

## THE ESPOIR COHORT STUDY.

### A FRENCH COHORT OF EARLY ARTHRITIS

**Steering committee:** A Cantagrel, B Combe, M Dougados, B Fautrel, F Guillemain, X LeLoet, MSD representative, Ph Ravaud, A Saraux, J Sibilia.

**Coordinating centre:** CHU Montpellier (B Combe, JP Daures)

#### 1. RATIONALE

Rheumatoid arthritis is the most frequent inflammatory arthritis, affecting 0.3 to 0.5% of the French 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 of them have to quit their professional activities or to seek for job adaptation less than 10 years after the start of the disease (4).

This disease has major cost consequences, recently dramatically increased by the new availability of biotherapies. It has a heterogeneous profile with several forms from mild to severe disease. The questions that practicing rheumatologists usually address can be distinguished in :

- **Diagnosis :** early diagnosis is particularly difficult in some forms. Classification criteria and diagnosis clinical standards are useful after one or two years of disease, but not at all times at first consultation. Furthermore, all practitioners may not use them the same way and do not classify early arthritis similarly (5). The combination of investigations over two or three of them do not seem to add complementary information to the diagnosis (6). A survey of French rheumatologist has shown that only blood count, ESR, rheumatoid factor and DNA antibodies and hand x-ray were prescribed routinely (7).
- **Prognosis :** some prognosis markers have been now clearly identified in early rheumatoid arthritis, like x-ray erosions, rheumatoid factor, acute phase reactants and HLA DR4. But their contribution in early arthritis, i.e. before arthritis be classified, has to be validated. Some markers like synovium immunohistologic markers might be contributive (8). Such markers would be important to identify with regards 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 estimates vary between 2 and 4 000 € per patient per year. Direct cost are high during the first year because of diagnosis investigations and early aggressive therapy, while indirect cost may secundarily increase in order to cope with social consequences of the disease (9,10).
- **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 (11).

These questions would be better addressed by obtaining periodic and prolonged follow-up over several years of early arthritis presenting patients.

#### References

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|-------------------------|-----------------------------------|
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## 2. RESEARCH OBJECTIVES

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

*Specific objectives* are in the following domains:

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

*Secondary objectives* are twofold:

- to monitor adverse events, particularly rare drug adverse events, in collaboration with other international studies
- 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.

## 2. DESIGN OF THE 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.

### 3a. Number of subjects to include.

Due to a great heterogeneity in prescribing practices and drugs availability, it is not yet possible to standardise guidelines for prescription in early arthritis. A sufficient number of subject 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 300 patients on a 10-year term, considered as reasonable and feasible. Data from the literature, as well as previous cohort study experiences in France have shown that proportion of loss to follow-up is in the range of 5 to 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 is planned to include 800 early arthritis patients.

### 3b. Inclusion criteria

- Patients aged over 18 and under 70
- Clinical diagnosis of rheumatoid arthritis as certain or probable
- 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 articular 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 6 weeks before inclusion
- Corticosteroids could be tolerated if prescribed for 1 week or less at least 1 month before the inclusion

### **3c. Non inclusion criteria**

- undifferentiated rheumatism with no potential chance to become RA
- other inflammatory rheumatisms clearly defined

### **3d. Patients recruitment**

Patients will be recruited over a period of 18 months in 15 university hospital rheumatology department. Criteria are set up to select participating centres:

- centres with investigators experienced in performing multicentre controlled trials, epidemiologic studies and genetic studies
- set-up quality standards shall be followed
- multiple procedures will be implemented to follow patients by direct contact, contact through rheumatologists and through general practitioners. Recruitment will be conducted in connection with local private practitioners.

Each centre is to include 35 patients per year on average over the recruitment period. Each centre will act as an observational centre, and not interfere with patient treatment, except if in charge of those patients. Not only those patients that are routinely treated in this centre, but also those routinely treated by private rheumatologists in the geographical area for recruitment will be incorporated, though not treated at the centre. An approach using several media will be 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 (family physician) or private rheumatologist in charge of routine care:

- it will be possible to see patients within less than 2 weeks upon request of GPs
- results of every patient investigations will be communicated to private rheumatologist in charge of patient care
- patient follow-up will not interfere with therapeutic decision made by her/his rheumatologist or GP.

### **3e. Patient follow-up**

All patients will be followed every 6 months during the first 2 years, then every year by the investigator in each centre. At this moment, it is planned to stop after 2 years the follow-up of patients with diagnosis other than RA.

## **3. DATABASES TO BE IMPLEMENTED**

Several databases have to be constituted to fit in the different objectives of this project.

Clinical database will be collected and computerised in each centre, then centralised in the coordinating centre (Montpellier)

Biological database will follow the same route, and will comprise an agreed-on list of routine investigations.

X-ray database will include at baseline a chest x-ray, both hand and wrist antero-posterior view and forefoot. At each follow-up hand, wrist and foot x-ray will be collected as well as other painful joints if necessary.

Serum, DNA, RNA, synovium liquid and tissue will be collected and double stored in adequate and definite conditions in each of 2 biological coordinating centre (Montpellier, Paris)

## **4. ORGANISATION AND COMMITTEES**

**Steering committee:** is in charge of organisational, administrative and financial coordination of the cohort study

Composition: A Saraux, B Combe, F Guillemin, Ph Ravaud, M Dougados, B Fautrel, X LeLoet, J Sibia, A Cantagrel, MSD representative

**Scientific committee:** includes steering committee members and one investigator of each participating centre. It will be in charge of following the cohort study process, and to examine and validate future projects to be using the cohort database.

Composition: steering committee members + P Fardellone, D Wendling, T Schaefferbecke, RM Flipo, X Mariette, O Meyer, Ph Goupille

**Coordinating centre:** will manage the data resources, the contact with each 15 clinical investigation centres, ethical aspects and quality control.

Centre: Montpellier hospital (B Combe, JP Daures)

**Biological coordinating centres:** will be 2 centres in charge of centralising and managing biological data collection, storage and analysis.

Centres: Montpellier (Pr Eliaou), Paris Bichat (J Benessiano)

**X-ray coordinating centre:** will be in charge of storing and organising the standardised x-ray readings.

Centre: Brest hospital (A Saraux).

**Funding sources:** An unconditional grant from Merck (MSD) is allocated for the first 3 years. An application for a grant from INSERM has been sought in february 2002. Additional grants per specific project will be sought.

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