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# The French early arthritis registry

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## ABSTRACT

*This report is focused on two French multicenter cohorts of patients with early rheumatoid arthritis (RA). The first one is a community-based study which was started in 1993. It was mainly designed to identify prognostic factors of joint destruction, disability and remission in patients with early RA. The 3-year and 5-year results have been recently reported. Briefly, progression of joint damage was best predicted at baseline by radiographic scores, ESR, CRP, rheumatoid factor and DRB1\*04 genes, and disability by disease activity including the HAQ score.*

*Recently, the French Society of Rheumatology initiated a large national multicenter registry (800 patients), the "ESPOIR cohort study", that could serve as a database to allow investigations not only on diagnostic and prognostic markers, but also on etiologic, pathogenic and medico-economic factors among patients with early inflammatory arthritis who could later develop RA. The objectives, design and organization of this early arthritis registry are described.*

## Introduction

In the past 10 years, several cohort observations have been initiated in France to study the characteristics of patients with early arthritis. At least two regional early arthritis cohorts (1, 2) and one multicenter national cohort of rheumatoid arthritis (RA) patients (3-11) were designed mainly to evaluate diagnostic criteria and prognostic factors in early RA.

Recently the French Society of Rheumatology initiated a large national multicenter registry, the so-called "ESPOIR cohort study," to allow investigations not only on diagnostic and prognostic markers, but also on etiologic, pathogenic, and medicoeconomic factors among patients with early inflammatory arthritis who could later

develop RA. This report is focused on the two multicenter cohorts.

## A FRENCH MULTICENTER COHORT OF PATIENTS WITH EARLY RA

This community-based study was started in 1993 and was mainly designed to identify prognostic factors of joint destruction and disability in patients with early RA. The 3-year and 5-year results have been recently reported (3-11).

## Inclusion criteria

All consecutive outpatients who: (i) fulfilled the American College of Rheumatology criteria for RA of <1 year; (ii) were referred from primary care physicians for the purposes of this study; (iii) had not been treated with disease-modifying antirheumatic drugs (DMARDs); and (iv) agreed to be enrolled in a 10-year followup study were included between March 1993 and October 1994 in 4 French centers (Montpellier, Paris-Cochin, Toulouse, and Tours). All patients were treated with DMARDs (usually methotrexate or sulfasalazine) that could be modified during the study according to efficacy and side effects. The study was approved by the Ethical Review Board in Montpellier.

## Assessments

### *Clinical and biologic assessment*

The following evaluation data were collected at baseline: age, sex, body mass index (BMI), disease duration, morning stiffness, pain on a visual analog scale, numbers of swollen and tender joints, Disease Activity Score (DAS), presence or absence of nodules and extra-articular manifestations (EAM), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels, antinuclear antibodies (ANA), IgA and IgM rheumatoid factor (RF) by enzyme-linked immunosorbent assay (ELISA), antikeratin antibodies by indirect immunofluorescence on cryostat

sections of rat esophagus, antiperinuclear antibodies by immunofluorescence on buccal epithelial cells, anti-cyclic citrullinated protein (CCP) antibodies by ELISA, anti-RA33 antibodies by immunoblotting, anti-Hsp90 antibodies by ELISA, anticalpastatin antibodies by ELISA, and YKL-40 by radioimmunoassay. HLA-DRB1\*, DQB1\*, and DMA-DMB genotyping were performed as previously described by our group. Each patient was followed up by the same investigator 6 months after inclusion and once a year for 5 years.

#### *Functional assessment*

Functional disability was assessed by the Health Assessment Questionnaire (HAQ) at baseline and at 3 and 5 years. This instrument has been adapted and validated in French. A continuous scale from 0 to 3.0 was used to relate the score of the functional state of the patients. Patients could be classified as mildly disabled (score 0-1), moderately disabled (score 1-2), or severely disabled (score > 2).

#### *X-ray measurement*

Hand, wrist, and foot radiographs were taken at baseline and at 3 and 5 years. They were evaluated in chronological order in a blinded manner by two independent observers according to the Sharp method modified by van der Heijde. For each patient an erosion score, a narrowing score, and a total damage score were noted for the hands and feet. Before the definite evaluation, the intra-class, intraobserver, and interobserver coefficients of correlation were calculated on 30 chosen pairs of x-rays of hands and feet, and these values were always > 0.85. No systematic differences were found in any of the scores. We then used the mean of the two observer scores for erosions, joint space narrowing, and total damage (hands and feet).

To determine a cut-off value for changes in joint space width that would define individual radiographic progression of RA unrelated to measurement errors (smallest detectable difference), we calculated the mean of differences between two analyses as described. We thus selected 30 pairs of x-rays of hands and feet that were representative

of the population under study. The mean  $\pm$  SD of the differences between the two analyses performed by the two observers were calculated for each score.

Radiographic progression was therefore defined by a change in radiographic scores greater than the upper bound of the 95% confidence interval of the differences (i.e., changes of at least 5.0, 4.9, and 4.1 in the erosion score, narrowing score, and total damage score, respectively).

#### **Prognostic factors of 3- and 5-year radiographic damage** (3, 4, 7, 9)

A multiparameter study for prediction of 3-year radiographic lesions was first performed (3): The mean  $\pm$  SD change in the total radiographic score was  $6.1 \pm 6.2$ . Radiographic progression was observed in 71 of the 172 patients for whom there were data at the end of the study. According to Fisher's exact test, radiographic scores and progression were closely correlated with baseline values of ESR, CRP level, IgM and IgA RF, antiperinuclear antibodies, radiographic scores, and RA-associated HLA-DRB1\*04 genes. No correlations were demonstrated for sex, age, DAS, swollen joints, EAM, HAQ score, anti-Hsp90 antibodies, anticalpastatin antibodies, anti-RA33 antibodies, ANA, YKL-40, antikeratin antibodies, and HLA-DRB1\*01. The logistic regression analysis revealed that the only baseline values able to predict the 3-year radiographic scores were IgM RF, DRB1\*04 genes, pain, and total radiographic score. Progression of joint damage was predicted by ESR, IgM RF, DRB1\*04 genes, and erosion score.

Later testing for anti-CCP antibodies and levels of matrix metalloproteinase 3 (MMP-3) also yielded associations with radiographic damage (4, 7)

A clinical model for prediction of 5-year joint damage was recently developed (9). When the outcome parameter was the Sharp score, the developed prediction models had low discriminative values (receiver operating characteristic [ROC] area under the curve [AUC] = 0.70). If erosion was used as the outcome parameter, 4 baseline predictive

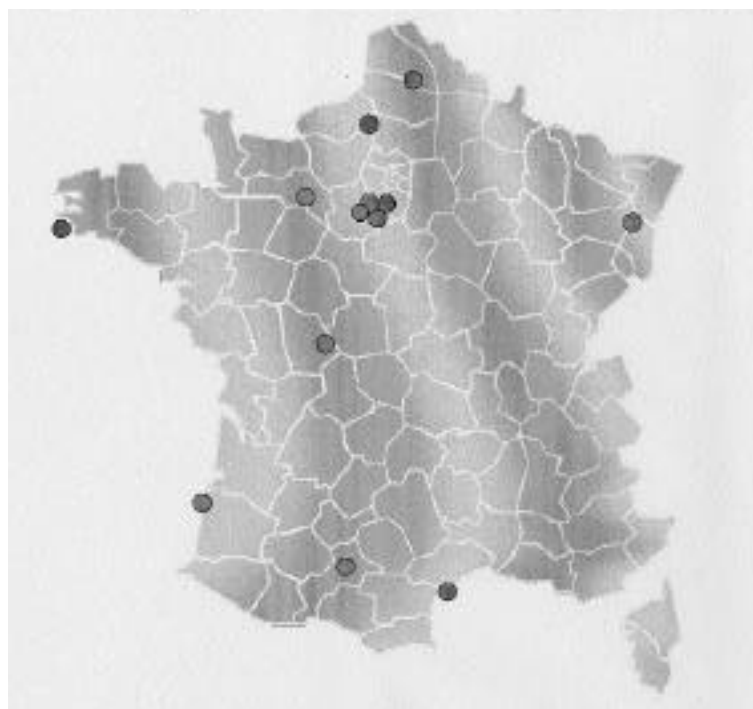
variables were selected: erosion, anti-CCP antibodies, IgA RF, and CRP level. The overall ability of model 2, including IgA RF and anti-CCP antibodies, to discriminate between erosive and non-erosive RA was significantly greater than that of model 1 without autoantibodies (ROC AUC + 0.85; SE = 0.15). When DRB1\*04 genes was added (model 3), the model was not improved. The selected model was simplified for clinical use by substituting coefficients with weighted scores. The simplified and original models had similar discriminative values. A clinical model for prediction of 5-year joint damage in early arthritis was developed which had excellent ability to discriminate at baseline between erosive and non-erosive RA. This simplified model with weighted scores can be easily applied to an individual patient.

#### **Factors predictive of 5-year disability in early RA** (6, 11)

##### *Factors predictive of HAQ disability in early RA* (6)

During the 5-year followup, the mean  $\pm$  SD HAQ score decreased from  $1.3 \pm 0.7$  to  $0.6 \pm 0.6$ . Ninety-eight patients (65.3%) had a HAQ score > 1 at baseline, while this was true for only 46 patients (27.4%) after 3 years and for only 34 patients (21.8%) after 5 years. Moreover, 90% of patients had improvement in their disability score. Final HAQ disability was associated with baseline values of HAQ score, pain, Ritchie Articular Index (RAI), tender joint count, DAS, ESR, CRP level, and presence of erosion. Multivariate analysis selected the baseline HAQ score, RAI, ESR, CRP level, and presence of erosion as independent prognostic factors of HAQ disability. Sex, age, IgM and IgA RF, other tested autoantibodies, and HLA class II genes did not significantly contribute to predicting disability after 5 years.

At baseline, mean  $\pm$  SD scores were  $3.6 \pm 7.7$  units for the total radiographic score,  $1.7 \pm 4.5$  units for the erosion score, and  $1.9 \pm 3.7$  units for the joint space narrowing score. After 5 years, these scores were  $17.9 \pm 22.3$  units,  $6.9 \pm 9.5$  units, and  $11.0 \pm 15.4$  units, respectively. No erosion was present at



**Fig. 1.** Study and follow-up of recent onset, undifferentiated polyarthritis.

baseline in 58.0% of patients, while 24.2% and 22.4% of patients had erosions at 3 years and 5 years, respectively. Global radiographic progression occurred in 87 patients (55.8%) during the 5 years. During the first 5 years of RA, radiographic damage increased progressively in half of the patients, while HAQ disability improved in most of them during the same period and could be predicted by baseline values of the HAQ score, RAI, ESR, CRP level, and the presence (or absence) of erosion.

#### *Factors predictive of 5-year quality of life (11)*

Using the Arthritis Impact Measurement Scales 2 (AIMS2) as the outcome variable, the logistic regression analysis revealed that the baseline values able to predict 5-year quality of life were as follows: HAQ score, ESR, and BMI for the physical domain; HAQ score, erosion score, and sex for the psychological health status; HAQ score, ESR, and IgA RF for the pain domain; antiperinuclear antibodies, MMP-3 level, joint space narrowing score, and tender joint score for the social domain; and HAQ score and age for the work status. According to Fisher's

exact test, no correlation was demonstrated with EAM, IgM RF, antikeratin antibodies, anti-Hsp90 antibodies, or HLA-DRB1\* genes. Prognostic factors for the 5-year quality of life in early RA were established and varied widely depending on the evaluated domain. The baseline HAQ score is the most important predictor of 4 of the 5 domains of the AIMS2.

#### **Prognostic factors for persistent remission in early RA (8)**

Forty-eight patients (25.1%) fulfilled the remission criteria at the 3-year followup visit, and 30 patients (15.7%) fulfilled these criteria at 3 and 5 years. According to univariate analysis by Fisher's exact test, remission at 3 years and persistent remission at 5 years were closely correlated with baseline values of the DAS, CRP level, RAI score, HAQ score, duration of morning stiffness, and, to a lesser extent, baseline total radiographic scores and RF negativity. No statistically significant correlation was demonstrated with sex, age, EAM, ESR, anti-CCP antibodies, antikeratin antibodies, anti-Hsp90 antibodies, anticalpastatin antibodies, ANA, or HLA-DRB1\* genotypes. Logistic regression analysis revealed

that the baseline independent variables predictive of remission were low baseline DAS, RAI score, morning stiffness duration, and total radiographic score. Baseline prognostic factors of remission in early RA were mainly clinical markers of disease activity and radiographic scores.

The next step will be to evaluate this RA cohort after 10 years of disease duration. Prognostic factors of 10-year radiographic damage, disability, and joint surgery will be determined.

#### **THE ESPOIR COHORT STUDY**

ESPOIR is the acronym for "Étude et Suivi des Polyarthrites Indifférenciées Récente" ("Study and Followup of Undifferentiated Early Arthritis"). The aim of this French multicenter study is to include 800 patients from the community and to follow them up for at least 10 years. The first patient was included in December 2002. Although several centers only joined in January 2003, more than 200 patients were included by May 1, 2003. Obviously, no data are yet available, and we will only describe here the objectives, design, and organization of this early arthritis registry.

#### **Rationale**

RA is the most frequent form of inflammatory arthritis, affecting 0.3% – 0.8% of the French population (12). Patients have significant disability and handicap after a few years of disease progression. At 10 years, 92% of these patients suffer significant decreases in their functional ability, and 50% need aid for some daily life activities (13, 14). Many either have to quit their professional activities or seek adaptive measures to enable them to perform their jobs less than 10 years after the start of the disease (15).

This condition has major economic consequences that have recently been dramatically increased by the availability of new biotherapies. RA has a heterogeneous profile with several forms ranging from mild to severe disease. The questions that practicing rheumatologists must usually address can be classified into the following categories: *Diagnosis*. Early diagnosis is particu-

larly difficult in some forms of RA. Classification criteria and standards for clinical diagnosis are useful after 1 or 2 years of disease, but are not always helpful at the first consultation. Furthermore, not all practitioners may use them in the same way, and not all practitioners classify early arthritis in a similar manner (16). The combined investigations of 2 or 3 clinicians do not seem to add complementary information to a given diagnosis (17). A survey of French rheumatologists has shown that only a blood count, ESR, RF, anti-DNA antibody testing, and hand x-ray are routinely carried out (18).

**Prognosis.** Some prognosis markers have now been identified for early RA, such as erosions on x-ray, RF, acute phase reactants, and HLA-DR4. However, their contribution in early arthritis (i.e., before arthritis can be classified) remains to be validated. Some, such as synovium immunohistologic markers, might help in the diagnosis (19). Such markers are important to identify with regard to early therapeutic decision making and the risk:benefit ratio of each therapy.

**Public health considerations.** Little data are available in France regarding the quality of life and socioeconomic consequences of arthritis. Direct cost estimates vary between 2,000 and 4,000 Euros per patient per year. Direct costs are high during the first year because of diagnostic investigations and early aggressive therapy, while indirect costs may increase as patients and society cope with consequences of the disease (20, 21).

**Pharmacogenomic developments.** A pharmacogenomic approach is becoming increasingly important in chronic disease, as it allows us to study the genetic component of the response to treatment and drug toxicity (22).

These questions would be best addressed by means of studies involving the prolonged followup (over several years with regular visits) of patients presenting with early arthritis.

### Research objectives

The primary objective of ESPOIR is to establish a multicenter cohort of patients with early arthritis (duration of <

6 months) in France that could serve as a database for various types of studies.

The specific objectives of the study lie in the following domains:

**Diagnosis:** to help determine among the many clinical, biologic, radiographic, and immunogenetic parameters available those that allow for the earliest possible diagnosis classification, in order to target early therapy.

**Prognosis:** to identify as soon as possible those patients at risk of severe disease by pursuing investigations of clinical, radiographic, biologic, genetic, and sociologic factors.

**Medicoeconomic:** to identify the costs and their determinants at various disease stages.

**Pathogenic:** to collect a databank of sera, DNA, RNA, and synovial fluids and tissues to allow various studies of RA pathogenesis, including transcripts and other genomic aspects, to be carried out.

Secondary objectives are:

- to monitor adverse events, particularly rare drug reactions, in collaboration with other international studies;
- to allow broader access to the data collected in this cohort study in order to facilitate new projects submitted to and approved by the scientific committee;
- to set up an educational program for general practitioners (GPs), focusing on early arthritis and early referral recommendations (23).

### Design of the ESPOIR cohort study

This is a longitudinal prospective cohort study of adults more than 18 and less than 70 years of age recruited from multiple regions across France.

#### Number of subjects to be included

Due to the broad heterogeneity in treatment practices and drug availability, it is not yet possible to standardize guidelines for treatment in early arthritis. A sufficient number of subjects would allow us to obtain reasonable estimates of prescribing practices after 10 years of followup, and to run reliable subgroup analyses. A compromise considered to be both reasonable and feasible has been formulated to obtain 300 patients for a 10-year period of study.

Data from the literature as well as previous cohort studies in France have shown that the proportion of patients lost to followup is in the range of 5–8% during the first 3 years, after which it stabilizes at 1–5%, depending on many different factors. Using intermediate estimates, it would be necessary to start with 400 RA patients. Given the probability that 50% of patients will probably not develop RA after 2 years, we plan to include 800 patients with early arthritis.

#### Inclusion criteria

- Patients >18 years and <70 years of age.
- Certain or probable clinical diagnosis of RA.
- Clinical diagnosis of undifferentiated arthritis that may potentially develop into RA.
- At least 2 inflammatory joints for the past 6 weeks: a swollen joint observed in 2 articular sites and present for at least the past 6 weeks.
- Arthritis starting within the past 6 months.
- The patient must never have been prescribed DMARDs or corticoids, unless they were prescribed more than 2 weeks before inclusion in the study or unless an intra-articular injection was received <4 weeks before inclusion
- Corticosteroids are authorized if they were prescribed for 2 weeks at least 2 weeks before inclusion and with a maximum mean dosage of 20 mg/day

#### Exclusion criteria

- Undifferentiated rheumatism with no potential to develop into RA
- Other clearly defined inflammatory rheumatisms

#### Patient recruitment

Patients will be recruited over a period of 18 months in 14 university hospital rheumatology departments (Fig. 1). The criteria established for the participating centers are:

- Centers must employ researchers experienced in performing multicenter controlled trials, epidemiologic studies, and genetic studies.

– Quality standards shall be followed in the set-up of local facilities for the study.

– Multiple procedures will be implemented to follow-up patients by direct contact, contact through rheumatologists, and contact through GPs.

Recruitment will be only conducted in connection with local private practitioners.

Each center is to include an average of 35 patients per year over the recruitment period. Each center will act as an observational center and will not interfere with patient treatment, unless the center is in charge of those patients. The patients will be routinely treated and followed up by private rheumatologists practicing in the geographic area. An approach using several communication media will be developed to invite patients and physicians in each regional area to participate.

Ethical rules have been set up to improve the followup of patients and to optimize the relationship between patients and their personal GPs or private rheumatologists in charge of routine care:

- It must be possible to see the patients in 2 weeks upon the request of GPs.
- The results of every test will be communicated to the private rheumatologist in charge of the patient.
- Patient followup will not interfere with therapeutic decisions made by patient's rheumatologist or GP.

#### Patient followup

All patients will be followed up every 6 months during the first 2 years, then every year by the same investigator in each center. The current plan is to stop the followup of patients with diagnoses other than RA or undifferentiated arthritis after 2 years.

#### Databases to be implemented

Several databases must be created to meet the different objectives of this project.

A clinical database will be established at each center and the data will be sent to the coordinating center in Montpellier.

A biologic database following the same route will comprise an agreed-upon list

of routine investigations. Serum, DNA, RNA, white blood cells, and synovial fluid and tissue will be collected and stored in duplicate under appropriate, clearly defined conditions at each of two biologic coordinating centers (Montpellier, Paris-Bichat).

An x-ray database will include baseline x-rays of the chest, forefoot, and anteroposterior views of both the hand and wrist. At each followup visit hand, wrist, and foot x-rays will be taken, as well as x-rays of other painful joints, where necessary. Ultrasonography and magnetic resonance imaging will also be performed on the hands and feet at selected centers.

#### Organization set-up and participating committees

*Steering committee.* The steering committee is in charge of organizational, administrative, and financial coordination of the cohort study and of following the cohort study process. It is composed of A. Saraux (Brest), B. Combe (Montpellier), F. Guillemin (Nancy), Ph. Ravaud (Paris-Bichat), M. Dougados (Paris-Cochin), B. Fautrel (Paris-Pitié), X. LeLoet (Rouen), J. Sibilia (Strasbourg), A. Cantagrel (Toulouse), and I. Logeart (MSD representative).

*Scientific committee.* The scientific committee includes the steering committee members, investigators of the participating centers, and external experts. It will be in charge of evaluating and validating future projects that may use the cohort database.

*Coordinating center.* The coordinating center (Montpellier University, B. Combe and J. P. Daures) will manage the data resources, the contact with each of the 14 clinical investigation centers, ethical aspects, and quality control.

*Biologic coordinating centers.* Two biologic resource centers (Montpellier, J. F. Eliaou; Paris-Bichat, J. Benesiano) are in charge of centralizing and managing biologic data collection, storage, and analysis.

*X-ray coordinating center.* The x-ray coordinating centre (Brest Hospital, A. Saraux) is in charge of storing and organizing the standardized x-ray readings.

*Funding sources.* An unrestricted grant from Merck (MSD) has been allocated for the first 3 years. An additional grant from INSERM was obtained to support part of the biologic database for the first 2 years. Abbott and Amgen are also supporting the ESPOIR cohort study.

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