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ORIGINAL ARTICLE

Vitiligo Treatment Impact score (VITs): development and validation of a vitiligo burden of treatment questionnaire using the ComPaRe Vitiligo e-cohort

J. Shourick,[1,2] J. Seneschal,[3,4] N. Andreu,[3] J.-M. Meurant,[5] I. Pane,[6,7] P. Ravaud,[6,7] V.-T. Tran,[6,7] K. Ezzedine[1,2,*]

[1]Service de Dermatologie, AP-HP, Hôpital Henri-Mondor, Créteil, France
[2]EpiDermE - Epidemiology in Dermatology and Evaluation of Therapeutics, Université Paris-Est Créteil, Creteil, France
[3]Service de Dermatologie, Centre de Référence des Maladies Rares de la Peau, Hôpital Saint André, CHU de Bordeaux, Bordeaux, France
[4]INSERM, BMGIC, U1035, Univ. Bordeaux, Bordeaux, France
[5]Association Française du Vitiligo, Paris, France
[6]Centre de Recherche Épidémiologie et StatistiqueS (CRESS - Université de Paris, INSERM UMR1153), Paris, France
[7]Centre d'épidémiologie clinique - Hôpital Hôtel-Dieu (AP-HP), Paris, France
*Correspondence: K. Ezzedine. E-mail: khaled.ezzedine@aphp.fr

Abstract

Background Vitiligo management is challenging and requires long-term adherence of patients who often complain of the burden associated with treatment.

Objective To develop and validate a patient reported measurement of the burden of treatment in vitiligo.

Methods The study was nested within the ComPaRe Vitiligo e-cohort, an online e-cohort of vitiligo patients in France. Items were derived from a literature review and from the qualitative analysis of a survey using open-ended questions of 204 patients with Vitiligo. Construct validity of the resulting instrument was assessed by comparing the instrument's score to the Dermatology Life Quality Index (DLQI), Vitiligo Impact Patient score (VIPs) and Treatment Burden Questionnaire (TBQ) scores. Reliability was assessed by test-retest with 15 ± 10 days of interval between both assessments.

Results In total, 343 adult participants participated in the validation of the Vitiligo Treatment Impact score (VITs). The VITs is a 19-item questionnaire assessing the burden of treatment in patients with vitiligo with results suggesting four domains ('Finding a doctor', 'Phototherapy', 'Topical treatment' and 'Impact on outdoor activities and photoprotection'). The VITs total score was well correlated with the DLQI, VIP and TBQ scores. Agreement between test and retest was good (ICC 0.705, 95% CI 0.491–0.818).

Conclusions We developed a patient reported measurement of the burden of treatment in vitiligo with good psychometric properties.

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Conflicts of interest

None to declare.

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Introduction

Vitiligo is a chronic depigmenting skin disease with a prevalence estimated at 0.1%–2% of the world's population.[1] Vitiligo can have a devastating impact on quality of life and self-esteem and psychiatric comorbidities such as depression and anxiety have been frequently reported in patients with vitiligo.[2] Vitiligo treatment is challenging and often requires combination therapies including oral or topical immunosuppressant, with light treatment.[3–7] These treatments are often long, costly and only allow partial repigmentation. Thus, the burden of vitiligo depends not only on disease severity and extent but is equally linked to its daily management.[8]

Being a patient is more than simply taking pills: it also implies activities such as finding a doctor, applying topical treatments or

changing one's lifestyle.[9] Therefore, the burden of treatment is a concept aimed at considering the full scope of the workload imposed by healthcare on patients, and its effect on quality of life.[10] The burden of treatment assessment is crucial to adapt treatments regimen to each patients' daily life.[11] However, it is rarely discussed or addressed during consultations.[12] Ignoring the burden of treatment is a public health issue as it's not only detrimental to the patient's own health and wellbeing, but equally worsen the workload of patient's relatives and more generally leads to an ineffective use of healthcare resources.[13] Recently, the Treatment Burden Questionnaire (TBQ) was designed as the first non-disease or context specific treatment burden score.[14] However, items included in the TBQ might miss the specificities of skin conditions and their management such as light or topical treatments.

Our study took place in the framework of ComPare, an ongoing e-cohort project dedicated to chronic diseases. Patients registered in ComPaRe are encouraged to play an active role in research by participating in the scientific committees or by proposing ideas for research. This study was recommended by patient members of the scientific committee of the vitiligo e-cohort who specifically queried to evaluate the burden of treatment in vitiligo.

In this context, we aimed at developing and validating a patient reported measurement of the burden of treatment in Vitiligo patients.

Methodology

We used a multistep method to develop a questionnaire to measure the burden of treatment in patients with Vitiligo. This study was conducted and reported in accordance with the COSMIN recommendations.[15] The development and validation of the questionnaire was led by a multidisciplinary working group involving researchers, methodologists, dermatologists and patients. The study was nested in the ComPaRe (Community of Patients for Research) Vitiligo e-cohort, a cohort dedicated to Vitiligo within ComPaRe. Briefly, ComPaRe is an ongoing e-cohort of patients with chronic conditions (www.compare.aphp.fr) involving 42 000 patients as of December 2020. Participants in ComPaRe are adults (>18 years old) who report having at least one chronic condition. Patients join the project to donate time to accelerate research on their conditions by answering regular patient-reported outcomes and patient-reported experience instruments.[16] ComPaRe and this study were approved by the local ethics committees of the University Hospital Centres of Paris [reference number 0008367] and conducted according to the Declaration of Helsinki.

Step 1: Elaboration of the questionnaire

We conducted a literature search on PubMed to identify published questionnaires or scoring systems related both to vitiligo's burden/quality of life impact and burden of treatment in dermatology. We found no questionnaires devoted to measuring the burden of treatment in dermatology (including vitiligo). However, among vitiligo quality of life scales, several instruments included few items related to treatment burden. The vitiligo impact scale,[17] the vitiligo impact patient scale[18,19] and the vitiligo life quality index[20] included respectively 3, 5 and 1 burden of treatment items exploring the costs of treatment, dietary modification, clinician search, change of lifestyle and everyday life treatment management.

Second, we involved 204 patients with Vitiligo from the ComPaRe vitiligo cohort [mean age 47.7 (±13) years; 147 women (72.1%)] who answered an online survey with open-ended questions exploring different aspects of vitiligo and treatment burden identified during the literature review. Their responses were analysed by two researchers with an experience in qualitative studies and led to the identification of 24 themes related to the burden of treatment for Vitiligo.

Finally, the multidisciplinary working group designed a preliminary questionnaire from the themes identified. Each theme was transformed in a questionnaire through items evaluated with a 4-point Likert scale: 'Disagree' (1), 'Slightly agree' (2), 'Agree' (3), 'Strongly Agree' (4) and 'Not concerned' (0).[21] Each item was introduced by the sentence 'During the last month' to define a precise time frame and limit memory bias.[22] Readability was assessed with a SMOG index corrected for French. Result was considered excellent (SMOG = 6.35).[23,24]

Step 2: Measurement properties of the questionnaire

The measurement properties of the questionnaire were assessed in six steps with a second sample of patients recruited in ComPaRe vitiligo. The steps involved: (i) reduction of the number of items, (ii) subscale repartition of items and assessment of factorial validity, (iii) assessment of construct validity, (iv) evaluation of the smallest detectable change (SDC) and the patient acceptable symptom state (PASS) for the questionnaire and (v) reliability.

Reduction of the number of items We reduced the number of items based on redundancy, which was suspected when the inter-item correlation evaluated by Spearman correlation coefficient was above 0.8.[25] Because we wanted our instrument to be able to capture all aspects of treatment burden in all patients and because some highly contextual items were dependant on the treatment regimen taken by the patient, we chose not to drop items based on floor effect or low inter-item correlation.

Subscale repartition of items and assessment of factorial validity We performed an exploratory factor analysis (EFA) using a promax rotation (using Thurstone criterium and assuming a positive interdimensional correlation) and polychoric correlations.[26,27] We assessed suitability of the dataset for factorial validity using a Kaiser-Meyer-Olkin (KMO) setting the

minimum score for each item at 0.7 (good).[28,29] We used scree plots with parallel analysis to visualise the best number of subscales keeping dimension with Eigen value of the original data greater than simulated values.[30] Items presenting a low factor loading (lower than 0.4) and a high cross factor loading (higher than 0.2) were excluded from the questionnaire.[25] The internal consistency of the questionnaire and its subscales was tested using Cronbach's alpha and McDonald's Omega coefficients, with Scores >0.7 generally indicating good homogeneity.[31,32]

Construct validity We hypothesised several relationships between the burden of treatment of vitiligo and other constructs. Specifically, a moderate correlation with the Dermatology Life Quality Index (DLQI) and the Vitiligo Impact Patient score (VIPs; r = 0.5–0.7) as quality of life related to the disease is only partially related to treatment burden.[33] Second, we expected a low correlation (r = 0–0.3) with the TBQ, because vitiligo's specific burden of treatment may represent a large subpart of the patients' total burden. Finally, we expected a low correlation with the Self Assessment Vitiligo Extent Score (SA-VES) considering the gap between objective and subjective assessment of disease severity and treatment needs in vitiligo.[34] The effect on the global score of being currently treated, currently receiving light treatment, having friction area involvement and having repigmentation thanks to treatment was assessed using Wilcoxon's test.

We also investigated if responses to the score could indicate different patterns of burden of treatment. To that end, we identified homogenous groups of patients depending on the similarity of their answers by using an ascendant hierarchical clustering with a Ward Method and Gower's distance.[35,36] The number of clusters was determined using the majority rule from a set of 30 indices.[37] We then compared the global score and each subscale score between the groups using Wilcoxon or Kruskal-Wallis test.

Evaluation of the SDC and of the PASS The SDC represents the smallest change that the instrument can detect reliably in a questionnaire and was determined using the standard error of the mean (SEM) method, determining the SDC to be $1.96*\sqrt{2}*SEM$.[38] The PASS is 'the highest level of symptom beyond which patients consider themselves well'.[39] It was determined with the following anchor question 'Thinking of all the things you do to take care of your vitiligo, do you think you could continue to invest the same amount of time, energy and money in caring for your vitiligo throughout your life?' with a yes/no answer. We used the anchor question as the independent variable and the global score of the vitiligo burden questionnaire as the dependent variable to produce a ROC to find the best cut-off point for the PASS.[40]

Reliability Participants answered the questionnaire twice with a 2-week interval, to perform a test-retest. Reliability between the two assessments was measured by the intraclass correlation coefficient ICC for agreement.[41] Agreement was represented by Bland and Altman plots.[42]

All data were analysed using R software version 3.4.4 for Windows. Significance was set for value <0.05.

Step 3: Online calculator

To ease the use of our questionnaire, we developed an online calculator determining the global score and each subscale score.[43]

Results

From October 2019 to February 2020, 343 patients from the ComPaRe vitiligo cohort were involved in the assessment of the measurement properties of the questionnaire. Their mean age was 46.5 years (±12.2); 257 were women (74.9%; Table 1). The mean duration of disease was 20.1 (±13.5) years. Fitzpatrick skin phototype was fair (phototype I-II-III) in 245 (71.4%) participants. From these patients, 78 (22.7%) were currently under treatment.

Reduction of the number of items

Inter-item correlation (Fig. S1, Supporting Information) allowed us to eliminate four items because of redundancy (Applying creams every day reminds me of my vitiligo, The times and rhythm of the phototherapy sessions are not

Table 1 Socio-demographic and clinical characteristics of patients included in the validation step.

	Absolute number or Mean (Percent or Standard deviation)
Sex	
Man	257 (74.9%)
Woman	86 (25.1%)
Age	46.5 (12.2 sd)
Duration of disease	20.1 (13.5 sd)
Phototype	
I–II	59 (17.3%)
III–IV	275 (80.6%)
V–VI	7 (2.1%)
Vitiligo type	
Acrofacial	116 (33.8%)
Generalized	217 (63.3%)
Segmental	10 (2.9%)
Friction area involvement	240 (73.8%)
Currently treated	78 (22.7%)
Phototherapy	36 (10.5%)
Repigmentation	
After sun exposure	53 (16.2%)
After treatment	69 (21.1%)
None	159 (48.6%)
Spontaneously	46 (14.1%)

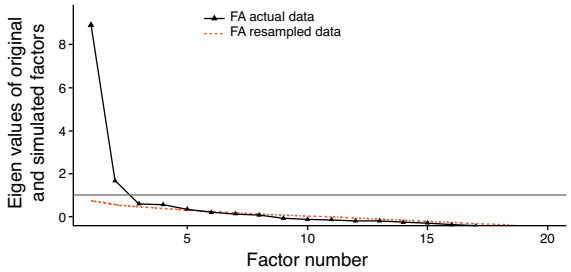

Figure 1 Scree plots representing Eigen value for each factor in the dataset and the simulated dataset. The number of dimensions (subscales) in the dataset is indicated by the number of dimensions with eigenvalue of the actual data greater than resampled data.

compatible with my daily activity, The treatments imposed by my vitiligo prevent me from certain hobbies or sports, The treatments have negative consequences on my social life).

Subscale repartition of items and assessment of factorial validity

All KMO scores were above 0.7. The scree plot determined four pertinent dimensions (Fig. 1). These were related to: 'Finding a Doctor' (three items), 'Topical treatments' (six items), 'Light treatment' (three items) and 'Impact on outdoor activities and photoprotection' (seven items). One item was eliminated due to both low factor loading and high cross factor loading (Not understanding the value of treatment disturbs me). Our final questionnaire therefore included 19-items (Table 2).

Table 2 Exploratory factor analysis with standardized regression coefficients from the final rotated factor pattern.

Question		Outdoor activities and photoprotection	Topical treatment	Light Therapy	Find a Doctor
Q1	Having a first appointment with a vitiligo specialist was not easy	0.115	0.07	-0.11	0.732
Q2	Finding a phototherapy cabin is very frustrating	-0.17	0.004	0.414	0.584
Q3	Getting a follow-up appointment is complicated	-0.026	-0.041	-0.152	1.112
Q4	Applying cream / ointment every day is difficult	-0.269	1.07	-0.019	0.008
Q5	Carrying out treatment without guarantee of success is frustrating	-0.001	0.672	0.182	0.065
Q6	I spend a lot of time applying creams / ointments	0.106	0.767	-0.062	0.03
Q7	Applying creams every day reminds me of my vitiligo	Redundant item			
Q8	I have a problem with applying creams under makeup	0.372	0.544	-0.083	-0.118
Q9	The time spent doing phototherapy sessions demotivates me	-0.149	0.069	0.862	0.046
Q10	The times and rhythm of the phototherapy sessions are not compatible with my daily activity	Redundant item			
Q11	The side effects of phototherapy scare me	0.077	0.032	0.831	-0.171
Q12	Phototherapy increases the contrast between normal skin and skin with vitiligo	-0.039	-0.116	1.06	-0.074
Q13	Finding the balance between sun exposure for re-pigmentation and sun protection is difficult	0.627	0.109	-0.057	0.015
Q14	Systematically having to protect myself from the sun (sunscreens, wearing long sleeves) is an annoyance	0.997	-0.209	-0.195	-0.011
Q15	The cost of non-reimbursed treatments (creams and phototherapy) demotivates me	0.522	-0.029	0.233	0.186
Q16	I deprive myself to protect myself from the sun with sunscreens	0.881	-0.143	-0.009	-0.014
Q17	Makeup and self-tanners are expensive	0.602	-0.02	0.122	-0.027
Q18	The treatments imposed by my vitiligo prevent me from having a normal vacation	0.733	0.156	-0.034	-0.018
Q19	The treatments imposed by my vitiligo prevent me from certain hobbies or sports	Redundant item			
Q20	Avoiding friction limits some of my daily activities (sport, shower, makeup for example)	0.687	0.056243	0.075	0.027
Q21	The creams necessary for the management of my vitiligo affect my sexuality and / or that of my partner	0.307	0.448	0.008	0.009
Q22	The consequences of the treatments on my physical appearance stress me out	0.259	0.539	0.064	0.019
Q23	The treatments have negative consequences on my social life	Redundant item			
Q24	Not understanding the value of treatments disturbs me	0.356	0.054	0.316	0.078

Cronbach's alpha coefficient reached 0.93 and McDonalds' Omega 0.9 [0.882, 0.915] for the entire questionnaire, reflecting its excellent internal coherence. All subscales presented a score above 0.7 for both indices.

Construct validity

The 19-item questionnaire correlated moderately with the DLQI 0.593 [0.511, 0.665], and the VIPs 0.587 [0.495, 0.666] and poorly with the SA-VES 0.161 [0.056, 0.263] and the TBQ 0.242 [0.14, 0.34] (Table 3, Fig. S2, Supporting Information). Total scores were significantly different between patients (i) currently receiving treatment vs. those not receiving any treatment (51.9 ± 19.5 vs. 38.6 ± 26, $P < 0.001$); (ii) currently receiving light therapy vs. those not receiving light treatment (61.4 ± 15.9 vs. 39.3 ± 25.1, $P < 0.001$); (iii) having vs. not having friction area involvement(36.2 ± 26 sd vs. 3.8 ± 25, $P = 0.013$) and (iv) having repigmented vs. not having repigmented following treatment (39.5 ± 26.2 vs. 49.9 ± 19.1 $P < 0.001$) (Table S1, Supporting Information).

Our hierarchical clustering divided the patients in two clusters, one with 146 patients and a mean total score of 59.9 (± 19.5) and one with 197 patients and a mean total score of 28.1 (±20). Comparison between these two groups for total score and each subscales scores were significantly different ($P < 0.001$). These findings confirmed that the total score reflected well the different response pattern.

Table 3 Convergent validity.

	Correlation	*P* value
DLQI		
Find a doctor	0.433 [0.33, 0.525]	<0.001
Topical treatment	0.514 [0.42, 0.596]	<0.001
Light therapy	0.357 [0.249, 0.457]	<0.001
Outdoor activities and photoprotection	0.594 [0.512, 0.666]	<0.001
Total score	0.594 [0.511, 0.665]	<0.001
VIP		
Find a doctor	0.359 [0.241, 0.467]	<0.001
Topical treatment	0.556 [0.46, 0.639]	<0.001
Light therapy	0.387 [0.271, 0.491]	<0.001
Outdoor activities and photoprotection	0.598 [0.509, 0.675]	<0.001
Total score	0.587 [0.496, 0.666]	<0.001
SAVES		
Find a doctor	0.018 [−0.088, 0.124]	0.733
Topical treatment	0.092 [−0.014, 0.196]	0.179
Light therapy	0.219 [0.116, 0.317]	<0.001
Outdoor activities and photoprotection	0.199 [0.095, 0.298]	<0.001
Total score	0.162 [0.057, 0.263]	0.008
TBQ		
Find a doctor	0.187 [0.082, 0.287]	0.001
Topical treatment	0.229 [0.126, 0.327]	<0.001
Light therapy	0.187 [0.083, 0.288]	0.001
Outdoor activities and photoprotection	0.18 [0.076, 0.281]	0.001
Total score	0.242 [0.14, 0.34]	<0.001

Correlation of DLQI, VIPs and SAVES correlate with each of the dimension subscale and to the total Vitiligo Impact treatment score.

Evaluation of the SDC and the PASS

The SDC was 10.6% and the PASS was 48.6% (Fig. S3, Supporting Information).

Reliability

The test-retest analysis was conducted on 151 patients. Reliability was good, with an ICC for agreement of 0.705, (95% CI, 0.49–0.82]. The Bland and Altman diagram is presented in Fig. 2.

Step 3: Online calculator

Our application is available at https://alden-score-calculator.shinyapps.io/Vitiligo_Burden/. To simplify interpretation of our results, we expressed the score and subscales on a 0%–100% scale in our application.

Discussion

In this study, we developed and validated a new patient reported instrument, the Vitiligo Impact Treatment score (VITs), that assesses the treatment burden of vitiligo. Our tool showed goodpsychometric and face validity. Our instrument complements existing measures of dermatologic quality of life such as the DLQI and VIPs by addressing the gap in evaluating the burden of dermatological care. Indeed, until today, there was no specifically developed dermatologic TBQ despite that these treatments are highly specific and include time-consuming light and topical therapies. In fact, the burden of treatment in dermatology is not specific to Vitiligo. Other chronic inflammatory skin diseases such as acne, psoriasis or atopic dermatitis require daily management of their care from the patients perspective over the long term, with difficulties to find reliable health care providers and sources of information.[44] In addition, dermatological treatments require a good adherence to treatment to enhance efficacy. Yet, burden of treatment can strongly affect adherence.[45] In particular, it may lead to 'rationalised non-adherence'.[13] Rationalised non-adherence refer to patients' perceiving that treatment benefits as lower than treatment burden and stopping some of their treatments. Because they know they should do differently, they may actively hide their non-adherence to caregivers.[46–48] Therefore, assessing the burden of treatment is crucial to both evaluate and improve adherence of patients. Future studies could explore how our patient reported instrument could be generalised to other chronic inflammatory skin diseases. Burden of treatment was defined as part of the core outcome set for vitiligo. Therefore our score fulfils an unmet need in vitiligo's clinical research.[49] Furthermore it could also help in developing clinical practice guidelines that are patient-centered. In addition, it could be used in clinical practice as a

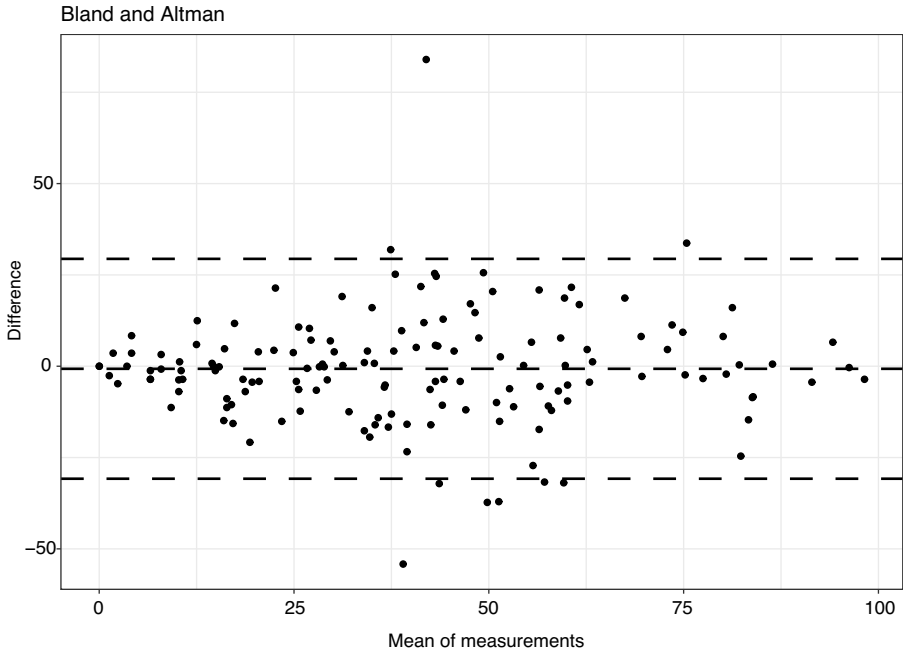

Figure 2 Bland and Altman graph for differences between test and retest total Vitiligo Impact Treatment score by their mean.

validated global score, that is, easy to calculate to identify patients overwhelmed by their treatment. For this purpose, we demonstrated that patients with a VITs score above 48.5 (the PASS) were at risk of being overwhelmed by treatment burden. Physicians managing these patients should reconsider treatment decisions to better fit their patients' goals and preferences. The ultimate aim would be to help physician and patient initiating and facilitating shared decision-making that can lower the burden of treatment in vitiligo patients.

The main limitation of our study is that it was conducted only in France. Thus, our results may not be generalisable to other cultural contexts. In particular, the French health system reimburses most of the treatments used in vitiligo, including phototherapy, which may have lowered the burden of treatment of patients in this study.

In conclusion, we have herein developed and validated a dermatologic specific burden score that we called VITs. This score was tested in a large vitiligo population and PASS was calculated and defined to help identifying patients overwhelmed by the treatment. This questionnaire will be of use to develop a patient-centred approach of vitiligo management involving the personalised adaptation of treatment regimens to find the best balance between treatment benefit and burden.

Data availability statement

Data is available on request, of note all data request will have to go through evaluation by Compare's scientific committee.

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Supporting information

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

Figure S1. Correlation matrix representing inter-items polychoric correlations

Figure S2. Dot Plot with regression lines for vitiligo total impact score and DLQI (dermatology life quality index), TBQ (Treatment burden questionnaire), SAVES (self assessment vitiligo extension scale) and VIP (vitiligo impact scale).

Figure S3. Cumulative distribution function of the total Vitiligo Impact Treatment score according to the yes or no answer of the patient to the anchor question) 'Thinking of all the things you do to take care of your vitiligo, do you think you could continue to invest the same amount of time, energy and money in caring for your vitiligo throughout your life?').

Table S1. Comparison of means of the total Vitiligo Treatment Impact score according to the presence or absence of friction areas involvement, current or past phototherapy, current treatment and repigmentation following treatment.