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ORIGINAL RESEARCH

Fluorescence-optical imaging as a promising easy-to-use imaging biomarker to increase early psoriatic arthritis detection in patients with psoriasis: a cross-sectional cohort study with follow-up

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ABSTRACT

Objectives To evaluate the ability of fluorescence-optical imaging (FOI) to detect preclinical musculoskeletal inflammatory signs in patients with skin psoriasis at risk of developing psoriatic arthritis (PsA).

Methods This investigator-initiated prospective exploratory study evaluated adult patients with psoriasis with musculoskeletal complaints and/or nail psoriasis within the last 6 months. Patients underwent a comprehensive rheumatological clinical examination (CE) along with musculoskeletal ultrasound (MSUS) and FOI of both hands at a single visit. Patients with CE–/MSUS–/FOI+ findings had MRI performed on the symptomatic or dominant hand within 7 days. If MRI was negative, the patients were followed over 2 years for the onset of clinically manifest PsA.

Results A total of 389 patients were referred from dermatology centres and evaluated at 14 rheumatology sites in Germany. Seventy-seven (20%) patients with CE–/US–/FOI– were considered to have psoriasis only. PsA was diagnosed in 140/389 patients (36%) based on CE alone and in another 55 patients (14%) by additional MSUS; overall, 50% of the patient cohort was diagnosed with PsA. One hundred sixteen patients (30%) were FOI+ (CE–) of which 40 (37%) were FOI+/MRI+. In the 2-year follow-up of the FOI+/CE– patients, clinical PsA was confirmed in another 12%.

Conclusion FOI is a promising method for the detection of signs of musculoskeletal inflammation in hands that may serve as an early imaging biomarker for transitions from psoriasis to PsA. This imaging technique has the potential to detect PsA in at-risk patients with psoriasis, reduce time to PsA diagnosis and improve patient outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Approximately 25% of patients with psoriasis eventually develop psoriatic arthritis (PsA), but there is currently no validated biomarker for identifying patients with psoriasis who are likely to develop PsA.

⇒ Fluorescence-optical imaging (FOI) allows assessment of disturbed microcirculation in the joints of both hands.

WHAT THIS STUDY ADDS

⇒ In the investigator-initiated XCITING study, rheumatological clinical evaluations (CE) confirmed a diagnosis of PsA in 50% of patients with psoriasis at risk for PsA and an additional 30% of patients were positive on FOI (FOI+).

⇒ In the 2-year follow-up period (XTEND study), these FOI+/CE– patients developed PsA at a higher incidence (12%) than expected based on published annual incidence rates (approximately 4% per year).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ FOI may detect a preclinical phase in the transition from psoriasis to PsA based on increased vascularisation that may evade detection by other imaging modalities (eg, MRI), and therefore could have potential as a screening method for non-rheumatologists, including dermatologists and general practitioners.

⇒ Additional studies are required to evaluate whether FOI has the potential to predict PsA development in patients with psoriasis.

INTRODUCTION

Psoriasis is a common chronic inflammatory skin disease that affects roughly 2% of individuals in Europe.[1] Approximately one-quarter of patients with psoriasis will develop psoriatic arthritis (PsA).[2–4] In most patients, skin symptoms precede joint involvement.[5] Patients with psoriasis therefore represent a specific

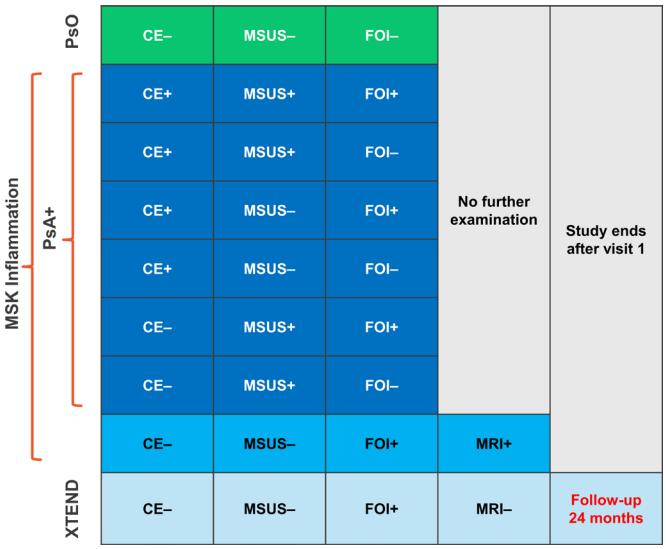

Figure 1 Study design of the XCITING and XTEND studies. CE, clinical examination; FOI, fluorescence-optical imaging; MSK, musculoskeletal; MSUS, musculoskeletal ultrasound; PsA, psoriatic arthritis; PsO, psoriasis.

population at elevated risk of arthritis that may benefit from early diagnostic efforts. Although several risk factors for musculoskeletal involvement have been suggested,[6–8] there is no rapid, reliable method for detection of early PsA or prediction of PsA onset in patients with psoriasis available. Since early initiation of PsA treatment is associated with improved long-term outcomes,[9] the marker-based identification of PsA-prone patients has important implications for disease course and patient function.

Even before the diagnosis of PsA, patients who ultimately develop the disease experience unspecific musculoskeletal symptoms, fatigue and stiffness.[10 11] The events underlying this transition from psoriasis to PsA are not well understood, although several models have been suggested.[12] Scher *et al* have proposed that the transition from psoriasis to symptomatic PsA involves three distinct phases.[12] In the earliest 'preclinical' phase, the immune system has been primed to initiate changes leading to PsA, but there are no obvious disease symptoms or markers. Later stages are marked by subclinical synovitis, alterations in biomarkers and the development of mild symptoms. Inflammatory changes at this stage can often be detected by sensitive imaging techniques such as musculoskeletal ultrasound (MSUS) or MRI. Currently, however, there is no validated detection procedure for identifying the earliest stage in the transition from psoriasis to PsA and asymptomatic synovio-entheseal abnormalities that may not end in PsA development.[13]

Changes in synovial vascularisation combined with increased expression of proangiogenic factors have been observed in patients with early PsA, consistent with dysregulated angiogenesis.[14] The pattern of new blood vessel formation differs from that observed in patients with rheumatoid arthritis (RA). In particular, PsA is marked by an increased number of immature blood vessels in the synovium and by elongated vessels that suggest proliferation through extension, as opposed to the branching patterns of new blood vessels observed in RA.[15] Given these differences, imaging techniques could potentially identify changes in vascularisation that might be useful for early detection and differential diagnosis of musculoskeletal disease.

Fluorescence-optical imaging (FOI) is an imaging method for detecting changes in microvascularisation and subclinical subdermal skin inflammation in both hands by use of a fluorescent dye, which accumulates in areas with vascular changes and inflammation, visualised by a special camera system.[16–20] By identifying areas of enhanced microcirculation and improving visualisation of inflamed musculoskeletal structures such as synovia and entheses, and subdermal skin, FOI may have the potential to assist in the early detection of patients at-risk and preclinical PsA in patients with psoriasis.[16 20] The goal of this investigator-initiated study was to evaluate the ability of FOI to detect preclinical musculoskeletal inflammation as a sign of early PsA in patients with psoriasis at risk of developing PsA.

METHODS

Study design

This investigator-initiated prospective, multicentre, two-part observational cohort study (XCITING and XTEND) involved rheumatology sites in Germany with trained joint assessors, affiliations with dermatologists who could refer patients with psoriasis and the capability and experience to perform FOI (Xiralite; Xiralite, Berlin, Germany), MSUS and MRI analysis. For the XCITING study, patients were seen at rheumatology centres between 28 January 2014 and 16 March 2017. Visits for XTEND were conducted 18–24 months after the XCITING visit; the last patient was seen on 16 March 2019.

The XCITING phase of the study was a cross-sectional study based on data obtained at an initial visit of patients with psoriasis at risk for PsA (figure 1). At this visit (visit 1), patients received a comprehensive clinical examination (CE), including swollen (66) and tender (68) joint counts, Disease Activity Score based on 28 joints, enthesitis (Leeds Enthesitis Index)[21] and dactylitis assessments, the Psoriasis Area and Severity Index, body surface area affected by psoriasis and the modified Nail Psoriasis Severity Index.[22] Laboratory investigations included erythrocyte sedimentation rate and C reactive protein levels. Laboratory values were based on reports from local laboratories. Patient-reported outcomes were obtained for pain (visual analogue scale of 0–10), function (the Funktionsfragebogen Hannover) questionnaire[23] and the Health Assessment Questionnaire-Disability Index,[24] and overall health-related quality of life (36 item short-form).[25] Patients were also asked to complete the Psoriasis Epidemiology Screening Tool (PEST),[26] with a score ≥3 indicating suspicion of PsA.

MSUS and FOI were performed on both hands at the time of the rheumatological examination (visit 1). MRI

of the hands was performed within 7 days in patients with signs of inflammation on FOI but no evidence of PsA during CE or MSUS (CE−/US−/FOI+, subsequently referred to as PsA−/FOI+). MSUS images were evaluated by the rheumatologist who performed the CE; a standardised assessment with predefined joint regions was used according to the Outcome Measures in Rheumatoid Arthritis (OMERACT) standard.[27 28] FOI images were read at a central location by a single reader who was blinded to patient information, including skin involvement (RHIO, Düsseldorf). MRI images were evaluated by radiologists at the site where imaging was performed using local protocols, and further classified as 'musculoskeletal inflammation' or 'normal' by a central reader at Fraunhofer ITMP, Frankfurt am Main, Germany.

In the subsequent longitudinal follow-up study (XTEND), the subcohort of patients with CE−/MSUS−/MRI−/FOI+ was followed over 2 years (assessments at months 18 and 24) to evaluate PsA development using the assessment setup from XCITING.

Study population

Adult (18–75 years) patients with a diagnosis of plaque psoriasis as confirmed by the referring dermatologist and who were considered at risk for musculoskeletal involvement, as defined by the current or known existence of nail psoriasis and/or report of musculoskeletal pain and/or swollen joints within the last 6 months, were eligible for inclusion in this study. Patients with a previous diagnosis of PsA, current or past treatment with biologic disease-modifying antirheumatic drug (bDMARD) therapy or evidence of significant uncontrolled or serious concomitant diseases were excluded. Hypersensitivity to fluorescence colour agents, particularly indocyanine green (ICG), wounded hands, iodine allergy, pregnant and breastfeeding women or specified thyroid conditions represented additional exclusion criteria.

Fluorescence-optical imaging

For FOI analyses, ICG, an agent approved in Europe for microcirculation imaging diagnostics, was injected intravenously as a bolus of 0.1 mg/kg; 360 images were obtained over a 6 min period. This imaging agent allows visualisation of blood flow and enhances detection of inflamed musculoskeletal structures. FOI activity scores (FOIAS) were calculated as previously reported by Werner *et al*[16 17]: 0=no enhancement, 1=low enhancement, 2=moderate enhancement and 3=strong enhancement. Clinicians were not aware of FOI scores during the clinical and MSUS examination. Following assessment of FOI, treating clinicians received an email notification of results (yes/no) and the site (right, left or both hands) of positive detection to allow planning of the MRI examination.

Objective and outcomes

The primary objective of this study was to evaluate the ability of FOI to detect signs of musculoskeletal inflammation in both hands in a population of patients with psoriasis at risk for PsA compared with clinical findings of CE and MSUS. Additional objectives included assessment of differences in baseline characteristics of patients based on diagnosis and imaging categories. The patients were categorised based on the following criteria:

- CE with MSUS: evidence of PsA as determined by the clinical judgement of the clinician based on the ClASsification criteria for Psoriatic Arthritis[29] and MSUS findings based on a standardised scoring system with assessment of synovitis/tenosynovitis (0–3) with power Doppler signal (0–3) and erosions (0/1) according to EULAR-OMERACT definitions and Naredo *et al* and Bruyn *et al*,[28 30–33] and adapted for PsA by inclusion of all joints (wrist, metacarpophalangeal, (proximal) interphalangeal, distal interphalangeal 1–5) and tendons of the hands (dorsal and palmar). Scores >0 were considered to indicate inflammation (synovitis/tenosynovitis). Patients with positive findings on either CE or MSUS were considered PsA+, and patients who were CE− and MSUS− were considered PsA−.
- FOI+: FOI scores ≥2 according to a central reader using the previously published scoring method FOIAS (see 'Fluorescence-optical imaging' section).[16 17]
- MRI+: MRI findings according to local report with confirmation of inflammation (synovitis/tenosynovitis) from a central reader.

Secondary outcomes included the evaluation of demographic and disease characteristics, concomitant medication and comorbidities by diagnosis/imaging subgroup.

Statistical analysis

Observed data are reported; data were not imputed. Mean (SD) are presented for continuous data unless data were skewed, in which case median (quartile (Q)1, Q3) data are shown. Sensitivity was assessed as the proportion of FOI+ patients who had a diagnosis of PsA (as determined by CE or MSUS) at visit 1, and specificity was assessed as the proportion of FOI− patients who were negative for PsA. Exact two-sided 95% Clopper-Pearson CIs were determined for sensitivity and specificity assessments. The predictive value of FOI to detect PsA was calculated by incidence rates over the 2-year observational period compared with the reported incidence from literature.

RESULTS

Patient classification

A total of 409 patients with psoriasis and at risk for PsA (nail psoriasis and/or tender/swollen joints within the past 6 months) enrolled in the study at 14 rheumatology centres throughout Germany. Eighteen patients were excluded, 17 due to missing data and 1 due to withdrawal. Of the 391 patients who underwent a rheumatology examination, 2 did not have FOI data. The final analysis cohort therefore consisted of 389 patients (figure 2). The overall rate of FOI+ in this psoriasis cohort was 265/389

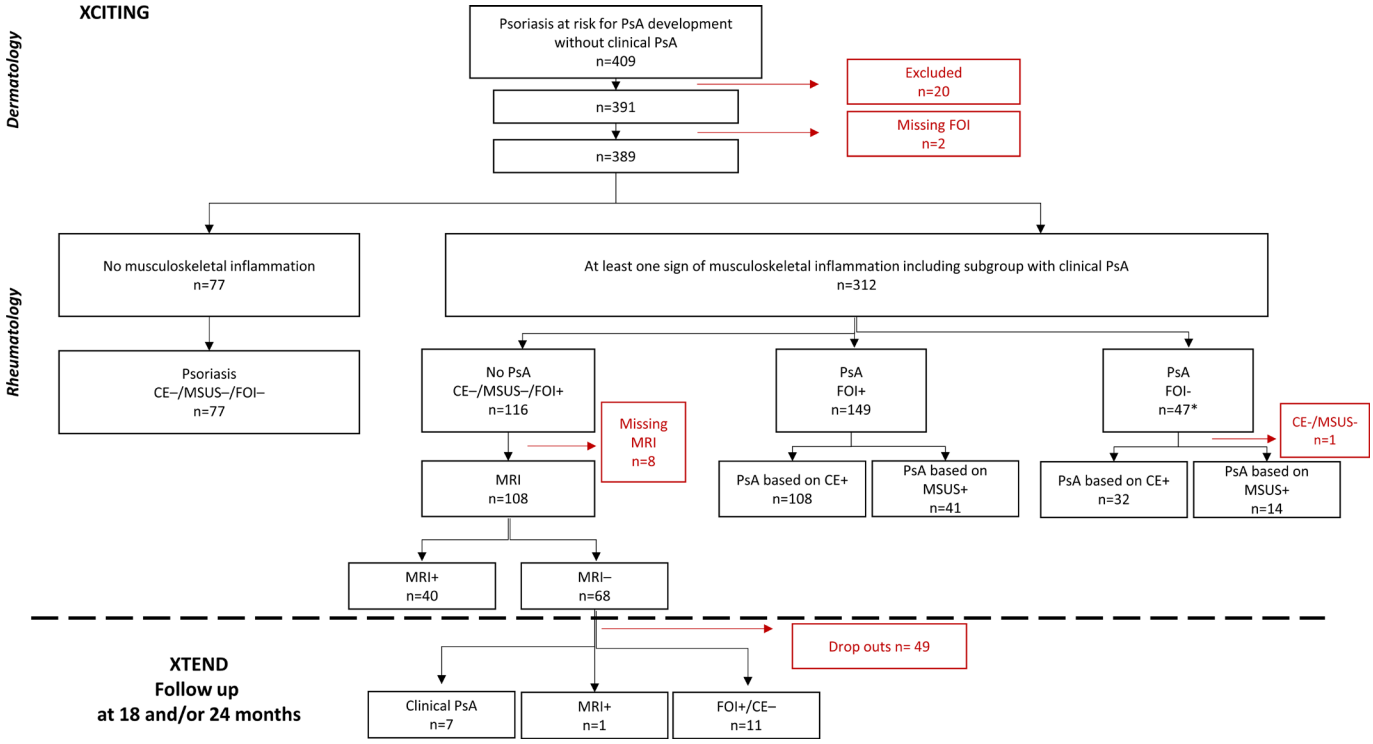

Figure 2 Clinical examination and imaging outcomes in the XCITING and XTEND (up to 24-month follow-up) studies. Only hand-dominant PsA was included in the analysis when patients were CE+/FOI–. CE, clinical examination; FOI, fluorescence-optical imaging; MSUS, musculoskeletal ultrasound; PsA, psoriatic arthritis.

(68.1%). Figure 3 shows representative FOI images with enhancement for FOI+ patients.

At visit 1, 77 (19.8%) patients showed no signs of musculoskeletal inflammation by CE, MSUS or FOI and were considered to have psoriasis only (online supplemental figure S1). The remaining 312 patients (80.2%) had at least one sign of musculoskeletal inflammation based on CE, MSUS or FOI; 265 were FOI+. In the 312 patients with at least one sign of musculoskeletal inflammation, PsA was diagnosed in 196 patients (50.4% of the full analysis cohort (n=389)), including 140 patients (36.0% of the full analysis cohort) based on CE alone and an additional 55 patients (14.1%) based on positive MSUS findings alone in patients for whom CE findings were not definitive. Overall, 115/140 (82.1%) CE+ patients were also MSUS+; the 25 patients who were CE+/MSUS– likely had musculoskeletal inflammation in anatomic regions other than the hands that led to the PsA diagnosis. About three-quarters (76.0%) of patients with a clinical PsA diagnosis were FOI+ in hand imaging.

One hundred sixteen patients (29.8%) were negative on CE and MSUS (PsA–) but FOI+. MRI data were available for 108 of the FOI+ patients. Forty of these patients (37.0% of the FOI+ subgroup with MRI data) were MRI+ and the remaining 68 patients (63.0%) were MRI– (figure 2).

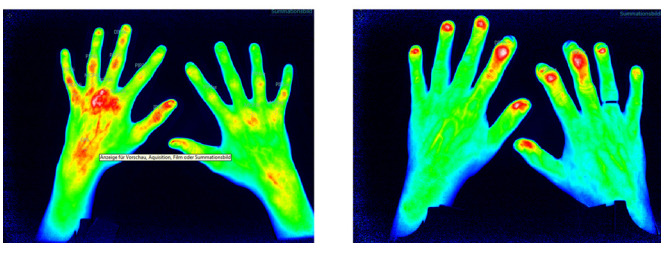

Figure 3 Fluorescence-optical images (FOI) of (A) asymmetric inflammation with strong enhancement in left hand (FOI+, summation image) and (B) distal-interphalangeal enhancement (FOI+, summation image). Images courtesy of Rheumatology Department, University Hospital Frankfurt.

Predictive value of FOI in preclinical detection of PsA

Twenty-eight of the 68 PsA–/FOI+/MRI– patients (41.2%) were included in the follow-up examinations (XTEND study) at months 18 and/or 24. The baseline characteristics of this subgroup were representative of the total CE–/FOI+ group. The remaining 40 patients dropped out of the study due to various reasons, primarily due to withdrawn of consent and loss of contact for appointment of follow-up. Up to month 24, another 8 patients (11.8% of the 68 PsA–FOI+/MRI– patients; 28.6% of the 28 patients with evaluable data) were diagnosed with PsA (documentation of external diagnosis, CE+ or MRI+) (figure 2).

Sensitivity and specificity of FOI compared with current PsA diagnosis

Sensitivity and specificity analyses were performed based on visit 1 findings. These analyses are therefore based on current diagnosis only and do not pertain to the ability of

FOI for detection of inflammatory signs or its predictive value for patients at risk for development of PsA.

One hundred forty-nine of the 196 patients with PsA confirmed by CE or MSUS were FOI+. The sensitivity of FOI for current PsA diagnosis was therefore 76.0% (95% CI 69.4 to 81.8). The sensitivity of FOI cannot be accurately compared with the sensitivity of MSUS because MSUS was part of the criteria used to determine PsA diagnoses. Of the 196 patients with PsA, 170 (86.7%) were MSUS+.

Of the 193 patients who did not have a diagnosis of PsA based on CE with MSUS, 77 were FOI–. The specificity of FOI for current PsA diagnosis was 39.5% (95% CI 32.6 to 46.7). It was not possible to explore comparative specificity as CE with MSUS was the reference for diagnosis and therefore no MSUS+ patients were considered negative for PsA.

Baseline characteristics

Baseline demographic characteristics were fairly well balanced across subgroups, but disease characteristics varied somewhat (table 1 and online supplemental table S1). As might be expected, the proportion of patients with at least one tender or swollen joint or at least one digit affected by dactylitis was highest in the confirmed PsA subgroup. In the PsA–/FOI+ subgroup, tender joint outcomes (mean/median tender joint count and number of patients reporting a tender joint) fell in between values for the psoriasis only and PsA groups; over 80% of patients in the PsA–/FOI+ subgroup reported at least one tender joint, even though these patients were not diagnosed with PsA by CE or MSUS. Swollen joint outcomes, which may reflect a later stage in PsA development, were similar between the psoriasis only and FOI+ subgroups. Patient-reported outcomes for the PsA–/FOI+ subgroup also fell in the middle of values reported by patients with psoriasis only and those with PsA. Psoriasis measures were generally comparable across subgroups, although psoriasis on the hands was more common in the PsA–/FOI+/MRI+ subgroup. The proportion of patients with ≥3 positive answers on the PEST questionnaire, a validated screening tool for PsA in patients with psoriasis,[23] was highest in the confirmed PsA subgroup followed by the PsA–/FOI+/MRI+ subgroup.

Treatment with systemic DMARDs was infrequent in this psoriasis population (table 2). The highest rates of DMARD usage occurred in the PsA–/FOI+/MRI+ subgroup; 17.5% of patients in this subgroup were treated with methotrexate (MTX). Non-steroidal anti-inflammatory drug (NSAID) usage was also highest in the PsA–/FOI+/MRI+ subgroup, particularly with respect to non-selective cyclooxygenase-2 inhibitors. Topical treatments for psoriasis, including topical steroids and topical vitamin D, were reported most frequently in the psoriasis-only subgroup.

The PsA–/FOI+/MRI+ subgroup had the highest rate of concomitant diseases (73%) and the PsA–/FOI+/MRI– subgroup had the lowest (44%) (table 3). Hypertension was the most common comorbidity in all subgroups. Rates of hypertension, type 2 diabetes and lipid metabolic disorders were substantially higher in the PsA–/FOI+/MRI+ subgroup compared with other subgroups.

DISCUSSION

Early detection of patients with psoriasis at high risk of developing arthritis is an important unmet need in rheumatology.[12] Multiple studies have shown that a large proportion of patients with psoriasis ultimately develop PsA,[2–4] and that this condition often goes undiagnosed for many years.[34] Barriers to prompt recognition of PsA pose a serious concern, as delayed initiation of PsA treatment may impair long-term outcomes, including functional ability.[9]

FOI allows the visualisation and detection of changes in microvascularisation and may provide a useful tool for identifying early changes in the disease transition from psoriasis to PsA as a predictive biomarker.[16–20] Its value in sensitive visualisation of musculoskeletal inflammation may exceed its ability to detect clinically manifest PsA at high sensitivity or specificity, but early visualisation is arguably of greater value as other imaging methods are currently available for detection of later stages of PsA. A technique allowing early identification of PsA may be especially valuable for non-rheumatologists, including dermatologists and general practitioners, and help expedite more efficient referral to specialists.

Sixty-eight per cent of the patients with psoriasis at high risk for PsA who were enrolled in this study showed signs of increased vascularisation by FOI. In the FOI+ cohort without findings on CE or MSUS, 34.5% also showed signs of inflammation in MRI assessments. In the subsequent 24 months, 11.8% of PsA–/FOI+/MRI– patients were identified with new-onset PsA using the assumption that all of the study dropouts remained PsA–; this proportion increased to 28.6% if only patients with evaluable data are considered. Literature data on yearly incidence rates in different national cohorts indicate an incidence rate of approximately 4.3% per year.[35–37] Accordingly, the calculated predicted percentage of patients with psoriasis with new onset of PsA during a 2-year follow-up period would be 8.6%, which is substantially lower than the 2-year overall incidence rate of 11.8% detected in the follow-up cohort (XTEND) using the most conservative estimate. In this respect, the high dropout rate of 58.8% during follow-up needs to be considered, since it may have affected the true PsA incidence rate in the XTEND cohort.

In the psoriasis cohort evaluated in this study, 50% of the patients had PsA based on CE or MSUS findings. Our entry criteria enriched the subpopulation for patients at risk of PsA, which likely explains the higher proportion of undiagnosed patients with PsA in our study compared with prevalence rates around 20% identified in earlier investigations of German patients with psoriasis.[2 3] In particular, nail psoriasis, which was found in over half of

Table 1 Baseline patient demographic and disease characteristics

Characteristic	Diagnosis/Imaging subgroup					All patients (n=389)
	PsO only* (n=77)	PsA on CE and/or MSUS (n=196)	CE–/MSUS–/FOI+ All† (n=116)	CE–/MSUS–/FOI+ MRI+ (n=40)	CE–/MSUS–/FOI+ MRI– (n=68)	
Demographics						
Age, years, mean (SD)	46.2 (12.9)	50.8 (12.0)	51.1 (11.7)	55.7 (12.8)	49.3 (9.9)	50 (12.2)
Sex, n female (%)	46 (59.7%)	112 (57.1%)	72 (62.1%)	23 (57.5%)	44 (64.7%)	230 (59.1%)
BMI, kg/m^2, mean (SD)	27.0 (5.3)	27.1 (4.8)	28.0 (5.5)	28.1 (4.5)	27.9 (6.1)	27.4 (5.1)
Current smokers, n (%)	24 (31.2%)	61 (31.1%)	46 (39.7%)	13 (32.5%)	29 (42.7%)	131 (33.7%)
Ethnicity, n white (%)	75 (97.4%)	193 (98.5%)	116 (100%)	40 (100%)	68 (100%)	384 (98.7%)
PsO disease duration, years, median (Q1, Q3)	12.5 (2, 32)	10 (2, 27)	11 (5, 25.5)	16.5 (8.5, 35)	10 (3, 21)	11 (2, 27)
Age of PsO onset, years, median (Q1, Q3)	19.5 (14, 34.5)	32 (18, 47)	32 (18, 43)	32 (15, 43.5)	30 (19, 40)	30 (16, 44)
PsA screening questionnaire, n (%) [n missing or not evaluable]						
PEST ≥3 questions positive	28 (36.4%)[9]	110 (56.1%)[34]	54 (46.6%)[18]	21 (52.5%)[6]	28 (41.2%)[12]	192 (49.4%)[61]
Arthritis measures						
TJC (0–76), median (Q1, Q3)	2 (0, 5)	4 (2, 9)	3 (1, 8)	5 (2, 9)	2 (1, 8)	4 (1, 8)
TJC76 >0, n (%)	53 (68.8%)	171 (87.2%)	97 (83.6%)	33 (82.5%)	56 (82.4%)	321 (82.5%)
SJC (0–74), median (Q1, Q3)	0 (0, 0)	1 (0, 3.5)	0 (0, 0)	0 (0, 0.5)	0 (0, 0)	0 (0, 2)
SJC74 >0, n (%)	10 (13.0%)	120 (61.2%)	15 (12.9%)	10 (25.0%)	4 (5.9%)	145 (37.3%)
LEI >0, n (%)	6 (7.8%)	32 (16.3%)	7 (6.0%)	1 (2.5%)	6 (8.8%)	45 (11.6%)
Dactylitis count >0, n (%)	2 (2.6%)	31 (15.8%)	0 (0%)	0 (0%)	0 (0%)	33 (8.5%)
PsO measures						
PASI, median (Q1, Q3)	2.6 (0.87, 7.9)	2.8 (1.0, 6.8)	2.4 (1.2, 5.1)	2.6 (1.6, 7.0)	2.4 (0.8, 4.2)	2.6 (1.0, 6.4)
BSA, median % (Q1, Q3)	4.5 (1, 9.5)	5 (2, 10)	5 (2, 7)	4.5 (2, 10)	5 (2, 6)	5.0 (2, 10)
Nail involvement, n (%)	40 (52.0%)	111 (56.6%)	56 (48.3%)	18 (45.0%)	35 (51.5%)	207 (53.2%)
mNAPSI >0, n (%)	41 (53.3%)	113 (57.7%)	58 (50.0%)	19 (47.5%)	36 (52.9%)	212 (54.5%)
PsO on hands, n (%)	15 (19.5%)	50 (25.5%)	26 (22.3%)	14 (35.0%)	12 (17.7%)	91 (23.4%)
Laboratory measures						
Anti-CCP positive, n (%)	3 (3.9%)	8 (4.1%)	3 (2.6%)	1 (2.5%)	2 (2.9%)	14 (3.6%)
Rheumatoid factor positive, n (%)	3 (3.9%)	11 (5.6%)	3 (2.6%)	1 (2.5%)	2 (2.9%)	17 (4.4%)
CRP, mg/L, median (Q1, Q3)	2.5 (1.0, 4.85)	2.4 (1.0, 4.9)	3 (1.2, 5)	1.8 (1, 5.2)	3.1 (1.6, 5.1)	2.5 (1, 5)
ESR, mm/hour, median (Q1, Q3)	10 (5, 17)	12 (6, 22)	12 (6, 24)	11 (4.5, 21)	12 (6, 24)	12 (6, 22)
Patient-reported outcomes, mean (SD) [n missing]						
PGA (VAS 100)	37.0 (25.8)[12]	47.0 (26.9)	43.8 (24.1)[16]	45.2 (23.8)[4]	43.7 (25.6)[12]	44.0 (26.1)[64]

Continued

Table 1 Continued

Characteristic	Diagnosis/Imaging subgroup					All patients (n=389)
	PsO only* (n=77)	PsA on CE and/or MSUS (n=196)	CE−/MSUS−/FOI+			
			All† (n=116)	MRI+ (n=40)	MRI− (n=68)	
Pain (VAS 100)	33.2 (25.7)[9]	46.2 (27.4)[33]	40.9 (25.8)[12]	42.7 (25.1)[4]	39.6 (27.4)[8]	41.9 (27.0)[54]
HAQ-DI (0–3)	0.4 (0.5)[6]	0.6 (0.6)[27]	0.5 (0.5)[8]	0.6 (0.5)[1]	0.4 (0.5)[7]	0.5 (0.6)[41]

*Negative on CE, MSUS and FOI.
†MRI data were not available for eight patients.
BMI, body mass index; BSA, body surface area; CCP, cyclic citrullinated peptide; CE, clinical examination; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; FOI, fluorescence-optical imaging; HAQ-DI, Health Assessment Questionnaire-Disability Index; LEI, Leeds Enthesitis Index; mNAPSI, modified Nail Psoriasis Severity Index; MSUS, musculoskeletal ultrasound; PASI, Psoriasis Area and Severity Index; PEST, Psoriasis Epidemiology Screening Tool; PGA, patient global disease activity; PsA, psoriatic arthritis; PsO, psoriasis; Q1, lowest 25th quartile; Q3, highest 25th quartile; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

the patients in this cohort, increases the risk of PsA by approximately threefold and has been identified as the strongest predictor of PsA in patients with psoriasis.[6 8] The higher proportion of patients with PsA in our study may also relate to the use of MSUS as a PsA criterion, which led to 15% of patients being classified with PsA in addition to those fulfilling PsA diagnosis by CE alone.

There were no clear differences in baseline skin symptoms across the different subgroups, but arthritis outcomes indicated increased joint involvement in the PsA group, as expected. Patients in the PsA−/FOI+ subgroup showed consistent, but modest, differences from the psoriasis-only subgroup; 40% were MRI+. Tender joint outcomes in the PsA−/FOI+ group fell in between values reported for psoriasis only and for PsA. Although numbers were small (n=40), the most pronounced differences were observed in the PsA−/FOI+/MRI+ subgroup, which showed elevations in several baseline characteristics compared with other subgroups, including psoriasis of the hands, MTX use and concomitant diseases, particularly conditions associated with metabolic syndrome such as hypertension, disorders of lipid metabolism and type 2 diabetes. MTX use may be an indication of more severe musculoskeletal manifestations in these patients. Other studies have shown a high prevalence of metabolic syndrome in patients with PsA,[38] but the association between metabolic syndrome and preclinical phases of PsA is unknown. The PsA−/FOI+/MRI+ and PsA subgroups had comparably high levels of NSAID use, suggesting more severe pain in these patients. The differences observed among subgroups appear to consistently reflect stages of progression from psoriasis only, with the lowest level of musculoskeletal involvement, to PsA−/FOI+/MRI−, to PsA−/FOI+/MRI+, to PsA. However, replication studies on larger patient populations will be required for further confirmation.

The subtle differences observed between baseline disease characteristics of imaging marker-defined subgroups of patients with psoriasis with musculoskeletal complaints illustrate the difficulty in diagnosing PsA at an early stage. Although careful CEs confirmed their value in uncovering undetected PsA in patients with psoriasis, a still relevant portion of oligosymptomatic cases at initial stages can be missed, and characterisation of reliable predictive markers for identifying patients at an increased risk for future PsA development remains a challenge. MRI is considered the gold standard for imaging of synovitis, but use of MRI may be restricted by cost, time and availability, while the requirement for a contrast agent has safety ramifications for some patients.[16] Moreover, validity of MRI findings depends on reader experience, as suspicious inflammatory changes might be associated with mechanical stress or other anatomic and physiological processes. In addition, because MRI primarily detects synovitis and structural changes, it may be better suited for identifying later stages in the transition from psoriasis to PsA.

Table 2 Baseline patient medications overall and by diagnosis/imaging subgroup

Characteristic	Diagnosis/Imaging subgroup					All patients (n=389)
	PsO only* (n=77)	PsA on CE and/or MSUS (n=196)	CE–/MSUS–/FOI+ All† (n=116)	CE–/MSUS–/FOI+ MRI+ (n=40)	CE–/MSUS–/FOI+ MRI– (n=68)	
Any DMARD‡	5 (6.5%)	15 (7.7%)	12 (10.3%)	7 (17.5%)	4 (5.9%)	32 (8.2%)
MTX	4 (5.2%)	14 (7.1%)	12 (10.3%)	7 (17.5%)	4 (5.9%)	30 (7.7%)
CSA	1 (1.3%)	1 (0.5%)	2 (1.7%)	1 (2.5%)	0 (0%)	4 (1.0%)
Any NSAID‡	18 (23.4%)	77 (39.3%)	27 (23.3%)	16 (40.0%)	11 (16.2%)	122 (31.4%)
Selective COX-2 inhibitor	4 (5.2%)	18 (9.2%)	6 (5.2%)	2 (5.0%)	4 (5.9%)	28 (7.2%)
Non-selective COX-2 inhibitor	15 (19.5%)	60 (30.6%)	23 (19.8%)	15 (37.5%)	8 (11.8%)	98 (25.2%)
Any topical therapy‡	66 (85.7%)	137 (69.9%)	92 (79.3%)	34 (85.0%)	52 (76.5%)	295 (75.8%)
Steroids	58 (75.3%)	121 (61.7%)	77 (66.4%)	27 (67.5%)	44 (64.7%)	256 (65.8%)
Vitamin D	33 (42.9%)	62 (31.6%)	30 (25.9%)	12 (30.0%)	15 (22.1%)	125 (32.1%)
Other	13 (16.9%)	40 (20.4%)	19 (16.4%)	7 (17.5%)	11 (16.2%)	72 (18.5%)
UV treatment	15 (19.5%)	40 (20.4%)	14 (12.1%)	9 (22.5%)	5 (7.4%)	69 (17.7%)
Systemic therapy for skin only	8 (10.4%)	30 (15.3%)	14 (12.1%)	4 (10.0%)	7 (10.3%)	52 (13.4%)
No skin treatment	10 (13.0%)	45 (23.0%)	17 (14.7%)	5 (12.5%)	12 (17.7%)	72 (18.5%)

Data are presented as n (% of patients).

*Negative on CE, MSUS and FOI.
†MRI data were not available for eight patients.
‡Patients could receive treatment with more than one agent within a drug class.
CE, clinical examination; COX-2, cyclooxygenase 2; CSA, ciclosporin A; DMARD, disease-modifying antirheumatic drug; FOI, fluorescence-optical imaging; MSUS, musculoskeletal ultrasound; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; PsO, psoriasis; UV, ultraviolet.

Methodology allowing detection of the proposed 'preclinical' phase of musculoskeletal inflammation that marks the transition from psoriasis to PsA[12] would be a valuable tool in identifying patients at high risk of PsA development. Our study suggests that FOI may have the capability to identify these early events. We envision FOI as complementing current imaging methodologies, such as MSUS and MRI, by identifying preclinical changes in vascularisation and subdermal inflammation in the hands that occur at the earliest stage of the transition from psoriasis to PsA in psoriatic disease. Accordingly, FOI+ findings could be used as an indicator for a closer follow-up during routine care or as an entry criterion for early intervention studies

Table 3 Baseline concomitant diseases overall and by diagnosis/imaging subgroup

Characteristic	Diagnosis/Imaging subgroup					All patients (n=389)
	PsO only* (n=77)	PsA on CE and/or MSUS (n=196)	CE–/MSUS–/FOI+ All† (n=116)	CE–/MSUS–/FOI+ MRI+ (n=40)	CE–/MSUS–/FOI+ MRI– (n=68)	
Any	40 (52.0%)	121 (61.7%)	64 (55.2%)	29 (72.5%)	30 (44.1%)	225 (57.8%)
Hypertension	15 (19.5%)	48 (24.5%)	29 (25.0%)	13 (32.5%)	14 (20.6%)	91 (23.4%)
Type 2 diabetes	2 (2.6%)	14 (7.1%)	14 (12.1%)	9 (22.5%)	4 (5.9%)	30 (7.7%)
Lipid metabolic disorders	3 (3.9%)	13 (6.6%)	7 (6.0%)	5 (12.5%)	2 (2.9%)	23 (5.9%)
Cardiovascular	0 (0%)	14 (7.1%)	4 (3.5%)	1 (2.5%)	2 (2.9%)	18 (4.6%)
Malignancies	2 (2.6%)	13 (6.6%)	2 (1.7%)	0 (0%)	2 (2.9%)	17 (4.4%)
Gout	3 (3.9%)	4 (2.0%)	1 (0.9%)	0 (0%)	1 (1.5%)	8 (2.1%)
Chronic infection	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)
IBD	1 (1.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)
Other	26 (33.7%)	71 (36.2%)	43 (37.1%)	24 (60.0%)	16 (23.5%)	141 (36.2%)

Data are presented as n (% of patients).
*Negative on CE, MSUS and FOI.
†MRI data were not available for eight patients.
CE, clinical examination; FOI, fluorescence-optical imaging; IBD, inflammatory bowel disease; MSUS, musculoskeletal ultrasound; PsA, psoriatic arthritis; PsO, psoriasis.

designed to explore prevention of the development of clinical PsA.

Limitations of this study include its non-randomised design and small numbers in some subgroups, particularly during the XTEND part of the study. Because our study was designed to evaluate 'standard of care' conditions in daily clinical practice, PsA diagnosis relied on the judgement of the clinician. It is possible that some patients had alternative conditions, including gout or osteoarthritis of the hands, that may have complicated interpretation of FOI findings. Patients were not asked to discontinue NSAIDs prior to imaging, which may have influenced results. However, only approximately 30% of patients were on NSAIDs, either occasionally or routinely, so we would expect any NSAID-related effects on imaging to be relatively minor. MRI scans were only obtained in the subset of PsA−/FOI+ patients, thereby preventing the availability of data needed to evaluate the comparative sensitivity/specificity of FOI and MRI. Further limitations include the restricted assessment of FOI to the hands, although the feet are also frequently affected in PsA. Moreover, the FOIAS as the quantitative measure for analysis is based on signal enhancement in the joints without focusing on other morphological changes such as enthesitis that are relevant periarticular manifestations of PsA. We acknowledge that patients with more musculoskeletal symptoms may have been more likely to attend follow-up visits, thus potentially resulting in a bias towards higher rates of PsA during the XTEND portion of the study. Additional limitations relate to the technical standardisation of FOI assessment including stable temperature and positioning of the device that must be considered during data acquisition to guarantee its validity.

In conclusion, our investigation provides evidence that FOI is a sensitive, safe and user-friendly method for the detection of early signs of joint inflammation in the hands that reflect altered patterns of vascularisation potentially related to incipient PsA. FOI assessment may uncover changes in synovial vascularisation at very initial stages in the transition from psoriasis to PsA, possibly capturing disease-specific features earlier than other imaging modalities and before onset of clinical symptoms. Accordingly, FOI may have the potential to improve patient outcomes in PsA by reducing the time to initiation of early treatment. Future studies are needed to reproduce these findings and to further evaluate the use of FOI in clinical rheumatology practice.

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