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Original article

What influences patients' opinion of remission and low disease activity in psoriatic arthritis? Principal component analysis of an international study

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Abstract

Objective. In PsA, the treatment objective is remission or low disease activity (LDA), but patients' perception of remission is poorly studied. This analysis aimed to identify factors associated with patient-defined remission.

Methods. This analysis uses ReFlaP data, an international PsA study, with remission defined as 'At this time, is your psoriatic arthritis in remission, if this means: you feel your disease is as good as gone?'. Variables associated with, first, patient-defined remission and, second, LDA were identified using multivariable logistic regression and principal component analysis (PCA) to explore correlated variables.

Results. Of 424 patients (50.2% male, mean age 52 years) with established disease, 94 (22.2%) reported themselves as being in remission and 191 (45.0%) as LDA alone. In multivariable analysis pain, psoriasis, impact of disease, physician opinion of symptoms from joint damage and Groll comorbidity index were independent predictors of remission. For LDA, results were similar. Using PCA, variance explained was 74% by five components for men and 80% by six components for women. The key component from PCA for remission was, for both sex, disease impact (Psoriatic Arthritis Impact of Disease, pain and HAQ) explaining 22.2–27.5% of variance. Other factors included musculoskeletal disease activity, chronicity/joint damage, psoriasis, enthesitis and CRP. For LDA, similar factors were identified but the variance explained was lower (64–68%).

Conclusion. Many factors impact on patients' opinion of remission, dominated by disease impact. Disease activity in multiple domains, chronicity/age, comorbidities and symptoms due to other conditions contribute to a robust model highlighting that patient-defined remission is multifaceted.

Trials registration. Clinicaltrials.gov, <http://clinicaltrials.gov>, NCT 03119805.

Key words: psoriatic arthritis, spondyloarthritis, remission, treat-to-target, outcome measures, low disease activity, disease activity, assessment

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Rheumatology key messages

- Many factors impact on patients' opinion of remission including disease activity, impact, chronicity and comorbidities.
- Similar different factors associate with low disease activity (LDA).
- The key component associated with remission and LDA was disease impact, including pain and function.

Introduction

PsA is an inflammatory musculoskeletal disease associated with psoriasis. In addition to involvement of the skin and peripheral joints, patients report other manifestations domains such as enthesitis, dactylitis, nails and axial disease. In 2015, the Tight Control of PsA (TICOPA) study showed that applying a treat-to-target (T2T) approach, aiming for achievement of the minimal disease activity (MDA) criteria, could improve clinical outcomes [1]. As a result of this study, international treatment recommendations have supported a T2T approach in routine practice [2, 3]. The increased interest in such a T2T approach in PsA, alongside increasing availability of effective therapeutics has focussed interest on the concepts of remission and low disease activity (LDA).

International T2T recommendations have suggested that remission should be the ultimate goal of therapy in PsA. Kavanaugh *et al.* proposed that remission in PsA should be characterized by 'a complete absence of disease activity, with no signs or symptoms of active disease' [4]. However, T2T recommendations recognize that remission may not be appropriate or attainable for all patients and low or minimal disease activity (LDA/MDA) may be a reasonable alternative target [5]. A number of different outcome measures have been recommended to define remission and LDA/MDA but few studies have addressed the patient perspective on remission/LDA.

The Remission and Flare in PsA (ReFlap) study was an observational study across 14 countries aiming to investigate the concepts of remission and flare in PsA (NCT 03119805). While there was a moderate-to-good agreement between potential targets based on outcome measures (such as the minimal disease activity criteria and disease activity in PsA definitions) and patients' opinion of remission/LDA, in a significant number of patients there was discordance between patients' opinion and the published outcome measure targets [6]. Little is known about the patients' perception of remission and what influences this opinion. The aim of this study was to utilize the ReFlap study data to further investigate the concept of patient-defined remission and identify which factors associate with patient-defined remission or LDA.

Methods**Study population**

Consecutive patients with rheumatologist-diagnosed PsA and more than 2 years' disease duration were

enrolled in 21 centres in 14 countries as part of the ReFlap Study (NCT03119805). The study design has been previously described [6]. This study uses only the baseline (cross-sectional) data. All patients gave written informed consent for their participation in the study. The ReFlap study was approved by the Institutional Review Board at the coordinating site (Sorbonne Universite, Paris, France) and at each participating site (Austria, Ethik Kommission Medizinische Universitat Wien; Brazil, Comissão Nacional de Ética em Pesquisa; Canada, Ottawa Health Science Network Research Ethics Board and Women's College Hospital Research Ethics Board; Estonia, Tallinna Meditsiiniuuringute Eetikakomitee; France, Comité de Protection des Personnes du Sud-Ouest et Outre-Mer 4; Germany, Ethik Kommission der Arztekammer Westfalen-Lippe und der Westfälischen Wilhelms-Universität; Italy, Comitato Etico dell'Università Sapienza; Romania, Consiliu Etic al Spitalului Clinic Sfanta Maria; Russia, VI Razumovskyy Saratov State Medical University Ethics Committee; Singapore, Singhealth Centralized Institutional Review Board; Spain, Comité Etico de Investigación Clínica del Hospital Clinic de Barcelona; Turkey, T.C. Hacettepe Üniversitesi Girisimsel Olmayan Klinik Arastirmalar Etik Kurulu; UK, South Central Oxford A Research Ethics Committee; and USA, Cleveland Clinic Institutional Review Board, Johns Hopkins Medicine Institutional Review Board). The ReFlap study complied with the Declaration of Helsinki.

Data collection

In addition to demographics, comorbidities [7] and disease characteristics, a PsA-specific data collection framework was used. Investigators recorded 66 swollen joint counts (SJC66, range 0–66) and 68 tender joint counts (TJC68, range 0–68), tender enthesal points using the Leeds Enthesitis Index (range 0–6), active psoriasis body surface area (range 0–100%), physician global assessment [numeric rating scale (NRS), 0–10 cm], and use of conventional systemic and biologic DMARDs (csDMARDs/bDMARDs). Comorbidities were quantified using the Functional Comorbidity Index or Groll index, which was developed to identify comorbidities particularly impacting on physical function rather than mortality. This index contains a wide range of comorbidities including diabetes, cardiovascular disease, depression/anxiety, gastrointestinal disease, degenerative spinal disease and obesity. Patient-reported outcomes (PROs) included pain, patient global assessment of overall disease activity, skin and joints (11-point NRS, 0–10), the Health Assessment Questionnaire

disability index (HAQ-DI, 0–3), and Psoriatic Arthritis Impact of Disease-12 items (PsAID, 0–10) [8, 9]. Higher PROs scores reflect worse patient status. After completing the physical examination for disease activity and the standard NRS, physicians were asked their opinion of the cause of the patient's symptoms. They scored on an NRS from 0 to 10 on how convinced they were that the symptoms were due to: (i) active inflammatory disease; (ii) severe disease (e.g. structural damage and deformed joints); and (iii) other diseases, not PsA (e.g. fibromyalgia, osteoarthritis and comorbidities) [10].

Remission and LDA separate questions for patients were developed with input from four patient research partners with PsA (France, Norway, Netherlands, UK) and was based on previous work in the field of rheumatoid arthritis [11, 12]. The phrasing was the following: 'At this time, is your psoriatic arthritis in remission, if this means: you feel your disease is as good as gone?' (for remission) and 'At this time, are you in low disease activity, if this means: your disease is in low activity but it's not as good as gone?' (for LDA). For analysis, remission was defined as those answering yes to the above remission question. LDA was defined as all those patients who identified as being in LDA excluding those patients who also reported that they were in remission.

Statistical analysis

Potential variables that may associate with the opinion of remission/LDA were analysed using univariate and then stepwise multivariable logistic regression using entry and exit *P*-values of 0.15 [13]. For this analysis only, rather than considering LDA patients separately, they were combined with remission for the LDA analysis. Otherwise, the non-LDA patients would have included both those in remission and those with high disease activity confusing the results. The variables included were demographic (age, sex, disease duration, Groll comorbidity index), disease-related (joint counts, psoriasis body surface area, enthesitis, CRP), PROs (pain, total PsAID score, HAQ) and physician opinion of cause of symptoms (symptoms due to PsA, to joint damage or to other disease all scored 0–10).

Correlation between the different variables was investigated using Spearman coefficients. We expected that the variables above would highly correlate due to the nature of the interaction between disease activity and impact. Therefore it was planned that if high levels of correlation (≥ 0.3) between variables were found, principal component analysis (PCA) was to be used to explore clustered components associated with both remission and with LDA (excluding remission) [14]. PCA was used to extract factors with orthogonal rotation. Factors with an eigenvalue ≥ 1 were included. As binary variables cannot be included in PCA analysis, PCA was performed separately for men and women to include sex in the model. Loading factors for key components (those with values $\geq \pm 0.5$ or second components with value $\geq \pm 0.3$) within each factor are provided alongside the eigenvalue and variance of each factor.

Results

Among 466 recruited patients, 31 did not meet inclusion criteria and 11 had missing data leaving 424 for analysis. A total of 94 (22.2%, $n = 59$ male) patients reported themselves as being in remission and 191 (45.0%, $n = 99$ male) in LDA/remission. The demographics of the patients included in the analysis (including the number of patients with missing data for each variable) is shown in Table 1.

When exploring factors associated with patients' opinion of remission using univariate analysis, many factors were associated with remission including sex, joint counts, psoriasis body surface area, enthesitis, pain, PsAID total score, HAQ and most of the physician global scores. Use of different therapies (conventional or bDMARDs) was not a predictor of remission although 61.7% of patients were receiving bDMARDs. In subsequent multivariable analysis, pain, psoriasis body surface area, PsAID total score, NRS of physician score of symptoms related to joint damage and Groll comorbidity index were identified as independent predictors. For LDA, results were similar except physician global score became significant and psoriasis measured by body surface area was no longer a significant predictor (Table 2).

Spearman correlation was used to explore the correlation between all these variables (Supplementary Table S1, available at *Rheumatology* online). A significant correlation was found between nearly all the variables with a particularly high correlation between the PROs, as expected. Correlation between joint counts (tender and swollen), physician global score, patient global score, PsAID, pain and HAQ was between 0.27 and 0.56 with correlation between patient global score, PsAID, pain and HAQ consistently over 0.8. Due to this high correlation, PCA was performed as planned.

In the PCA, the variables predicting remission were reduced to five (men) or six (women) components with eigenvalues of ≥ 1 , containing variables that correlated together. When combined, these five and six components explained a high proportion of the variance of remission (74% for men in five components and 80% for women in six components) suggesting that other factors had a minimal impact across individuals. The component that associated most strongly with remission across individuals, for both sex, appeared to reflect 'disease impact' (consisting of the correlated variables of PsAID score, pain and HAQ). 'Disease impact' accounted for 22–28% of the variance. Other components significantly associated with remission included musculoskeletal disease activity, chronicity/joint damage, psoriasis body surface area, enthesitis and CRP. For women, physician's opinion of symptoms related to other disease (e.g. fibromyalgia, osteoarthritis, comorbidities) was identified as a separate factor independent of the other variables (Table 3). For LDA, similar factors were identified (Table 4) but the percentage variance explained was lower (64–68%), suggesting more variation between individuals was explained by other elements not included in the model.

TABLE 1 Characteristics of 424 PsA cases included in the analysis

| Variable | All (n = 424) | Patient-defined remission (n = 94) | Patient-defined LDA (n = 191) | Other (n = 139) | Missing |
|--|-------------------|------------------------------------|-------------------------------|----------------------|---------|
| Male, n (%) | 213 (50.2) | 59 (62.8) | 99 (51.8) | 55 (39.6) | 0 |
| Age, years, mean (s.d.) | 52.1 (12.6) | 51.7 (13.1) | 53.4 (12.5) | 50.7 (12.3) | 0 |
| PsA duration, median (IQ) | 8 (4, 15) | 8 (4, 17) | 8 (4, 15) | 9 (4, 13) | 7 |
| Current smoker, n (%) | 75 (17.7) | 10 (10.6) | 30 (15.7) | 35 (25.2) | 45 |
| Current csDMARDs, n (%) | 252 (59.4) | 57 (60.6) | 115 (60.2) | 80 (57.6) | 0 |
| Current biologic, n (%) | 238 (56.1) | 58 (61.7) | 110 (57.6) | 70 (50.4) | 0 |
| Current steroid use, n (%) | 65 (15.3) | 9 (9.6) | 25 (13.1) | 31 (22.3) | 64 |
| Groll index, median (IQ) | 1 (0, 2) | 0 (0, 1) | 1 (0, 2) | 1 (0, 2) | 21 |
| Tender joint count, median (IQ) | 1 (0, 4) | 0 (0, 1) | 1 (0, 3) | 3.5 (1, 10.25) | 2 |
| Swollen joint count, median (IQ) | 0 (0, 2) | 0 (0, 0) | 0 (0, 1) | 1 (0, 4) | 2 |
| No psoriasis, n (%) | 145 (34.2) | 46 (48.9) | 67 (35.1) | 32 (23) | 22 |
| Mild psoriasis, n (%) | 219 (51.7) | 41 (43.6) | 101 (52.9) | 77 (55.4) | |
| Moderate psoriasis, n (%) | 31 (7.3) | 3 (3.2) | 15 (7.9) | 13 (9.4) | |
| Severe psoriasis, n (%) | 7 (1.7) | 0 | 2 (1) | 5 (3.6) | |
| Enthesitis score, median (IQR) | 0 (0, 0) | 0 (0, 0) | 0 (0, 0) | 0 (0, 2) | 0 |
| CRP, mg/dL, median (IQR) | 0.3 (0.1, 0.9) | 0.17 (0.06, 0.95) | 0.3 (0.1, 0.73) | 0.5 (0.13, 1.6) | 13 |
| Patient pain, median (IQR) | 4 (2, 6) | 1 (0, 3) | 3 (2, 5) | 7 (5, 8) | 0 |
| Patient global, median (IQR) | 4 (2, 6) | 2 (0, 4) | 3 (2, 5) | 7 (5, 8) | 1 |
| PsAID, median (IQR) | 2.85 (1.35, 4.95) | 1.2 (0.3, 2.4) | 2.28 (1.35, 4.10) | 4.95 (3.80, 6.85) | 1 |
| HAQ, median (IQR) | 0.375 (0, 1) | 0 (0, 0.375) | 0.25 (0, 0.875) | 0.875 (0.375, 1.375) | 6 |
| Physician global, median (IQR) | 2 (1, 5) | 1 (0, 2) | 2 (1, 4) | 5 (3, 7) | 3 |
| Physician active disease, median (IQR) | 4 (1, 8) | 1 (0, 4) | 3 (1, 8) | 7 (2.5, 9) | 41 |
| Physician damage, median (IQR) | 1 (0, 3) | 0 (0, 2) | 1 (0, 3) | 1 (0, 4) | 3 |
| Physician other disease, median (IQR) | 1 (0, 4) | 0 (0, 2) | 1 (0, 4) | 2 (0, 5) | 3 |

Results are reported as mean (s.d.) for normally distributed data or median (IQ) for non-normal data. csDMARD: conventional systemic DMARD; IQR: interquartile range; LDA: low disease activity; PsAID: Psoriatic Arthritis Impact of Disease.

TABLE 2 Multivariable analysis of factors associated with patients' opinion of remission and LDA

| Variable | Remission | | | LDA | | |
|---|------------|--------------|---------|------------|--------------|---------|
| | Odds ratio | 95% CI | P-value | Odds ratio | 95% CI | P-value |
| Groll functional comorbidity index | 1.216 | 0.958, 1.543 | 0.11 | 1.286 | 1.032, 1.603 | 0.03 |
| Psoriasis body surface area | 0.541 | 0.335, 0.875 | 0.01 | | | |
| Patient pain score | 0.776 | 0.636, 0.948 | 0.01 | 0.780 | 0.655, 0.929 | 0.01 |
| PsAID total score | 0.731 | 0.571, 0.935 | 0.01 | 0.746 | 0.610, 0.911 | <0.01 |
| Physician global of arthritis | | | | 0.821 | 0.717, 0.939 | <0.01 |
| Physician score of symptoms due to joint damage | 1.113 | 0.999, 1.240 | 0.05 | 1.110 | 0.987, 1.249 | 0.08 |

LDA: low disease activity; PsAID: Psoriatic Arthritis Impact of Disease.

Discussion

This study is the first to try to explore what remission and LDA mean to patients with PsA using patient-reported and physician assessments specific to PsA. Development of clinical remission criteria in PsA has highlighted the importance ascribed to disease activity perceived and measured by clinicians using physical examination (e.g. tender/swollen joint counts, Psoriasis area and severity index (PASI) score etc). This analysis showed that while doctors may consider remission in

terms of musculoskeletal and skin disease activity, disease symptoms and impact (reflected by pain, physical function impairment and high PsAID scores) are the strongest drivers for the patients' opinion. Reflecting the multidimensional nature of PsA, in addition to this main component, disease activity in all domains, chronicity/age, comorbidities and other conditions also contributed, highlighting how multifaceted remission can be for individuals. The PCA, particularly for those in remission, resulted in a robust model accounting for 74–80% of the variance.

TABLE 3 PCA of factors associated with patients' opinion of remission with percentage of variance explained

| Factor | Men | | | | Women | | | |
|--------|---------------------------------|----------------|------------|----------|---------------------------------|----------------|------------|----------|
| | Components | Factor loading | Eigenvalue | Variance | Components | Factor loading | Eigenvalue | Variance |
| 1 | Pain | 0.815 | 5.1 | 27.5 | Pain | 0.881 | 3.3 | 22.2 |
| | PsAID | 0.745 | | | PsAID | 0.872 | | |
| | HAQ | 0.599 | | | HAQ | 0.787 | | |
| | TJC | 0.610 | | | Physician global | 0.741 | | |
| | SJC | 0.778 | | | | | | |
| 2 | Physician global | 0.914 | 1.7 | 17.2 | TJC | 0.966 | | |
| | Age | 0.724 | | | SJC | 0.815 | | |
| | Comorbidities | 0.711 | | | Enthesitis | 0.961 | | |
| | Symptoms from joint damage | 0.674 | | | | | | |
| | Other diseases causing symptoms | 0.591 | | | | | | |
| 3 | Psoriasis | 0.764 | 1.3 | 10.6 | Age | 0.452 | 1.8 | 11.6 |
| | Enthesitis | 0.697 | | | Comorbidities | 0.854 | | |
| | | | | | Psoriasis | -0.616 | | |
| 4 | Disease duration | -0.922 | 1.1 | 9.99 | Disease duration | 0.810 | 1.2 | 9.27 |
| | TJC | 0.460 | | | Symptoms from joint damage | 0.520 | | |
| 5 | CRP | 0.908 | 1.0 | 7.99 | CRP | 0.924 | 1.1 | 9.13 |
| | | | | | Psoriasis | 0.482 | | |
| | | | | | Other diseases causing symptoms | 0.939 | 1.0 | 9.11 |

PsAID: Psoriatic Arthritis Impact of Disease; SJC: swollen joint count; TJC: tender joint count.

TABLE 4 Principal component analysis of factors associated with patients' opinion of LDA with percentage of variance explained

| Factor | Men | | | | Women | | | | |
|--------|---------------------------------|----------------|------------|----------|--------|---------------------------------|----------------|------------|----------|
| | Components | Factor loading | Eigenvalue | Variance | Factor | Components | Factor loading | Eigenvalue | Variance |
| 1 | Pain | 0.863 | 3.7 | 19.6 | 1 | Pain | 0.676 | 3.4 | 20.6 |
| | PsAID | 0.896 | | | | PsAID | 0.804 | | |
| | HAQ | 0.628 | | | | HAQ | 0.687 | | |
| | SJC | 0.359 | | | | Physician global | 0.727 | | |
| | Physician global | 0.663 | | | | TJC | 0.564 | | |
| 2 | Comorbidities | 0.623 | 2.1 | 15.1 | 2 | Other diseases causing symptoms | 0.616 | 1.9 | 13.3 |
| | Symptoms from joint damage | 0.738 | | | | Comorbidities | 0.533 | | |
| | Other diseases causing symptoms | 0.768 | | | | Age | 0.678 | | |
| | TJC | 0.870 | 1.5 | 14.6 | 3 | Disease duration | 0.628 | 1.5 | 12.3 |
| | Enthesitis | 0.842 | | | | CRP | 0.611 | | |
| 4 | Age | 0.773 | 1.3 | 11.0 | 4 | SJC | 0.554 | 1.3 | 9.8 |
| | CRP | -0.675 | | | | Psoriasis | 0.475 | | |
| | Psoriasis | 0.811 | 1.1 | 9.0 | | Symptoms from joint damage | 0.633 | | |
| | Disease duration | 0.548 | | | | | | | |
| | CRP | 0.356 | | | | | | | |

LDA: low disease activity; PsAID: Psoriatic Arthritis Impact of Disease; SJC: swollen joint count; TJC: tender joint count.

This study provides insight into remission in PsA using data from a large international study with strong involvement of patient research partners in the study design, outcome selection, analysis and interpretation. A large range of disease-specific and generic clinical and PROs were collected within the ReFlaP study allowing detailed analysis and insight into predictors of remission. The study population represents a wide range of disease activity, burden and treatment representative of a real-world population. The analysis is the first to focus quantitatively rather than qualitatively on what influences a patients' perspective of remission. It also highlights some sex differences previously identified in this dataset [15] and other PsA studies, although disease impact (reflected by pain, PsAID and HAQ) was a key factor associated with remission in both sexes.

This study does have some limitations. The study recruited patients with over 2 years' disease duration to ensure that patients had experience of living with PsA. It was thought that this would help with their judgement of disease states such as remission and flare. However, this does mean that generalization to patients with early disease should be done with caution and additional investigation is recommended in this group. Around half of the patients were receiving bDMARDs which may also limit generalizability but in the analyses, current class of treatment (csDMARDs, bDMARDs and steroids) was not a significant predictor of remission. Across the entire cohort, disease activity was relatively low, particularly in terms of skin disease, which is reflective of our routine practice but may limit generalizability to other patient groups, for example those reviewed in dermatology services who typically have more severe skin disease.

This study provides insight into patients' opinion of remission, showing that many factors contribute but it is dominated by disease symptoms and impact reflected by pain, limitations in physical function and high PsAID scores. The multifaceted nature of PsA is highlighted by additional contribution of disease activity in multiple domains, chronicity/age, comorbidities and other conditions, which all combine into a robust model. This reflects previous work on key domains of psoriatic disease identified by patients when developing the 2016 Outcome Measures in Rheumatology (OMERACT) core domain set [16] and the PsAID score [8, 17]. Previous work has identified that the PROs within treatment targets, such as the patient's global assessment of disease, are less often achieved [18]. It was suggested by Queiro [18] that important aspects that the patient attributes to their illness are not fully captured in the PsA composite measures and the data reported here provide further details on these aspects.

These data improve our understanding of the focus on remission as perceived by patients with PsA. Understanding the patient perspective of remission is key to improving the definition of efficacy and effectiveness and to establishing optimal treatment outcomes. While disease impact may not always relate directly to disease

activity, both must be considered when making therapeutic decisions. This understanding can support effective physician-patient communication and shared decision making, particularly when using a T2T approach.

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Data availability statement

The data underlying this article were provided by the ReFlaP team by permission. Data will be shared on request to the ReFlaP corresponding author (L. Gossec) with permission of the ReFlaP study steering committee.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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