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ORIGINAL ARTICLE

Evaluation of Serum Interleukin-6 Level as a Surrogate Marker of Synovial Inflammation and as a Factor of Structural Progression in Early Rheumatoid Arthritis: Results From a French National Multicenter Cohort

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Objective. **Interleukin-6 (IL-6) is a key cytokine in rheumatoid arthritis pathogenesis. We aimed to analyze the association between IL-6 serum levels and joint inflammation at baseline and the correlation of time-integrated IL-6 values with structural damage during the first 36 months of early arthritis.**

Methods. **IL-6 was assessed by 2 different methods in 813 patients of the French early arthritis cohort ESPOIR (Etude et Suivi des Polyarthrites Indifférenciées Récentes) over 36 months. IL-6 and C-reactive protein (CRP) changes were correlated to radiographic progression assessed by the total Sharp/van der Heijde score (SHS). Synovium inflammation was assessed in a subgroup of 126 patients by ultrasonography (US). The relationship between SHS change and IL-6 or CRP levels at baseline was investigated by a univariate regression and a multivariable analysis. A longitudinal model nested by visit and patient was conducted to assess the role of IL-6 on SHS at each visit.**

Results. **At baseline, IL-6 was more strongly correlated with the swollen joint count than CRP level. In the univariate analysis, the time-integrated value of IL-6 was more strongly correlated with the swollen joint count and the variation of SHS than time-integrated CRP level. Baseline IL-6 was not independently associated with SHS change. Longitudinal models nested by patient showed that IL-6 levels were associated with structural damage independently from the Disease Activity Score in 28 joints, smoking status, rheumatoid factor, and anti–citrullinated protein peptide antibody serology, treatments, and CRP levels.**

Conclusion. **IL-6 level was a marker of US synovitis at baseline. Repeated measurements of IL-6 are associated with structural damage.**

INTRODUCTION

Rheumatoid arthritis (RA) is characterized by a progressive joint destruction leading to a substantial disability. It is now well established that the first few months following the onset of inflammatory arthritis are critical in a patient's management. RA management was dramatically improved this past decade. Huge endeavors have been made to diagnose the disease earlier, since early treatment leads to better outcomes (1). Despite the establishment of

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Significance & Innovations

- Interleukin-6 (IL-6) correlates with ultrasonography synovitis in early rheumatoid arthritis (RA).
- IL-6 levels are associated with structural damage in early RA independently from disease activity, anti–citrullinated protein antibody/rheumatoid factor serology, treatments, and C-reactive protein levels.

clinical criteria and matrices predicting the structural damages (2), the detection of patients with poor radiographic prognosis is still challenging, mainly because reliable predictors of disease course are lacking. Ultrasound (US) and magnetic resonance imaging (MRI) evaluations are more sensitive techniques to identify synovitis than clinical examination and are better than conventional radiography to detect bone erosion (3). The exact position of US in RA management has been recently clarified (4). However, the benefit from these imaging procedures is hampered by their limited availability, which emphasizes the urgent need for widely available soluble biomarkers.

Several studies have emphasized correlations between interleukin-6 (IL-6), a pleiotropic cytokine massively produced locally by both resident and infiltrating cells in inflamed joints (5), and C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), disease activity, and morning stiffness without providing any evidence for usefulness of this potential biomarker in clinical practice. Although IL-6 is involved in the worsening of synovial inflammation of RA (6), only a few studies have evaluated IL-6 as a surrogate marker of joint inflammation and predictor of structural damage, with divergent results (1,7).

A recent study showed that baseline IL-6 was significantly higher in early RA than in undifferentiated early arthritis (8). Despite the fact that CRP synthesis is notoriously IL-6 dependent, this study showed that patients with detectable IL-6 at enrollment displayed higher risk for radiographic progression independently of systemic inflammation assessed by CRP level. Given this possible association, independent of systemic inflammation, between IL-6 and structural damage, we hypothesized that IL-6 was a reliable biomarker of synovitis. First, we aimed to analyze the correlation between US synovitis and both IL-6 and systemic inflammation assessed by CRP level. Then we studied the impact of cumulative levels of systemic inflammation and IL-6 on radiographic progression in the French early arthritis ESPOIR (Etude et Suivi des Polyarthrites Indifférenciées Récentes) cohort during the first 36 months of followup.

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PATIENTS AND METHODS

Patients. ESPOIR is a French national observational cohort of patients with at least 2 joints affected by synovitis for more than 6 weeks and less than 6 months at baseline (9) and is for patients not undergoing treatment with synthetic or biologic disease-modifying antirheumatic drugs (DMARDs) at inclusion. Patients were enrolled from 2002 to 2005 in hospitals or in private practice and were followed every 6 months in the first 2 years and are now being followed every year, with an expected followup of 10 years. During followup, patients with a diagnosis other than RA were excluded. The following data from all patients included in the ESPOIR Cohort were recorded at baseline and at 6, 12, 18, 24, and 36 months: sex, age, smoking status, pharmaceutical treatment, ESR, joint count including swollen joint count (SJC) and tender joint count (TJC), Disease Activity Score in 28 joints based on ESR (DAS28-ESR), Health Assessment Questionnaire (HAQ), anti–citrullinated protein/peptide antibody (ACPA), and HLA–DRB1 genotype. Shared epitope alleles were HLA–DRB1 *0101, *0102, *0401, *0404, *0405, *0408, *0410, and *1001 (10). Patients were considered taking synthetic or biologic DMARDs treatment when taking, at 2 consecutive visits, methotrexate $\geq$10 mg/week, leflunomide, or any biologic agent treatment. The Montpellier Ethics Committee approved the study protocol. Written consent forms were obtained from each patient before inclusion.

IL-6. Serum samples obtained at baseline and at 6, 12, 18, 24, and 36 months were immediately frozen and stored at -80°C. A single biologic resource center was in charge of centralizing and managing the biologic data collection. IL-6 concentration was assessed using 2 different methods: 1) an immunoassay (Roche Diagnostics) according to supplier's recommendations with a detection range from 1.5 to 5,000 ng/liter, with normal values in healthy individuals being $<$7 ng/liter, and 2) multianalyte profiling beads (R&D Systems), with a detection range from 9.5 to 6,900 ng/liter (11).

Structural damage assessment. Two trained rheumatologists scored radiographs of wrists and hands (anteroposterior views) and feet (anteroposterior and oblique views) taken at baseline and at 6, 12, 24, and 36 months, using the total Sharp/van der Heijde scoring (SHS) method. Readers were blinded from each other and had no information about the patients. Intraobserver and interobserver reliabilities were good (12).

Baseline US evaluation was performed in a sample of 126 patients in 4 evaluation centers at baseline. Six joints (metacarpophalangeal joints [MCP] 2 and 5 and metatarsophalangeal [MTP] joint 5), were targeted for erosion detection and 10 joints (MCP joints 2–5 and MTP joint 5) were targeted for synovitis (13). Briefly, the palmar, dorsal, and lateral or medial sides of MCP joint 2, MCP joint 5 and MTP joint 5 were assessed for bone

erosion, while synovitis in B mode (gray-scale US) were assessed as present or not on MCP joint 2, MCP joint 5, and MTP joint 5, according to Outcome Measures in Rheumatology guidelines (14). Synovitis was also quantified in power Doppler mode using a semiquantitative score, where grade 0 = no flow in the synovium; grade 1 = flow ≤ one-third; grade 2 = flow ≤ two-thirds; and grade 3 = flow > two-thirds (15). The interexaminer reliability was assessed on 20 images in B mode and 30 images of synovitis, blinded from clinical data and other examiner results. The reliability among the 4 examiners was good (13).

Statistical analysis. Baseline demographic parameters of the 126 patients with US evaluation were compared to the whole ESPOIR cohort using the Mann-Whitney or the Fischer test where appropriate. Time-integrated values of DAS28-ESR, TJC, SJC, HAQ, CRP level, and IL-6 were estimated as area under the curve (AUC). The relationship between continuous outcome measures was investigated by Spearman's rank test either at baseline or from month (M) 0 to M36.

Baseline predictors of radiologic progression were investigated by several general linear models, including the following independent covariates: smoking status, synthetic or biologic DMARDs, radiographic erosion at baseline, HLA–DRB1 genotype (1 if shared epitope single dose, 2 if shared epitope double dose, and 0 if not), ACPA serology, and rheumatoid factor (RF) serology (1 if negative, i.e., less than or equal to the upper limit of normal [ULN] for the laboratory and assay; 2 if low positive, i.e., higher than the ULN but ≤3 times the ULN; and 3 if high positive, i.e., values that are >3 times the ULN for the laboratory and assay [10]). Analysis included the following models: model 1 = age, sex, and smoking status; model 2 = model 1 + baseline erosion + HLA–DRB1 genotype + RF serology + ACPA serology; model 3 = model 2 + baseline IL-6; model 4 = model 2 + baseline CRP; and model 5 = model 2 + baseline CRP + baseline IL-6.

Longitudinal models nested by patient and visit were conducted to investigate the role of IL-6 in the progression of SHS from baseline to M36. At each visit, the independent variable was the SHS score and the dependent covariates were DAS28, synthetic DMARD (i.e., methotrexate ≥10 mg/week or leflunomide), biologic DMARD and steroids (intramuscular and/or intravenous and/or oral steroids >5 mg/day), baseline smoking status, baseline RF, and baseline ACPA serology. A stepwise backward multivariable analysis was conducted to determine the best model (model 1). Then we forced IL-6 (model 2) or CRP level (model 3) or both (model 4) into this model. Baseline smoking status, baseline RF, and baseline ACPA serology were added in model 5. Missing data (5.8–17.1% according to the outcome measure) were replaced using last observation carried forward methodology. The intraclass correlation coefficient (ICC) and 95% confidence interval (95% CI) assessed the reliability of IL-6 concentrations measured by an immunoassay relative to the multianalyte profiling. Statistical analysis was performed using SAS software, version 9.1.

RESULTS

Study population. In all, 812 of the 813 patients could be assessed for IL-6 serum level at baseline and during the 36 months of followup. Demographic parameters are shown in Table 1. A total of 558 (17.1%) radiologic assessments were missing from baseline to M36. Mean, median, SD, and interquartile range of radiologic studies by patient were, respectively, 3.31, 4.00, 1.07, and 1.00. The demographic characteristics of the 126 patients assessed for US synovitis and erosion were not different from the whole cohort.

Baseline IL-6 as a predictor of synovitis and radiologic progression. IL-6 concentrations assessed by both methods were highly correlated (ICC 0.790, 95% CI 0.529–0.914). For subsequent analyses, we used the IL-6 immunoassay. IL-6 and CRP level were not detectable in, respectively, 17 patients (13.5%) and 15 patients (11.8%) at baseline and, respectively, 1,498 samples (30.8%) and 388 samples (8.0%) from baseline to M36.

Baseline IL-6 levels correlated with the SJC ($\rho = 0.497$, $P < 0.001$), US synovitis in B mode ($\rho = 0.198$, $P < 0.025$), US synovitis Doppler mode ($\rho = 0.259$, $P < 0.003$), and US erosion ($\rho = 0.202$, $P < 0.023$). Baseline CRP levels correlated with the SJC ($\rho = 0.142$, $P < 0.001$) (Table 2 and Supplementary Figure 1, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22513/abstract). IL-6 was more significantly correlated with clinical synovitis assessed by SJC than CRP level (Table 2).

Baseline IL-6 was correlated with SHS change from baseline to M36 independently from sex, age, smoking status, baseline erosion, HLA–DRB1 shared epitope, RF, and ACPA, but not from baseline CRP level (Table 3).

Role of IL-6 in the progression of SHS. Whereas $AUC_{IL\text{-}6}$ and AUC_{CRP} correlated with AUC_{HAQ} ($\rho = 0.220$, $P < 0.001$ and $\rho = 0.214$, $P < 0.001$, respectively), AUC_{SJC} was more strongly correlated with $AUC_{IL\text{-}6}$ ($\rho = 0.382$, $P < 0.001$) than AUC_{CRP} ($\rho = 0.159$, $P < 0.001$) (Table 4). SHS change from baseline to M36 was more strongly correlated with $AUC_{IL\text{-}6}$ ($\rho = 0.296$, $P < 0.001$) than with AUC_{CRP} ($\rho = 0.089$, $P < 0.012$) in the univariate analysis.

A total of 793 patients were included in longitudinal models nested by patient and visit. DMARD and steroid treatment were independently correlated with SHS score at each visit, whereas DAS28 was not (Table 5, model 1). IL-6 and CRP level were also independently correlated with SHS at each visit (Table 5, models 2–4).

DISCUSSION

In this 3-year followup study of early arthritis patients, we showed that IL-6 level at baseline was more correlated with clinical synovitis than CRP level. Baseline IL-6 was not independently associated with SHS change. However, longitudinal models nested by patient showed that IL-6 levels were associated with structural damage independently from DAS28, treatments, and CRP levels.

Table 1. Baseline demographics*

	ESPOIR cohort (n = 812)	US assessment (n = 126)	Univariate analysis, *P*
Female sex, %	76.7	77.2	0.913
Age, years	50.1 (38.8–57.2)	53.3 (40.7–59.2)	0.065
Disease duration, months	3.6 (2.2–5.3)	3.5 (2.2–5.1)	0.516
DAS28-ESR	5.1 (4.2–5.9)	5.1 (4.2–5.8)	0.772
HAQ (range 0–3)	0.9 (0.4–1.5)	0.8 (0.3–1.3)	0.057
SHS (range 0–448)	2.0 (0.0–7.0)	3.0 (0.0–7.0)	0.388
At least 1 bone erosion, %	34.0	31.7	0.614
1987 ACR criteria positive, %	56.9	61.4	0.338
ACPA positive, %	37.6	46.8	0.051
HLA–DRB1 genotype, no. (%)†			0.776
Shared epitope single dose	322 (41.8)	52 (43.0)	
Shared epitope double dose	82 (10.7)	10 (8.3)	
Shared epitope negative	366 (47.5)	59 (48.8)	
ESR, mm at 1 hour	22.0 (12.0–38.0)	25.0 (12.0–46.0)	0.369
CRP, mg/liter	9.0 (4.0–24.0)	7.0 (4.0–18.0)	0.100
IL-6, ng/liter	9.9 (2.7–30.6)	10.4 (2.9–33.3)	0.496

* Values are the median (interquartile range) unless indicated otherwise. ESPOIR = Etude et Suivi des Polyarthrites Indifférenciées Récentes; US = ultrasonography; DAS28-ESR = Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; HAQ = Health Assessment Questionnaire; SHS = total Sharp/van der Heijde score; ACR = American College of Rheumatology; ACPA = anti–citrullinated protein antibody; CRP = C-reactive protein; IL-6 = interleukin-6.
† Shared epitope = HLA–DRB1 *0101, *0102, *0401, *0404, *0405, *0408, *0410, and *1001 (10).

One of the main strengths of this study was the head-to-head correlation of time-integrated values of IL-6 and CRP level based on repeated measurements and structural damage in the largest prospective cohort of early arthritis in which biologic, immunologic, and radiologic data were thoroughly collected. Moreover, IL-6 concentration was detected using sensitive techniques (8). Furthermore, we could study the 3-year radiologic progression, whereas most of the other studies focused on the short-term, usually 12 months, radiologic progression.

The precise origin of circulating IL-6 in inflammatory arthritis is still unclear. In healthy individuals, one-third of the circulating IL-6 level is produced by adipose tissue (16). However, in early RA IL-6 levels are not correlated with body mass index (17), showing that adipose tissue is a marginal source of IL-6 in inflammatory arthritis. Our data, showing a correlation between baseline IL-6 levels and both swollen joint count and US synovitis, support the hypothesis that the increased blood level of IL-6 in RA patients is mainly due to the release of IL-6 from inflamed synovium (18), and could be a surrogate marker of synovitis in untreated early RA contrary to CRP level, which was barely correlated with SJC and was not correlated with US synovitis.

Several studies showed a very weak relationship between the SJC and erosions in RA (19,20). Therefore, a direct causal relation between clinically inflamed synovitis and structural damage progression seems unclear (11). However, the predictive value of subclinical synovitis, assessed by US or MRI, on structural damage has been suggested in RA patients treated with tumor necrosis factor blockers (21) and for patients in clinical remission (22).

Moreover, cumulative measures of US (23) and MRI synovitis (24) independently predicted radiographic progression, suggesting a direct role of subclinical synovitis on joint destruction. Hence, IL-6 is more likely to influence radiographic progression by a local fibroblast-like

Table 2. Baseline correlation between swollen joint count US evaluation, IL-6, and CRP*

	Baseline IL-6		Baseline CRP		
	$\rho_{IL\text{-}6}$ Spearman's coefficient	*P*	ρ_{CRP} Spearman's coefficient	*P*	$\rho_{IL\text{-}6}$ vs. ρ_{CRP}, *P*
Swollen joint count	0.497	< 0.001	0.147	< 0.001	0.002
US synovitis B mode	0.198	0.025	0.087	0.330	0.365
US synovitis Doppler mode	0.259	0.003	0.066	0.462	0.103
US erosion	0.202	0.023	0.138	0.124	0.605

* Data are stated as correlation between baseline ultrasonography (US) evaluation and either baseline interleukin-6 (IL-6) or C-reactive protein (CRP) levels.

synoviocytes proliferation (6) and an osteoclast stimulation (25), rather than a systemic effect on the immune system. In RA, the systemic levels of cytokine released by subclinical synovitis in small joints do not reflect cytokine concentration in synovium, explaining, at least partly, that the time-integrated levels of IL-6 are uncoupled from radiologic progression. Moreover, IL-6 is rapidly and dramatically decreased by RA pharmaceutical treatments (26). Hence, the dependence of IL-6 levels on treatment is likely to explain why IL-6 was not an independent factor of structural progression in our multivariable analysis. CRP production is also dependent on IL-1β and anaphylatoxin C5a generated as a consequence of complement activation (27). Therefore, CRP levels reflect IL-6 as well as C5a (28–30) and IL-1β (31,32) levels, which are both involved in synovium inflammation and joint destruction. This might explain that the time-integrated level of CRP was correlated with radiographic progression and IL-6 was not.

Previous studies showing a correlation between cumulative levels of systemic inflammation and joint destruction assessed cumulative CRP burden as a proxy of joint inflammation (23,24,33). Interestingly, our data suggested that the impact of systemic inflammation on radiologic progression was independent from joint inflammation. The upregulation of the receptor activator of RANKL expression in RA synovium intimal lining layer correlating with systemic inflammation assessed by CRP level has already been described (34) and might explain the correlation between systemic inflammation and joint destruction. Nevertheless, the extent of such a correlation was less important than the correlation between joint destruction and initial bone erosion, RF/ACPA serology, or disease-modifying treatment.

Some limitations of this study should be emphasized. First, US synovitis was analyzed in a cross-sectional manner. Although the significance of changes of US evaluation during followup is not clearly defined as yet (3), a paired comparison of time-integrated values of IL-6 levels and US synovitis might bring further insight in the relationship between IL-6, persistent synovitis, and structural damage. Second, biologic DMARDs and steroids inhibit inflammatory markers and specifically IL-6 along with radiographic progression. Most of the patients (515 of 813) did not take steroids at baseline (35), but short-term steroid intakes might influence our data as IL-6 is very sensitive to these antiinflammatory agents. During the first 5 years of followup, only 18.3% of the patients received a biologic DMARD (36), and only a few were treated with tocilizumab. Free IL-6 may combine to a soluble IL-6 receptor α (sIL-6Rα), which modulates IL-6 bioactivity. As sIL-6R/IL-6 complex, which we were not able to detect in our study, plays a role in synovitis and bone resorption in RA mouse model (37) through the up-regulation of receptor activator of RANKL by synovial fibroblasts, the additional assessment of both sIL-6R/IL-6 and IL-6 levels may be more closely correlated to clinical outcomes. Finally, preanalytical conditions might be considered. For instance, variations in IL-6 concentration have been reported according to subjects' age (38) and food intake (39). Physical exercise also increases serum IL-6 in healthy subjects but not in RA patients (40). Stress and emotional problems have been suggested to influence IL-6 levels (41). However, studies yielded contradictory data with decrease (42,43), and psychological distress has not been proven to be a risk factor for exacerbation of disease activity (44). Clot formation during serum preparation has also been suggested to increase cytokine levels through myeloid cell activation (45); IL-6 concentration in serum and plasma is well correlated (46,47), but might be influenced by anticoagulant (47,48). Although time sample collection was synchronized in the morning in order to obtain comparable and meaningful results, $AUC_{IL\text{-}6}$ based on repeated measurement is an

Table 3. Baseline independent predictors of 3-year radiographic progression assessed by changes of total Sharp/van der Heijde score from baseline to month 36 (general linear model)*

Independent covariates	Estimated coefficient ± SE	*P*
Model 1		
Sex	−0.27 ± 1.78	0.768
Age	0.09 ± 0.03	0.004
Baseline smoking status	−0.32 ± 0.77	0.681
Model 2		
Sex	−0.96 ± 0.91	0.289
Age	0.07 ± 0.03	0.016
Baseline smoking status	0.03 ± 0.76	0.968
Baseline erosion	3.08 ± 0.81	< 0.001
Shared epitope	0.22 ± 0.60	0.717
RF	0.95 ± 0.57	0.094
ACPA serology	2.50 ± 0.58	< 0.001
Model 3		
Sex	−1.13 ± 0.91	0.213
Age	0.07 ± 0.03	0.014
Baseline smoking status	−0.02 ± 0.76	0.974
Baseline erosion	2.90 ± 0.81	< 0.001
Shared epitope	0.30 ± 0.60	0.611
RF	0.92 ± 0.57	0.103
ACPA serology	2.38 ± 0.58	< 0.001
Baseline IL-6	0.02 ± 0.006	0.006
Model 4		
Sex	−1.50 ± 0.91	0.100
Age	0.07 ± 0.03	0.024
Baseline smoking status	0.12 ± 0.76	0.875
Baseline erosion	3.05 ± 0.81	< 0.001
Shared epitope	0.19 ± 0.59	0.753
RF	1.03 ± 0.56	0.067
ACPA serology	2.36 ± 0.57	< 0.001
Baseline CRP	0.05 ± 0.01	< 0.001
Model 5		
Sex	−1.52 ± 0.91	0.096
Age	0.07 ± 0.03	0.022
Baseline smoking status	0.08 ± 0.76	0.911
Baseline erosion	2.97 ± 0.81	< 0.001
Shared epitope	0.23 ± 0.59	0.694
RF	1.01 ± 0.56	0.074
ACPA serology	2.31 ± 0.57	< 0.001
Baseline CRP	0.04 ± 0.01	< 0.001
Baseline IL-6	0.01 ± 0.01	0.2059

* RF = rheumatoid factor; ACPA = anti–citrullinated protein antibody; IL-6 = interleukin-6; CRP = C-reactive protein.

Table 4. Correlation between time-integrated changes of outcome measures, total SHS score change from baseline to month 36, IL-6, and CRP*

	AUC_{IL-6}		AUC_{CRP}		
	$\rho_{AUC\ IL-6}$ Spearman's coefficient	*P*	$\rho_{AUC\ CRP}$ Spearman's coefficient	*P*	$\rho_{AUC\ IL6}$ vs. $\rho_{AUC\ CRP}$, *P*
$AUC_{DAS28-ESR}$	0.279	< 0.001	0.268		0.824
AUC_{TJC}	0.105	0.003	0.069	< 0.001	0.463
AUC_{SJC}	0.382	< 0.001	0.159	0.051	< 0.001
AUC_{HAQ}	0.220	< 0.001	0.214	< 0.001	0.904
$\Delta_{SHS\ M36-M0}$	0.296	< 0.001	0.089	0.012	< 0.001

* Data are stated as correlation between time-integrated (area under the curve [AUC]) changes from month 0 (M0) to month 36 (M36) of rheumatoid arthritis–related outcome measures, interleukin-6 (IL-6), and C-reactive protein (CRP). SHS = total Sharp/van der Heijde score; DAS28-ESR = Disease Activity Score in 28 joints using the erythrocyte sedimentation rate; TJC = total joint count; SJC = swollen joint count; HAQ = Health Assessment Questionnaire.

approximation of the real cumulative cytokine load, and may not be accurate enough to reflect the subtle cytokine variations in RA patients.

In summary, our study suggests that IL-6 level at baseline was associated with US synovitis but was not independently associated with SHS change. Longitudinal models nested by patient showed that IL-6 levels were associated with structural damage independently from DAS28, treatments, and CRP levels.

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Table 5. IL-6 as a predictor of radiologic progression; longitudinal models nested by patient and visit, exploring the predictors of structural damage assessed by total Sharp/van der Heijde score from month 6 to month 36*

	Coefficient					
Independent covariates	**Baseline**	**M6**	**M12**	**M24**	**M36**	***P***
Model 1						
DMARD		−4.94	−3.29	−2.51	0.00	< 0.001
Steroids		−1.36	−0.29	0.44	1.09	< 0.001
Model 2						
DMARD		−4.88	−3.29	−2.49	0.00	< 0.0001
Steroids		−1.27	−0.31	0.47	1.01	0.004
IL-6		−0.011	0.00	0.00	0.01	< 0.001
Model 3						
DMARD		−4.78	−3.14	−2.44	0.00	< 0.001
Steroids		−1.29	−0.25	0.47	1.09	< 0.001
CRP		−0.06	−0.05	−0.02	0.00	< 0.001
Model 4						< 0.001
DMARD		−4.77	−3.16	−2.45	0.00	< 0.001
Steroids		−1.23	−0.26	0.47	1.05	< 0.001
CRP		−0.05	−0.04	0.12	0.00	0.006
Il-6		−0.01	0.00	0.00	0.01	0.049
Model 5						
DMARD		−4.95	−3.29	−2.50	0.00	< 0.001
Steroids		−1.27	−0.29	0.46	1.04	< 0.001
CRP		−0.01	−0.042	0.12	0.00	0.006
Il-6		−0.01	0.00	0.00	0.01	0.034
Baseline smoking status	0.52					0.289
Baseline RF	−0.43					0.258
Baseline ACPA	1.37					< 0.001

* IL-6 = interleukin-6; M = month; DMARD = disease-modifying antirheumatic drug; CRP = C-reactive protein; RF = rheumatoid factor; ACPA = anti–citrullinated protein/peptide antibody.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Baillet had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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