ActiPso: definition of activity types for psoriatic disease: A novel marker for an advanced disease classification

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Abstract

Background Assessment of psoriasis is exclusively done measuring severity using somatic scores such as the psoriasis area and severity index or patient-reported outcomes such as the dermatology life quality index. There is no established tool to measure a patient’s individual psoriasis activity over time.

Objectives Development of a new tool to classify psoriasis activity types.

Methods Open patient interviews were performed and adapted in several steps and by using different groups of patients. Wording of the tool’s axis and description how to use it was optimized with the input of patients. The final ActiPso tool was used in a prospective study in psoriasis patients.

Results Four activity types could be identified describing psoriasis intensity (e.g. severity, itch, pain) over one typical year and an event/trigger type describing flares. In the study in 586 psoriasis patients of the 536 patients eligible for analysis 40.9% self-classified as type 1 (‘stable’), 22.6% as type 2 (‘unstable’), 30.6% as type 3 (‘winter type’) and 6.0% as type 4 (‘summer type’), respectively. Flares of psoriasis as identified by the event/trigger type were reported in 36.1% of patients with activity type 1, 67.8% with type 2, 73.8% of type 3 and 59.4% of type 4, respectively.

Conclusions Interviewed patients were able to describe their course of psoriatic disease and to name potential triggering factors. By doing so, activity types of psoriasis were defined for the first time and the importance of events/ triggers for flares described and integrated into ActiPso types as a basis for advanced patient-centric management. A limitation of ActiPso is that in regions with no seasonal variations types 3 and 4 may not apply.

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Introduction

Psoriatic disease is a chronic inflammatory condition for which there is no cure. The most common form is plaque psoriasis presenting with a rather heterogeneous phenotype regarding lesional characteristics, affected body areas and extent.1

After first onset, psoriasis has an unpredictable often lifelong course with substantial inter- and intraindividual variation. This is at least in part due to the influence of risk and trigger factors such as obesity with a body mass index (BMI) above 30 and tobacco smoking.2,3 Known trigger factors include psychosocial stress, infections such as streptococcal throat infection and periodontitis.4 Psoriasis has a devastating effect on health-related quality of life due to stigmatization and disease and treatment burden.5

Classification of psoriasis is nearly exclusively done by assessing disease severity. For this purpose, tools such as the psoriasis area and severity index (PASI), body surface area (BSA) or physician’s global assessment (PGA) are used. These are supplemented today by tools measuring symptoms such as itch (mostly numerical rating scales) and patient-reported outcome (PRO) instruments such as the dermatology life quality index.6 They all have in common that such an assessment only represents a snapshot within an individual disease history. Psoriasis severity tools
and PROs are used to grade psoriasis into mild vs. moderate-to-severe in order to apply appropriate treatment according to the label of respective drugs and treatment procedures including topicals and UV light. However, there is a very high variability in treatment responses and predictors for therapeutic outcomes are not yet available.

When interviewed patients are able to accurately describe their individual disease course and are able to name triggering events. Treatment failures can often be attributed to changes in disease activity following a trigger episode or the prominent involvement of risk/aggravating factors. Until today there has been no published tool to assess psoriatic disease activity.

The aim of the ActiPso approach was to identify common profiles of psoriatic disease courses that can be used for classification of activity types. Patient interviews were performed and structured, and the outcomes were used to define a first set of activity types. Thereafter, patients were asked to refine the profiles and the wording used for the instructions how to use the tool. The final version was subsequently employed for a first study in 586 patients with psoriasis.

Patients and methods
The study was performed during regular care in non-selected outpatients with psoriasis consecutively presenting to the Psoriasis Center Kiel. Approval for patient interviews, pilot assessments and the following study using the final ActiPso tool was obtained from the Ethics Committee of the University of Kiel (AZ: D435/19).

Selection of patients for the first interviews was performed using the method of purposeful sampling. All patients were recruited from the outpatient service of the Psoriasis Center Kiel.

The process to generate the tool involved continuous interaction with psoriasis patients in order to create a final version with a maximum of understandability to limit insufficient use. The flow of steps is shown in Fig. 1.

The first cohort consisted of 10 psoriasis patients. The task was explained to the patients in a 1 : 1 communication setting by a trained specialist in psychosomatic medicine and psychotherapy (RvS). Patients were asked to draw a picture of their individual course of psoriasis on a blank sheet of paper. Advice was only provided when actively demanded.

The results obtained from this first group activity were then translated into a preliminary tool with five different types of activity, followed by a proposal for labelling of y- and x-axis and instructional text was achieved in a second group of patients (n = 21).

Thereafter, an initial ActiPso score sheet was created including written instructions on how to use the tool by a next group of patients.

After having received the response of an additional group of patients (n = 30) and after amending the ActiPso sheet for better understanding, the prefinal ActiPso tool was created. Thereafter, a final test and adjustment were performed in a group of 150 psoriasis patients to create the final tool to be used subsequently.

The ActiPso tool was handed out to all patients presenting to the outpatient service of the Psoriasis Center from 03.12.2019 to 24.03.2020 and evaluated thereafter.

Statistical analysis
Descriptive statistics were used to obtain data about the frequencies of the different activity types and their relationship to clinical and demographic data using SPSS version 26.0.0.0 (IBM, Armonk, NY, USA). Continuous data are expressed as mean ± standard deviation (SD) unless otherwise stated while categorical data are presented as number (percentage). For comparison of categorical data, the chi-square test was used, both globally across all activity types and for pairwise comparisons. Continuous data were compared globally using analysis of variance (ANOVA), followed by pairwise t-tests with P-value adjustment using the Bonferroni method. Pairwise tests were only performed if the global comparison was significant. P-values <0.05 were considered statistically significant.

Results
Patient-focused definition of activity types of plaque psoriasis
In the first 1 : 1 guided effort, patients were able to draw a curve resembling their individual psoriasis activity over a period of time resulting in the creation of curves in a coordinate system. In the second group, patients agreed about the labelling of the y-axis as intensity and of the x-axis as the period of 1 year. There was debate among patients whether the x-axis labelling should describe seasons (e.g. spring, summer, fall, winter) or months. As the tool was designed for a potential global use, it was decided to use labelling with months from January to January with April, July and October in between. This approach resulted in the definition of four activity types. However, many patients mentioned that during certain episodes f. ex. following stressful life events psoriasis activity was higher over a period of time before returning to their individual baseline. Thus, an additional event/trigger type was created and integrated into the preliminary ActiPso tool. For the event/trigger type, the y-axis label remained as intensity but the x-axis was only labelled with time because patients described that the flares mainly last from days to weeks or months. To better define flare, examples of important triggers (e.g. stress, infections) were named and integrated into the cartoon. Patients receiving treatment and having major improvement or even clearing of lesions were asked to think about their disease course before treatment was initiated.

A text on how to use the tool was consented. To better characterize the nature of flares, additional information needed to be
provided when this activity type was ticked in addition to one of the four basic types.

To descriptively name the four basic types, they were tentatively classified as follows: type 1 = 'stable', type 2 = 'unstable', type 3 = 'winter type', type 4 = 'summer type', and event type/trigger type.

In the third group, the ActiPso types and draft instructions were tested and amendments were implemented where appropriate and a final test conducted in a separate cohort of 150 psoriasis patients. Subsequently, the final ActiPso tool was defined (Fig. 2) (Original German ActiPso tool Fig. S1).

**ActiPso study evaluation**
The ActiPso tool was handed to 586 psoriasis patients during routine care and 536 questionnaires were eligible for analysis.

Demographic data were lacking in 25 cases (4.3%), and in the remaining 25 data sets, there was incomplete information regarding ActiPso types (4.3%).

Patients’ demographics are shown in Table 1. Of the 536 patients, 40.86% were self-classified as type 1 (stable), 22.57% as type 2 (unstable), 30.6% as type 3 (winter type) and 5.97% as type 4 (summer type), respectively (Fig. 3).

Regarding a correlation between ActiPso types and demographic factors, it was found that patients identifying their psoriasis as type 1 (stable) were significantly older as compared to those of type 3 (winter type; \( P < 0.037 \); Fig. 4).

ActiPso type 2 (unstable) was more frequently identified in female patients as compared to type 3 (winter type; \( P < 0.011 \)).

Flares of psoriasis as identified by the event/trigger type were reported in 36.1% of patients with activity type 1, 67.8% with
type 2, 73.8% of type 3 and 59.4% of type 4, respectively (Fig. 5). Treatment at the time of patients’ judgement had no influence on the distribution of ActiPso types (Figs S2 and S3).

The most important trigger factor was stress reported by 92.0% of the patients with event/trigger type, followed by infections (33.1%, with 5.5% tonsillitis) and drugs (3.7%; Fig. 6). Of those reporting infections, as a trigger, 21.2% named common cold as event. Other trigger factors were present in 9.5% of the patients. In ActiPso type 3 patients (winter type) stress at work, school or education was significantly more frequently named as in ActiPso type 1 patients (stable; \( P < 0.03 \)).

Psoriasis patients who selected the event/trigger type in addition to ActiPso types 1–4 were significantly younger compared to event/trigger type-negative patients (47.17 ± 14.0 vs. 53.75 ± 16.2 years, mean and SD, \( P < 0.001 \)). Female patients identified significantly more frequently the event/trigger type in addition to ActiPso types 1–4 than male (68.3% vs. 48.7%, \( P < 0.001 \); Fig. S4).

There was no correlation between ActiPso types 1–4 with or without event/trigger type and BMI (Fig. S5).

**Discussion**

By today assessment of psoriasis, severity is the pillar of classification and is mainly used to grade the disease into mild and moderate-to-severe for later application of, respectively, labelled treatments and to define treatment goals.\(^8\) Physicians seeing patients only occasionally are unable to describe the individual course of psoriasis over a year or more because of the snapshot-like character of their assessments.

The ActiPso approach as a new patient-reported outcome tool aimed to fill this gap by defining activity types that can be identified by the patients themselves. It was therefore essential, that patients mainly drove the process and major emphasis was put on giving clear instructions on how to use the score sheet.

The term ‘intensity’ used as the label for the \( y \)-axis of the diagrams was found to best describe a complex of lesional severity, extent, involvement of impactful areas (e.g. visible sites, genitals) and symptoms such as itch or pain. Patients clearly preferred the label of the \( x \)-axis using the names of months from January to January describing a 1-year period. It needs to be considered that variation activity types 3 and 4 may not be relevant for patients living in countries with only little seasonal variation compared to patients exposed to a winter–summer climate. Although data on the influence of climate on psoriasis is sparse, patients more frequently report a negative impact of winter and coldness.\(^9\) Our first study during regular care showed that patients with a stable disease course (ActiPso type 1) reported about flares significantly less frequent (36.07%) compared to activity types type 2 67.77% and type 3 73.78%.

An interesting finding of the first study in patients from the outpatient service of the Psoriasis-Center Kiel was the frequently identified ActiPso event/trigger type particularly in combination
with ActiPso types 2 or 3 and that the majority of those patients could define a specific trigger.

Risk and trigger factors are known to be significantly modifying psoriatic disease. First onset or flares even during otherwise efficacious treatment are mostly induced by trigger events. They are of major importance for successful treatment outcomes and predictability of response. Starting a new therapy is likely to be less effective when patients are in a phase of increased disease activity during or after a trigger as compared to the phase of decreasing activity. Although textbook knowledge emphasizes the importance of trigger factors, data regarding the frequency and importance of such events are rare. Defining the individual ActiPso type enables to identify triggers in patients with ActiPso event/trigger type and to manage these patients according to their type.

| Demographics of patients in the study using the final ActiPso tool (n = 536). Continuous data are expressed as mean ± standard deviation (SD) while categorical data are presented as number (percentage) |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| **Full cohort**                 | **Type 1 ("stable")**          | **Type 2 ("unstable")**         | **Type 3 ("winter-type")**      | **Type 4 ("summer-type")**     | **Trigger-type**                 | **Missing values**               |
| **n (%)**                       | 536 (100)                       | 219 (40.9)                      | 121 (22.6)                      | 164 (30.6)                      | 32 (6.0)                        | 301 (56.2)                      |
| **Age, years**                  | 50.06 (15.4)                    | 52.21 (15.8)                    | 49.92 (15.7)                    | 47.88 (13.8)                    | 47.02 (16.1)                    | 47.18 (14.0)                    |
| **Sex m, f**                    | 335 m (62.5)/200 f (37.5)       | 142 m (64.8)/77 f (35.2)        | 61 m (50.4)/60 f (49.6)         | 112 m (68.7)/51 f (31.3)        | 1 (37.5)                        | 137 f (45.5)                    |
| **BMI**                         | 27.51 (6.8)                     | 29.14 (6.5)                     | 28.85 (6.5)                     | 28.31 (6.5)                     | 26.31 (5.6)                     | 28.77 (6.4)                     |
| **Trigger-type**                | 301 (56.2)                      | 79 (36.1)                       | 82 (67.8)                       | 121 (73.8)                      | 19 (59.4)                       | —                               |
| **Smoker**                      | 199 (38.7)                      | 77 (36.2)                       | 50 (43.9)                       | 58 (36.7)                       | 14 (48.3)                       | 122 (42.2)                      |
| —valid/missing                  | 514/22                          | 213/6                           | 114/7                           | 158/6                           | 29/3                            | 289/12                         |
| **Treatment**                   | 493 (94.4)                      | 206 (95.4)                      | 110 (92.4)                      | 150 (94.9)                      | 27 (93.1)                       | 275 (93.9)                      |
| —valid/missing                  | 522/14                          | 216/3                           | 119/2                           | 158/6                           | 29/3                            | 293/8                           |

**Figure 3** Distribution of patients (n = 536) regarding the four ActiPso types.

**Figure 4** Distribution of age among the four ActiPso types.

**Figure 5** Proportion of patients reporting an effect of event/trigger factors related to the four ActiPso types.

**Figure 6** Frequency of various event/trigger factor in psoriasis patients.
their individual needs. Patients reporting about the event/trigger type were highly significantly younger than those without event/trigger factor. Stress was reported as triggering event in more than 90% of the patients who experience flares during their psoriatic disease course with more female than male patients. In a recent meta-analysis of 39 studies including more than 32,500 patients with psoriasis stress, as a trigger factor was described in 19 studies (n = 26,099) and 46% of patients believed that psoriasis was reactive to stress. In our study, 59.25% of the entire cohort reported about events/triggers aggravating psoriasis and of those 92% named stress as major factor. According to a systematic review, stress may occur episodically and this observation fits well with the description of the event type of ActiPso.

Stress induces pro-inflammatory cytokines and favours T-cell activation. Among infections reported by 33.1% of the patients identifying the event/trigger type, common cold was the most frequently named. Drugs as potential aggravating factor were only identified by 3.7%. These data for the first time classify trigger factors regarding their frequency and nature from the patients’ perspective and are important to adjust management procedures accordingly. Finally, the definition of ActiPso types resulted in the classification of eight types that can be documented and used for advanced psoriasis classification (Table 2).

Table 2 ActiPso types

| ActiPso Types               | Without additional event/trigger type | With additional event/trigger type |
|----------------------------|---------------------------------------|-----------------------------------|
| Type 1 ("stable")         | ActiPso 1                             | ActiPso 1                          |
| Type 2 ("unstable")       | ActiPso 2                             | ActiPso 2                          |
| Type 3 ("winter type")    | ActiPso 3                             | ActiPso 3                          |
| Type 4 ("summer type")    | ActiPso 4                             | ActiPso 4                          |

ActiPso scoring is preferentially suited for psoriasis patients living in areas with a summer–winter rather than with a constant climate. However, the global prevalence of psoriasis is highest in areas with changing seasons and this may be directly related to the impact of weather on psoriasis as described in many studies. In fact, the proportion of patients reporting trigger events was highest in ActiPso type 3 (winter type).

A limitation of the ActiPso approach may be the need for understanding the score sheet and how to interpret the curves exemplifying the four different activity types by the patients. However, with the final version of the ActiPso score sheet developed together with patients in several steps the rate of dropouts due to inconsistent information in the first study in 586 patients was very low (4.3%).

This new classification of patient-centric psoriatic disease activity may be suitable for an improved definition of individual disease courses and characteristics and to personalize management accordingly. The ActiPso classification enables to detect trigger factors and to initiate measures to prevent future flares. The data of the first study using ActiPso suggest that clinicians are encouraged to include stress as the main trigger factor into their psoriasis assessment and consider psychological interventions as adjuncts, particularly in those who identify as ‘stress-responders’.

ActiPso may be helpful in planning of treatment and discussion with patients about the expected therapeutic response. If the patient is an ActiPso type 2 (‘unstable’), the patients can be asked if activity is increasing or decreasing at the time of treatment initiation and to communicate f. ex. a less than expected response in a phase of increasing psoriasis activity at presentation.

Studies are in progress to confirm the validity of the different groups identified and to correlate ActiPso types with treatment success and failures particularly during long-term maintenance therapy. In clinical trials, selection of patients based on their ActiPso type could help to generate well-balanced cohorts regarding psoriatic disease activity. As a further outlook, it will be interesting to investigate whether a patient’s ActiPso type can be modified by long-term management of psoriasis.

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

Figure S1. ActiPso tool as the original German template.

Figure S2. Influence of treatment vs. no treatment related to the distribution of ActiPso types (Corrected Bonferroni P = 0.696).
Figure S3. Influence of local, systemic, or combination treatment on the distribution of ActiPso types (Corrected Bonferroni P > 0.05).
Figure S4. Distribution of gender in relation to the four ActiPso types.
Figure S5. Distribution of body weight (BMI) in relation to the four ActiPso types.