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# Clinical & Experimental Dermatology and Therapies

Eysteinsdóttir JH, et al. . Clin Exp Dermatol Ther 2017: CEDT-123.

DOI: 10.29011/2575-8268/100023

Research Article

# Trozak Histological Assessment Score of Psoriasis Vulgaris: Correlation with Disease Severity, Other Histological Findings and Quality of Life Assessment

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**Citation:** Eysteinsdóttir JH, Ólafsson JH, Agnarsson BA, Jónasdóttir S, Sigurgeirsson B (2017) Trozak Histological Assessment Score of Psoriasis Vulgaris: Correlation with Disease Severity, Other Histological Findings and Quality of Life Assessment. Clin Exp Dermatol Ther 2017: J123. DOI: 10.29011/2575-8268/100023

**Received Date:** 05 May, 2017; **Accepted Date:** 26 May, 2017; **Published Date:** 3 June, 2017

## Abstract

Reliable assessment of severity in psoriasis is essential to document treatment responses in clinical research. Here we correlate the Trozak histological assessment score in chronic plaque psoriasis with Psoriasis Area Severity Index (PASI), histopathological markers and quality of life score (Dermatology Life Quality Index (DLQI)) in a sub study parallel to prospective randomized clinical trial. Skin biopsies were collected from twenty-one patients. PASI and DLQI were evaluated at the same time points. Trozak histological score was significantly reduced from 10.3 before treatment to 5.1 after two weeks and 3.2 after 6 weeks ($p<0.0001$). This correlated strongly with the reduction in PASI ($r=0.41$, $p<0.001$), DLQI ($r=0.61$, $p<0.01$) and Epidermal Thickness (ET) ($p<0.001$). ET correlated strongly with Trozak score ($r=0.68$, $p<0.0001$) but not with PASI. This implies that Trozak histological assessment of psoriasis plaques may provide a useful method to use in combination with clinical severity and quality of life scores in psoriasis research.

**Keywords:** Histological Score; Outcome Measure; Psoriasis; Quality of Life

## Introduction

Psoriasis is a chronic skin disease with a worldwide prevalence of around 2% [1] and high economic burden [2]. Reliable outcome measures of the disease severity are critical in clinical trials to measure the efficacy of an investigational treatment and very important in evidence-based medicine to provide comparisons among similarly designed trials. The ideal outcome measure to evaluate the severity of psoriasis should have a high specificity and sensitivity, a low inter- and intra-observer variation and take into account the psychosocial impact of the disease [3]. None of the currently available psoriasis score systems fulfils all of the validation criteria [4]. The Psoriasis Area and Severity Index (PASI) [5] is considered as gold standard to assess the clinical severity of psoriasis [4,6,7] but it has limitations such as low responsiveness in mild disease and low response distribution [4,6,7]. Another reliable clinical score is the "Lattice System Physician´s Global Assessment" (LS-PGA) [8] which has lower intra-observer and inter-observer variation than PASI [8].

Psoriasis has a major impact on health-related Quality of Life (QOL) [9] which is not necessarily in proportion to clinical severity [10]. In an effort to yield a comprehensive view of the impact of psoriasis and to complement the PASI, a patient-reported quality of life score is often added to the outcome measures in clinical practice and clinical trials [11,12]. The most widely used measure for assessing quality of life related to psoriasis is the quality of life

score Dermatology Life Quality Index (DLQI) [13].

Since clinical severity and quality of life scores are lacking in objectivity and have several limitations in measuring psoriasis severity, more observer-independent methods have been established such as biophysical methods [14-16] and biopsies from target lesions. Epidermal Thickness (ET)is often used as a secondary outcome measure in clinical trials as well as markers for epidermal proliferation (Ki-67) and immunohistochemically scoring of T cell activity in the epidermis and dermis (CD3, CD4, CD8, CD25 and CD45RO) [17-19]. Many researchers have validated the characterizing histological features of psoriasis before and after treatment [17,19-22]and few have used various histological scoring systems in an effort to quantify the degree of [23-26]. Histological assessment grading of psoriasis as suggested by Trozak [26] (Trozak score) is the only grading system which examines the specificity and sensitivity of these histological characteristics, but it has not been widely used in psoriasis research [15,27-29].

This study is a sub study to a randomized clinical trial that evaluates and compares three different psoriasis treatment regimens; traditional Narrow-Band Ultraviolet-B (NB-UVB) therapy and two treatment regimens including bathing in geothermal seawater combined with NB-UVB therapy in sixty-eight chronic plaque psoriasis patients. The results of the clinical trial have been published elsewhere [27]. Briefly, the data showed that bathing in geothermal seawater combined with NB-UVB therapy induces faster improvement in PASI and Lattice clinical scores as well as in the Trozak score.

In this sub study the objective is to validate the use of the Trozak score by comparing it to other histological and immunohistochemically scoring methods of biopsy material commonly used in conjunction with clinical scoring. We found out that the Trozak score correlated well with clinical severity and quality of life scoring and Epidermal Thickness (ET). The Trozak histological assessment of psoriasis plaques may be a useful method to use in combination with clinical severity and quality of life scores in psoriasis research.

## Materials and Methods

### Patients

The Icelandic National Bioethics Committee and the Icelandic Data Protection Authority approved the study protocol. Patients provided written consent to participate in the study. Eligible patients were recruited to the study from September 2009 to May 2010 and followed up for 2 years. Skin biopsies were collected from 21 patients of total 68 patients included in the randomized clinical trial [27]. Key inclusion criteria were:

1. Diagnosis of chronic plaque psoriasis.
2. Psoriasis Area and Severity Index score (PASI score) [5] of 7 or higher.
- Patients who were non-responsive to topical treatment and were candidates for phototherapy or systemic treatment.

Patients with other forms of psoriasis (e.g. guttate, pustular or erythrodermic) or skin diseases that could interfere with study evaluations, were excluded. All on-going psoriasis treatment was stopped at least 4 weeks prior to inclusion in the study.

### Treatment Regimens

A total of 68 patients were randomly assigned to receive one of the following three treatments: (i) Outpatient bathing in geothermal seawater combined with UVB therapy three times/week for 6 weeks (n=22), (ii) In-patient treatment daily for two weeks (bathing in geothermal seawater two times/day combined with UVB therapy) followed by outpatient UVB therapy two-three times/week for 4 weeks (n=22). (iii) Conventional UVB therapy three times/week for 6 weeks (n=24). Clinical evaluation with PASI and LS-PGA score was performed at baseline and week 1, 2, 4, 6 and 10 weeks after beginning the treatment. Quality of life assessment with DLQI was assessed before treatment and after 10 weeks. For the sub study 4-mm punch biopsy from a target lesion was obtained at baseline, week 2 and 6 from 7 patients in each treatment group. The target lesion was selected as the thickest lesion on the extremities and the follow-up biopsies were obtained from the same localization. The clinical characteristics of these 21 patients is summarized in (Table 1).

| Characteristics | GSW (N= 7) | IT-GSW (N=7) | UVB (N=7) | P Value † |
|---|---|---|---|---|
| Age - yr | 46.1 (±10.8) | 38.4 (±16) | 37.9 (±14.4) | 0.37 |
| Male sex - no. (%) | 3 (43%) | 2 (29%) | 3 (43%) | 0.82 |
| Body mass index (BMI) | 32 (±5) | 30.2 (±5.4) | 28.8 (±7.1) | 0.96 |
| Duration of psoriasis - yr | 23 (±14) | 18.8 (±11) | 12.3 (±8.1) | 0.09 |
| Participants with psoriatic arthritis - no.(%) | 0 (0%) | 1 (14%) | 0 (0%) | 0.71 |
| Participants with nail psoriasis - no. (%) | 3 (43%) | 3 (43%) | 1 (14%) | 0.61 |
| Psoriasis area and severity index (PASI) | 13.8 (±5.2) | 11.6 (±6.2) | 11.1 (±4.9) | 0.22 |
| Lattice system physician´s global assessment | severe | severe | severe | 1.00 |
| Dermatology Life Quality Index score | 7 (±4.2) | 11.6 (±6.2) | 8.3 (±5.1) | 0.038* |
| Participants treated previously - no.(%) | | | | |
| Blue Lagoon | 5 (71%) | 4 (57%) | 2 (29%) | 0.57 |
| Topical agent | 6 (86%) | 7 (100%) | 7 (100%) | 1.00 |
| Phototherapy | 7 (100%) | 7 (100%) | 6 (86%) | 0.51 |
| Systemic therapy | 1 (14%) | 0 (0%) | 0 (0%) | 0.61 |
| Smoking | 3 (43%) | 3 (43%) | 2 (29%) | 0.77 |
| Family history | 6 (86%) | 4 (57%) | 4 (57%) | 0.35 |

**Table 1:** Clinical Characteristics of Patients Included in the Sub-Study Parallel to.

### Outcome Measures

#### Histological Assessment

Trozak score-Trozak´s histologic grading system for psoriasis [26] was used for histological blinded assessment of the skin biopsies stained with hematoxylin and eosin. It comprises

10 different histomorphological features: elongated rete ridges, club-shaped rete ridges, edema and elongation of dermal papillae, perivascular infiltrate in the upper dermis, absent granular layer, parakeratosis, thinning of the suprapapillary plate, suprabasal mitosis, the presence of Munro micro abscesses and / or Kogoj pustules, each taking a score of 1, 2 or 3, depending on their histological specificity for psoriasis and relevance to disease activity. The cumulative score (0-19) is recorded for each biopsy (Table 2). The scoring was investigator-blinded and performed by the same investigator (the author JHE) before treatment, after 2 and 6 weeks of treatment.

Name of Study: _____

Slide Accession Number: _____

HISTOLOGIC GRADING SYSTEM FOR PSORIASIS

| Microscopic Criteria | | Value/Criteria | Score |
|---|---|---|---|
| 1. Regular elongation of the rete ridge | | 1 | |
| 2. Club shaped rete ridges | | 2 | |
| 3. Elongation and edema of the dermal papillae | | 1 | |
| 4. Perivascular mononuclear infiltrate in the upper dermis of papillae | | 1 | |
| 5. Absent granular layer | a. focal | 1 | |
| | b. total | 2 | |
| 6. Parakeratosis | a. focal | 1 | |
| | b. total | 2 | |
| 7. Suprapapillary plate thinning | | 2 | |
| 8. Mitosis above basal cell layer | | 2 | |
| 9. Munro microabscesses | | 3 | |
| 10. Spongiform pustule | | 3 | |
| | Score total: | 19 | |
| | | | |
| Epidermal Thickness | | | |
| Suprabasilar Mitosis Average per 8 HPF | | | |

Comments: _____

_____

Investigators Signature_____ Date _____

Adapted from (Trozak, 1994) original paper.

**Table 2:** Trozak´S Histologic Grading System for Psoriasis.

## Epidermal Thickness (ET)

ET is defined as the average distance in mm, between the base of stratum corneum and the tip of rete ridges, measured in different locations. In this study ET was measured using a calibrated microscope micrometer in three different locations. All ET measurements were investigator-blinded and performed by the same investigator (BAA) before treatment, after 2 and 6 weeks of treatment.

## Immunohistochemistry

The following markers were investigated: CD3, CD4 and CD8 to evaluate T cell infiltration in the skin, and Ki-67-positive keratinocytes to evaluate epidermal proliferation. Ki-67 serves as a marker of proliferative activity in neoplasms and other diseases with excessive cell proliferation such as psoriasis [30]. Sections were cut at 3µ, mounted on star frost slides and heated for one hour at 60°. After deparaffination they were heated in Envision-Flex Target-Retrieval Solution High pH (DM 828, Dako) for 25 minutes in a water bath. Immunohistochemical staining was done in AutostainerLink 48 (Dako), and a two-step polymer method Envision TM Flex K8000 (Dako) was used. All antibodies were incubated for 30 minutes. Slides were developed with DAB reagent and counterstained with hematoxylin. Four different antibodies were used: polyclonal rabbit anti- human CD3 (Dako) 1:250., mouse monoclonal anti-human CD4 (Leica Novocastra) 1:25, monoclonal mouse anti-human CD8 (Dako) 1:100, and monoclonal-mouse anti-human Ki-67MIB1 (Dako) 1:200. All antibodies were diluted in Envision-Flex Antibody Diluent (DM830, Dako). The slides were evaluated using Leica Application Suite 3.5.0 and the cells were counted at 400x magnification.

## Clinical Scores

### Psoriasis Area and Severity Index score (PASI score)

PASI is the most commonly used clinical score for assessing the clinical severity and extent of psoriasis and the current gold standard. It evaluates severity of the main three clinical signs of psoriasis: erythema, desquamation and infiltration from 0 to 4, weighted by the area of involvement. The whole body is divided into four regions (head, body, upper and lower extremities separately) weighted according to its approximate percentage of the total body surface area. PASI is expressed in numerical values from 0 to 72 [5].

### Lattice System Physician´s Global Assessment Score (LS-PGA)

LS-PGA was also used as a clinical score to provide additional information. It quantifies psoriasis severity into eight descriptive categories from ‘Clear’ to ‘Very Severe’ where it incorporates the involved Body Surface Area (BSA) and the overall plaque morphology [8]. The BSA percentage involved is measured in categories of 0, 1-3, 4-9, 10-20, 21-29, 30-50 and 51-100%. LS-PGA score has been shown to correlate with PASI and studies have shown that the inter-observer variation is lower for LS-PGA compared with PASI [8,31]. The clinical scores were evaluated before treatment, after 2, 6 and 10 weeks by the same investigator (JHE).

## Quality of Life Measures

As clinical assessments alone are not sufficient enough to evaluate psoriasis severity in clinical research [32], the Quality of Life (QoL) questionnaire Dermatology Life Quality Index (DLQI)was used [13]. It is a 10-item questionnaire that determines whether psoriasis affects patient-reported QoL over the previous week, with overall scores ranging from 0 (not at all) to 30 (very much) [13]. These 10 questions cover 6 domains of health status; symptoms, feelings, daily activities, leisure, work or school, relationships and side effects from therapeutic management. It was assessed at baseline and after 10 weeks.

## Statistical Analysis

Efficacy data from all randomized patients were analyzed on an intention-to-treat basis. Patients who discontinued study treatment

due to unsatisfactory therapeutic effect or who did not follow the study treatment protocol were regarded as treatment failures. For analysis in such cases, missing values were replaced with the most recently available values for all efficacy variables (last observation carried forward). The proportions of patients responding to treatment were compared using the two-sided Fisher´s exact test. Continuous response variables were compared with the use of analysis of variance (ANOVA). Also, we used Pearson´s correlation coefficient to show the correlation between different parameters including all visits. All statistical tests were two sided and performed at an alpha level of 0.05.

# Results

## Histological Response to Treatment

### Trozak Histological Score

Untreated patients showed typical histopathological changes for psoriasis patients such as hyperkeratosis, elongated rete ridges, perivascular mononuclear cell infiltrate and Munro abscesses (see Figure1). Patients showed significant decrease in histologic changes as measured by the Trozak score after only two weeks of treatment, or from 10.3±3.7 to 5.1±4.1 ($p<0.001$; (Table 3) and (Figure 1). The histological features were further reduced after 6 weeks of treatment or to 3.2±3.3 ($p<0.001$), (Table 3). No significant difference was observed when the treatment groups were compared with each other. The Trozak score significantly correlated with the PASI score (Pearson´s $r=0.41$, $p<0.001$, (Table 3) and (Figure 2), LS-PGA score (Pearson´s $r=0.48$, $p<0.0001$), epidermal thickness (Pearson´s $r=0.68$, $p<0.0001$) and Ki-67 antigen expression in lesional skin (Pearson´s $r=0.28$, $p<0.05$) (Figure 2). In addition, changes in the Trozak´s score correlated well with changes in DLQI score (Pearson´s $r=0.61$, $p<0.01$).

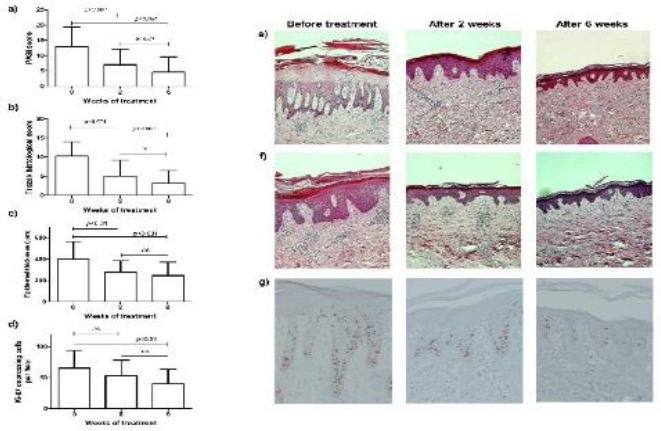


**Figure 1:** Patients Showed Significant Decrease in Psoriatic Changes with Treatment as Measured by **a)** the PASI Score, **b)** the Trozak Score, **c)** Epidermal Thickness (ET) and **d)** Ki-67 Expression in Epidermis. Representative Photographs from **e)** One Patient in the GSW Group and **f)** One Patient from the IT-GSW Group and **g)** Ki-67 Expression with Treatment. Data is represented as mean±SD. ns = non-significant.

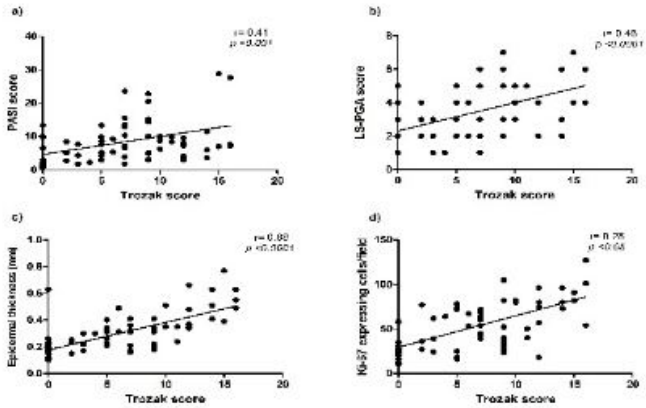


**Figure 2:** Correlation of a) the PASI Score, b) the LS-PGA Score, c) Epidermal Thickness of Lesional Skin and d) Ki-67 Antigen Expression in the Epidermis of Lesional Skin with Trozak's Histological Score.

| | Before treatment (n =21) | After 2 weeks (n =21) | *p* value | After 6 weeks (n =21) | *p* value | Correlation with PASI; *r* | *p* value |
|---|---|---|---|---|---|---|---|
| Biopsy grading (Trozac score) | 10,3 | 5,1 | < 0,001 | 3,2 | < 0,001 | 0,41 | < 0,001 |
| Epidermal thickness (µm) | 397,4 | 277 | < 0,01 | 246,5 | < 0,001 | 0,13 | ns |
| Ki-67 (positive cells/field) | 65,3 | 53,4 | ns | 40,3 | < 0,01 | 0,28 | 0,025 |
| CD3 (positive cells/field) | 134,8 | x | x | 47,8 | < 0,01 | 0,27 | ns |
| CD4 (positive cells/field) | 74 | x | x | 22 | < 0,001 | 0,16 | ns |
| CD8 (positive cells/field) | 56,6 | x | x | 17,9 | < 0,01 | 0,36 | ns |
| PASI score | 12,9 | 7,1 | < 0,001 | 4,7 | < 0,001 | x | x |
| LS-PGA score | 5 | 3 | < 0,001 | 2,3 | < 0,001 | 0,88 | < 0,0001 |
| DLQI score | 10 | x | x | 6,1** | < 0,01 | 0,48 | < 0,01 |

**Table 3:** Mean Values for All Variables Used in The Study. * p value compared with before treatment. Statistically significant difference at $p<0.05$. **DLQI after 10 weeks, not 6 weeks. r: Pearson Correlation Coefficient.

## Epidermal Thickness (ET)

ET of untreated lesional psoriasis skin was 397,4 µm on average when all participants were analyzed together and significantly decreased to 277 µm after only two weeks of treatment ($p<0.01$) and to 246,5 µm after six weeks of treatment ($p<0.001$), (Table 3) and (Figure 1). No significant difference was observed when the treatment groups were compared with each other. Interestingly, even though there was a significant correlation between ET and the histopathological Trozak score, it did not correlate with either of the clinical scores used in this study; the PASI score (Pearson´s $r=0.13$, $p=0.28$) and the LS-PGA score (Pearson´s $r=0.20$, $p=0.10$). However, ET correlated significantly with Ki-67 antigen expression (Pearson´s $r=0.58$, $p<0.0001$).

## Immunohistochemical Staining for CD3, CD4, CD8 and Ki-67 Antigen Expression

Before treatment 65.3 epidermal cells stained positive for Ki-67antigen expression per field in lesional psoriatic skin when all participants were analyzed together. No significant difference was found after two weeks of treatment but after six weeks the expression decreased significantly to 40.3 positive cells per field

(p<0.01); (Table 3) and (Figure 1). There was a significant difference in the amount of CD3+, CD4+and CD8+ positive epidermal T-lymphocytes before and after six weeks of treatment in lesional skin (p<0.01), (Table 3). No immunohistochemical staining was performed for CD3, CD4and CD8 on biopsies taken after two weeks of treatment, only after six weeks. CD3, CD4 and CD8 expression did not correlate with the PASI score, however, Ki-67 antigen expression shows weak significant correlation with the PASI score (Pearson´s r=0.28, p=0.025) and the LS-PGA (Pearson´s r=0.37, p<0.01). As mentioned before, Ki-67 expression shows weak correlation with the Trozak´s score (Pearson´s r=0.28, p<0.05) and strong correlation with ET (Pearson´s r=0.58, p<0.0001). No significant difference was observed when the treatment groups were compared with each other.

### Clinical Efficacy

PASI score changed significantly after only two weeks of treatment from 12,9 to 7,1 (p<0,001) on average for all participants analyzed together and after six weeks of treatment the PASI score has reduced to 4,7 (p<0,001), (Table 3) and (Figure1). The LS-PGA score shows same reduction as the PASI and there is a high correlation between the two clinical scores (Pearson´s r=0.88, p<0.0001; (Table 3). The PASI score showed strong correlation with the reduction of Trozak score (Pearson´s r=0.41, p<0.001) but no correlation with ET (Pearson´s r=0.13, p=0.28).

### Quality of Life Assessment

DLQI baseline scores were significantly higher before the treatment compared with after 10 weeks for all treatment groups analysed together (Table 3). Five patients out of twenty-one achieved a DLQI score of 0 or 1 by week 10. As mentioned before changes in the DLQI scores correlated well with changes in the clinical scores, the PASI score (Pearson´s r=0.48, p<0.01) and the LS-PGA score (Pearson´s r=0.46, p<0.01). The reduction of DLQI correlated well with the reduction of the Trozak score (r=0.61, p<0.01)

## Discussion

Although the material is small the results indicate that the histological score of Trozak is a potential objective assessment tool for showing psoriasis severity in combination with the global clinical severity PASI score [4]. Although histological normalization in an index plaque does not always correlate with global clinical improvement here we show that the Trozak score has a strong correlation with two clinical severity scores, PASI and LS-PGA. In addition, the Trozak score correlated well with ET in lesional skin and has a weak but significant correlation with Ki-67 antigen expression in lesional skin and DLQI. Interestingly, we found weak correlation of DLQI with the PASI, which is used as an almost universal outcome measure in psoriasis trials. This finding is consistent with other studies [7].

Our ET measurement showed thicker ET in untreated lesions than in treated lesions which was 397,4 µm before treatment and 246,5 µm after six weeks of treatment attributed to the normalization of the epidermis. These observations are in good agreement with previous studies that show ET of untreated lesions to be 266.7-352.5 µm and after treatment 312-131 µm [15,18,33]. It may be speculated that these differences are due to differences in disease severity, regional variation in the target lesions studied and different treatment periods.

The most commonly used histopathological outcome measures in recent clinical trials are ET, markers for epidermal proliferation (Ki-67) and immunohistochemical scoring of T cell activity in lesional skin before and after treatment [17-19,24,34-37]. There is conflicting data whether these findings correlate with clinical psoriasis scoring systems, where some studies show correlation and others do not [15,23-25,27]. Of these markers, there seems to be most convincing data for ET and Ki-67 antigen expression [17,18,25,37,38]. Morsy, et al. 2010 found correlation of DLQI and Trozak score with ET, but surprisingly no correlation between ET and PASI [15]. They do not mention any correlation analysis of the Trozak score and PASI, however we showed strong correlation between PASI and Trozak score in our study [27]. We found weak correlation between Ki-67 positive cells in lesional skin and PASI before and after treatment, but no correlation with CD3, CD4 and CD8 positive T cells which is consistent with [23] and [18]. In addition, we did not find any correlation between changes of ET in lesional skin and changes in PASI with treatment which is also consistent with previous studies [15]. This may indicate that the Trozak score reflects disease severity better than ET, both before and after therapy.

Histopathology is not often used to quantify inflammatory skin disease. Nevertheless, it has been suggested as a more observer-independent assessment tool than clinical assessment, as clinical severity scores may have innate limitations when used alone [3]. Few studies use histopathological assessment as a secondary outcome measure in combination with clinical score [18,24,34-36] but the data is conflicting because there is no uniformity in the techniques used and the assessment is often made at different time points which makes comparison difficult. The Trozak score is not widely used in psoriasis research today and only a few researchers have used it in their studies [15,27,28]. However, some previous studieshave useda quantitative histological grading system as a severity assessment tool for psoriasis, which is similar to the Trozak score [23-25]. Othersuse no scoring system, only a general histopathological examination which makes correlation with clinical severity of the disease and comparison with other studies difficult [17,20-22].

In conclusion, more observer-independent assessment tools are needed in Randomized Controlled Psoriasis Trials (RCT) to assess the disease with more objectivity. We propose the histologi-

cal assessment score of Trozak can be used in psoriasis RCT in combination with clinical and quality of life assessments.

### Acknowledgements

The authors would like to thank Esther Hjálmarsdóttir RN, Ingileif Jónsdóttir PhD, Elísabet Reykdal MD and Grímur Sæmundsen MD for their contribution and assistance, as well as the staff at the Dermatology and Immunology Departments, Landspitali University Hospital, for their assistance collaboration and valuable inputs. The Landspitali University Hospital Research Fund and The Technology Development Fund supported this work.

### Declaration of Interest

This study was primarily sponsored by the "Icelandic Technology Development Fund" and the "Landspitali University Hospital Research Fund". The Blue Lagoon Ltd. offered the treatment and the expenses free of charge. Study investigators designed the study with practical input from the employees of the Blue Lagoon. Study investigators collected data, which was maintained in a database in the University Hospital of Iceland.

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