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Concise report

Anti-citrullinated protein antibodies are linked to erosive disease in an observational study of patients with psoriatic arthritis

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Abstract

Objective. ACPAs are associated with bone destruction in RA. The aim of this study was to evaluate the association between ACPA and bone destruction in patients with a distinct inflammatory disorder, PsA.

Methods. We used baseline data from a large observational study of PsA patients preparing to initiate treatment with adalimumab to analyse demographic and disease characteristics by ACPA status. To ensure a homogeneous PsA study population, only patients with active psoriatic skin manifestations who met Classification of Psoriatic Arthritis criteria for PsA were included in the analyses, thereby minimizing the risk of including misdiagnosed RA patients. Multiple logistic regression analyses were used to explore potential associations between ACPA seropositivity and bone destruction.

Results. Of 1996 PsA patients who met the strict inclusion criteria, 105 (5.3%) were positive for ACPA. ACPA-positive patients had significantly higher swollen joint counts and 28-joint DAS values than ACPA-negative patients and significantly higher rates of erosive changes and dactylitis. Multiple logistic regression analysis confirmed the association of ACPA seropositivity with a 2.8-fold increase in the risk of erosive disease.

Conclusion. As has been previously shown for RA, ACPA is associated with bone destruction in PsA, suggesting that the osteocatabolic effect of ACPA is not confined to RA but is also detectable in the different pathogenetic context of a distinct disease entity.

Trial registration: ClinicalTrials.gov, NCT01111240

Key words: adalimumab, anti-citrullinated protein antibodies, psoriatic arthritis, osteoporosis, erosions, observational study

CLINICAL SCIENCE

Rheumatology key messages

- Approximately 5% of patients with PsA were seropositive for ACPA.
- ACPA seropositivity was associated with higher rates of erosive disease, osteoporosis and dactylitis.
- The osteocatabolic effect of ACPA may extend to disease states distinct from RA.

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Introduction

Recent studies support an association between ACPAs and bone destruction in RA [1–4]. Furthermore, the transfer of ACPAs against citrullinated vimentin to lymphocyte-deficient mice results in bone loss [2], implying that ACPAs can directly mediate bone destruction in the absence of other RA-associated factors.

In humans, it is difficult to separate the presence of ACPAs from the RA disease state, as ACPA seropositivity

is rare in other patient populations. We took advantage of the availability of baseline data from a large observational study of patients with PsA preparing to initiate treatment with the TNF inhibitor adalimumab to further explore the role of ACPAs in bone pathology. Although ACPAs are less common in PsA than in RA [5], up to 17.5% of PsA patients have been reported to be ACPA seropositive [5–15]. We reasoned that a sufficiently large population of PsA patients would provide the tools to explore the potential association between ACPAs and bone loss in patients who are not affected by RA.

Patients and methods

Study design and patient selection

This study utilized baseline data from PsA patients preparing to initiate treatment with adalimumab in a multicentre non-interventional study (ClinicalTrials.gov, trial registration NCT01111240) as described by Behrens *et al.* [16]. All patients were under the routine medical care of 317 physicians (52% rheumatologists, 25% dermatologists and 23% other specialists) in Germany.

Adult patients ($\geqslant$18 years of age) were required to have a diagnosis of active PsA, a clinical indication for treatment with a TNF inhibitor and no contraindications. Patients were enrolled in this study between August 2005 and January 2013. All patients were informed of the objectives of the study and gave written consent for their voluntary participation in the study and the anonymous use of personal data in statistical analyses. Because of the non-interventional nature of this study, ethics approval was not required by German law.

A possible obstacle to analysing the effect of autoantibodies in PsA patients is the potential for misdiagnosis, as it can be difficult to distinguish PsA from RA with concomitant psoriasis [8]. To minimize the risk of including RA patients in the PsA population analysed here, we adopted a modified version of the Classification of Psoriatic Arthritis (CASPAR) criteria [17]. In addition to inflammatory arthritis, patients were required to have current active psoriasis and to fulfil at least one additional CASPAR criterion from available data (nail psoriasis, dactylitis or negative RF). We did not have access to information for other conditions specified in CASPAR criteria (personal/family history of psoriasis, history of dactylitis or juxta-articular new bone formation). All patients who did not meet these strict criteria were excluded from the analyses reported here. We also excluded patients who lacked ACPA laboratory tests or adequate documentation of baseline disease characteristics.

Baseline characteristics

Demographic and disease characteristics, including the 28-joint DAS (DAS28), were recorded at the baseline visit prior to initiation of adalimumab therapy. Baseline evaluations included demographic characteristics and disease assessments, including the type of joint involvement and the presence of enthesitis and dactylitis as judged by the investigator. Measures of arthritis disease activity included tender and swollen joint counts (TJCs and SJCs) performed on 78 and 76 joints, respectively, and DAS28. Psoriasis was assessed by use of the target lesion score, which ranged from 0 (absent) to 15 (severe erythema, scaling and infiltration), and body surface area measurements. The patient's medical history was reviewed and concomitant diseases, as indicated by the use of relevant medications or listed in the patient's medical history, were recorded. As this was an observational study, BMD tests were not routinely available. Erosive changes were identified from the most recent available radiographs. A central reading and scoring of radiographs was not possible due to the standard-of-care design of this non-interventional study. Laboratory tests were performed at local facilities and ACPA seropositivity was determined based on local guidelines and the cut-off values recommended by commercially available assays. Patient function was evaluated by use of the Funktionsfragebogen Hannover patient questionnaire on a scale of 0% (maximal impairment) to 100% (maximal functional capacity) [18].

Data analyses

Descriptive statistics were computed for all data as appropriate. Missing data were not imputed. P-values for comparisons between baseline characteristics (ACPA-positive *vs* ACPA-negative patients) were calculated by Wilcoxon rank sum tests for all continuous variables. For discrete variables, the Fisher's exact test (two-sided) was used. Associations between baseline characteristics and erosive changes or osteoporosis were identified by multiple logistic regression analyses using SAS statistical software (version 9.2; SAS Institute, Cary, NC, USA). This process produced an impact ranking for 44 possible predictor variables. The most influential variables ($P < 0.01$) were used for the final models.

Results

Demographic, disease and treatment characteristics

The cohort of 1996 patients with PsA, as determined by a modified version of the CASPAR criteria (see Patients and Methods section), had a mean age of $\sim$50 years and long-standing disease (psoriasis symptoms for a mean duration of 18.3–18.6 years and arthritis symptoms for a mean duration of 8.5–9.3 years) (Table 1). Of these patients, 105/1996 (5.3%) were seropositive for ACPA. Compared with ACPA-negative patients, ACPA-positive patients had increased rheumatologic disease activity, including significantly higher SJCs, DAS28 and ESR levels (Table 1). ACPA-positive patients also had significantly higher rates of osteoporosis, dactylitis and erosive changes. The time interval between the most recent available radiograph and first visit was similar between the two groups (a median of 122.5 and 119.0 days for the ACPA-positive and ACPA-negative groups, respectively; P = NS). Joint involvement patterns and psoriasis measures were similar in both subgroups.

Table 1 Baseline characteristics of PsA patients by ACPA status

Characteristics	ACPA-positive patients (n = 105)	ACPA-negative patients (n = 1891)	P-values
Demographic characteristics			
Age, mean (S.D.), years	50.2 (11.3)	49.4 (11.6)	0.74
BMI, mean (S.D.), kg/m^2	27.5 (5.0)	28.6 (5.4)	0.039
Female, %	52.9	44.2	0.086
Duration of arthritis symptoms, mean (S.D.), years	8.5 (8.6)	9.3 (8.5)	0.15
Duration of psoriasis symptoms, mean (S.D.), years	18.6 (13.3)	18.3 (12.9)	0.92
Disease characteristics			
Tender joint count, mean (S.D.)	18.4 (16.7)	16.6 (16.4)	0.16
Swollen joint count, mean (S.D.)	15.1 (16.7)	8.5 (10.5)	<0.0001
DAS28, mean (S.D.)	5.26 (1.44)	4.77 (1.32)	0.0016
FFbH, % remaining functional capacity, mean (S.D.)	67.3 (19.9)	70.2 (21.5)	0.12
Erosive changes, % of patients	72.2	52.9	0.0003
Osteoporosis, % of patients	11.7	4.5	0.0034
Dactylitis, % of patients	67.6	50.6	0.0006
Enthesitis, % of patients	28.6	31.4	0.59
Nail psoriasis, % of patients	71.4	65.7	0.25
Joint involvement, % of patients			
Polyarthritis	64.8	61.3	0.54
Mono-/oligoarthritis	23.8	30.0	0.19
DIP involvement	26.7	24.2	0.56
Axial involvement	19.0	18.3	0.80
Arthritis mutilans	0	2.6	0.11
Target lesion score, mean (S.D.)	7.3 (4.0)	7.1 (3.5)	0.45
BSA, % of patients[a]			
<3%	15.4	21.3	
3–10%	38.5	39.5	0.37
11–20%	25.0	19.9	
>20%	21.2	19.2	
Laboratory parameters, mean (S.D.)			
CRP, mg/l	19.2 (54.5)	12.1 (23.2)	0.20
ESR, mm/h	28.0 (24.1)	22.6 (19.0)	0.049

Demographic and disease characteristics of PsA patients at baseline (prior to initiation of adalimumab therapy) by ACPA status. P-values were calculated using the Wilcoxon rank sum test for continuous variables and the Fisher's exact test for discrete variables. [a]Values do not total 100% due to rounding. BSA: body surface area; FFbH: Funktionsfragebogen Hannover patient function questionnaire (higher scores correspond to greater function).

As ACPA formation is closely associated with RF formation, we also addressed the possible role of RF in bone destruction. The proportion of patients seropositive for RF was increased in ACPA-positive PsA patients (43.7 *vs* 4.5% in ACPA-negative patients; $P < 0.0001$). However, RF was not significantly associated with erosive disease (60.6% of RF-positive patients *vs* 53.2% of RF-negative patients; $P = 0.168$ by Fisher's exact test) in contrast to the findings for ACPA status. Although the data cannot fully exclude a contribution of RF to erosive disease in ACPA-positive PsA patients due to the high percentage of patients who were positive for both serum markers, they clearly support a dominant role of ACPA as a risk factor. A comparison of the patients who were seropositive for RF alone (73 patients, 41 erosive and 32 non-erosive) with those who were positive for ACPA alone (50 patients, 38 erosive and 12 non-erosive) revealed that the proportion of patients with an erosive disease course was significantly increased in the ACPA-positive, RF-negative group ($P = 0.035$, Fisher's exact test).

Regression analyses of the association between baseline characteristics and bone loss

Because of potential confounding factors, including disease activity, we used multiple logistic regression models to assess whether ACPA seropositivity was an independent biomarker that was significantly associated with bone loss in patients with PsA. ACPA seropositivity was found to be the strongest risk factor for erosive changes (Table 2). Other factors associated with an increased likelihood of erosive changes were arthritis mutilans, DIP involvement, nail psoriasis, dactylitis, a longer duration of arthritis symptoms and higher ESR levels. Factors associated with an increased risk of osteoporosis were older age, systemic glucocorticoid use, female gender, SJC and ESR.

Discussion

In this observational study of a large, well-characterized cohort of PsA patients preparing to initiate adalimumab

TABLE 2 Baseline variables associated with increased likelihood of erosive changes

Variable	Odds ratio (95% CI)	P-values
ACPA seropositivity	2.771 (1.634, 4.697)	0.0002
Arthritis mutilans	2.653 (1.072, 6.567)	0.0349
DIP involvement	1.549 (1.197, 2.005)	0.0009
Nail psoriasis	1.469 (1.177, 1.834)	0.0007
Dactylitis	1.421 (1.149, 1.757)	0.0012
Duration of arthritis symptoms, years	1.045[a] (1.031, 1.059)	<0.0001
ESR, mm/h	1.011[a] (1.005, 1.017)	0.0001

Baseline disease and demographic variables associated with an increased likelihood of erosive changes as determined by multiple logistic regression analysis. [a]Odds ratio for 1 unit difference, for x units, risk equals the odds ratio to the power of x. No factors were identified that contributed to a decreased likelihood of erosive changes. Modelling was based on 1553 PsA patients with complete data sets. CIs and P-values were determined by the Wald test.

therapy, 5.3% were ACPA seropositive. This rate is in good agreement with smaller studies of PsA patients, which have reported ACPA-positive rates ranging between 3.1 and 17.5% [5–15]. Although some studies [8, 12], including a recent study from the CORRONA database (n = 958) [14], did not identify significant differences in measures of disease activity between ACPA-positive and ACPA-negative PsA patients, others have reported higher rates of erosive disease [7, 9, 10] and more involved joints [10, 11, 13, 15] in PsA patients who were positive for ACPA. However, the conclusions of these studies are somewhat limited by their small size; the largest study reporting an association between ACPA seropositivity and disease activity included 192 PsA patients, of which 15 were ACPA-positive [11]. Another potential issue is the possibility of misdiagnosis, as it can be difficult to distinguish between PsA and RA with psoriasis [8]. Accordingly, published reports have not been able to convincingly confirm an association between ACPA seropositivity and disease activity or bone loss in a non-RA population.

The population in our study was of sufficient size to allow exclusion of data from patients who did not fulfil the modified CASPAR criteria for PsA used in this study, thereby largely eliminating concerns of misdiagnosis. The remaining PsA cohort consisted of 1996 patients, including 105 ACPA-positive patients. ACPA-positive patients had a significantly higher incidence of osteoporosis, erosive changes and dactylitis than ACPA-negative patients and significantly higher baseline SJCs and DAS28 scores. The differences between our study and those that did not detect higher disease activity in ACPA-positive patients may relate not only to the larger number of patients included here, but also to the patient population that was assessed. Patients in our study were preparing to start biologic therapy and, as might be expected, had more severe baseline disease activity than in the CORRONA study (a mean DAS28 of 5.15 *vs* 3.25) [14].

Logistic regression analyses confirmed that ACPA seropositivity was associated with a 2.8-fold increase in the risk of erosive disease, suggesting that ACPA is associated with a general osteocatabolic effect. Although ACPA was not identified as an independent risk factor for osteoporosis in multivariate regression analyses, this biomarker may be more easily detectable as a contributing factor in erosive disease due to the greater number of ACPA-positive PsA patients with this condition (n = 76) compared with the small population with osteoporosis (n = 12). Alternatively, the significantly higher rate of osteoporosis in ACPA-positive PsA patients may be due to an ACPA-associated increase in systemic inflammation rather than to a direct effect on bone metabolism; ESR was significantly increased in ACPA-positive patients and was a risk factor for both osteoporosis and erosive changes.

Due to the limitations of observational studies, it is possible that some patients with osteoporosis were omitted, as the presence of osteoporosis was determined by the patient's medical history and confirmatory BMD tests were not systematically documented. Another limitation of our study is that central laboratories were not used for evaluation of ACPAs and autoantibody titres were not systematically recorded. In addition, a central reading and scoring of radiographs was not performed, so neither the timing nor the evaluation of radiographs was standardized. Because we did not have access to all of the information included in the CASPAR criteria [17], such as patient history of psoriasis, family history of psoriasis or radiographic evidence of new bone formation, it is possible that we excluded some patients with true PsA from the analysis. Alternatively, by relying on only a subset of CASPAR criteria to identify patients with PsA, the RF-positive patient population could potentially have been enriched for risk factors of more severe disease, as those patients did not qualify for the criterion of negative RF and therefore required at least one manifestation associated with an erosive PsA course (nail involvement or dactylitis) to fulfil the inclusion criteria. However, the occurrence of erosive disease did not significantly differ between RF-positive and RF-negative patients despite an increased prevalence of dactylitis in the RF-positive subgroup (73.8 *vs* 49.7%), and there was no significant difference in psoriatic nail disease between the groups (71.5 *vs* 71.4%) (data not shown). Accordingly, a potential selection bias due to the use of a modified CASPAR criteria for study inclusion is unlikely to account for the association between erosive PsA and ACPA seropositivity in our study.

Recent studies have begun to elucidate the functional connection between autoimmunity and bone loss in patients with RA [3]. The ability of ACPAs with specificity for citrullinated vimentin to stimulate systemic bone loss and osteoclast formation following adoptive transfer into mice [2] strongly suggests that ACPAs directly promote bone destruction, even in an experimental setting that excludes the interference of other RA-specific factors. Our data on the association between ACPAs and bone destruction in

PsA are compatible with this hypothesis. Our results indicate that the significance of ACPAs in inflammation-associated bone destruction is not confined to RA, but is likely also operative in other underlying disease states, analogous to the above-mentioned animal model system [2].

Our data suggest that ACPA-positive patients with PsA should be carefully evaluated for osteoporosis, erosive changes and other forms of bone destruction, as fragility fractures are a significant concern in PsA patients [19]. We hope these data will prompt further exploration into the pathogenetic mechanisms of autoantibody-associated bone destruction.

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