ESPOIR and the French database management: what have we learned from the first years of follow-up?

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ABSTRACT

ESPOIR (Etude et Suivi des POlyarthrites Indifférenciées Récentes) is a multicentre national cohort sponsored by the French Society for Rheumatology. The patients had early arthritis (< 6-month disease duration), had a certain/probable clinical diagnosis of RA or undifferentiated arthritis potentially becoming RA and were DMARDs or glucocorticoids naïve. ESPOIR is a cohort of early arthritis, highly enriched for rheumatoid arthritis (RA) patients, since in patients followed for 5 years more than 90% met ACR/EULAR criteria for RA. A total of 813 patients were enrolled between December 2002 and March 2005 in 14 academic regional centres with the participation of a network of private rheumatologists.

Today, 104 clinical research projects have been selected by the scientific committee of the cohort. The projects focus on data from the first 5 years of follow-up. Many studies are in progress, and 54 original articles have been published. The research projects cover a wide range of topics, including environmental factors, diagnosis, evolution, and prognosis, evaluation of disease, imaging, genetics, biomarkers, medical economics and therapeutic strategies.

Introduction

ESPOIR (Etude et Suivi des Polyarthrites Indifférenciées Récentes) is a multicentre cohort from France sponsored by the French Society for Rheumatology. A total of 813 patients were enrolled between December 2002 and March 2005 in 14 academic regional centres with the participation of a network of private rheumatologists (1).

The objective of establishing the ESPOIR cohort was to create a database of early inflammatory arthritis, particularly rheumatoid arthritis (RA), for scientific clinical, physiopathological or medico-economic analysis. The second objective was to integrate the database in international projects, train practitioners in the diagnosis and early treatment of inflammatory peripheral rheumatism and improve patient care.

Therefore, ESPOIR is a cohort of early arthritis, highly enriched for RA patients since, among the patients followed for 5 years, more than 90% met the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for RA (2, 3).

Patients 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 centres in France. The objective and design of the cohort have been described previously (1).

The primary objective was to establish a multicentre cohort of patients with early arthritis (<6 months' disease duration) to produce 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' duration; clinical diagnosis of RA certain or probable or undifferentiated arthritis potentially becoming RA; and never receiving disease-modifying anti-rheumatic drugs or glucocorticoids (the latter only if prescribed for <2 weeks with a maximum mean dosage of 20 mg/day prednisone or intra-articular injection <4 weeks before inclusion).

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

The sample size calculation: A sufficient number of subjects would allow for obtaining reasonable estimates of practice after 10 years of follow-up and reliable subgroup analyses. A compromise was formulated to have at

least 300 patients with RA for 10-year follow-up. Data from the literature and previous cohort studies have shown that the proportion of lost to follow-up ranges from 5% to 8% during the first 3 years, then stabilises between 1% and 5%, depending on many factors. With intermediate estimates, 400 RA patients are needed. Given the probability than 50% of patients will probably not show RA after 2 years, the plan was to include 800 patients with early arthritis.

Patient recruitment and follow-up

The patients were routinely treated and followed by their rheumatologists according to standard care and without predefined therapeutic strategies. All patients were seen at each regional centre every 6 months during the first 2 years, then every year, and were seen by the same investigator in each centre. Procedures were established to avoid "lost to follow-up" as much as possible. At baseline and at each visit, data were obtained for a set of clinical and biological variables recommended for the management of early arthritis (1). At each visit, RA was classified according to the 1987 ACR criteria and retrospectively to the 2010 ACR/EULAR criteria. Patients were tested for baseline erythrocyte sedimentation rate; C-reactive protein level (local testing; normal <10 mg/l); IgM and IgA rheumatoid factors (ELISA, Menarini, France: positive >9 UI/ml), anti-cyclic citrullinated peptide 2 (anti-CCP2) antibodies (ELISA, DiaSorin, France; positive >50 U/ml), and human leukocyte antigen (HLA) DRB1* alleles (Immunology Department, Montpellier University Hospital) by the same procedures in a central lab. At each visit, the patients completed function and quality-of-life questionnaires including the Health Assessment Questionnaire Disability Index (HAQ DI), and Arthritis Impact Measurement Scale (AIMS2) version 2 short form, a medico-economic questionnaire, and globally assessed disease on a visual analogical scale. They underwent radiography of the hand and wrist (face) and foot (face and oblique). X-ray films were stored in the radiological coordinating centre (Brest) and were evaluated by the van der Heijde-modified Sharp score.

The protocol for 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.

What we have learned from the first years of follow-up of the ESPOIR cohort?

Main results

Today, 104 clinical research projects have been selected by the scientific committee of the cohort. The projects focus on data from the first 5 years of follow-up. Many studies are in progress, and 54 original articles have been published in the most-widely read rheumatology journals (3-54). The research projects cover a wide range of topics, including environmental factors, diagnosis, evolution, and prognosis, evaluation of disease, imaging, genetics, biomarkers, medical economics and therapeutic strategies.

Environment and genetics

Among environmental factors, tobacco is regarded as an important susceptibility factor, but its effect on disease progression remains controversial. In the ESPOIR cohort, smoking as well as hormonal treatment of menopause may have a protective effect on the production of anti-citrullinated peptide antibodies (ACPA) and the development of early bone erosions, with obvious interactions with the genetic factors (5). Another parallel work has shown that exposure to tobacco seems to protect against radiographic progression at 3 years (6). Whether smoking has a protective effect on the development of RA has not been demonstrated and certain assumptions can implicate the anti-inflammatory effect of nicotine (6). These data reinforce previous works which have failed to show a negative effect of smoking on RA outcome (55).

Menopause and hormone replacement therapy appear to play a role, because hormone therapy reduces the risk of ACPAs and also the risk associated with presence of HLA DRB* 01 and RA/* or 04 (the two elements can be linked) (7). In addition, the season when the first symptoms appeared affects radiographic progression in the short term (6 months) (8). This finding was replicated in a Dutch cohort (56). Various hypotheses have been advanced to explain this observation and further work, including the effect of vitamin D on early RA, is ongoing.

The allele C20W PTPN22 was found associated with ACPA production in early RA (7). Another study showed the association of interleukin 2RA (IL-2RA) and IL-2RB and erosions in early RA (9). Recently, the ESPOIR cohort was used to demonstrate the association of the genetic variants rs9138 and STP1 rs114239060 and risk of RA, especially for ACPA-negative patients (10). In these patients, the variant rs9138 SSP1 apears to contribute to the severity of radiological lesions.

Diagnosis, evolution and prognosis

The ESPOIR cohort was a primary early arthritis cohort used by the ACR and EULAR for developing the new 2010 criteria for classification of RA (2). Because of its number of patients and the importance of its database, the ESPOIR cohort was the first used to test the working hypothesis for these criteria. It was secondarily used with other cohorts for validation of the ACR/EULAR criteria (11, 12). The criteria are primarily classification criteria and were developed first from European and Canadian cohorts of early arthritis and second from case scenarios of patients with early inflammatory arthritis. The criteria can be used in case of doubt to guide diagnosis in practice. In 2013, the EULAR used the ESPOIR and Leiden cohorts to define *erosions typical of RA* (13, 14). The finding of radiographic bone erosion in three joints of the hands, wrists or feet was considered highly specific to RA.

ESPOIR cohort data have been widely evaluated for remission status (15-17). The ACR/EULAR remission criteria for RA, developed from clinical trials, have been validated in patients in real life in the ESPOIR cohort (15). In addition, it was confirmed that the rate of patients achieving early and sustained remission in early RA varied depending on the criteria used, the Disease Activity Score in 28 joints (DAS28) being the most permissive (16). Analysis also revealed good correlation between ACR/

EULAR and the Simple Disease Activity Index score. In addition, and this is reassuring, whatever the criteria used to define remission, predictive factors of remission for 6 months were similar: low initial activity level, menopausal status, and younger age (16). Finally, it was found that an Index without formal joint countes based on Routine Assessment of Patient Index Data 3 (RAPID3) RAPID3<3 and one or no swollen joints gave results quite similar to the Boolean criteria established by a EULAR/ACR committee (17).

The five-year follow-up of the ESPOIR cohort confirmed that RA outcome is in general benign as compared with analysis of previous decades' cohorts that was based on structural progression, functional disability and achieved remission (3). The analyses identified many initial factors predictive of the development of radiographic progression, remission or functional disability and met criteria already known in the literature (3, 8, 18, 19). New predictive biomarkers have been tested, which will be discussed later.

Analysis of comorbidities and their impact on the outcome of RA is an objective of the ESPOIR Cohort but will occur mainly after the 10th year. Nevertheless, initial results for cardiovascular risk confirmed that traditional cardiovascular risk factors differed in early RA as compared with controls (20). A recent publication showed that patients in the ESPOIR cohort have, early in their disease, a higher risk of cardiovascular mortality than the French population control at 10 years.

Work disability was also evaluated in the ESPOIR cohort. We have few French data on this subject. Loss of productivity at work (work interruption, etc.) was significant in the first 3 years of the disease and especially related to functional disability (HAQ) (21). In addition, early remission in the first 6 months of the disease reduced the number of days of work interruption in the first 5 years of the disease (22). A medico-economic analysis of the early years of the disease was published recently (54).

Patient criteria

Patient-reported outcomes (PROs) have been widely studied in the ESPOIR cohort, with many questionnaires developed at the beginning of the study and at follow-up. As noted, the self-administered questionnaire RAPID3 produced a relevant score for assessing disease activity, including remission (17, 23). Fatigue is an important factor for patients and a few studies have been performed in patients with early RA. Analysis of the ESPOIR cohort confirmed that fatigue has a multifactorial origin and cannot be considered the only consequence of disease activity (24). At baseline, factors independently associated with fatigue are varied and include age, sex, education, tobacco use, DAS28, morning stiffness and quality of life. Depression and anxiety are manifestations of early RA, found in nearly half of the ESPOIR cohort. These symptoms generally improve with treatment and during follow-up, with control of the disease (25). The HAQ score is the best predictor of depression and anxiety. Scores of quality of life and utility, EQ-5D and SF-6D also have been assessed in the ESPOIR cohort (26-28).

Imaging

Patients in the ESPOIR cohort underwent standard radiography of the hands, wrists and feet, systematically performed at baseline and at most follow-up visits. MRI of the hands and ultrasonography of the hands and feet were also part of the evaluation (1). Analysis of the ESPOIR cohort has provided data on radiographic progression over time (3) and that oblique radiographs of the feet allow for better detecting bone erosions in early RA than anteroposterior radiographs (29). MRI evaluation allowed for a simple assessment of joint damage to the hands in early RA (30). Finally, ultrasonographic evaluation of joints was confirmed to have a large place in the early diagnosis and evaluation of prognosis of RA (31-33). Ultrasonography appeared more sensitive than clinical data for detecting synovitis and more sensitive than plain radiographs for detecting erosions. Finally, early ultrasonography detected non-radiographically visible erosions that can predict future radiographic erosions (33).

Biomarkers

Biological data from the ESPOIR cohort allows for the evaluation of many biomarkers. The ESPOIR cohort has been analysed by several private companies to test biomarkers for diagnostic, prognostic or evolution in early RA. The use of "standard" biological tests in the diagnosis of early arthritis assessment showed that viral serology, including hepatitis B and C serology, was not useful for systematic detection (34-37). Among the autoantibodies, ACPA have been mainly studied (38-41). The analysis revealed no need to repeat anti-CCP (or anti-CCP2) testing during RA because seroconversion or seronegativity was rare (38). Besides the determination of anti-CCP2 antibodies, currently performed routinely, testing for the other ACPA such as citrullinated vimentin antibodies or citrullinated fibrinogen anti-human antibodies (AhFibAs) does not improve the diagnostic performance of ACPA (39.40). AhFibAs are good prognostic markers of bone erosion (40).

The clinical presentation of RA with or without auto-antibodies has been described (41). Levels of some serum B-lymphocyte activation markers were increased in early RA and correlated with disease activity (42); interleukin 6 and 21 levels (43), adiponectin (44) and Dickkopf-1 markers were associated with radiographic progression of RA.

Treatments and therapeutic strategies

Many studies have focused on the evaluation of treatments and therapeutic strategies in early RA in daily practice. Methotrexate has symptomatic and structural efficacy in early RA, but the optimal use with a rapid increase in dose up to a maximum of 20 to 25 mg/week, if well tolerated, gave better results (45). Nearly 50% of patients in the cohort received corticosteroids, more than 10% for more than 5 years (3). The impact of corticosteroids is currently being evaluated. Furthermore, the contribution of biologics, including anti-tumor necrosis factor (anti-TNF) agents, received by approximately 22% of RA patients during the first 5 years, is important. Several studies have evaluated

the therapeutic strategies in early RA (22, 46-51) and have found that with the importance of early detection, the use of an effective treatment for early RA, when used in the first 3 months of the disease, reduces radiographic progression at 1 year. Follow-up based on a validated activity score to adapt, as quickly as possible, a therapeutic strategy, is crucial. The need for early clinical remission to prevent and reduce complications in the medium- and long-term has clearly been demonstrated (22, 53) and provides additional scientific support for the most recent recommendations of RA management (57, 58). Finally, a discrepancy between current practice guidelines and strategies of care in daily practice was identified (47), whereas adherence by patients and rheumatologists to recommendations such as those of EULAR can limit structural progression and functional disability in RA (51).

Conclusions

The ESPOIR cohort has allowed the creation of an important database of information on early inflammatory arthritis, especially for patients with RA. Because of the number of patients included and followed, the amount of information available and the quality of the data, it is a well-known cohort, by international rheumatologist researchers, particularly in Europe and North America. Many French and international scientific teams have developed high-quality projects. The database at 8-year follow-up is now frozen, and the data for the 10-year follow-up will be available in late 2015. We should have data for more than 500 patients at 10 years, and considering this important group, they are expected to be followed up to 20 years. During the second decade, some issues, such as analysis of comorbidities, tolerance and the effect of treatment as well as long-term outcome and economic impact will be highlighted. Information concerning the ESPOIR cohort is at www.lacohorteespoir.fr.

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