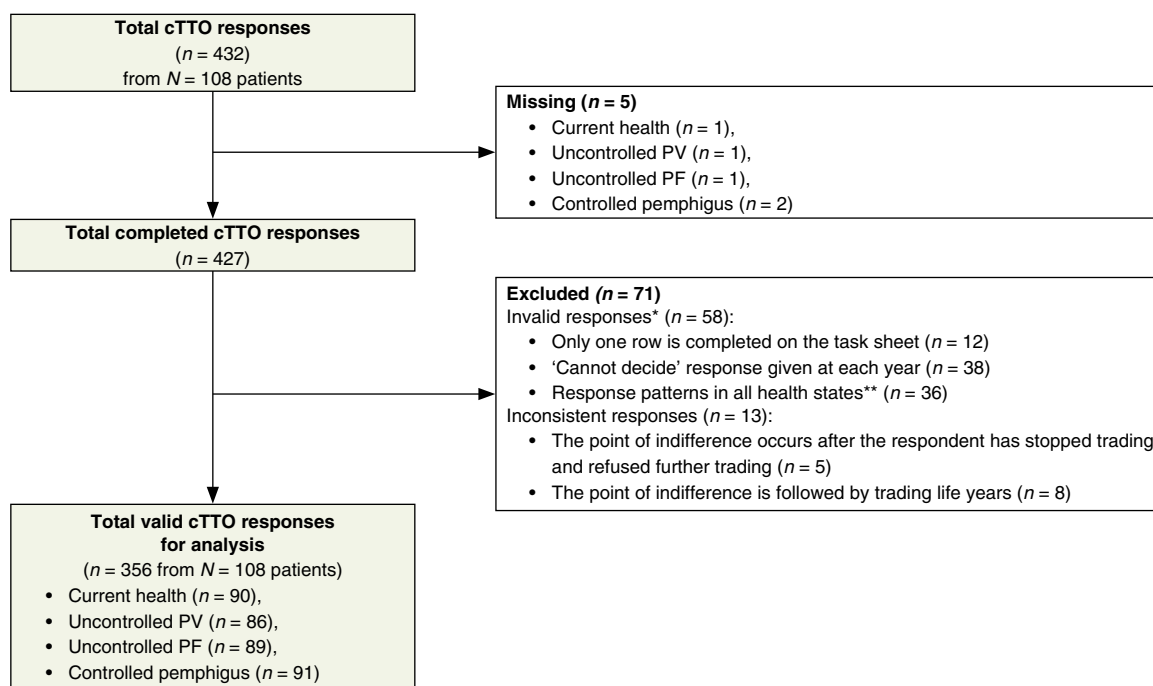
Figure 1 Study flow diagram. *A single response might be invalid due to more than one reason. **The patient provided exactly the same response pattern for each cTTO with the exception of non-trading behaviour, when following a pattern is acceptable. cTTO, composite time trade-off; PF, pemphigus foliaceus; PV, pemphigus vulgaris.

Table 2 cTTO utilities for current health and hypothetical pemphigus health states

	Pemphigus patients (n = 108)			General population (n = 108)[19]			Mean difference	P-value
	n	Mean (SD)	Median	n	Mean (SD)	Median		
Current health	90	0.76 (0.30)	0.90	N/A	N/A	N/A	N/A	N/A
Uncontrolled PV	86	0.41 (0.45)	0.40	104	0.35 (0.38)	0.40	0.07	0.278
Uncontrolled PF	89	0.52 (0.42)	0.50	106	0.52 (0.32)	0.50	0.00	0.974
Controlled PV/PF	91	0.66 (0.36)	0.80	107	0.75 (0.31)	0.80	−0.09	0.056

Source of data on general population values: Rencz et al.[19]
cTTO, composite time trade-off; N/A, not applicable; PF, pemphigus foliaceus; PV, pemphigus vulgaris.

Mean cTTO utility for patients' current health was 0.76 on a scale anchored on 0 (=death) and 1 (=full health). To put this in another way, patients were willing to trade 24% of their remaining hypothetical 10-year life expectancy to be free from pemphigus. The relatively low utility values in pemphigus compared to other skin diseases reflect the large impact of PV and PF on the life of these patients.[29–37] In other studies, patients with various chronic dermatological conditions valued their actual health as follows (mean values): hidradenitis suppurativa 0.63,[31] systemic sclerosis 0.76,[33,34] psoriasis 0.88,[32] melasma 0.92,[35] atopic dermatitis 0.93,[32] port wine stains 0.95[36] and acne 0.96.[37] However, results of these studies are not directly comparable to those of our study due to differences in the TTO methodologies, such as varying length of time frame in the TTO task.

In our study, cTTO utilities for current health demonstrated a weak correlation with disease severity. Previously, a large number of studies in various diseases found no or at most modest correlation between disease severity measures and health utilities.[38] Examples from the field of dermatology include Melasma Area Severity Index, Investigator's Static Global Assessment score in acne and Hurley staging in hidradenitis suppurativa.[31,35,37] Evidence suggests that clinical variables may explain only a part of health utilities, while person-related variables such as socioeconomic status, having children and attitudes towards death represent the major source of variation.[39]

Table 3 Predictors of cTTO utility values (multiple linear regressions)

	Coeff. (b)	SE	*P*-value
cTTO hypothetical			
Intercept	0.982	0.108	<0.001
Hypothetical pemphigus health states			
Uncontrolled PV	−0.306	0.054	<0.001
Uncontrolled PF	−0.156	0.043	<0.001
Clinical and demographic characteristics of patients			
Age	−0.0070	0.0018	<0.001
ABSIS	0.0088	0.0032	0.006
ABSIS^2	−0.00016	0.00004	<0.001
cTTO current health			
Intercept	0.486	0.058	<0.001
Hypothetical controlled PV/PF health state cTTO utility	0.555	0.079	<0.001
Clinical and demographic characteristics of patients			
Having a caregiver	−0.131	0.065	0.042
Worst pain intensity VAS	−0.017	0.008	0.038
ABSIS	−0.0080	0.0035	0.023
ABSIS^2	0.00016	0.00004	<0.001

Unrestricted generalized least squares (GLS) estimates. R-squared: 0.387 for current health VAS, 0.244 for hypothetical cTTO and 0.492 for current health cTTO. Independent variables: *ABSIS*: score on Autoimmune Bullous Skin Disorder Intensity Score (0–206); *Age* = patient's age (years); *Having a caregiver*: no = 0; yes = 1; *Hypothetical controlled PV/PF health state cTTO utility:* cTTO utility for the hypothetical controlled PV/PF health state on a −1 to 1 scale; *Hypothetical uncontrolled PF health state*: no = 0, yes = 1; *Hypothetical uncontrolled PV health state*: no = 0, yes = 1; *Worst pain intensity VAS*: worst pain experienced in the past 3 months on a 0–10 visual analogue scale.
ABSIS, Autoimmune Bullous Skin Disorder Intensity Score; cTTO, composite time trade-off; PF, pemphigus foliaceus; PV, pemphigus vulgaris; VAS, visual analogue scale.

Our results are in accordance with earlier studies assessing HRQoL and its predictors in patients with pemphigus by using EQ-5D, SF-36, WHOQOL-BREF, DLQI and Skindex-29.[14,40–47] Moreover, having a caregiver was associated with lower utilities for current health. Pemphigus may not only adversely affect HRQoL of patients but also places a burden on caregivers. The European Academy of Dermatology and Venereology (EADV) quality of life task force advocates that the impact of a skin disease on family and caregivers should be measured as part of any thorough evaluation of the burden of a disease.[48]

Regarding the hypothetical health states, the mean cTTO utilities were 0.41 for uncontrolled PV, 0.52 for uncontrolled PF and 0.66 for controlled PV/PF. Utilities may be obtained from patients or the general population. Our results show that in case of the three hypothetical pemphigus health states, preferences of patients and the general public are not significantly different. This is in line with results of a meta-analysis of 22 TTO studies by Peeters *et al.*[49] who reported that when patients rated hypothetical health state descriptions, their values were, in fact, very similar to those obtained from non-patients (*P* > 0.05).

Utility values from our study can be used to estimate QALYs in cost-effectiveness models. The large differences in utilities between the uncontrolled and controlled health states suggest that the successful treatment of pemphigus may generate a significant QALY gain. In many countries including the United States, Canada and most European countries, health technology assessment (HTA) bodies require cost/QALY estimates for every new medication seeking reimbursement.[50–55] High-quality and timely evidence on cost-effectiveness may make a substantial impact on speeding up access to innovative medicines for patients in need.

A strength is that this study is the first to elicit health utility values directly from patients with pemphigus. Other strengths include the relatively large sample size in comparison with previous HRQoL studies in pemphigus,[13] especially in light of the rarity of the condition. The patient population was heterogeneous with regard to demographic as well as clinical characteristics, which satisfies the purpose of this valuation study. Our study had some limitations. First, patients were mostly well-controlled and just a few patients with severe symptoms entered the study. Secondly, disease activity was measured by only one instrument (ABSIS). Compared to the ABSIS, Pemphigus Disease Area Index indicated somewhat better measurement properties in patients with mild disease activity.[22] Thirdly, a total of 17.6% of cTTO responses were invalid or inconsistent which suggests that the cTTO task is challenging, despite supervision by a dermatologist.

In conclusion, our findings inform physicians, policymakers and funders about the overall extent of health loss in pemphigus. Health utilities for current and hypothetical health states confirmed that pemphigus is associated with a detrimental impact on patients' HRQoL. Given the recent availability of highly

effective therapy such as first-line rituximab, the assessment of pemphigus-related outcomes based on treatment is essential. Utility values from this study allow to quantify the burden of pemphigus in a way that is compatible with the medical and financial decision-making processes.

Acknowledgements

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Example for a utility assessment task for cTTO.
Appendix S2. Health state descriptions.