

Measurement of patient-relevant benefits in the treatment of chronic hand eczema – a novel approach

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Background: The assessment of patient-relevant treatment benefit gains importance in treatment evaluation. The 'Patient Benefit Index' (PBI) is a validated instrument for the assessment of such benefits in patients with skin diseases. Patients rate the importance of specific treatment needs before treatment and benefits achieved after treatment. To date, no specific instrument for chronic hand eczema (CHE) has been published.

Objectives: Development and validation of a specific PBI for treatment evaluation in patients with CHE.

Methods: Items reflecting disease burden and treatment needs were collected in 20 patients with CHE. Relevant items were selected by an expert panel of dermatologists, psychologists, and patients. The resulting 'Patient Benefit Index for chronic hand eczema' (PBI-HE) was validated in an open label treatment study with alitretinoin in $n = 249$ patients.

Results: Cronbach's alpha was 0.93. High convergent validity was demonstrated for clinical improvement and treatment success (Spearman $r = 0.60$ – 0.78 , $P < 0.001$); 84.3% of patients reached a $\text{PBI} \geq 1$, indicating more than minimum patient-relevant benefit of alitretinoin. Feasibility was high, with a rate of missing data $< 1\%$.

Conclusions: The PBI-HE is a feasible, reliable, and valid instrument for the assessment of patient-relevant treatment benefits in CHE.

Key words: chronic hand eczema; outcomes research; patient-reported outcomes; patient benefit index; quality of life; questionnaire. © John Wiley & Sons A/S, 2009.

Conflicts of interest: M.A. is the licence holder of the PBI and has received consultancy fees from Basilea. C.B. and S.J.R. are members of the working group led by M.A. J.M. is an employee of Basilea Pharmaceutica International Ltd, Basel, Switzerland. Basilea was the sponsor of study protocol NCT00309621. The study was registered at the ClinicalTrials.gov study registry. Basilea funded the development of the PBI-HE and the assessment of PBI data. There were no restrictions given by Basilea with respect to the development and validation of the PBI. T.D. was the principal investigator for the study protocol NCT00309621 and has received lecture and consultancy fees from Basilea.

Accepted for publication 1 February 2009

Background

Chronic hand eczema (CHE) is a distressing disease with major impact on occupation and work ability as well as private and social functioning (1, 2). Highly relevant reductions in quality of life (QoL) have been reported. If mild cases are included, the 1-year prevalence of hand eczema is estimated to be up to 10% in the general population (3, 4).

Management of CHE is complex and includes sound diagnostic, therapeutic and preventive measures (5). For patients with severe CHE, standard treatments such as corticosteroids yield mostly unsatisfactory results. The use of conventional systemic immunosuppressants like ciclosporin is limited by contraindications and side-effects (6). Recently, oral alitretinoin has been

licensed for the treatment of severe CHE. Results from the clinical development programme indicate efficacy rates of up to 48%, as determined by Physicians Global Assessment (PGA) of clear or almost clear hands, and a tolerability profile consistent with that of the retinoid substance class (6). However, for the lack of specific instruments, there are no more data available regarding patient-relevant benefits in the treatment of hand eczema with alitretinoin or any other drug.

Patient-relevant benefit assessment gains importance in evaluating therapies. Proof of therapeutic benefit of drugs is demanded for cost reimbursement in 15 countries recently studied (7) including Australia, Canada, France, and Great Britain. In Germany, the current regulation explicitly states that patient benefit has to be assessed primarily from the patient's perspective (8, 9). Moreover, it was found that physicians' and patients' perceptions of treatment needs differ considerably (10). Thus, patient-relevant benefit of treatments can only be judged by the patients themselves.

To date, patient-relevant benefit is usually measured by change in QoL. These questionnaires, however, neglect differences in importance of treatment needs within and between patients and do not allow for a weighing of benefits according to the patients' preferences.

Recently, a method was developed that allows patients to select and rate the importance of treatment needs and weighs the achieved benefits according to these individual needs. This 'Patient Benefit Index for Skin Diseases' (PBI-S) therefore provides a method for the assessment of patient-relevant benefit in conformity with the legal requirements. The PBI has been validated in various skin diseases (11). In addition, PBI versions for specific diseases have been developed, such as for patients with vitiligo (12) or chronic wounds (unpublished data).

In this article, the development and validation of a specific PBI for patients with CHE is presented.

Objectives

Development and validation of an instrument for assessing patient-relevant treatment benefit in patients with CHE.

Methods

Generation of need and benefit items and development of the questionnaire

The methods for instrument development followed common international standards of psychometric and biometric test development (13–17).

20 patients with CHE were recruited consecutively from two dermatology practices and at the

Department of Dermatology, University Clinics of Hamburg. The patients completed an open questionnaire asking for (i) disease burdens and impairments because of CHE and (ii) individually important treatment needs.

A panel of three dermatologists, one psychologist, one methodologist (all from the department of dermatology, University Clinics, Hamburg), and two patients with severe hand eczema under treatment with topical steroids discussed these items and compared them with those included in the PBI-S. It was decided to add CHE-specific need and benefit items to the item list of the validated standard version of the PBI (11).

Structure of the questionnaire

The PBI-HE, just as the standard version PBI-S, consists of two questionnaires.

- (1) The 'Patient Needs Questionnaire' (PNQ) is filled in by the patients before therapy. It contains 27 standardized items on the patient's needs (treatment objectives) such as 'to no longer experience itching' and 'to be able to lead a normal everyday life'. Patients rate the importance of each need on a 5-step Likert scale ranging from 0 = 'not at all important' to 4 = 'very important'.
- (2) The 'Patient Benefit Questionnaire' (PBQ) is filled in by the patients during or after therapy. It consists of the same items as the PNQ, but the instruction differs: patients rate the extent to which the treatment needs have been fulfilled by therapy on a Likert scale ranging from 0 = 'treatment didn't help at all' to 4 = 'treatment helped a lot'.

An item not applicable to a patient is checked as 'does not apply to me' in the PNQ and 'did not apply to me' in the PBQ. These items are considered irrelevant for further procedure.

Computation of the PBI

The PBI is calculated from the importance of needs before therapy (rated in the PNQ) and the achievement of these needs (rated in the PBQ) according to the following algorithm: each importance rating of a treatment need is divided by the sum of all importance ratings of a patient to obtain relative importance weights. To calculate the PBI, each benefit rating is multiplied by the respective relative importance rating and the products are summed. The PBI ranges from 0 (no benefit) to 4 (maximal benefit).

Validation

The instrument was validated in an open label study on the safety and efficacy of oral alitretinoin in 249 patients with severe hand eczema lasting at least 6 months since initial diagnosis and refractory to standard therapy including topical corticosteroids. Patients received 24 weeks of treatment with 30 mg oral alitretinoin daily and filled in the PNQ before and the PBQ after therapy.

As recommended by the German National Guideline on QoL Assessment in Dermatology (18), the following characteristics of the patient benefit index for chronic hand eczema (PBI-HE) were examined:

- (1) Distributional characteristics (frequencies, means, and standard deviations of items and total score).
- (2) Amount of missing values.
- (3) Reliability (Cronbach's alpha of PNQ).
- (4) Convergent validity: Spearman correlations between PBI and following criteria:
 - Clinical severity: patient's Global Assessment (1 = 'clear or almost clear' to 6 = 'worsening')
 - Clinical severity: Physician's Global Assessment (PGA) (1 = 'clear' to 6 = 'severe disease')
 - Treatment success as rated by the patient, regarding:
 - physical well-being
 - mental well-being
 - capabilities at work and in daily life
 - social contacts
 - leisure time activities
 - general QoL (1 = 'not at all successful' to 5 = 'very successful').
 - Symptoms [modified total lesion symptom score (mTLSS); sum of physician's ratings of seven symptoms: erythema, scaling, lichenification/hyperkeratosis, vesiculation, oedema, fissures, pruritus/pain; 0 = 'none' to 3 = 'severe'; corresponding to a sum score ranging from 0 to 21].
 - Pain (rated by the patient on a 10-cm visual analogue scale with end-points of 0 = 'no pain' and 10 = 'most intense pain imaginable').
 - Pruritus (rated by the patient on a 10-cm visual analogue scale with end-points of 0 = 'no pruritus', 10 = 'most intense pruritus imaginable').

To control for pretreatment differences in 'symptoms', 'pain', and 'pruritus', linear regression analyses of respective pretherapy values on post-therapy values were performed, and the rank values of the resulting unstandardized residuals

were used as criterion variables. For physician's global assessment of severity of disease, statistical control was not necessary because 'severe' CHE was an inclusion criterion.

Missing on-treatment data in physician's global assessment of severity of disease, symptoms, pain, and pruritus were imputed using the Last Observation Carried Forward method.

Statistical analysis

Results of the clinical study were obtained with SAS[®] version 8.1 and higher. Validation analyses were performed with SPSS[®], version 15.0 for Windows.

Ethics

For the non-interventional item collection survey, no ethics approval was necessary. In the validation study, only preexisting anonymized data were used. Thus, no ethics approval was necessary. Approval from the local ethics committee had been obtained for the open label study on alitretinoin treatment.

Results

Item selection

From a total of 65 benefit items collected in the open survey, 18 non-redundant items were taken into consideration. Sixteen of these items were part of the standard version of the PBI. Accordingly, two items not covered in the PBI-S were added to the questionnaire: 'to not need gloves in everyday life and at work anymore' and 'to be able to touch other people'. One item of the PBI-S was changed from 'to be healed of all skin alterations' into 'to achieve improvement of the skin alterations'. Two items were excluded because the patients considered them to be not relevant ('to have no fear that the disease will become worse' and 'to be able to have a normal sex life'). The resulting 'PBI for patients with CHE' (PBI-HE) contained a total of 23 non-redundant and relevant items covering both disease-specific and dermatology-generic need and benefit items in CHE.

Patient characteristics

The sample included 249 patients with CHE aged 18–75 years (mean 48.1). 47.0% of the patients were female. A hyperkeratotic eczema was diagnosed in 227 patients (91.2%), a pompholyx in 54 (21.7%), a fingertip eczema in 80 (32.1%), and 41 patients had other types of CHE. At enrolment, patients had a median duration of diagnosis of

5.1 years and the present episode had lasted for a median of 5.3 months.

The PNQ was completed by 245 patients and 228 completed the PBQ. Both PNQ and PBQ were completed by 225 patients. For these, the PBI was computed.

Clinical results are published elsewhere (1). In sum, alitretinoin was highly effective in 48% of the patients as demonstrated by PGA ratings of 'clear' or 'almost clear' hands at the end of the treatment period (primary study end-point).

Distributional characteristics of the PBI

When applying a threshold of minimal benefit of 1 (2), it is found that 84.3% of the patients had achieved at least minimal benefit from alitretinoin (Fig. 1). In a relatively high proportion of patients (14.1%), the personal treatment needs were completely fulfilled, and thus they achieved the upper bound of the PBI (4.0).

Judging from the histogram shown in Fig. 1, there seem to be three subgroups of patients: those who achieve no relevant benefit ($PBI < 1$), those with moderate benefit ($PBI = 1\text{--}2.2$) (both with a right-skewed distribution), and those with high benefit ($PBI > 2.4$) and a left-skewed distribution.

Patient-defined needs (PNQ) and benefits (PBQ)

All but 4 of the 23 items were rated as 'quite' or 'very important' by at least 50% of the patients, indicating that there is a wide range of patient-relevant treatment needs in CHE (Table 1). Most

importantly, patients wanted to have their skin lesions improved, have confidence in therapy, and get rid of itching (all quite or very important to $> 90\%$ of the patients). The fourth most important need was to find a clear diagnosis and therapy (88.1%). Treatment needs of relatively low importance ($< 50\%$) were reduction of social impairments regarding relatives, friends, and others, and to feel less depressed.

After alitretinoin therapy, all treatment needs had been achieved by at least 57% of the patients to whom the respective objective had been applicable (patients who did not check 'does not apply to me') (Table 2). The need best achieved by alitretinoin treatment was 'to be able to lead a normal daily life' (74.1%). 8 of the 10 aims best achieved were among the 10 needs that were most important to the patients.

Missing values

The mean rate of missing values was 0.44% for the 23 need items and 0.95% for the benefit items. Missing values were evenly spread among the items with no more than 2.2% in any of them (Tables 1 and 2).

Reliability

The internal consistency of the PNQ (Cronbach's $\alpha = 0.93$) was considerably high.

Construct validity

Correlations between the PBI-HE and therapy success indicators were high ($r = 0.60\text{--}0.78$) and highly significant ($P < 0.001$; Fig. 2).

Of the clinical improvement measures (upper five bars in Fig. 2), overall symptom reduction (mTLSS) correlated highest with the PBI ($r = 0.70$). Pain and pruritus reduction, representing two single parts of the overall symptom pattern, correlated highly with the PBI-HE ($r = 0.60$ for pain and $r = 0.63$ for pruritus).

Among the domains of treatment success ratings (lower five bars), physical well-being and general QoL correlated highest with the PBI ($r = 0.78$). High correlations were also found in the other domains work/daily life, mental well-being, leisure time activities, and social contacts ($r = 0.70\text{--}0.74$).

Discussion

The assessment of patient-relevant benefits with the PBI is a novel approach in the treatment of CHE as well as in dermatology in general.

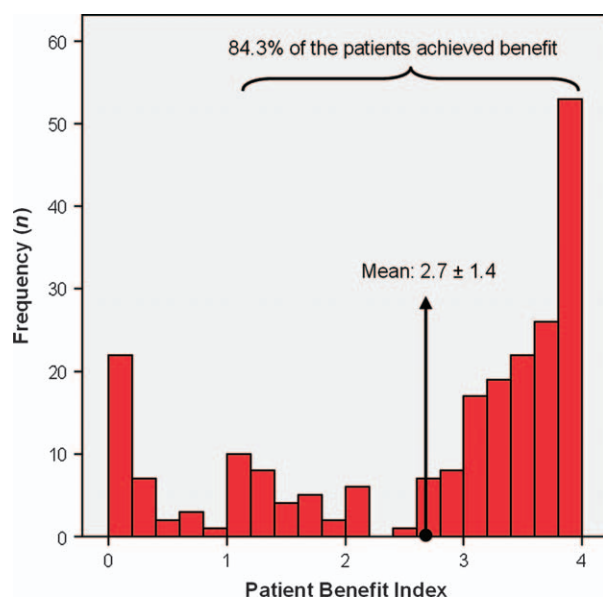
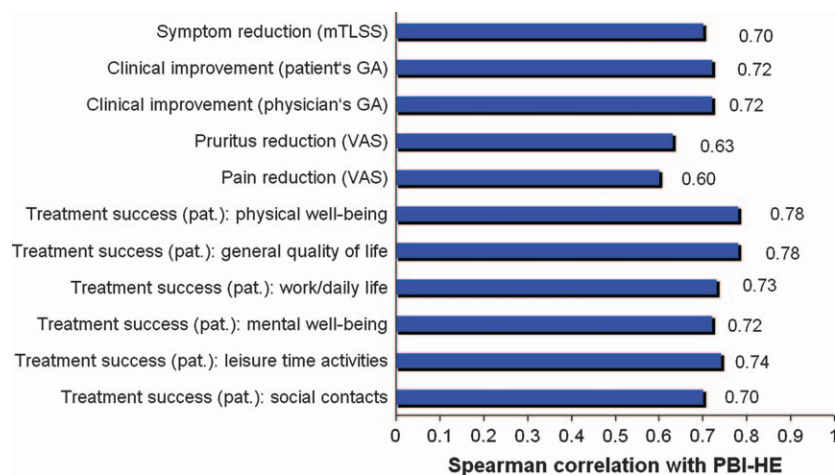


Fig. 1. Frequency distribution of the Patient Benefit Index for chronic hand eczema (PBI-HE), $n = 225$; threshold of minimal clinical benefit: $PBI = 1$.

Fig. 2. Spearman correlations of Patient Benefit Index for chronic hand eczema and validation criteria (all $P < 0.001$; $n = 210$ –223); modified total lesion symptom score, Patient's Global Assessment (GA), and physician's GA: statistically controlled for pretreatment values. Pat., patient; VAS, visual analogue scale.



Especially innovative is the combination of importance ratings of patient needs with achieved benefits in the respective domains to get a single weighted index of treatment benefit.

The object of this study was to develop a PBI version specific for use in CHE patients and to test it for feasibility, reliability, and validity. The methodological procedures followed international standards of test development (1–5) and guideline-based QoL assessment (6). The generation of items from the results of the open survey on patient needs by a 7 person-expert panel corre-

sponds with these international standards. Although it cannot be ruled out that a different expert panel would not have come to identical results, patient participation compensated for a 'professional bias' in the expert panel.

The PBI-HE was found to be highly reliable. It was valid with regard to a wide range of validation criteria including clinical improvement and treatment success ratings by patients and physicians. As the PBI is the first instrument to measure patient-relevant benefit, there is no ideal validation criterion, and both clinical improvement and

Table 1. Patient needs questionnaire: importance of treatment needs (PNQ) in patients with chronic hand eczema^a

Item no.	Patient needs	Mean ^b	SD ^b	Applies to me (%)	Does not apply to me (%)	Quite or very important (%)	n
4	Get an improvement of the skin lesions	3.8	0.5	99.6	0.4	96.3	244
23	Have confidence in the therapy	3.8	0.6	99.2	0.8	95.1	244
2	Be free of itching	3.7	0.7	97.1	2.9	92.2	245
22	Find a clear diagnosis and therapy	3.7	0.9	96.7	3.3	88.1	244
3	No longer have a burning sensation on the skin	3.7	0.8	90.5	9.5	85.5	242
1	Be pain-free	3.5	1.0	94.3	5.7	82.9	245
18	Require less doctor and clinic appointments	3.4	1.0	94.3	5.7	81.2	245
19	Need less time for daily treatment	3.4	1.0	93.9	6.1	79.6	245
8	Be able to lead a normal daily life	3.5	0.9	88.1	11.9	77.0	244
20	Have lower personal treatment costs	3.3	1.2	90.2	9.8	73.0	244
21	Experience fewer side-effects	3.4	1.1	86.4	13.6	72.4	243
13	Lead a professional and daily life without wearing gloves	3.5	1.0	82.9	17.1	72.2	245
9	Be more capable in daily life	3.3	1.1	80.3	19.7	66.8	244
11	Be able to participate in normal leisure time activities	3.3	1.2	83.1	16.9	65.4	243
16	Be able to touch others	3.2	1.2	82.4	17.6	65.2	244
12	Be able to lead a normal working life	3.5	1.0	73.6	26.4	64.9	242
7	Experience a greater enjoyment of life	3.1	1.3	76.3	23.7	57.6	245
15	Want to show yourself more in public	2.8	1.4	74.7	25.3	53.1	245
5	Be able to sleep better	3.0	1.4	70.1	29.9	51.5	241
10	Be less of a burden to relatives and friends	2.9	1.4	66.8	33.2	47.5	244
17	Be less burdened in your partnership	2.9	1.4	69.4	30.6	47.3	245
14	Be able to have more contact with other people	2.7	1.5	67.3	32.7	44.1	245
6	Feel less depressed	2.7	1.5	68.2	31.8	41.3	242

^aItem range: 0 = not at all, 1 = somewhat, 2 = moderately, 3 = quite, 4 = very important.

^bMean and SD refer to those patients who did not check 'does not apply to me'.

Table 2. Patient Benefit Questionnaire: treatment benefits achieved in patients with chronic hand eczema after alitretinoin treatment^a

Item no.	Treatment benefit	Mean ^b	SD ^b	Applied to me (%)	Did not apply to me (%)	Treatment quite or very helpful (%) ^b	n
8	Be able to lead a normal daily life	2.9	1.4	81.5	18.5	74.1	227
1	Be pain-free	3.0	1.4	89.9	10.1	73.5	227
23	Have confidence in the therapy	3.0	1.5	97.8	2.2	72.9	226
2	Be free of itching	2.8	1.5	93.8	6.2	70.4	227
3	No longer have a burning sensation on the skin	2.9	1.5	86.7	13.3	70.4	226
9	Be more capable in daily life	2.7	1.6	77.9	22.1	69.3	226
4	Get an improvement of the skin lesions	2.9	1.5	99.1	0.9	69.2	226
20	Have lower personal treatment costs	2.8	1.5	82.1	17.9	67.9	224
11	Be able to participate in normal leisure time activities	2.7	1.5	77.5	22.5	67.6	227
19	Need less time for daily treatment	2.8	1.5	91.6	8.4	67.1	226
16	Be able to touch others	2.7	1.6	81.1	18.9	66.8	227
18	Require less doctor and clinic appointments	2.7	1.6	85.7	14.3	66.5	223
22	Find a clear diagnosis and therapy	2.7	1.6	93.3	6.7	65.9	223
21	Experience fewer side-effects	2.6	1.6	77.9	22.1	64.2	226
12	Be able to lead a normal working life	2.6	1.6	68.3	31.7	64.1	224
17	Be less burdened in your partnership	2.5	1.6	61.7	38.3	63.6	227
15	Want to show yourself more in public	2.6	1.6	69.0	31.0	63.5	226
10	Be less of a burden to relatives and friends	2.5	1.6	66.4	33.6	62.7	226
7	Experience a greater enjoyment of life	2.5	1.6	74.7	25.3	61.9	225
14	Be able to have more contact with other people	2.5	1.6	67.7	32.3	60.1	226
13	Lead a professional and daily life without wearing gloves	2.5	1.7	79.7	20.3	58.0	227
6	Feel less depressed	2.3	1.6	60.4	39.6	57.4	225
5	Be able to sleep better	2.4	1.6	63.0	37.0	57.3	227

^aItem range 0 = not at all, 1 = somewhat, 2 = moderately, 3 = quite, 4 = very helpful.

^bMean, SD, and 'quite or very helpful' refer to those patients who did not check 'did not apply to me'.

success ratings are surrogate parameters. Therefore, content validity was of particular importance in the development of the PBI. By valuing the results of an open survey involving 20 patients with CHE and a systematic review of and selection from the resulting item pool by an interdisciplinary panel of experts in dermatology, methodology and CHE, i.e. patients, the most relevant treatment needs in patients with CHE were identified. The instrument was validated in a group of patients with severe CHE refractory to standard therapy. However, patients with less severe hand eczema can be assumed to not have different treatment goals but rather less goals or goals of less importance. The option 'does not apply to me' in the PBI makes sure that only the individual goals of each patient are included in the total score.

In conclusion, the PBI for patients with CHE is the first standardized, reliable, and valid instrument for the assessment of patient-relevant benefit in the treatment of hand eczema. It can be conveniently used in research as well as in clinical practice.

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