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Joint Bone Spine

Review

Early lessons from the recent-onset rheumatoid arthritis cohort ESPOIR

Bernard Combe*, Nathalie Rincheval

Département rhumatologie, université Montpellier I, hôpital Lapeyronie, 34295 Montpellier cedex 5, France

ARTICLE INFO

ABSTRACT

ESPOIR is a French multicenter cohort of patients with undifferentiated arthritis enrolled within six months of symptom onset, naive to disease-modifying antirheumatic drugs and corticosteroid therapy, and either having rheumatoid arthritis (RA) or being at risk for progression to RA. The cohort is sponsored by the French Society for Rheumatology (Société française de rhumatologie [SFR]). Between December 2002 and March 2005, 813 patients were enrolled at 14 regional university hospitals, with the participation of a network of community-based rheumatologists. The objective was to establish a database on recent-onset inflammatory joint disease and, more specifically, on RA to serve for scientific research in the clinical, epidemiological, pathophysiological, and healthcare-cost fields. Ten years after enrolment were started, the cohort still has about 500 patients. The scientific committee has approved 104 clinical research projects, of which many are ongoing, and 54 original articles written by numerous French and international groups have been published. These projects cover a vast spectrum of topics including environmental factors, diagnosis, outcomes, prognosis, disease evaluation, imaging, genetics, biomarkers, costs, and RA management strategies.

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1. Introduction

A major meeting of all the research groups having worked on the ESPOIR cohort since its initiation in December 2002 was held on September 3, 2013, in Paris, France, providing the opportunity to draw a comprehensive picture of the research projects developed over the last decade. *Étude et suivi des polyarthrites indifférenciées récentes* (ESPOIR), research and outcomes in recent-onset undifferentiated polyarthritis, is a French multicenter cohort sponsored by the French Society for Rheumatology (*Société française de rhumatologie* [SFR]). With participation from a network of community-based rheumatologists, 14 regional university hospitals included 813 patients between December 2002 and March 2005 [1]. The primary objective was to establish a database on recent-onset inflammatory joint disease and, more specifically, on rheumatoid arthritis (RA), to serve for scientific research in the clinical, pathophysiological, and healthcare-cost fields. Secondary objectives included incorporation of the database into international research projects, training of physicians in the diagnosis and early management of patients with peripheral inflammatory joint disease, and improvement of patient management. The steering committee determined that the likelihood of meeting these objectives would be greatest if 300 patients with RA were monitored for at least 10 years. Given the estimated numbers of patients who would be lost to the cohort (via loss to follow-up, patient refusal of follow-up, relocation outside the region, or death) or who would receive a definite diagnosis other than RA, the estimated sample size was about 800 patients. The goal was therefore to include patients who had either recent-onset RA or undifferentiated arthritis with a potential for progression to definite RA. This goal explains the large proportion of patients with RA in the ESPOIR population of patients with recent-onset arthritis. Thus, among patients followed-up for five years, over 90% met ACR/EULAR criteria for RA [2,3].

The method used to include and to monitor the ESPOIR patients has been described in detail elsewhere [1,3,4]. The main inclusion criteria were as follows: age, 18–70 years; inflammatory arthritis involving at least two peripheral joints; symptom duration of six weeks to six months; and absence of treatment with disease-modifying antirheumatic drugs (DMARDs) or corticosteroids for longer than two weeks [4]. The exclusion criterion was early inflammatory joint disease meeting criteria for a definite diagnosis other than RA or exhibiting features that ruled out progression to RA. All included patients were evaluated every six months for the first two years then once a year. No restrictions were placed on treatments or other aspects of patient management, which were entirely at

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* Corresponding author. Tel.:.; +33 467 338 710; fax: +33 467 337 311.
E-mail address: b-combe@chu-montpellier.fr (B. Combe).

the discretion of the rheumatologist in charge of the patient, in compliance with the current standard of care.

The ESPOIR cohort [1] involves the participation of 14 regional university hospitals, each of which works with a network of community-based rheumatologists; a coordinating center (Montpellier); a biological resource center (Bichat Hospital in Paris) where patient sera, DNA, and urine specimens are stored; an imaging center (Brest); a steering committee that developed the protocol, established the cohort, and has managed it since its initiation; and a scientific committee that has been meeting twice a year since enrolment ended in 2005, to evaluate submitted research projects. For the first three years, only the investigators, steering committee members, and scientific committee members were allowed to submit projects. Since then, the ESPOIR database has been made available to other French and international researchers.

To draw a clear picture of the clinical and scientific advances allowed by the ESPOIR cohort, we will review the research projects based on ESPOIR data. The scientific committee has approved 104 clinical research projects based on the data collected during the first five years of patient follow-up. Many of these projects are ongoing, and 54 original articles have been published in the best rheumatology journals, by numerous research groups [3–54]. These projects cover a vast spectrum of topics including environmental factors, diagnosis, outcomes, prognosis, disease evaluation, imaging, genetics, biomarkers, costs, and RA management strategies.

2. Environmental and genetic factors

Among environmental exposures, smoking is one of the best documented risk factors for developing RA. However, the potential effect of smoking on the course of the disease remains controversial. A study of the ESPOIR cohort suggests that both smoking and menopausal hormone therapy may protect against the development of anticitrullinated protein antibodies (ACPAs) and of early bone erosions, in the absence of patent interactions with the genetic background [5]. Along the same line, cigarette smoke exposure seemed to protect against radiographic progression during three years of follow-up [6]. The mechanism by which smoking may protect against RA progression has not been identified, although hypotheses have been put forward, such as the antiinflammatory effect of nicotine [6]. The effect of the menopause and menopausal hormone therapy may involve not only the abovementioned decrease in the risk of ACPA production, but also a decrease in the risk of developing RA related to the HLA DRB*01 and/or *04 genes, and these two mechanisms may be related to each other [7]. Another interesting finding is that the season of symptom onset influences short-term (six months) radiographic progression in patients with recent-onset arthritis [8]. This finding has been replicated in a cohort from The Netherlands. A number of hypotheses generated by this finding are under investigation, most notably by studies of potential vitamin D effects in recent-onset RA in the ESPOIR cohort.

Among genetic factors, a study has confirmed that the PTPN22 C20W allele is associated with ACPA production in recent-onset RA [7]. Another study demonstrated an association between the IL-2RA and IL-2RB genes and the development of erosions in recent-onset RA [9]. ESPOIR was used very recently for a study establishing that the STP1 rs9138 and rs114239060 genetic variants were associated with the risk of RA, particularly in the subset of ACPA-negative patients [10]. In this subset, the SSP1 rs9138 variant may contribute to the severity of the radiological lesions.

3. Diagnosis, course, and prognosis

ESPOIR was the main early-arthritis cohort used by the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) to develop new RA classification criteria, in 2010 [2]. The large number of patients and comprehensive dataset led to selection of ESPOIR as the first cohort for testing the working hypotheses put forward to develop the new criteria. Subsequently, other methods were applied to ESPOIR to validate the ACR/EULAR criteria [11,12]. These criteria, which are primarily intended for classification purposes, were developed based on European and Canadian cohorts of patients with recent-onset arthritis and on clinical vignettes of patients with recent-onset inflammatory joint disease. They can therefore provide rheumatologists with diagnostic orientation in doubtful cases seen in everyday practice. In 2013, the EULAR used ESPOIR and the Leiden cohort to define erosive disease typical for RA [13,14]. A radiographic erosion involving the bone in at least three separate joints in the hands, wrists, and feet was considered highly specific of RA.

Criteria for RA remission have been extensively evaluated in the ESPOIR cohort [15–17]. ESPOIR enabled the validation in the real-life setting of the ACR/EULAR criteria for RA remission developed based on therapeutic trials [15]. An ESPOIR study confirmed that the proportion of patients achieving an early and sustained remission in recent-onset RA varied according to the criterion used and was highest with the DAS28 [16]. A close correlation was demonstrated between the ACR/EULAR criteria and the Simplified Disease Activity Index (SDAI). Finally, a fortunate finding is that, regardless of the criterion used to define a remission, the factors predicting an at least 6-month-long remission were the same, namely, low baseline disease activity, nonmenopausal status, and younger age [16]. Finally, the group led by Ted Pincus has established that the self-report RAPID3 score, which does not involve joint counts, performs well for evaluating RA remission [17].

Studies of 5-year outcomes in ESPOIR patients have confirmed that the overall prognosis of RA is better than in past decades, most notably regarding structural disease progression, functional impairments, and disease remission [3]. Many baseline predictors of radiologic disease progression, remission, or functional impairment have been identified and found consistent with previously reported criteria [3,8,18,19]. The potential predictive significance of new biomarkers has been tested in ESPOIR patients, as discussed below. An assessment of comorbidities and of their impact on outcomes of patients with RA is among the objectives of the ESPOIR cohort but will become a strong focus only after 10 years of follow-up. Nevertheless, preliminary data on the cardiovascular risk have confirmed that traditional cardiovascular risk factors differ between patients with recent-onset RA and controls [20]. A submitted study demonstrates an increased 10-year risk of cardiovascular death among ESPOIR patients at disease onset compared to matched controls from the general population in France.

Work disability has also been evaluated in ESPOIR patients. Data on this point are extremely scarce in France. Loss of work productivity (e.g., related to sick leaves) was highly significant during the first three years after disease onset and was chiefly ascribable to functional impairment (Health Assessment Questionnaire [HAQ]) [21]. Obtaining a remission within six months after disease onset was associated with a decrease in the number of days off work during the first five years of the disease [22]. Data on healthcare costs during the first few years after disease onset were published recently [54] and further studies on this topic are under way and will continue as work on the cohort moves forward.

4. Usefulness of patient-reported outcomes (PROs)

Patient-reported outcomes (PROs) have been the focus of wide-ranging studies in the ESPOIR cohort via numerous questionnaires completed at baseline and during follow-up. In the US, the group led by I. Castejon and T. Pincus established that the self-report RAPID3

score was effective in evaluating RA activity, including the identification of remission [17,23]. Fatigue is a major burden for patients but has received little research attention in recent-onset RA. A study in the ESPOIR cohort identified fatigue as a multifactorial symptom that was not fully explained by disease activity [24]. A broad array of baseline features were associated with fatigue including age, gender, educational background, smoking history, the DAS28, morning stiffness, and quality of life. Anxiety and depression, two other manifestations of recent-onset RA, were found in nearly half the ESPOIR patients. Overall improvements in these symptoms were documented after treatment initiation and during follow-up, in relation to the degree of disease control [25]. The HAQ score is the best predictor of anxiety and depression. The EQ-5D and SF-6D quality-of-life and utility scores have also been evaluated in the ESPOIR cohort [26–28].

5. Imaging

The various imaging studies performed in ESPOIR patients include routine standard radiography of the hands, wrists, and forefeet at baseline and at each follow-up visit. In addition, a subset of patients underwent magnetic resonance imaging (MRI) of the hands and ultrasonography of the hands and feet [1]. The ESPOIR cohort has not only provided information on radiographic disease progression over time [3], but also shown that oblique radiographs of the feet are superior over anteroposterior radiographs for detecting bony erosions in recent-onset RA [29]. A simplified MRI score has been developed to assist in the evaluation of hand joint lesions in recent-onset RA [30]. Proof has been obtained that ultrasonography contributes to the early diagnosis and prognostic evaluation in RA [31–33]. Thus, ultrasonography was more sensitive than the physical examination for detecting synovitis and was also more sensitive than standard radiographs for detecting erosions. Ultrasonography has been proven useful for evaluating a diagnosis of RA based on ACR/EULAR criteria. Finally, early ultrasononographic erosions predict the subsequent detection of radiographic erosions [33].

6. Biomarkers

The ESPOIR biobank has provided valuable opportunities for evaluating a host of biological markers and will continue to allow biomarker studies in the future. Several private corporations have asked to use the ESPOIR database to test biomarkers under development as diagnostic, monitoring, or prognostic tools for recent-onset RA.

The contribution of standard laboratory tests to the diagnosis of recent-onset arthritis has been established. Serological tests for viral infections including hepatitis B or C are not performed routinely [34–37]. Among autoantibodies, the most extensively studied are ACPAs [38–41]. Repeated anti-cyclic citrullinated peptide antibody (anti-CCP) assays during the course of RA are unhelpful, as changes from positive to negative or vice versa are extremely rare [38]. When performed in addition to the now standard anti-CCP2 assay, assays of other ACPAs such as anti-citrullinated vimentin or anti-human citrullinated fibrinogen antibodies (AhFibAs) do not improve the diagnostic performance of ACPAs [39,40]. However, AhFibAs are good predictors of bony erosions [40]. The clinical presentations in RA patients with and without autoantibodies have been described [41]. Increased levels of several serum markers for B-cell activation have been demonstrated in patients with recent-onset RA and shown to correlate with disease activity [42]. Interleukin (IL)-6 and IL-21 [43], as well as adiponectin [44] and Dickkopf-1, correlate with radiographic disease progression.

7. Treatments and management strategies

Numerous studies have evaluated treatments and management strategies for recent-onset RA. In everyday practice, methotrexate demonstrated symptomatic and structural efficacy in recent-onset RA, and results were best with an optimized methotrexate regimen consisting in rapid dosage escalation to a maximum of 20–25 mg/week if well tolerated [45]. Nearly 50% of ESPOIR patients received corticosteroid therapy, which was used for more than five years in over 10% of cases [3]. The impact of this treatment is being assessed. Also under evaluation is the contribution of biologics, particularly TNFα antagonists, which were used during the first five years in about 22% of ESPOIR patients with RA. Several studies evaluated management strategies for recent-onset RA [23,46–51,53]. The results confirmed the beneficial effects of early rheumatologist referral of patients with early arthritis; early administration of effective DMARD therapy, which decreased 1-year radiographic progression when started within three months after disease onset; and tight disease control based on a validated activity score to allow prompt treatment adjustments. The need to achieve an early clinical remission in order to prevent and limit the development of mid- and long-term complications has been convincingly demonstrated [22,53] and constitutes additional scientific support for the latest recommendations on managing RA [55,56]. Finally, management strategies currently used in everyday practice are not always fully consistent with clinical practice [47]. This finding raises concern, since adhesion of patients and rheumatologists to recommendations such as those issued by the EULAR limits structural disease progression and functional impairments in RA [51].

8. Conclusion

The ESPOIR cohort has enabled the development of a vast wealth of data on recent-onset inflammatory joint disease, stemming chiefly from patients with RA. Unique features of ESPOIR include the large number of patients with baseline and follow-up data, the extensive information obtained on each patient, and the high quality of the database. These features have brought ESPOIR to the attention of rheumatologists leading international research efforts, most notably in Europe and North America. Many research groups in the French and international rheumatology communities have developed high-quality scientific projects based on the ESPOIR cohort. The 8-year database was locked very recently, and the 10-year data for the overall cohort will become available in late 2015. Over 500 patients are expected to undergo evaluation at the 10-year time point, and the large size of this population still in the cohort has prompted the decision to extend follow-up to 20 years, thus conferring to the ESPOIR cohort a unique position on the international research scene. During the second decade of follow-up, special attention will be directed to several topics such as comorbidities and treatment safety and effectiveness, although evaluations of long-term outcomes and disease costs will constitute the main priorities.

Comprehensive information on the ESPOIR cohort is available online at www.lacohorteespoir.fr.

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