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Automated, computer-guided PASI measurements by digital image analysis versus conventional physicians' PASI calculations: study protocol for a comparative, single-centre, observational study

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ABSTRACT

Introduction Reliable and accurate assessment of severity in psoriasis is very important in order to meet indication criteria for initiation of systemic treatment or to evaluate treatment efficacy. The most acknowledged tool for measuring the extent of psoriatic skin changes is the Psoriasis Area and Severity Index (PASI). However, the calculation of PASI can be tedious and subjective and high intraobserver and interobserver variability is an important concern. Therefore, there is a great need for a standardised and objective method that guarantees a reproducible PASI calculation. Within this study we will investigate the precision and reproducibility of automated, computer-guided PASI measurements in comparison to trained physicians to address these limitations.

Methods and analysis Non-interventional analyses of PASI calculations by either physicians in a prospective versus retrospective setting or an automated computer-guided algorithm in 120 patients with plaque psoriasis. All retrospective PASI calculations by physicians or by the computer algorithm are based on total body digital images. The primary objective of this study is comparison of automated computer-guided PASI measurements by means of digital image analysis versus conventional, prospective or retrospective physicians' PASI assessments. Secondary endpoints include (1) the assessment of physicians' interobserver variance in PASI calculations, (2) the assessment of physicians' intraobserver variance in PASI assessments of the same patients' images after a time interval of at least 4 weeks, (3) the assessment of the deviation between physicians' prospective versus retrospective PASI calculations, and (4) the reproducibility of automated computer-guided PASI measurements by assessment of two sets of total body digital images of the same patients taken at one time point.

Ethics Ethical approval was provided by the Ethics Committee of the Medical Faculty of the University of Heidelberg (ethics approval number S-379/2016).

Trial registration number DRKS00011818; Results.

Strengths and limitations of this study

- For the first time the diagnostic performance of an automated computer-guided Psoriasis Area and Severity Index (PASI) measurement will be evaluated on a large scale in daily clinical routine.
- The primary and secondary objectives of this study address open questions of major importance for future clinical trials using PASI measurements.
- A 'golden standard' for PASI measurements is lacking. Therefore, all statistical analyses can only provide insight into differences of the level of concordance and reproducibility between PASI calculations by physicians and the computer algorithm.
- Limitations of this study are the non-randomised and single-site setting.

INTRODUCTION

Background and preliminary work

Psoriasis is a chronic, inflammatory skin disease that affects 1.5%–2% of the population in Western industrialised countries. Without adequate treatment, patients with psoriasis experience a high burden of disease and a substantial restriction in quality of life.[1] Plaque psoriasis is the most common clinical form of the disease and is characterised by sharply demarcated erythrosquamous plaques which most frequently occur on the extensor sides of the extremities.[1] Assessment of disease progress is performed by means of the Psoriasis Area and Severity Index (PASI). Accurate severity scoring in psoriasis is of paramount importance for determination of a medical indication for systemic therapy and the subsequent surveillance of treatment efficacy. Furthermore, considerable significance is given concerning the use of PASI calculations in the context of clinical trials

investigating new pharmaceutical drugs in psoriasis. First, a certain disease severity (as measured by PASI) is a prerequisite for patient inclusion in these trials. Second, the assessment of the efficacy of any investigational drug in psoriasis treatment is mostly expressed by the percentage of reduction of the baseline PASI. Thus, PASI calculations represent an important measure to achieve regulatory approval for marketing of antipsoriatic drugs. The PASI assessment is based on a complex calculation including the percentage of the body area covered by psoriatic lesions, the extent of erythema, scaling and thickness of psoriatic plaques. For the scoring, the body is divided into the four anatomical regions: head, trunk, and upper and lower extremities. Both the severity of psoriatic skin lesions and the extent of the covered body surface are calculated separately. Erythema, induration and scaling are each measured on a 0–4 visual analogue scale and the involved body surface area (BSA) is measured using a 0–6 visual analogue scale.[1] The PASI score varies from 0 to 72. Higher scores indicate more severe disease manifestations.[1] A 75% reduction of the baseline PASI (PASI 75) was suggested as a current benchmark for many antipsoriatic drugs under investigation in clinical trials.[2] The primary endpoint in these trials calculates the percentage of patients reaching PASI 75 after a certain time interval under treatment with the investigational drug. The PASI was developed by Fredriksson and Pettersson in 1978 as an objective means to measure the effectiveness of a retinoid during the course of the study.[3] In several subsequent studies it became apparent that the BSA measurement is one of the major limitations of the PASI. Besides the 'rule of nine' the BSA calculation was often based on the 'one hand method' since it was assumed that the area of a flat patients' hand represents 1% of his total BSA.[4] In most cases the involved body surface was significantly overestimated by physicians and noticeable variations between the assessors were observed. Even trained and experienced personnel showed a lack of concordance in scoring the extent of psoriasis in the same patient.[5–8] Meanwhile, it has been shown that one hand actually represents 0.70%–0.76% of the BSA which might be one possible explanation for surface overestimation.[9] Additionally, time pressure during the consultation is undoubtedly another important influence on the high intraobserver and interobserver variability. Of note, PASI is not taking relevant patient-reported outcomes such as pain and itch into account. Therefore, several alternative scores for psoriasis severity assessment were implemented more recently.[10] For example, an innovative and alternative severity score based on the dermoscopic vascular pattern of psoriatic skin lesions was suggested by Carlesimo *et al*.[11] Finally, a further limitation of the PASI is that it is not routinely used by many clinicians. However, PASI allows for historical comparisons between clinical trials evaluating different antipsoriatic drugs and will therefore still be widely applied.

Rationale of the study

A reproducible, standardised and objective assessment of disease severity in psoriasis is of utmost importance in order to evaluate the indication for systemic treatment or treatment efficacy in daily clinical practice. To date, the most extensively studied and validated assessment tool is the PASI, which, therefore, represents the current standard. However, significant concerns arise from PASI's inherent level of subjectivity and high interobserver and intraobserver variability. Therefore, within this study we will investigate the precision and reproducibility of automated, computer-guided PASI measurements in comparison to trained physicians.

DESIGN/METHODS

Study design

This is a retrospective, single-centre, non-interventional study to evaluate an automated computer-guided PASI measurement (ACPM) by digital image analysis of 120 patients suffering from plaque psoriasis in comparison to conventional PASI assessments by physicians.

Study objectives

The primary objective of this study is to investigate the precision of ACPMs by means of digital image analysis versus conventional, prospective or retrospective physicians' PASI assessments. Secondary endpoints include (1) the statistical assessment of physicians' interobserver variance in PASI calculations, (2) the statistical assessment of physicians' intra-observer variance in PASI assessments of the same patients' images after a time interval of at least 4 weeks, (3) the statistical assessment of variance between physicians' prospective versus retrospective PASI calculations, and (4) the reproducibility of ACPMs by assessment of two sets of total body digital images of the same patients taken at one time point.

Study population and criteria for inclusion/exclusion

One hundred and twenty patients suffering from plaque psoriasis, undergoing medical treatment at the Department of Dermatology, University of Heidelberg, and at least 18 years of age will be included in this study. Patients with other clinical types of psoriasis, for example, erythrodermic or pustular psoriasis, shall be excluded from this study.

Methods

The prospective PASI calculation will be performed during regular consultation and physical examination of the patient by a trained physician (*pPASI 1*). Directly afterwards, total body imaging with the FotoFinder Automated Total Body Mapping (ATBM) system will be performed (automated total body imaging 1+2). Digital images will then be used for automated computer-guided measurements (ACPM) of PASI (*computerised cPASI 1+2*) with the approved FotoFinder PASI Software for Psoriasis Quantification (PASIvision). ATBM and computerised

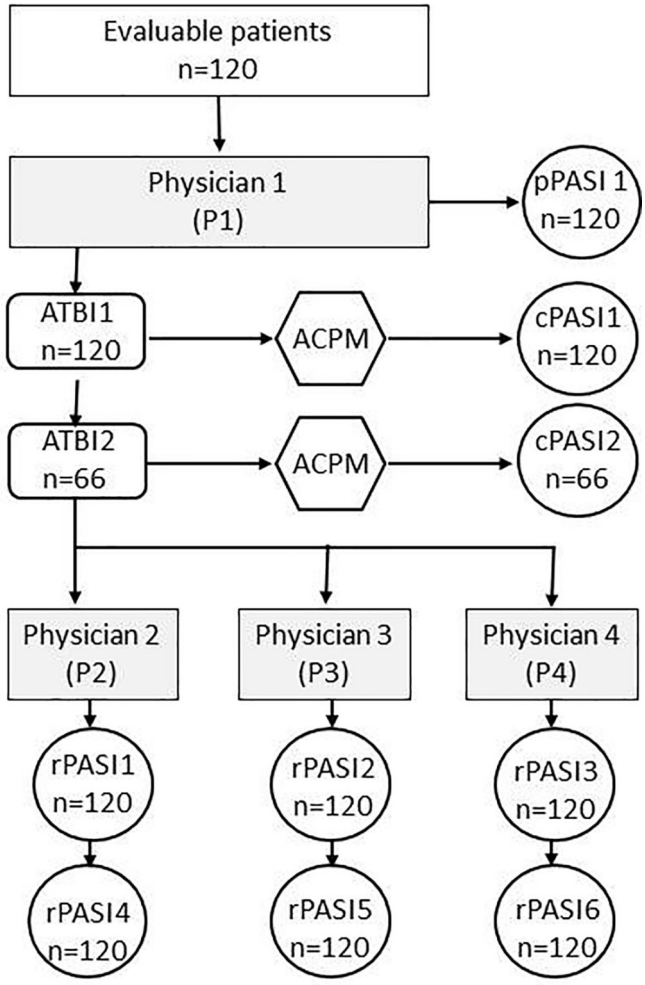

Figure 1 Flow chart of the study. At the first consultation each patient will be examined by a PASI trained physician (P1) who will prospectively attain pPASI 1. Each patient will then be sent for automated total body imaging (ATBI) and calculation of the computerised PASI (cPASI 1+2) by automated computer-guided PASI measurements (ACPM). ATBI and ACPM will be done twice consecutively for measurement of consistency and reproducibility. The digital pictures of the total body imaging will then be used for PASI calculation by three further trained physicians (P2–P4) resulting in rPASI 1–3. After at least 4 weeks the same three physicians will perform a second assessment of the total body images and calculate rPASI 4–6. PASI, Psoriasis Area and Severity Index.

PASI measurements will be done twice consecutively for measurement of consistency and reproducibility. Next, three other PASI-trained physicians *(P2–4)* will assess the PASI based on the analysis of the total body images (*rPASI 1–3*) for measurement of interindividual consistency. Additionally, a repeated PASI calculation of the same images at least 4 weeks after first calculation by the identical three physicians (*rPASI 4–6*) will be done for measurement of intraindividual consistency (see figure 1). Physicians were considered experienced PASI raters if they had been formally trained and had been involved in at least 20 clinical psoriasis trials over the last 3 years. FotoFinder PASI Software for Psoriasis Quantification (PASIvision) is an approved medical class I device. The software automatically calculates the PASI based on 16 polarised digital images covering the whole body surface made with the FotoFinder ATBM system. ATBM enables standardised documentation of the entire skin surface, except hairy scalp and genital area. Of note, for this study we will use the computerised PASI scores without any further adjustments. However, the software offers physicians the opportunity to customise and adjust the computerised PASI in a final step before storage. The calculation and presentation of the computerised PASI score complies with the validated method of standardised PASI scoring.[12] Study data will be collected and managed by the Institute of Medical Biometry and Informatics at the University of Heidelberg using the Research Electronic Data Capture (REDCap) tool. REDCap is a secure, web-based application designed to support data capture for research studies providing an intuitive interface for validated data entry, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages and procedures for importing data from external sources.[13] The individual values of the PASI will be directly entered in the REDCap database by the physicians during evaluation of the total body images. After PASI data for all patients have been entered by the three physicians (*rPASI 1–3*) the database will be locked for 4 weeks and PASI assessments can then be repeated (*rPASI 4–6*) at the earliest availability of the three physicians. The time interval of at least 4 weeks between the two assessments is sufficiently long to exclude that physicians remember earlier PASI scorings of the 120 patients. Physicians will have neither access to their previously entered data nor to PASI scores of other physicians or to the computerised PASI scores.

Statistical considerations

Sample size calculation

This is a retrospective non-interventional analysis of digital images of 120 patients with plaque psoriasis. Only descriptive statistics will be applied. The general objective of this study is not proving superiority of one method over the other, but to evaluate concordance and reproducibility of PASI calculations. We did not perform a formal sample size calculation because there was no available a-priori knowledge about intraclass correlation coefficient (ICC) values that could be expected for the comparison of computerized PASI measurements versus PASI measurements of physicians. However, assuming that ICCs will reach values of around 0.7 a sample size of 120 patients will be sufficient to obtain a 95% confidence interval of width 0.2 around the estimated ICCs. Therefore, a sample size of 120 fully evaluable patients is sufficient to assess the performance of the computer algorithm as well as interobserver and intraobserver variability.[14]

Statistical analysis

All PASI score results will be analysed descriptively by tabulation of the mean and SD. The intraclass correlation coefficient will be used to measure the agreement between computerised and physicians' PASI, the reproducibility of computerised PASI and the inter-rater and intrarater reliability. Bland-Altman plots will be used to visualise the agreements. Mean bias between the PASI measurements and limits of agreement will be calculated. The analyses will be carried out using R (V.3.3.1) with the packages car (V.2.1–5), multilevel (V.2.6), MASS (V.7.3–45), nlme (V.3.1–128), xtable (V.1.8–2) and psychometric (V.2.2).[15]

Ethical considerations, dissemination plan and regulatory obligations

The information contained in this protocol and the implementation of the study is consistent with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (2013), the principles of International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines (E6) and the current laws. This study will be performed in the context of the approved standard operating procedures (SOP) which are based on ICH-GCP guidelines (E6) and the German implementation of Good Clinical Practice for clinical work. Before initiation of the study, the protocol was presented to the independent Ethics Committee of the Medical Faculty of the University of Heidelberg. Ethics approval was granted by the ethics committee in September 2016 (ethics approval number S-379/2016). All included patients shall provide written informed consent which is required for the acquisition and further processing of digital total body images. This study falls within the legal category of 'in-house research' according to the German 'Landesdatenschutzgesetz' §15 section 3 (Rechtsgrundlagen der Datenverarbeitung). All digital images processed in this study were collected within the framework of routine medical care according to the SOPs of the Department of Dermatology at the University of Heidelberg and current treatment guidelines. This implies that the presented study does not require any direct patient-related procedures. The names of patients and all confidential data are subject to professional discretion and the German Federal Data Protection Act (Bundesdatenschutzgesetz, BDSG). Processing of medical data will only take place in pseudonymous form. Third persons will not be allowed access to patient data. There is no personal benefit and no additional risks for study participants. The design and the final results of the study will be published and made available to the public in the form of congress presentations, press releases and manuscripts submitted to scientific journals. Data storage is in accordance with the German Federal Data Protection Act (BDSG). Study records will be kept for 10 years.

Contributors CF, CK, LU and HAH participated in the development and the implementation of the study (writing of the protocol, submission to ethics committee, data management). CF, CK, LU and HAH helped to draft and to review the paper. All authors read and approved the final manuscript.

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Competing interests None declared.

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