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Five-year Favorable Outcome of Patients with Early Rheumatoid Arthritis in the 2000s: Data from the ESPOIR Cohort

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ABSTRACT. ***Objective.*** To report the 5-year outcome of a large prospective cohort of patients with very early rheumatoid arthritis (RA), and to identify factors predictive of outcome.

Methods. Patients were recruited if they had early arthritis of < 6 months' duration, had a high probability of developing RA, and had never been prescribed disease-modifying antirheumatic drugs (DMARD) or steroids. Logistic regression analysis was used to determine factors that predict outcome.

Results. We included 813 patients from December 2002 to April 2005. Age was 48.1 ± 12.6 years, delay before referral 103.1 ± 52.4 days, 28-joint Disease Activity Score (DAS28) 5.1 ± 1.3, Health Assessment Questionnaire (HAQ) 1.0 ± 0.7; 45.8% and 38.7% had rheumatoid factor or antibodies to cyclic citrullinated peptide (anti-CCP), respectively; 22% had hand or foot erosions; 78.5% fulfilled the American College of Rheumatology/European League Against Rheumatism criteria for RA at baseline and 93.8% during followup. At 5 years, 573 patients were evaluated. The outcome was mild for most patients: disease activity (median DAS28 = 2.5) and HAQ disability (median 0.3) were well controlled over time; 50.6% achieved DAS28 remission and 64.7% low disease activity. Radiographic progression was low (2.9 Sharp unit/year) and only a few patients required joint surgery. Nevertheless, some patients developed new comorbidities. During the 5 years, 82.7% of patients had received at least 1 DMARD (methotrexate, 65.9%), 18.3% a biological DMARD, and about 60% prednisone at least once. Anti-CCP was the best predictor of remaining in the cohort for 5 years, of prescription of synthetic or biologic DMARD, and of radiographic progression.

Conclusion. The 5-year outcome of an early RA cohort in the 2000s was described. Anti-CCP was a robust predictor of outcome. The generally good 5-year outcome could be related to early referral and early effective treatment, key processes in the management of early RA in daily practice. (First Release Aug 15 2013; J Rheumatol 2013;40:1650–7; doi:10.3899/jrheum.121515)

Key Indexing Terms:
ESPOIR COHORT RHEUMATOID ARTHRITIS EARLY ARTHRITIS
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Rheumatoid arthritis (RA) is the most frequent inflammatory arthritis, affecting 0.3% to 0.8% of the population[1]. Patients experience significant disability and handicap after a few years of disease progression. Results published before 2000 showed that at 10 years, more than 80% of patients had greatly decreased functional ability, 50% needed personal aid for some daily life activities, and many have to quit their professional activities or alter their jobs[2,3,4,5,6]. In addition, patients with active and severe disease showed increased cardiovascular morbidity and reduced life expectancy[7].

In the past 10 years, tremendous changes have occurred in the management of RA. These changes are explained by the scientific validation of important processes (very early treatment, tight control, intensive strategies)[8,9,10,11,12,13,14,15,16], effective treatments such as biologics[17,18,19,20], and the development of international guidelines aiming for remission[16,21,22,23]. These concepts have been validated by clinical trials, but outside of clinical trials, little is known about the outcome of RA in patients whose disease began in the last decade, and whose treatment was based on standard care.

In 2002, the French Society of Rheumatology initiated the development of a large national multicenter cohort, the ESPOIR cohort, for investigating diagnostic and prognostic markers and also pathogenic mechanisms and economic consequences among patients with early undifferentiated, inflammatory arthritis that could later progress to RA[24]. ESPOIR is an acronym for *Etude et Suivi des POlyarthrites Indifférenciées Récentes* (Study and Monitoring of Early Undifferentiated Arthritis). The primary objective of our current study was to report the 5-year outcome of patients included in the ESPOIR cohort and to identify factors that predict outcome: remaining in the cohort, 5 years disability, prescription of synthetic or biologic disease-modifying antirheumatic drugs (DMARD), and 3-year radiographic evidence of damage.

MATERIALS AND METHODS

ESPOIR is a longitudinal prospective cohort of adults with possible early RA who are ≥ 18 and < 70 years old. Patients were referred by rheumatologists and general practitioners to one of 14 regional centers in France. The objective and design of the cohort have been described in detail[24].

The primary objective was to establish a multicenter cohort of patients with early arthritis (< 6 months' disease duration) that could result in a database for studying early RA, including diagnosis, prognosis, medico-economic factors, genetics, and pathogenesis.

The main inclusion criteria were at least 2 inflammatory joints for at least 6 weeks up to 6 months; clinical diagnosis of RA as certain or probable or undifferentiated arthritis potentially becoming RA; never prescribed DMARD or glucocorticoids except if the latter were prescribed for < 2 weeks with a maximum mean dosage of 20 mg/day prednisone or intraarticular injection < 4 weeks before inclusion.

The main exclusion criteria were other inflammatory rheumatism or connective tissue diseases clearly determined according to usual criteria.

Sample size calculation. A sufficient number of subjects would allow reasonable conclusions after 10 years of followup and reliable subgroup analyses. A compromise has been formulated to obtain at least 300 patients with RA on a 10-year term, to first evaluate the clinical and structural severity of the disease including main comorbidities and the predictive factors of outcome. Data from the literature, as well as previous cohort study experiences, have shown that proportion of loss to followup is in the range of 5% to 8% during the first 3 years, then stabilizes between 1% and 5%, depending on many different factors. Using intermediate estimates, it would be necessary to start with 400 patients. Given the probability that 50% of patients will not have RA after 2 years, it was planned to include 800 patients with early arthritis.

Patient recruitment and followup. Patients were routinely treated and followed by their rheumatologists according to standard care and without predefined therapeutic strategies. All patients were referred to each regional center every 6 months during the first 2 years, then every year, and were seen by the same investigator in each center. Procedures were set up to avoid patients lost to followup as much as possible. At baseline and at each visit, we recorded data for a set of clinical and biological variables recommended for the management of early arthritis[24]. At each visit, RA was classified according to the 1987 American College of Rheumatology (ACR) criteria[25] and retrospectively to the 2010 ACR/European League Against Rheumatism (EULAR) criteria[26]. Patients underwent testing by the same procedures in a central laboratory for baseline erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level (normally < 10 mg/dl), IgM and IgA rheumatoid factors (RF; determined by ELISA; positive > 9 IU/ml), antibodies to cyclic citrullinated peptide (anti-CCP; determined by ELISA; positive > 50 U/ml), and HLA-DRB1* alleles (Immunology Department, Montpellier University Hospital).

At each visit, patients completed function and quality-of-life self-administered questionnaires including the Health Assessment Questionnaire-Disability Index (HAQ-DI), Arthritis Impact Measurement Scales version 2 short form[27], a medicoeconomic questionnaire, and globally assessed disease, pain at rest and pain during motion on a visual analog scale (VAS). Patients underwent radiographs of the hand and wrist (face) and foot (face and oblique). Radiographs were stored in the radiological coordinating center (Brest) and then were evaluated by the van der Heijde-modified Sharp score[12,28].

The protocol of the ESPOIR cohort study was approved in July 2002 by the ethics committee of Montpellier (no. 020307). All patients gave their signed informed consent before inclusion.

Our study describes the 5-year course for the 813 included patients. The primary outcomes were the clinical and functional variables. Secondary outcomes included radiographic damage, immunologic changes, therapeutic management, and comorbidities. We also aimed to identify predictive factors of outcome.

Statistical analysis. Univariate analysis of the association of all baseline values and outcome measures involved Pearson's chi-square or Fisher's exact test. Continuous variables were transformed into categorical variables with the median value as the cutoff (or the cutoff provided by the manufacturer for biological data). Unconditional logistic regression analysis was used to determine independent baseline variables to predict outcome. Five different analyses were performed to explain the outcomes: remaining in the cohort for 5 years, poor HAQ-DI score (higher than median value), prescription of a synthetic or a biologic DMARD, and 3-year radiographic progression. The explanatory variables included in each model were selected at $p < 0.15$ from results of the univariate analysis. A (forward) stepwise procedure was used to select variables to be retained in the multivariate model. Significance was defined as $p < 0.05$ for variables in the multivariate model. Data were

analyzed by use of SAS 9.2 (SAS Institute) by the EA2415 biostatistical team of Montpellier I University.

RESULTS

Baseline patient characteristics. The main baseline characteristics of the whole cohort are reported in Table 1. The mean age of the 813 patients was 48.1 ± 12.6 years (median 50.1); 76.7% (n = 624) were women. In total, 50 (6.1%) patients had a personal history of psoriasis and 129 (15.9%) a familial history of inflammatory arthritis (RA = 113). Cardiovascular diseases were the main comorbidity (Table 2). The mean time between the first occurrence of swollen joints (diagnosed by a physician) and the referral was 103.12 ± 52.42 days. Patients had active disease, with a mean 28-joint Disease Activity Score (DAS28) of 5.11 ± 1.31 (median 5.1, range 1.5–8.8) and a mean HAQ-DI score of 0.98 ± 0.68 (median 0.9, range 0–2.9). In all, 71.3% (n = 578) patients fulfilled the 1987 ACR criteria for RA and 78.5% (n = 641) the 2010 ACR/EULAR criteria for RA. ESR and CRP levels were increased; 316 patients (38.9%) had abnormal CRP level; 45.8% patients (n = 372) were positive for IgM RF, and 38.7% (n = 315) had anti-CCP. A total of 54.4% of patients (56.7% with RA based on 2010 ACR/EULAR criteria) were positive for HLA-DRB1*01 or *04 RA-associated alleles with the following genotypes: 01/X (16.4%), 04/X (29.4%), 01/01 (0.6%), 01/04 (4.9%), 04/04 (3.1%), and X/X (45.6%; where X = neither 01 nor 04 HLA DRB1*-associated alleles). At baseline, the total van der Heijde-modified Sharp score[28] was 4.97 ± 7.14; 22.3% of patients (160 of 715) had typical RA erosions on hands and/or feet, as defined by each rheumatologist investigator.

No significant differences among regional centers were observed.

Patients lost to followup. We could evaluate data for 573 of 813 patients with RA or undifferentiated arthritis at 5 years in the regional centers: 49 patients missed the 5-year visit but were still followed in ESPOIR, 62 patients (7.5%) received a diagnosis other than RA or undifferentiated arthritis and were excluded, and 9 patients died. In all, 120 patients were truly lost to followup (n = 44, 5.4%) or had moved or refused to continue the planned longitudinal followup (n = 76, 9.3%). For patients who stayed in the cohort and were seen at 5 years, at baseline (Table 1) they were significantly older (p = 0.029); were more often positive for anti-CCP, IgM or IgA RF (p < 0.0001), and HLA-DRB1-associated alleles (p = 0.005); and had more radiographic damage (p = 0.012) than the whole cohort. On multivariate analysis, predictors of being in the cohort at 5 years were baseline anti-CCP (OR 3.59, 95% CI 2.31–5.80, p < 0.0001), age > 50 years (OR 1.81, 95% CI 1.24–2.62, p = 0.0019), and pain during motion on a 100 mm VAS (OR 0.68, 95% CI 0.46–0.98, p = 0.041).

Clinical and functional outcome. At 5 years, most patients

Table 1. Characteristics of the ESPOIR cohort with early rheumatoid arthritis at baseline. Data are mean ± SD, median (range), unless otherwise indicated.

Variable	Whole Cohort, n = 813	Patients with 5-Year Followup, n = 573
Symptom duration*	103.1 ± 52.4	103.2 ± 52.1, 92 (5–192)
Swollen joints (0–28)	7.2 ± 5.3	7.5 ± 5.4, 6 (2–28)
Tender joints (0–28)	8.4 ± 7.0	8.4 ± 6.9, 6 (2–28)
Patient global assessment (mm, VAS)	59.9 ± 25.6	59.3 ± 25.6, 64 (0–100)
Physician global assessment (mm, VAS)	50.7 ± 22.5	50.9 ± 22.3, 50.5 (0–91)
Pain at rest (mm, VAS)	30.6 ± 27.5	30.8 ± 27.6, 34.0 (0.0–100)
Pain during motion (mm, VAS)	53.7 ± 26.1	54.0 ± 25.6, 54.5 (0.0–100)
DAS28	5.11 ± 1.31	5.12 ± 1.31, 5.07 (1.51–8.8)
HAQ-DI score	0.98 ± 0.68	0.99 ± 0.68, 0.88 (0–2.88)
ESR, mm/h	29.4 ± 24.6	28.8 ± 24.3, 22 (0–130)
CRP level, mg/dl	20.3 ± 32.4	22.0 ± 34.8, 19 (0–384)
ACPA positivity, n (%)	315 (38.7)	256 (44.7)
IgM-RF positivity, n (%)	372 (45.8)	292 (51.0)
IgA-RF positivity, n (%)	359 (44.2)	265 (46.2)
HLA-DRB1*01, n (%)**	178 (21.9)	118 (20.6)
HLA-DRB1*04, n (%)**	304 (37.4)	235 (41.0)
van der Heijde-modified total Sharp score	4.9 ± 7.1	5.3 ± 6.8, 2 (0–56)
Erosion score	1.4 ± 3.6	1.6 ± 3.4, 0 (0–38)
1987 ACR criteria, n (%)	578 (71.3)	427 (74.5)
2010 ACR/EULAR criteria, n (%)	641 (78.5)	471 (82.2)

* Since first swollen joints on ESPOIR screening. ** HLA-DRB1*0101, 0103, 0401, 0404, 0405, or 0408. VAS: visual analog scale; DAS28: Disease Activity Score in 28 joints; HAQ-DI: Health Assessment Questionnaire-Disability Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ACPA: anticitrullinated protein antibodies; RF: rheumatoid factor; ACR: American College of Rheumatology; RA: rheumatoid arthritis; EULAR: European League Against Rheumatism.

Table 2. Past and present comorbidities in the ESPOIR cohort.

Conditions	Baseline n = 813 (%)	Baseline n = 573 (%)*	5-year Followup, n = 573 (%)
Hypertension	139 (17.1)	98 (17.1)	148 (25.8)
Hypercholesterolemia	125 (15.4)	89 (15.5)	180 (31.4)
Hypertriglyceridemia	28 (3.4)	18 (3.1)	77 (13.4)
Myocardial ischemia	8 (1.0)	6 (1.1)	15 (2.6)
Stroke	4 (0.5)	2 (0.4)	6 (1)
Lymphoproliferative disorder	5 (0.6)	3 (0.5)	5 (0.9)
Cancer	25 (3.1)	21 (3.7)	35 (6.1)
Gastrointestinal event	44 (5.4)	31 (5.4)	42 (7.3)
Diabetes	31 (3.8)	17 (3.0)	26 (4.5)
Thyroid disorder	90 (11.1)	65 (11.3)	89 (15.5)
Tuberculosis	35 (4.3)	26 (4.5)	32 (5.6)
HIV infection	1 (0.1)	1 (0.2)	1 (0.2)
Hepatitis B	4 (0.5)	3 (0.5)	4 (0.7)
Hepatitis C	6 (0.7)	5 (0.9)	8 (1.4)
Vertebral fracture	0	0	2 (0.4)

* Patients with a visit at 5 years. HIV: human immunodeficiency virus.

(92.8%, 532/573) met the 2010 ACR/EULAR criteria, and among the whole cohort of 813 patients, 763 (93.8%) had fulfilled these criteria at least once during followup (Table 3). Because this high rate of patients fulfilling the RA classification criteria was in line with the inclusion criteria, the whole cohort was considered an early RA cohort.

Most of the time, disease activity was well controlled. DAS28 decreased to 3.4 ± 1.4 (median 3.3, range 0–7.4) at month 6 and 2.7 ± 1.3 (median 2.5, range 0–7.1) at 5 years. HAQ-DI score decreased to 0.5 ± 0.6 (median 0.4, range 0–2.5) at month 6 and 0.5 ± 0.6 (median 0.3, range 0–2.5) at 5 years. Scores for patient global assessment on a 0–10 VAS, ESR, and CRP levels were improved as well. At the 2-year and 5-year visits, 47.6% (n = 321) and 50.6% (n = 290) of patients, respectively, achieved DAS28 remission, and 64.6% (n = 437) and 64.7% (n = 371) had DAS28 low disease activity. At 5 years, 33.0% of patients (n = 189) had achieved sustained (> 12 months) DAS28 remission.

Because of efficient data management, the rate of missing data was low (0.16% to 0.65%; Table 3).

Predictors of poor 5-year HAQ disability were baseline HAQ-DI score, older age, female sex, and joint pain at rest (VAS; Table 4).

Radiographic outcome. Structural progression was weak, with a mean change of 8.8 in total modified Sharp score [smallest detectable difference (SDD) = 1] and 2.6 in erosion score during the first 3 years. During this time, 79% (n = 447) showed progression of the total Sharp score and 53.7% (n = 304) change of at least 5 points. HAQ-DI and radiographic scores were not associated.

Predictors of 3-year radiographic progression were baseline anti-CCP positivity and erosion score (Table 4).

Immunologic changes. Autoantibody positivity showed no

Table 3. Disease activity, functional and structural outcome in the ESPOIR cohort over 5 years. Data are mean ± SD except where indicated.

	Baseline, n = 813	Month 6, n = 757	Month 12, n = 731	Month 24, n = 692	Month 36, n = 636	Month 60, n = 573	Baseline*, n = 573
DAS28	5.1 ± 1.3	3.4 ± 1.4	3.1 ± 1.4	2.9 ± 1.4	2.9 ± 1.4	2.7 ± 1.3	5.1 ± 1.3
Swollen joints, n	7.2 ± 5.4	2.4 ± 3.3	2.1 ± 3.1	1.6 ± 3	1.3 ± 2.5	1.2 ± 2.5	7.5 ± 5.4
Tender joints, n	8.4 ± 7.0	4.4 ± 5.8	3.7 ± 5.6	2.9 ± 5.2	3.0 ± 5.3	2.7 ± 5	8.4 ± 6.9
Patient global assessment	59.8 ± 25.6	34.7 ± 26.8	31.1 ± 26.4	28.0 ± 26.4	28.8 ± 26.2	25.9 ± 25.4	59.3 ± 25.6
HAQ-DI score	1.0 ± 0.7	0.5 ± 0.6	0.5 ± 0.6	0.5 ± 0.6	0.5 ± 0.6	0.5 ± 0.6	1 ± 0.7
ESR, mm/h	29.4 ± 24.6	16.2 ± 14.0	15.2 ± 13.8	15.6 ± 14	14.9 ± 13.2	14.5 ± 13.3	28.8 ± 24.3
CRP level, mg/dl	20.3 ± 32.4	22.2 ± 33.6	8.8 ± 19.9	7.4 ± 12.2	7.0 ± 12.6	6.8 ± 11.7	22.0 ± 34.8
mTS** score	4.9 ± 7.1			10.7 ± 1.3	13.8 ± 14.7		5.3 ± 6.8
Erosion score	1.4 ± 3.6			3.1 ± 7.4	4.0 ± 7.8		1.6 ± 3.4
Missing values, %***	0.25	0.24	0.16	0.23	0.64	0.65	0.23

* For patients with a visit at 5 years. ** van der Heijde-modified total Sharp score. *** Any missing values that are not reported here, including those from quality-of-life and medicoeconomic questionnaires. DAS28: Disease Activity Score in 28 joints; HAQ-DI: Health Assessment Questionnaire-Disability Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table 4. Baseline predictors of outcome in the ESPOIR cohort (multivariate analysis).

Predictors	OR	(95% CI)
Three-yr radiographic progression		
ACPA	2.16	(1.37 ± 3.40)
Baseline erosion score	2.30	(1.39 ± 3.79)
Five-yr HAQ disability		
Baseline HAQ	2.90	(2.00–4.19)
Older age	1.91	(1.32–1.77)
Female sex	1.60	(1.02–2.50)
Baseline pain at rest	1.69	(1.17–2.44)
Prescription of at least 1 DMARD		
ACPA	4.85	(2.46–9.56)
2010 ACR/EULAR criteria	2.52	(1.58–4.01)
Baseline pain	2.19	(1.37–3.48)
Biologics prescription		
ACPA	3.12	(1.80–5.43)
Baseline tender joint count	2.34	(1.51–3.61)
Baseline pain	2.16	(1.39–3.34)
Rheumatoid factor positivity	1.90	(1.07–3.35)

ACPA: anticitrullinated protein antibodies; HAQ: Health Assessment Questionnaire; DMARD: disease-modifying antirheumatic drug; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism.

significant change over time: at baseline and 5 years, 45.8% and 43.2% of patients, respectively, were positive for IgM RF and 38.7% and 45.7% for anti-CCP.

Disease management. Most patients (82.7%, n = 672) from the whole cohort had received at least 1 synthetic DMARD during the followup. This rate increased to 90.4% when only patients (n = 573) with a visit at 5 years were considered. Most started this therapy during the first 6 months after the first synovitis.

The most commonly prescribed synthetic DMARD (65.9%, n = 536) was methotrexate [MTX; median dosage 12.97 (range 5–25) mg/week], then hydroxychloroquine (20.8%, n = 169), sulfasalazine (18.1%, n = 147), leflunomide (15.6%, n = 127), and injectable gold (4.1%, n = 33); 69 patients (8.49%) received a combination of at least 2 synthetic DMARD. The patients had received 1.83 ± 1.05 DMARD, on average.

Predictors of prescription of at least 1 synthetic DMARD were baseline anti-CCP, meeting 2010 ACR/EULAR criteria, and increased pain at rest (VAS; Table 4).

During the 5-year followup, 149 patients (18.3%) of the whole cohort received a biological DMARD (21.8% of the 573 patients with a visit at 5 years), mainly a tumor necrosis factor (TNF) blocker (etanercept 78, adalimumab 85, infliximab 16); 49 patients (6.0%) had received > 1 biologic and some received a non-anti-TNF DMARD (abatacept 4, rituximab 15, tocilizumab 1). Finally, 40 of these patients (26.8%) received the biologic as monotherapy, without any associated synthetic DMARD.

Predictors of prescription of at least 1 biologic DMARD were baseline anti-CCP, increased number of tender joints, increased pain at rest level (VAS), and IgM RF positivity (Table 4).

As for glucocorticoids, more than half the patients (59.8%, n = 486) had received prednisone at least once; 45.3% of those (n = 368) received steroids during the first 6 months. In total, 38.5% of patients (n = 312) had received daily oral steroids for more than 1 year and 11.2% (n = 64) continuously during the whole 5 years. For patients taking steroids, the mean prednisone dosage was 8.8 ± 7.7 mg/day (median 6, range 1.0–60.0).

In total, 24 (3%) patients required joint surgery as a result of their arthritis: 4 hip arthroplasties, 3 knee arthroplasties, 7 synovectomies, 5 foot or wrist arthrodesis, and 5 forefoot procedures.

Nine patients died: 3 from preexisting severe cardiovascular disease, 3 severe infections, 2 malignancies, and 1 car accident. Compared to baseline, at 5 years, some patients showed new comorbidities, mainly hyperlipidemia and hypertension, and despite low number of events, myocardial ischemia and strokes (Table 2).

DISCUSSION

Although our report is mainly descriptive and has some limitations, including the absence of a comparison group, it provides the 5-year outcome for 813 patients with very early arthritis who received the standard of care available from 2003 to 2010 from their rheumatologists. At baseline, 78.5% of patients fulfilled the 2010 ACR/EULAR criteria for RA, and 93.8% did so at least once during followup. At baseline, 71% of patients met the 1987 ACR criteria for RA; the discrepancies between the 2 sets of criteria in the ESPOIR cohort have recently been published and discussed[29].

Patients had active arthritis at entry, as confirmed by the DAS28 score and HAQ-DI. The 5-year outcome was rather mild in most of the patients, and disease activity was well controlled. At 5 years, the median DAS28 was 2.5, HAQ-DI score was within normal limits for > 50% of patients (median 0.3), and the annual rate of radiographic disease progression was low (van der Heijde-modified Sharp score 2.9 units/year), even though 79% of patients showed structural disease progression (smallest detectable difference 1). Almost half the patients achieved DAS28 remission in the first 2 years, one-third showed sustained remission (> 1 year) at 5 years, and only a few patients required joint surgery. However, some patients developed new comorbidities, mainly hyperlipidemia and cardiovascular diseases, which seems in line with some previous reports of early RA[30]. Only 573 of the 813 selected patients at baseline were followed up. The loss of followup patients may induce bias in the data interpretation. However, the baseline characteristics of the whole cohort and of the patients who were seen at 5 years did not indicate major differences between these 2 groups. Further, anti-CCP and radiographic damage,

which usually indicate more severe disease, were significantly higher in the followup patients, suggesting that the missing patients may have had milder disease.

Most patients (90.4%) had received at least 1 DMARD during the 5-year followup, mainly MTX, according to the usual guidelines[21,22]. DMARD were mainly prescribed as monotherapy (89.7%), which could seem very high. French rheumatologists do not really trust the effectiveness of synthetic DMARD combinations, which have been used extensively, with disappointing results. In addition, such combinations are still not strongly recommended by our national and EULAR guidelines[22]. Most of the patients started DMARD during the first 6 months; we previously showed with this cohort that patients who received their first DMARD within 3 months after the onset of the first synovitis had better radiographic outcome at 1 year[12]. In the current study, 21.8% of patients at their 5-year visit had received a biological DMARD, one-quarter as monotherapy; this relatively high rate could be related to the French guidelines, which place almost no limit on the prescription of licensed biologics. Finally, about 60% of the whole cohort had received prednisone at least once during the 5 years, with a mean dosage 8.8 ± 7.7 mg/day. Unfortunately, this seems quite high with reference to the national and international guidelines, which recommend that glucocorticoids be used with caution and preferably for only short periods, in combination with synthetic DMARD[22].

The proportion of patients with positivity for RF and anti-CCP at baseline, 45.8% and 38.8%, respectively, remained stable during followup, which suggests no need to recheck for these autoantibodies. These rates are lower than those for a previous smaller early RA cohort started in France in 1993[31] and for other early RA cohorts, with positivity for RF and anti-CCP of about 60% and 50%, respectively[32,33]. This difference may be related to our rate of patients fulfilling RA classification criteria at baseline: 78.5% versus 100% for the other RA cohorts. Nevertheless, our results are in line with the autoantibody positivity reported for other early arthritis inception cohorts[34,35].

Despite the absence of a comparison group, the favorable 5-year outcome that we observed in this early arthritis cohort may be related to several factors that have been highlighted in recommendations for managing RA[16,20,21]. These factors include early referral to a rheumatologist (mean 103.1 days after the first symptoms; about half the patients were seen by a rheumatologist within the EULAR-recommended timeframe[36]); early effective treatment (DMARD: 82.7%; MTX: 65.9%)[30]; and a high rate of remission. The trend toward milder disease in RA since the beginning of the year 2000 has been suggested by some clinical studies but never demonstrated in real life[32,37,38,39]. The trend is probably attributable to better therapeutic strategies, including the extensive use and optimization of effective antirheumatic treatment such as MTX. Because fewer than 20% of our patients received biologics, the benefit of these relatively new therapies on RA outcome is difficult to evaluate.

Our data also confirm anti-CCP positivity as a robust predictor of outcome with early RA. Anti-CCP positivity at baseline was the best predictor of remaining in the cohort after 5 years, prescription of synthetic or biologic DMARD, and 3-year radiographic disease progression. The finding that anti-CCP were associated with the prescription of synthetic DMARD is probably explained by the diagnostic value of this biomarker, which was highlighted by the 2010 ACR/EULAR classification criteria for RA[26], and because international guidelines strongly recommend the prescription of a DMARD as soon as the diagnosis of RA is made[21,22]. Older age and female sex were mainly associated with HAQ disability, as reported[40,41]. Age > 50 years was also predictive of being in the cohort at 5 years. Despite some discrepancies, older age has been frequently reported as a poor prognostic marker in patients with RA[40,41,42]. In addition, it has been shown that in patients with early undifferentiated arthritis, age was an independent predictive variable for persistence and development of RA[43]. Baseline pain at rest was selected as a predictive factor of HAQ disability but also of both synthetic and biologic DMARD prescriptions, which confirms the importance of patient perspective in treatment decisions in RA. Interestingly, the extensive biological database of the ESPOIR cohort will help determine other biomarkers associated with outcome. Indeed, we recently showed that, along with anti-CCP positivity, baseline interleukin 6 level was an independent risk factor of structural disease progression[44].

We report the 5-year outcome of a large cohort that was established in the early 2000s of patients with very early RA. Anti-CCP was a robust predictor of outcome, including remaining in the cohort for 5 years, prescription of synthetic or biologic DMARD, and radiographic progression. The favorable outcomes for this cohort support the need for early referral and early effective treatment in managing early RA in daily practice.

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