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Original article

Current favourable 10-year outcome of patients with early rheumatoid arthritis: data from the ESPOIR cohort

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Abstract

Objective. To report the 10-year outcome of an inception cohort of patients with early rheumatoid arthritis (RA), the ESPOIR cohort, and predictors of outcome.

Methods. From 2003 to 2005, 813 patients were included if they had early arthritis (<6 months) with a high probability of RA and had never been prescribed DMARDs. Multivariate analysis was used to evaluate predictors of outcome.

Results. In total, 521 (64.1%) RA patients were followed up for 10 years; 35 (4.3%) died, which appears to be similar to the French general population. Overall, 480 (92.1%) patients received a DMARD; 174 (33.4%) received at least one biologic DMARD, 13.6% within 2 years. At year 10, 273 (52.4%) patients were in DAS28 remission, 40.1% in sustained remission, 14.1% in drug-free remission, 39.7% in CDAI remission. Half of the patients achieved a health assessment questionnaire-disability index (HAQ-DI) < 0.5. SF-36 physical component and pain were well controlled. Structural progression was weak, with a mean change from baseline in modified Sharp score of 11.0 (17.9). Only 34 (6.5%) patients required major joint surgery. A substantial number of patients showed new comorbidities over 10 years. Positivity for anti-citrullinated peptides antibodies (ACPA) was confirmed as a robust predictor of long-term outcome.

Conclusions. We report a very mild 10-year outcome of a large cohort of patients with early RA diagnosed in the early 2000s, which was much better than results for a previous cohort of patients who were recruited in 1993. This current favourable outcome may be related to more intensive care for real-life patients.

Key words: ESPOIR cohort, rheumatoid arthritis, early arthritis, outcome, disability, remission

CLINICAL SCIENCE

Rheumatology key messages

- Current 10-year outcome of patients with early RA is better than in previous decades
- Structural progression, HAQ disability, rates of major joint surgery and of mortality are currently low
- This favourable outcome may be related to more intensive care for real-life patients

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Introduction

Rheumatoid Arthritis (RA) is a heterogeneous disease, and the outcome is challenging to predict. Most patients experience significant disability and structural damage after a few years of disease progression and patients with severe disease show increased cardiovascular morbidity and reduced life expectancy [1]. However, the outcome of the disease seems to have improved in recent years with the availability of effective therapies and recognition that early treatment and use of treat-to-target strategy are key points in the management [2, 3]. Results published before 2000 showed that at 10 years' disease duration, many patients had greatly decreased functional ability and had to quit their professional activities [4, 5]. However, evidence is still limited for the outcome of RA patients in whom disease began after 2000, although recent data seem to support improvement in disease activity, structural damage and cardiovascular mortality [6, 7].

In 2003, the French Society for Rheumatology initiated an inception cohort (ESPOIR cohort), in patients with early arthritis that could progress to RA. The 5-year outcome was previously reported [8]. The current study describes the 10-year outcome of RA patients included in the ESPOIR cohort and aimed to identify predictors of outcome. We also compared the findings with data reported for a previous French cohort with disease onset in 1993–1994 [9].

Patients and methods

ESPOIR cohort

Patients were referred by rheumatologists and general practitioners to one of the 14 regional centres (ClinicalTrials.gov: NCT03666091). The objective and design of the cohort are described elsewhere [8]. The main inclusion criteria were at least two inflammatory joints (6 weeks to 6 months); clinical diagnosis of RA as certain or probable; and never prescribed disease-modifying anti-rheumatic drugs (DMARDs) or glucocorticoids. The main exclusion criteria were other inflammatory arthritis determined according to usual classification criteria. Patients received standard of care and were followed without predefined therapeutic strategies. At baseline and at each yearly visit, data of variables recommended for managing early arthritis were recorded and patients completed function and quality-of-life questionnaires (health assessment questionnaire-disability index (HAQ-DI), SF-36 scores, pain and fatigue on a visual analogue scale). Patients underwent radiography of hands and feet. Central X-ray readings were performed by multi-reader assessment [10]. The data manager of the cohort (NR) froze the yearly database when all queries had been answered. Only patients who met at least once during the follow-up, the 2010 ACR/EULAR criteria [11], were selected for the current study.

The protocol of the ESPOIR cohort study was approved by the Ethics Committee of Montpellier, France (July 2002; no. 020307). All patients gave their signed informed consent.

Outcomes

The 10-year outcome variables were selected according to the major objectives in RA management [2, 3]: clinical remission, absence of significant functional disability (HAQ-DI < 0.5) [12], prevention of structural damage and comorbidities. Deaths were collected by both the clinical centres and the national epidemiologic centre on the causes of death. The rate of deaths was compared with that in the French general population stratified for age (cepidc-data.inserm.fr).

Statistical analysis

Descriptive statistics are presented as mean (S.D.) or number (%) as appropriate. The non-parametric Mann–Whitney *U* test was used to compare continuous variables and χ^2 test (or Fisher's exact test) for categorical variables. Continuous variables were transformed to categorical variables with the median or a predetermined threshold.

Multivariate logistic regression analysis was used to determine the association between potential predictive variables and outcome measures at 10 years. The explanatory variables that could explain the outcome and were associated on univariate analyses at $P < 0.20$ were considered in the multivariate analysis. A stepwise procedure was used. Odds ratios (OR) and 95% CI were calculated.

Survival analysis was performed to identify the risk factors for a patient leaving the study. This event could be related to death, refusal, lost to follow-up or non-RA diagnosis. The survival time was defined as the difference between baseline date and the last follow-up visit date or cut-off date (5 November 2015). Potential predictive factors were investigated with the Kaplan-Meier estimate of time to event and were compared by the log rank test on a first-step univariate analysis. A Cox proportional-hazards model was then built to determine the factors that may affect the occurrence of the event, based on selected parameters from univariate analysis. Entered parameters were selected by a log rank test at 20%.

Hazard ratios (HR) and 95% CI were estimated. $P < 0.05$ was considered statistically significant, and all statistical tests were two-sided. Statistical analyses involved use of SAS V.9.4 (SAS Institute, Cary, NC, USA).

Results

Patients

The ESPOIR cohort enrolled 813 patients; 88.6% satisfied the ACR/EULAR criteria for RA; 521 (64.1%) of them were followed up until 10 years. Thirty-five patients died, 36 were lost to follow-up, 120 refused further follow-up and 101 (12.4%) received a diagnosis other than RA or undifferentiated arthritis. Baseline characteristics of the 521 patients (Table 1) were similar to those of the whole cohort that were previously reported [8]. Probability of staying in the cohort for 10 years was associated with baseline anti-citrullinated peptides

Table 1 Baseline characteristics in the ESPOIR cohort and outcome in ESPOIR and 1993 cohorts of patients who were followed up to 10 years

	ESPOIR cohort baseline *n* = 521	ESPOIR cohort 10 years *n* = 521	1993 cohort 10 years *n* = 112
Variable			
Age (years)°	48.6 (11.6) 0°	58.6 (11.6) 0°	60.4 (12.5)
Female, *n* (%)	408 (78.3) 0°	–	90 (80.3)
Symptom duration*	103.4 (50.1) 0°	–	–
Swollen joints (*n*)	7.6 (5.3) 0°	0.9 (2.1) (3.6)°	3.3 (4.2)
Tender joints (*n*)	8.5 (7.0) 0°	2.1 (4.3) (3.8)°	3.4 (4.5)
Patient global assessment (mm, VAS)	59.7 (25.9) (0.4)°	24.0 (24.0) (4)°	26.2 (13.8)
Physician global assessment (mm, VAS)	52.0 (22.2) 0°	14.9 (18.1) (4.6)°	–
DAS28 ESR	5.1 (1.3) (1.5)°	2.5 (1.3) (11.6)°	–
DAS44	–	–	2.2 (0.9)
SDAI	29.6 (14.5) (1.7)°	7.5 (8.7) (6.9)°	–
CDAI	27.4 (13.4) (0.4)°	6.8 (8.3) (5.0)°	–
DAS28 ESR remission, *n* (%)	–	273 (52.4)	–
CDAI remission	–	207 (39.7)	–
DAS28 sustained remission, *n* (%)	–	209 (40.1)	–
DAS28 drug-free remission, *n* (%)	–	73 (14.1)	–
DAS28 ESR low disease activity	–	336 (64.5)	–
HAQ-DI score	1.0 (0.7) 0°	0.5 (0.6) (1.3)°	0.8 (0.7)
HAQ-DI < 0.5, *n* (%)	–	280 (54.5) (1.3)°	–
SF36 MCS	40.2 (11.1) (1.2)°	46.7 (10.5) (1.9)°	–
SF36 PCS	36.7 (8.5) (1.2)°	44.6 (9.2) (1.9)°	–
Pain (mm, VAS)	37.0 (27.9) (0.4)°	16.6 (20.6) (4.4)°	23.2 (23.0)
Fatigue (mm, VAS)	47.3 (27.9) (0.4)°	31.4 (27.0) (4.4)°	–
Rheumatoid nodules	6 (1.2) (0.2)°	39 (7.5) 0°	–
Sicca syndrome	154 (29.7) (0.4)°	314 (60.3) 0°	–
ESR (mm/h)	29.4 (25.2) (0.9)°	14.4 (14.0) (11.5)°	18.4 (16.5)
CRP level (mg/l)	20.2 (33.6) 0°	6.4 (16.5) (4.6)°	9.3 (11.7)
Normal CRP (<5 mg/l), *n* (%)	–	336 (67.6) (4.6)°	–
Total mSharp score***	2.8 (5.0) (22.8)°	13.7 (19.6) (23.6)°	35.4 (46.1)
Erosion score	0.8 (2.3)	4.9 (9.4)	18.4 (26.5)
Joint narrowing score	2.1 (3.4)	8.9 (12.1)	32.1 (23.2)
Joint surgery	–	82 (15.7)	26 (23.2)
Joint arthroplasty/arthrodesis	–	34 (6.5)	20 (17.9)
ACPA (anti-CCP2) positivity, *n* (%)	248 (47.6) 0°	–	50 (57.9)
IgM-RF positivity, *n* (%)	274 (52.6) 0°	–	113 (59.1)
IgA-RF positivity, *n* (%)	261 (50.1) 0°	–	115 (60.2)
HLA shared epitope, *n* (%)	291 (58.1) (3.8)°	–	78 (70.2)
Current smoker, *n* (%)	105 (20.2) 0°	–	–
Never smoker, *n* (%)	277 (53.2) 0°	–	–

Data are mean (S.D.) unless indicated. °Rate of missing data. *Days between first swollen joints and ESPOIR screening. **At least at one yearly visit. ***van der Heijde-modified total Sharp score. °Median (range) 50.4 (17.4–72.7). VAS: visual analogue scale; DAS28: disease activity score in 28 joints; HAQ-DI: Health Assessment Questionnaire Disability Index; SF36 MCS: Medial Outcomes Study 36-item Short Form mental component summary; SF36 PCS: Medical Outcomes Study 36-item Short Form physical component summary; ACPA: anti-citrullinated peptide antibodies; CCP2: cyclic citrullinated peptide; CDAI: Clinical Disease Activity Index; SDAI: Simple Disease Activity Index.

antibodies (ACPA) positivity, positive diagnosis of RA by a rheumatologist additive arthritis *vs* polyarticular onset and high familial income (Supplementary Table S1, Fig. S1, available at *Rheumatology* online).

Disease management

Most patients (*n* = 480, 92.1%) had received at least one DMARD during the 10-year follow-up, usually started during the first 6 months; 411 (78.9%) patients received methotrexate and 65 (12.5%) a combination of at least two conventional synthetic DMARDs (Supplementary Table S2, available at *Rheumatology* online).

A biologic DMARD (bDMARD) was prescribed in 174 (33.4%) patients, mainly a TNF blocker; 57 (10.9%) received at least one non–anti-TNF bDMARD. Overall, 71 (13.6%) and 122 (23.5%) patients received a bDMARD within 2 and 5 years, respectively.

Predictors of at least one bDMARD prescription were baseline ACPA positivity high physician global assessment, IgM RF positivity, increased SF36 MCS, additive arthritis, no current smoking, and young age (Supplementary Table S1, available at *Rheumatology* online).

More than half of the patients ($n = 343$; 65.8%) had received prednisone at least once during the 10-year follow-up. The mean dosage was 8.3 (8.5) mg/day during the glucocorticoids period intake, with a mean cumulative dose of 8.7 (8.6) g.

Comorbidities

Thirty-five (4.3%) patients died. This rate appears similar to the general population despite differences by age groups, with a trend towards lower mortality in ESPOIR patients >65 years (Supplementary Table S3, available at *Rheumatology* online). As compared with baseline, a high number of patients had new comorbidities at 10 years (Table 2).

Clinical remission

At 10 years, disease activity seemed well controlled (Table 1); 273 (52.4%) patients achieved DAS28-ESR remission, 39.7% CDAI remission, 64.5% DAS28 low disease activity, 40.1% DAS28 sustained remission (remission at both 9- and 10-year visits), and 14.1% drug-free remission.

Functional disability, quality of life, structural damage, joint surgery

At 10 years, HAQ-DI score decreased to a median of 0.3 (0–2.5) (Supplementary Fig. S2, available at *Rheumatology* online). Half of the patients did not have significant disability. A similar satisfactory outcome was observed for the SF36 physical component and pain (Table 1). Fatigue and SF36 MCS were improved but still impaired. Structural progression was weak, with a mean modified total Sharp score (mTSS) change from baseline of 11.0 (17.9). Joint space narrowing explained two thirds of the radiographic progression (Table 1). Eighty-two (15.7%) patients required joint surgery; 34 (6.5%) patients had major palliative procedures including 13 hip arthroplasties, 11 knee arthroplasties, 10 arthrodesis.

Table 2 Comorbidities in the ESPOIR cohort ($n = 521$)

Diseases*	Baseline	10-year follow-up
Hypertension	89 (17.1)	175 (33.6)
Hypercholesterolaemia	84 (16.1)	207 (39.7)
Hypertriglyceridemia	19 (3.7)	90 (17.3)
Myocardial ischaemia	4 (0.8)	18 (3.5)
Stroke	2 (0.4)	11(2.1)
Lung disease	52 (10.0)	38 (7.5)
Lymphoproliferative disorder	2 (0.4)	8 (1.5)
Cancer	17 (3.3)	53 (10.2)
Gastrointestinal event	26 (5.0)	44 (8.5)
Diabetes	16 (3.1)	40 (7.7)
Thyroid disorder	62 (11.9)	89 (15.5)
Active tuberculosis	8 (1.5)	10 (1.9)
Hepatitis B	3 (0.6)	5 (1.0)
Hepatitis C	3 (0.6)	6 (1.2)
Osteoporotic fracture	1 (0.2)	18 (3.5)
Severe infection	7 (1.3)	45 (8.6)°

Data are number of patients (%). *Past and present comorbidities. °Severe infections were more frequently observed in patients having received at least one bDMARD (12.6% *vs* 5.2%) and/or glucocorticoids (7.6% *vs* 2.4%).

Baseline predictors of 10-year outcomes

Probability of achieving DAS28 remission at 10 years was associated with low pain at rest, better SF36 MCS. Sustained remission was in addition predicted by absence of cardiovascular disease, increased personal income, ACPA negativity and drug-free remission by ACPA negativity, young age, intermittent onset. Predictors of HAQ-DI < 0.5 were mainly young age, low fatigue score, increased personal income, absence of lung disease, or current smoking. Predictors of radiographic progression were ACPA positivity, older age, swollen joint count (Supplementary Table S1, available at *Rheumatology* online).

Discussion

The 10-year outcome for 521 patients with early RA who were enrolled in the ESPOIR cohort and received standard of care between 2003 and 2015 was rather good. Disease activity was well controlled; 52.4% of the patients were in DAS28 remission, and 40.1% in DAS28 persistent remission. Half of the patients did not have a significant functional disability. Radiographic progression was low, with an annual rate of progression of 1.1 units/year. By comparison, in an early arthritis cohort set up in 1993 by four of us (191 patients; disease duration 8.4 (26.3) months but similar other characteristics), mean HAQ-DI was moderately increased but structural damage was much higher [mean mTSS 35.4 (46.1) *vs* 13.8 (19.6) for ESPOIR] and major surgeries as well (Table 1) [9].

The ESPOIR cohort showed an increase in cardiovascular events, dyslipidaemia and serious infections during the 10-year follow-up, which is consistent with the comorbid conditions-associated risk in RA [1]. However, there was no clear impact on mortality since the rate of death was low, lower than in the 1993 cohort (4.5% *vs* 11.0%) and similar to that in the general population. This rate of mortality agrees with recent reports of RA showing a trend towards absence of mortality rate differences *vs* the general population [7, 13, 14].

Most of the recent inception cohorts of early RA patients showed control of disease activity over time [6, 14–17]. Clinical remission rate has been infrequently shown in the long term. Gullick *et al.* [18] found only 29% DAS28 remission after 10 years in patients with established RA. However, in another RA outpatient

clinic population, Haugeberg *et al.* [17] reported DAS28 and CDAI remission rates of 55% and 31.7% at 10 years, which is consistent with the ESPOIR findings. In contrast to our results, most prospective studies still report a 10-year impairment of functional disability and structural damage in RA patients [6, 14, 15]. Gwinnutt *et al.* reported a median HAQ-DI of 1.00 (0.25–1.88) after 10 years [14]. In the BARFOT study, patients did not show less HAQ disability over 8 years as compared with a previous cohort [15]. We have to note that our patients are slightly younger than those of these cohorts; nevertheless in agreement with our study, an improvement over time in HAQ-DI and remission rate has also been reported for autoantibody-positive patients and a treat-to-target approach [16]. Long-term follow-up data for radiographic progression in recent cohorts of early RA are scarce. Carpenter *et al.* showed a substantial reduction of structural damage compared with a previous cohort, but the mean annual rate of change was still 2.5 [19], which is more than double our rate. Fatigue was still a concern for the ESPOIR patients, but this outcome measure is usually multifactorial, including other factors than the disease process [20].

To our knowledge, such a very good 10-year outcome in early RA patients has not yet been reported. It may be related to several factors that have been highlighted in international recommendations [2, 3]. As previously reported in ESPOIR [8], these factors include early referral to a rheumatologist, early DMARDs start, regular monitoring, and a high rate of early remission. This favourable outcome is also probably attributable to an intensive therapeutic strategy; 33.4% of patients received a bDMARD during the 10 years, including 23.5% within 5 years, whereas in the 1993 cohort, 24.1% received bDMARDs, all started after at least 8 years. Some studies [16, 17] also suggest that the recent treatment regimens have greatly improved the long-term outcome of patients with RA in real life.

Our findings also confirm, in the long term, ACPA positivity as a robust predictor of severe outcome in patients with early RA, including structural progression, not achieving sustained or drug-free remission, and prescription of bDMARDs. Other features not directly related to the disease process (age, fatigue, personal income, smoking or mental health status) may also affect long-term outcome, as previously reported [21].

This study has important strengths. It is one of the largest inception cohorts of patients with early RA that has been prospectively followed for at least 10 years. RA was routinely managed according to standard of care, and the database was rigorously built and controlled, which has allowed this cohort to be used by many task forces [11]. The study has some limitations inherent to observational cohorts. Only 521/813 patients were followed for 10 years; however, these patients did not have significant differences in baseline characteristics as compared with the whole cohort.

In conclusion, we report the very favourable 10-year outcome of a recent large cohort of patients with early RA. This mild outcome may be related to an early and adapted management that was recommended and implemented in daily practice during the last 15 years.

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B.C. takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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