Swollen joint count in psoriatic arthritis is associated with progressive radiological damage in hands and feet

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Abstract

Objectives
Psoriatic arthritis (PsA) may progress to joint damage. Determining clinical predictors of joint damage assessed by radiography is important. The aim of this study was to determine clinical factors as possible predictors for radiological damage in hands and feet of PsA patients with a 12-month follow-up.

Methods
We conducted a retrospective study on 53 PsA patients who were taking disease-modifying anti-rheumatic drugs (DMARDs) and/or tumour necrosis factor (TNF)-alpha-blockers at a fixed dosage. The patients were observed in 118 follow-up visits (intervals of 12 months ± 3 months), according to a clinical and radiological protocol which included the documentation of the number of swollen and tender joints in hands and feet, the applied therapy, psoriasis, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and global health assessment. Outcome was defined as radiographic damage of hands and feet (Ratingen score). For the statistical analysis the Chi-Square test for 2x2 crosstables (with Fisher’s correction, as required) was used.

Results
Progressive radiological damage was more frequent among patients with an increasing swollen joint count (8 of 26 visits; 30.8%) than among those with a stable or decreased number of swollen joints (5 of 89 visits; 5.6%; p=0.001). The analysis of the patients stratified into the different treatment modalities resulted in a significant higher rate of radiological progress (20.8%) in patients on DMARD therapy compared with TNF-alpha blocking agents (0%) (p=0.009).

Conclusion
During a 12-month follow-up of PsA patients, an increasing number of swollen joints heralds progression of radiological damage. TNF-alpha-blocker therapy appears to be superior to DMARDs in the protection from radiological progress.

Key words
psoriatic arthritis, radiography, risk factors, tumour necrosis factor alpha inhibitors
Introduction
Psoriatic arthritis (PsA) is a heterogeneous inflammatory rheumatologic disorder with inflammation of the spine, enthesitis, and peripheral joints, affecting 6–39% of the patients suffering from psoriasis (1, 2). In previous studies, 20% of the patients were found to have >5 deformed joints at the first visit to the clinic. In addition, 11% showed a significant decline in the physical function (3). Other investigators have found that 47% of the patients developed erosive disease within 2 years of onset of symptoms (4).
Patients often suffer from joint destruction and a reduced quality of life (5). Moreover, PsA is prone to progressive disability and is associated with an increased risk of health-related retirement and an increased mortality rate compared to the general population (6).
If patients could be detected at an early stage, physicians could adapt their treatment to the course of PsA. The treatment includes DMARDs like methotrexate, ciclosporine A, and leflunomide (26); in addition, the effectiveness of the TNF-alpha antagonist agents in the treatment of inflammatory arthritis in PsA patients have been proved in several studies (7–9). Other studies have examined the role of clinical assessment tools in the course of disease (10, 11). Genetic variations in candidate genes encoding for TNF-alpha, PTPN22 or MHC (e.g. Human leukocyte antigen Cw6), are supposed to be associated with the occurrence and severity of PsA in the population (12–15). Further work has investigated the possible role of clinical variables as prognostic factors for progressive damage: the number of active inflamed joints, particularly swollen joints, the current level of damage, the disease duration at presentation and the initial ESR level (11, 25). Furthermore, the recently published study of Cresswell et al. (25) has demonstrated that tenderness and swelling of the joints of the foot and/or hand seem to predict radiological joint damage in PsA.
In PsA conventional x-ray is basically inferior to other imaging modalities like CT or MRI; however, most of the studies with a follow-up design of imaging prefer conventional radiography because of the practical character and established radiological scoring systems. The aim of the current study was therefore the identification in PsA patients of clinical variables as possible predictors for radiographic damage in a 12-month follow-up.

Patients and methods

Patient selection
The medical records of 69 PsA patients with documented follow-up over more than 12 months were available, of whom 53 patients were included in the analysis. Sixteen patients were excluded because the follow-up was incomplete: either the clinical data including drug administration and/or the radiographic data were insufficient.
We conducted a retrospective study on 118 follow-up visits of 53 patients treated between 2004 and 2009 at the rheumatology departments of Saarland University Medical School and the city hospital of Ludwigshafen, Germany. All patients satisfied the CASPAR criteria for PsA (16). Inclusion criteria were: PsA patients under therapy with DMARDs and/or TNF-alpha-blockers; documented clinical and radiological course of disease during the follow-up of the PsA patients (including baseline x-ray imaging and at least one follow-up imaging of the hands and feet). Table I shows the demographic and baseline clinical characteristics of the study participants. Relating to the different treatment regimes, the study population was stratified into patients treated with DMARDs and those receiving TNF-alpha blocking agents.

Treatment regime
The different anti-rheumatic drugs and their dosages administered to the study participants are outlined in Table I and II. Only patients abiding by the medication and the dosage regime were included in the study. Seven patients were excluded from the study: three patients stopped the DMARD therapy after more than three-fold elevation of liver enzyme levels. Three patients discontinued treatment with DMARDs, two because of a lack of efficacy and one patient had increasing serum creatinine concentrations. TNF-alpha block-
ers were given in the following mean doses: etanercept 50 mg/week and adalimumab 40 mg every two weeks. One patient stopped the treatment with adalimumab due to inefficiency. No severe allergies or infectious complications were observed among the study population.

In addition to the specific antirheumatic therapy with DMARDs or TNF-α blockers, 26 patients (49%) were on concomitant treatment with fixed doses of NSAIDs and 19 patients (35.8%) on corticosteroids (10 mg per day prednisolone or less) for the time of observation.

Study protocol
The follow-up of PsA patients was documented in medical records containing the medical history and a physical examination including rheumatologic assessment of tender and swollen joints. Furthermore, physicians recorded demographic characteristics of the patients such as sex, age, family history, arthritis duration, time of onset of psoriasis, and the medication actually taken by the patient; a routine laboratory assessment including C-reactive protein (CRP) and elevated sedimentation rate (ESR) was carried out. For all patients x-ray radiographs of both hands and feet were available. Patients were followed up at 12-month (±3-month) intervals. The radiologist was responsible for reading the x-rays and evaluating them according to the scoring system (see below) at the end of the study.

Assessment of clinical activity of PsA
Patients were seen at baseline and then at intervals of approximately 12 months by the same rheumatologist. The physical function and clinical disease activity of the joints were recorded at all visits. Physicians examined the clinical disease activity using the American College of Rheumatology (ACR) 66/68 counts for swollen and tender joints. The following 68 joints were assessed for tenderness: all these joints, except the hips, were also examined for swelling.

The global health assessment was evaluated by patients using a scoring system ranging from 0 (no activity) to 4 (very high disease activity), according to the functional class model previously published (11). The severity of psoriasis was determined by the presence of nail lesions and the percentage of the body surface area (BSA) involved. The psoriasis was rated as mild (<5% of the BSA), moderate (5–20% of the BSA, or lower if the hands and feet were involved), moderate-severe (20–30% of the BSA, or lower if the hands and feet were involved) and severe (>30% of the BSA). Finally, the documentation of the medication regime by each patient was complete. It included the circumstances in case the treatment regime had been changed during the follow-up interval.

Assessment of radiological damage in PsA
An x-ray radiography was performed by posterior-anterior and optional semisupine projections of the hands and feet. The radiographic damage grade was measured with the Osirix medical imaging software. Radiographic joint damage was defined as progressive if new lesions like erosions or proliferations had been detected or if pre-existent lesions had increased.

In order to classify radiological damage accurately, the evaluation of any radiographic joint damage was performed according to the scoring system established by the American Society for Radiation Oncology (12,30). This method is based on a semiquantitative scale ranging from 0 to 4 (normal articular structures to severe damage).

Table I. Characteristics of patients at first observational interval.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>53</td>
</tr>
<tr>
<td>Female/male</td>
<td>20/33</td>
</tr>
<tr>
<td>Mean age at clinic entry (years) (min–max)</td>
<td>54.8 (23–73)</td>
</tr>
<tr>
<td>Mean duration of disease before therapy (months) (min–max)</td>
<td>39.7 (0–240)</td>
</tr>
<tr>
<td>Family history of psoriasis (arthritis) (number of patients)</td>
<td>56.8% (25/44)</td>
</tr>
<tr>
<td>Mean number of tender joints (all joints) (min–max)</td>
<td>6.6 (0–29)</td>
</tr>
<tr>
<td>Mean number of swollen joints (all joints) (min–max)</td>
<td>4.7 (0–30)</td>
</tr>
</tbody>
</table>

Physician global assessment (number of patients)
- good: 13.2% (7/53)
- medium: 52.8% (28/53)
- poor: 34% (18/53)

Medication
- NSAIDs: 49% (26/53)
- corticosteroids: 35.8% (19/53)
- DMARDs: 74% (39/53)
- TNF-α blocker: 26% (14/53)


Table II. Anti-rheumatic drugs with their therapeutic ranges and the number of application intervals.

<table>
<thead>
<tr>
<th>Drugs used</th>
<th>Dosage (mean)</th>
<th>Ranges</th>
<th>Number of observation intervals n=118 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ibuprofen</td>
<td>828.6±458.9 mg/day</td>
<td>600–2400 mg</td>
<td>12 (10.2%)</td>
</tr>
<tr>
<td>diclofenac</td>
<td>86±48 mg/day</td>
<td>25–150 mg</td>
<td>10 (8.5%)</td>
</tr>
<tr>
<td>rofecoxibe</td>
<td>25 mg/day</td>
<td>25 mg</td>
<td>6 (5.1%)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>4.8±4.9 mg/day</td>
<td>2.5–10 mg</td>
<td>41 (34.8%)</td>
</tr>
<tr>
<td>(prednisone-equivalent)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DMARDs
- sulfasalazine | 1947.4±437.6 mg/day | 1000–3000 mg | 23 (19.5%) |
- methotrexate | 15.8±3.8 mg/week | 10–20 mg | 80 (67.8%) |
- leflunomide | 19.4±2.5 mg/day | 10–20 mg | 19 (16.1%) |
- cyclosporine A | 225±86.6 mg/day | 150–300 mg | 4 (3.4%) |
| TNF-α blocker | etanercept | 45.8±9.58 mg/week | 25–50 mg | 19 (16.1%) |
| | adalimumab | 40 mg/every 2 weeks | 40 mg | 16 (13.6%) |

logical damage was based on the Ratingen scoring system that was developed specifically for PsA (17). It includes 40 joints of the hands and feet: eight distal interphalangeal joints, two interphalan-
geal joints of the thumbs, eight proximal interphalangeal joints, ten metacar-
pophalangeal joints, both wrists, both IPs of the great toes, and second to fifth metatarsophalangeal joint.
All joints were scored separately for destruction (on a 0–5 scale) and proli-
feration (on a 0–4 scale), which could be summed up to give the total score (0–360).
Joint surface destruction was catego-
rised on a 0–5 scale as: 0. normal, 1. de-
struction <10% of the total joint surface,
2. destruction of 11–25%, 3. destruction of
26–50%, 4. destruction of 51–75%,
5. destruction >75%.
The proliferation grade was determined
on a 0–4 scale: 0. normal, 1. bone
growth less than 25% of the original
diameter of the bone, 2. bone growth
between 25–50%, 3. bone growth be-
tween 51–75%, and 4. ankylosis.

Statistical analysis and
principal outcome variables
The aim of this retrospective study was
to investigate if any of the mentioned
clinical variables had a predictive value
for progressive radiological damage. As x-rays were taken at a mean time of
12-month intervals, only visits at which
both clinical and radiological damage
were assessed were evaluated.
The main outcome was the progres-
sion of radiographic damage between
two clinic visits; it was estimated by
subtracting the initial score of dam-
age from the score measured after one
year. To analyse the relations between
the clinical variables and their possi-
ble association with the development
of radiological progression, the data
were stratified into two groups in order
to describe the changes in the scores
of joint destruction and clinical damage
after one year: the first group showed
a stable or regressive damage score and
the second group had a worse damage
score compared to the last examination.
For statistical analyses the Chi-square
test for 2x2 crosstables (with Fisher’s
correction, as required) was used, and

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Radiological joint damage</th>
<th>Odds ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>progressive</td>
<td>stable or regressive</td>
<td></td>
</tr>
<tr>
<td>Clinical health assessment</td>
<td></td>
<td></td>
<td>0.822</td>
</tr>
<tr>
<td>progressive stable or regressive</td>
<td>10% (3/30)</td>
<td>90% (27/30)</td>
<td>[0.210–3.214]</td>
</tr>
<tr>
<td>Number of tender joints</td>
<td></td>
<td></td>
<td>2.141</td>
</tr>
<tr>
<td>progressive stable or regressive</td>
<td>17.1% (6/35)</td>
<td>82.9% (29/35)</td>
<td>[0.668–6.967]</td>
</tr>
<tr>
<td>Number of swollen joints progressive</td>
<td></td>
<td></td>
<td>7.503</td>
</tr>
<tr>
<td>stable or regressive</td>
<td>30.8% (8/26)</td>
<td>69.2% (18/26)</td>
<td>[2.187–25.490]</td>
</tr>
<tr>
<td>ESR level</td>
<td></td>
<td></td>
<td>0.891</td>
</tr>
<tr>
<td>progressive stable or regressive</td>
<td>10.5% (4/38)</td>
<td>89.5% (34/38)</td>
<td>[0.242–3.274]</td>
</tr>
<tr>
<td>CRP level</td>
<td></td>
<td></td>
<td>1.257</td>
</tr>
<tr>
<td>progressive stable or regressive</td>
<td>11.8% (4/34)</td>
<td>88.2% (30/34)</td>
<td>[0.342–4.622]</td>
</tr>
<tr>
<td>Psoriatic skin damage progressive</td>
<td></td>
<td></td>
<td>0.850</td>
</tr>
<tr>
<td>stable or regressive</td>
<td>9.1% (1/11)</td>
<td>90.9% (10/11)</td>
<td>[0.098–7.352]</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td>53.772</td>
</tr>
<tr>
<td>DMARDs</td>
<td>20.8% (14/67)</td>
<td>79.2% (53/67)</td>
<td>[0.491–33.647]</td>
</tr>
<tr>
<td>TNF-α blocker</td>
<td>0% (0/28)</td>
<td>100% (28/28)</td>
<td></td>
</tr>
</tbody>
</table>

(…): number of observation intervals; […]: confidence interval; PsA: psoriatic arthritis; ESR: eryth-
rocyte sedimentation rate; CRP: C-reactive protein; DMARD: disease modifying antirheumatic drug;
TNF-α-blocker: tumour necrosis factor-α blocker.

Radiological damage and
level of treatment
Altogether, 67 follow-up intervals were eval-
uated, during which 39 patients
were treated with DMARDs (Table I
and II). In 14 of 67 (20.8%) intervals
(12 patients), a progression of radi-
ological damage was found (Table III).
The mean change in the Ratingen Score
was +2.27±3.58. Six patients discon-
tinued the treatment with DMARDs and
changed to the biological arm. In
the further follow-up all patients showed an
inhibition of radiographic progression
(Ratingen score -0.71±1.11).
Biologics were administrated in a total
of 28 follow-up intervals of 14 patients
(Table I). None of these patients showed
a radiological progression (Ratingen
score -0.22±0.66) (p=0.009) (Table III,
Fig. 1).

Radiological damage and
swollen joint count
The number of actively inflamed joints also correlated with radiographic dam-

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In 8 of 26 visits (30.8%) of the follow-up, patients with swollen joints also showed radiological progress (Ratingen score +2.55 ±3.94), whereas only 5 of 89 visits (5.6%) of the follow-up patients with a stable or even decreased swollen joint count showed new or progressive radiological damage (Ratingen score +1.75 ±1.5) (p = 0.001) (Table III, Fig. 2).

The numbers of tender joints, skin damage, nail involvement, ESR, CRP and global health assessment did not correlate with any radiographic outcome (Table III).

Discussion

This study on PsA patients documents that an increasing number of swollen joints is significantly associated with progression of radiological damage. In PsA, joint damage as determined by previously published assessment tools and histology is an important outcome measure (18, 19). Some patients develop damage early and rapidly progress towards an “arthritis mutilans” with massive joint destruction. It is therefore important to detect these patients at an early stage of disease and to start an appropriate treatment. In this context, the meaningfulness of different clinical parameters as potential predictors for progressive radiological damage is of great importance. In agreement with our data, previous studies pointed to the role of clinical variables as prognostic factors for progressive radiological damage in the long-term observation: the number of actively inflamed joints, particularly the swollen joints, the number of clinically damaged joints and the initial ESR at presentation. These variables could be associated with progression of joint disease and early mortality in PsA (11, 20). Furthermore, a polyarticular joint inflammation at first clinic presentation was found as a possible predictor for progression as well (11, 21). In addition, the recently published data from Cresswell et al. (25) presented a clear association of both joint tenderness and welling with radiological damage in hands and feet. In that study, all patients did not show any radiographic damage at the beginning of the follow-up period.

In the present study, the radiological examination also focussed on the joints of the hands and feet as these are the joints that are primarily involved in the inflammatory process. However, the evaluation of the radiological data is based on follow-up intervals and not on patients. This procedure means that one patient is evaluated in one observation interval as “stable or regressive” and possibly in the next interval as “progressive”. Furthermore, in contrast with previous studies, PsA patients were also included into the analysis with already proved radiological damage. This strategy allowed a dynamic observation of different developments in the course of disease over the observation intervals. However, the limitation of this procedure model is the presence of inter- and intraindividual interferences influencing the meaningfulness of the presented data with regard to statistically significant differences. Furthermore, the study has recruited a relatively small number of participants (only fifty-three) for the retrospective analysis based on clinical and radiological data out of medical records; therefore, a sensible statistical analysis by a multivariate analysis model was not possible. Nevertheless,
the data also seem to verify the importance of the clinical parameter of swelling joint count as a predictive factor for radiological damage.

The radiological joint destruction was quantified with the Ratingen score (17). In this study, the Ratingen score was preferred over Larson score because it only scores bony changes of the joints: we did not consider soft tissue swelling as a criterium, because its evaluation might be influenced by the quality of the radiograph, especially the hardness of the x-ray source. In addition, it only reflects the activity of the inflammatory process in the soft tissues and is often quickly reversible.

In our study, 20.8% of the patients taking DMARDs had a progressive erosion score. In contrast, none of the patients treated with anti-TNF agents showed an increased radiological joint damage. Although the influence of the treatment modality was not the primary aim of the present study, the subgroup analysis of the data showed that PsA patients on medication with TNF-alpha-blockers, unlike the patients on DMARDS, developed neither new erosions nor a progression of existent erosions. This result supports earlier studies, which observed that anti-TNF agents actually have higher clinical and radiological response rates in PsA patients than DMARDS. In addition to a beneficial effect on the clinical symptoms of joint inflammation, the anti-TNF antagonist agents also showed potential to slow down, and to some extent even revert, radiographic joint damage in PsA (7-9, 22-24, 27).

Conclusion
The presented data indicate that an increasing swollen joint count in patients with PsA is associated with progression of radiological damage.

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Authors’ contributions
P. Simon collected and analysed the data and wrote the main paper. G. Assmann conceived and supervised the study, corrected the paper and gave conceptual advice and support. R. Bergner provided additional clinical data from the rheumatological centre of the city of Ludwigshafen. M. Schreiber scanned and converted conventional x-rays into high quality digital files (OsiriX). C. Pröhler provided derma
tological data to help us estimate their course of psoriasis. M. Pfreundschuh was involved in the interpretation of the clinical data. All the authors were included in the writing and correction of the manuscript, and they all read and approved the final manuscript.

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