

Original article

The ESPOIR cohort: A ten-year follow-up of early arthritis in France: Methodology and baseline characteristics of the 813 included patients

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Abstract

Objectives: The French Society of Rheumatology initiated a large national multicenter, longitudinal and prospective cohort, the so-called “ES-POIR cohort study” in order to set up databases to allow various investigations on diagnosis, prognostic markers, epidemiology, pathogenesis and medico-economic factors in the field of early arthritis and rheumatoid arthritis.

Methods: Patients were recruited if they had undifferentiated arthritis or rheumatoid arthritis, of less than 6 months disease duration and if they were DMARD and steroids naïve. Patients have then to be followed every 6 months during the first 2 years then every year during at least 10 years. Clinical, biological, radiographic and medico-economic databases have been constituted to fit in the different objectives of the project and more than 20 scientific studies have already been accepted by the scientific committee.

Results: 813 patients were included (76.75% were female). The mean age was 48.07 ± 12.55 years. The mean delay from the onset of symptoms to referral to the rheumatologist was 74.8 ± 76.6 days. Baseline swollen and tender joint counts were 7.19 ± 5.37 and 8.43 ± 7.01 ; DAS28 score

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was 5.11 ± 1.31 . CRP was abnormal in 38.9% of the patients; 44.2%, 45.8% and 38.8% had respectively IgM rheumatoid factor (RF), IgA RF and anti-CCP antibodies. HLA DRB1*01 or 04 genes were found in 56.7% of them. Finally, 22% of these patients had erosions on hand or feet at baseline.

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1. Introduction

Rheumatoid arthritis (RA) is the most frequent inflammatory arthritis, affecting 0.3–0.8% of the population [1]. Patients suffer significant disability and handicap after a few years of disease progression. At 10 years, 92% of them have an important decrease of their functional ability, 50% need personal aid for some daily life activities [2,3]. Many patients have to quit their professional activities or to seek for job adaptation less than 10 years after the start of the disease [4–6]. In addition, cardiovascular morbidity is increased and life expectancy significantly reduced in patients with active and severe disease [7].

This disease has major cost consequences, recently dramatically increased by the new availability of biotherapies. However, these new therapies have been shown to control the disease progression [8] and to dramatically improve outcome if prescribed before irreversible damage [9,10]. RA has a heterogeneous profile with several forms from mild to severe disease. The questions that rheumatologists usually address can be distinguished in:

- *Diagnosis*: early diagnosis is a key point to improve outcome but frequently difficult since gold standard does not exist. Classification criteria and diagnosis clinical standards are useful after one or two years of disease, but not always at first consultation. Furthermore, all practitioners may not use them the same way and do not classify early arthritis similarly [11]. The combination of investigations over two or three of them do not seem to add complementary information to the diagnosis [12,13].
- *Prognosis*: some prognosis markers have been now clearly identified in early rheumatoid arthritis, including X-ray erosions, anti-CCP antibodies, rheumatoid factor, acute phase reactants and HLA DRB1*04 genes [14–16]. However, their contribution in early arthritis, i.e. before arthritis may be classified, has to be clearly validated at individual level. Some markers like synovium immunohistologic markers might be contributive [17]. Such markers would be important with regards to early therapeutic decision, and risk/benefit ratio of each therapy.
- *Public health perspective*: few data are available in France about quality of life and socioeconomic consequences of arthritis. Direct cost are high during the first year because of diagnosis investigations and early aggressive therapy, while indirect cost may secondarily increase in order to cope with social consequences of the disease [18,19].

- *Pharmacogenomic*: Such approach becomes increasingly important in chronic disease, in that they would allow for studying the genetic part of response to treatment and drug toxicity.

These questions would be better addressed by obtaining periodic and prolonged follow-up over several years of early arthritis presenting patients. In the past ten years several observational cohorts have been initiated in France to study the characteristics of patients with early arthritis. At least two regional early arthritis cohorts [20,21] and one multicentre national cohort on RA patients [16,22,23] were designed to mainly evaluate diagnostic criteria and prognostic factors in early RA. Despite interesting data, their value seems limited in the current context. Consequently, the French Society of Rheumatology initiated a large national multicentre cohort, the so-called “ESPOIR cohort study” to allow investigations on diagnostic and prognostic markers but also etiologic, pathogenic and medico-economic factors among patients with early inflammatory arthritis that could later develop RA. ESPOIR is an acronym sounding in French for “Etude et Suivi des Polyarthrites Indifférenciées Récentes”, “study and follow-up of undifferentiated early arthritis”.

2. Methods

2.1. Objective of ESPOIR

The primary objective is to set-up a multicentre cohort of early arthritis (less than 6 months disease duration) in France that could serve as a database to studies of various natures.

Specific objectives are in the following domains:

- *diagnosis*: to help to determine among clinical, biological, radiographic and immunogenetics parameters those allowing for the earliest diagnosis classification as possible, in order to target early therapy;
- *prognosis*: to early identify those patients at risk of severe disease by investigating among clinical, radiological, biological, genetic and sociologic factors;
- *medico-economic*: to identify the costs and their determinants at various disease stage;
- *pathogenic*: to collect a databank of sera, DNA, RNA, synovial fluids and tissues in order to allow various studies on RA pathogenesis including transcriptomics and other genomics.

Secondary objectives are:

- *Safety*: to monitor adverse events, particularly rare drug adverse events, in collaboration with other international studies.
- *Research platform*: to allow access to the data collected in this cohort study in order to facilitate new projects submitted to and approved by the scientific committee.
- *Continuous medical education*: to set up an educational program for the general practitioners (GPs) focus on early arthritis and early referral recommendations [24].

2.2. Design of the ESPOIR cohort study

This is a longitudinal prospective cohort study in adults aged over 18 and under 70 years from multiple regional samples recruited across France.

2.2.1. Number of subjects to include

A sufficient number of subjects would allow to obtain reasonable estimates of practices after 10 years of follow-up and run reliable subgroup analyses. A compromise has been formulated to obtain at least, 300 patients with RA, on a 10-year term. Data from the literature [11,15,20,22], as well as previous cohort study experiences have shown that proportion of loss to follow-up is in the range of 5–8% during the first 3 years, then stabilise between 1 and 5%, depending on many different factors. Using intermediate estimates, it would be necessary to start with 400 RA patients. Given the probability than 50% of patients will probably not turn into rheumatoid arthritis after 2 years, it was planned to include 800 early arthritis patients.

2.2.2. Inclusion criteria

- Patients aged over 18 and under 70.
- Clinical diagnosis of rheumatoid arthritis as certain or probable or clinical diagnosis of undifferentiated arthritis potentially becoming RA.
- At least 2 inflammatory joints since 6 weeks: a swollen joint has to be observed in two joint sites and be present since at least 6 weeks.
- Arthritis starting since less than 6 months.
- Never prescribed DMARDs, corticoids, except if less than 2 weeks or except intra-articular injection less than 4 weeks before inclusion.
- Corticosteroids may be authorized if prescribed for 2 weeks or less at least 2 weeks before the inclusion and with a maximum mean dosage of 20 mg/day prednisone.

2.2.3. Exclusion criteria

- Other inflammatory rheumatisms or connective tissue diseases clearly defined.
- Early arthritis with no potential chance to become RA.

2.2.4. Patients recruitment

Patients had to be recruited over a period of 24 months in 14 regional centres (16 university hospital rheumatology departments). Criteria were set up to select participating centres:

- centres with investigators experienced in performing multicentre controlled trials, epidemiologic studies and genetic studies;
- set-up quality standards had to be followed;
- multiple procedures were implemented to follow patients by direct contact, contact through rheumatologists and through general practitioners.

Recruitment was only conducted in connection with local private practitioners.

Each centre acted as an observational centre, and did not interfere with patient treatment, except if in charge of a patient. The patients were routinely treated and followed by private rheumatologists of the geographical area. An approach using several media was developed to invite patients and physicians to participate in each regional area.

Ethical rules have been set-up for improvement of patients follow-up and good relationship with their personal general practitioner or private rheumatologist in charge of routine care:

- each center had to be able to see patients within less than 2 weeks upon request of general practitioners (GPs);
- results of every patient investigations had to be communicated to private rheumatologist in charge of patient care;
- patients follow-up did not have to interfere with therapeutic decision made by his rheumatologist.

2.2.5. Patient follow-up

All patients have to be followed every 6 months during the first 2 years, then every year by the same investigator in each centre during at least 10 years. It was planned to stop 2 years after inclusion the follow-up of patients achieving diagnosis other than RA or undifferentiated arthritis.

Procedures were set up to avoid as much as possible lost of follow-up patients. Newsletters are sent every 6–12 months to each included patient. As soon as a patient misses a planned visit each centre has to call him or his doctor to organize a new appointment. If this is not successful a special letter is sent by the regional and the national coordinating centre both to the patient and his doctor. Finally, if a new visit cannot be done shortly a questionnaire with the main items is proposed to be filled in by phone.

2.2.6. Clinical and biological evaluation

At baseline and at each visit a set of clinical and biological variables were recorded according to recommendations in the management of early arthritis [24]. Baseline CRP ($N < 10$ mg/l), IgM and IgA rheumatoid factor (Elisa, Menarini, France; Positive >9 UI/ml) and anti-CCP2 antibodies (Elisa, DiaSorin, France; Positive >50 U/ml) were performed for all the patients

using the same technique in a central lab (Paris-Bichat). HLA DRB1* genotypes were determined in each centre.

Furthermore quality of life questionnaires including HAQ, SF36, Euroqol and AIMS-2 short form [25–27], a medico-economic questionnaire, and hand-wrist (face), feet (face and oblique) radiographs were also performed at each visit. Ultrasonography and Magnetic Resonance Imaging were performed on hands and feet in selected centres.

2.3. Databases

Several databases had been constituted to fit in the different objectives of this project.

Clinical (including standard biology) data and medicoeconomic data were collected and computerised at each visit in each centre, then centralised in the general database at the coordinating centre (Montpellier).

Biological database followed the same route, and comprised an agreed-on list of routine investigations. Serum, DNA, urine, white blood cells synovium liquid and tissue (when possible) were collected at baseline. Serum and urine were also obtained at each follow-up visit. They were then sent and double stored in adequate and definite conditions in the biological coordinating centre (Paris-Bichat).

X-ray database included at baseline a chest X-ray, both hand and wrist antero-posterior view and forefoot. At each follow-up visit hand, wrist and foot X-ray were collected as well as other painful joints if necessary. All original X-rays were stored in the radiological coordinating centre (Brest).

2.4. Organisation and committees

Steering committee: The steering committee (BC, AC, MD, BF, FG, IL, XL, PhR, AS, JS) is in charge of organisational, administrative and financial coordination of the cohort study and of following the cohort study process.

Scientific committee: The scientific committee includes steering committee members, investigators of participating centres and external experts. It is in charge of evaluating and validating scientific projects to be performed using the cohort databases.

Coordinating centre: The Coordinating centre (Montpellier University, BC, JPD, NR) manage the data resources, the contact with each clinical investigation centres, ethical aspects and monitoring and quality control.

Biological coordinating centres: One biological resources centre (Paris-Bichat, JB) is in charge of centralising and managing biological data collection.

X-ray coordinating centre: The X-ray coordinating centre (Brest hospital, AS) is in charge of storing and organising the standardised X-ray readings.

Funding sources: An unrestricted grant from Merck Sharp and Dohme (MSD) was allocated for the first 5 years. Two additional grants from INSERM were obtained to support part of the biological database. The French Society of Rheumatology, Abbott, Amgen and Wyeth also supported the ESPOIR cohort study.

2.5. Ethical committee

The protocol of ESPOIR Cohort study was approved in July 2002 by the ethical committee of Montpellier. All the patients signed an informed consent form before inclusion.

3. Results

3.1. Patients inclusion

A total of 814 patients with early arthritis were included between December 2002 and march 2005. All the centres were active and each regional centre recruited between 29 and 86 patients. One patient removed his consent form.

3.2. Demographic data

The mean age of the patients was 48.1 ± 12.5 (median: 50.1), 624 (76.7%) were females and 189 (23.2%) males. Fifty patients (6.1%) had a history of psoriasis and 129 (15.9) a familial history of inflammatory arthritis (RA = 113). Cardiovascular diseases were the main co-morbidity (Table 1).

3.3. Baseline clinical data

The main baseline clinical informations are shown on Table 2. The main delay between the first symptoms and the first consultation with a rheumatologist is still high around two months and a half. Patients had an active disease with a mean swollen joint count of 7.19 ± 5.37 , a mean tender joint count of 8.43 ± 7.01 and a mean DAS28 score of 5.11 ± 1.31 . A total of 578 (71.3%) of patients fulfilled the ACR criteria for RA confirming that patients at risk of developing RA have been recruited.

3.4. Baseline biological data

Erythrocyte sedimentation rate and C-reactive protein were increased with a mean of $29.4 \text{ mm/h} \pm 24.5$ (median = 22) and $22.2 \text{ mg/l} \pm 34.0$ (median = 9) respectively. A total of

Table 1
ESPOIR Cohort: past and present comorbidities at baseline

Diseases	n	%
HTA	139	17.1
Hypercholesterolemia	124	15.2
Hypertriglyceridemia	26	3.2
Myocardial ischemia	8	0.9
Stroke	4	0.4
Lymphoproliferative disorder	5	0.6
Cancer	25	3.0
Gastro-intestinal event	44	5.4
Diabetes	31	3.8
Thyroid disorder	87	10.7
Tuberculosis	35	4.3
HIV infection	2	0.2
Hepatitis B	4	0.4
Hepatitis C	7	0.8

Table 2
ESPOIR Cohort: Clinical variables at baseline

Variable	Mean \pm SD	Median (range)
1st symptom to GP visit*	26.35 \pm 41.08	15 (1–370)
1st symptom to rheumatologist visit *	74.89 \pm 76.59	60 (1–850)
1st symptom to ESPOIR screening*	214 \pm 253.18	146 (8–1691)
1st swollen joints to ESPOIR screening*	103.12 \pm 52.42	94 (5–546)
Swollen joints (nb)	7.19 \pm 5.37	6 (2–28)
Tender joints (nb)	8.43 \pm 7.01	6 (2–28)
Patient global evaluation	59.85 \pm 25.63	65 (0–100)
Physician global evaluation	50.67 \pm 22.46	50 (0–99)
DAS28	5.11 \pm 1.31	5.07 (1.51–8.8)
HAQ score	0.98 \pm 0.68	0.88 (0–2.88)
ACR criteria positive	71.3%	

*Delay (days) between symptom and 1st visit to a general practitioner (GP), a rheumatologist or to ESPOIR screening (days).

316 patients (38.9%) had an abnormal CRP. IgM and IgA rheumatoid factors were positive in 359 (44.2%) and 372 (45.8%) patients and 315 (38.7%) patients had anti-CCP antibodies. Antinuclear antibodies were positive in 284 cases (35.3%). Finally, 56.6% of the patients had HLA DRB1*01 or HLA DRB1*04 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%; X/X = 35.3%; (X = none 01 or 04 HLA DRB1* genes).

3.5. Radiological data

At baseline, the erosion score on hand and feet was 2.46 ± 4.61 and the joint narrowing score was 3.52 ± 6.91 . The total van der Heijde modified Sharp score [28] was 5.97 ± 10.14 ; 160 out of 715 (22.3%) patients had erosions on hand and/or feet.

4. Discussion

We have presented the design, the demographic characteristics and the baseline clinical, biological and radiographic data of the ESPOIR cohort. The objective of this program was to recruit and follow during at least 10 years more than 300 patients with RA and to create important clinical, biological and medico-economic databases on early arthritis and RA in order to develop clinical and basic scientific projects. Patients with a definite diagnosis other than RA or undifferentiated arthritis were excluded. A total of 813 patients were included. They were all DMARDs and steroids naïve. The baseline data of ESPOIR show us the current face of early undifferentiated arthritis in France.

Almost 75% of the patients fulfilled ACR criteria for RA, 45% had IgM RF positivity, 39% had anti-CCP antibodies and 56% had at least one RA-associated HLA DRB1* genes suggesting that most of the patients of this cohort will further develop RA. This is reinforced by the fact that 22% of the patients had erosions on hand or feet radiographs at baseline. Patients have active arthritis as confirmed by the mean DAS28 score (5.11 ± 1.32). Comparison with other international early arthritis cohorts is difficult since inclusion criteria were

different between these cohorts [16,21,29–33]. Some database selected only patients with early RA according to ACR criteria, others only patients with undifferentiated arthritis. The mean age of our patients (48.1 ± 12.5 years) is consistent with other early arthritis cohorts. In addition, disease duration at entry is also variable (3–24 months) as well as baseline therapies. Since the selected populations are heterogeneous, comparison of clinical, biological or immunological characteristics is of limited value.

The delay between first symptoms and inclusions in ESPOIR could seem high (mean = 214 ± 253 days) however the mean delay between the first swollen joint, which is the usual definition of arthritis, and inclusion was only 103.1 ± 52.4 days which is consistent with early arthritis of less than 6 months disease duration. Even if the delay for referral to a rheumatologist seems shorter than previously reported [34] this period (mean 75 days) is much longer than the maximum 6 weeks delay recently recommended by EULAR [24]. Consequently, since this delay for referral and start of effective treatment and management has been shown to impact the outcome of early RA [34,35] educational programs with the general practitioners are of great importance and should be set up in order to improve the management of early arthritis in daily practice. The clinical, biological and imaging database of ESPOIR should allow to answer to multiple scientific questions on early arthritis and rheumatoid arthritis in various fields such as diagnosis, prognosis, epidemiology, pathogenesis, management or medico-economy. Already, more than twenty scientific projects have been approved by the scientific committee and are ongoing and the database is now open to the scientific community.

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