CONCISE REPORT

Rheumatoid arthritis in Spain: occurrence of extra-articular manifestations and estimates of disease severity

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Objectives: To characterise RA in a sample of Spanish patients by estimating mean clinical activity, functional ability, and radiological damage, and current and cumulative prevalence of extra-articular manifestations.

Methods: Cross sectional analysis of a cohort of patients with RA randomly selected from the clinical databases of 34 centres. Standard definitions and measurements were used, and radiographs read centrally. Estimates and confidence intervals were adjusted to sampling.

Results: Data were available for 788 patients. Extra-articular RA was present in 285 (36.2%) patients. Cumulative prevalence and 95% confidence intervals of extra-articular manifestations were estimated: nodules 24.5% (21.5 to 27.5), Sjögren's syndrome 17.0% (14.4 to 19.6), atlantoaxial subluxation 12.1% (9.8 to 14.4), carpal tunnel syndrome 10.7% (7.8 to 13.6), interstitial lung disease 3.7% (2.4 to 5.0), serositis 2.5% (1.4 to 3.5), eye disease 2.5% (1.1 to 3.9), vasculitis 1.3% (0.5 to 2.1), amyloidosis 0.6% (0.1 to 1.2), and Felty's syndrome 0.3% (<0.6). Mean (SD) activity/progression indexes were: DAS28-3 3.4 (1.2), HAQ 1.6 (0.4), Larsen score 54.7 (26.4). Less than 5% of the patients were in remission. 205 (72%) patients were receiving disease modifying antirheumatic drugs (DMARDs).

Conclusion: Spanish patients with RA ever seen by a rheumatologist have, on average, a moderate degree of activity, despite widespread use of DMARDs. Measures of the degree of progression do not show a benign disease. The proportion of extra-articular manifestations in Spanish patients with RA is similar to that found in other Mediterranean populations, and lower than that reported in Anglo Saxon countries.

Many reports on the differences in the prevalence of rheumatoid arthritis (RA) in the world have been published, and evidence provided to show that the clinical expression and outcome may vary between populations.[1] These differences in the clinical expression and outcome may underlie the discrepancies in response to treatments, which might have unexpected implications when planning international efficacy studies. Moreover, if these differences really existed, some practice guidelines developed in Anglo Saxon countries might not apply completely in Mediterranean or Asian countries, and should be adapted to regional disease expression and outcome. The Spanish Society of Rheumatology (SER) supported the assembly of a national cohort of patients with RA in which to characterise RA in Spain by estimating the mean clinical activity, functional ability, and radiological damage, and the occurrence of extra-

articular manifestations (EAMs) in unselected Spanish patients. This cohort, from hereon called EMECAR (Estudio de la Morbilidad y Expresión Clínica de la Artritis Reumatoide), is the basis for future estimations and outcome studies.

MATERIALS AND METHODS

The databases of 34 participating rheumatology clinics were searched for patients with RA ever registered. These patients were then selected by cluster random sampling at a central facility and the lists produced sent to the participating rheumatologists, who then confirmed that the selected patients fulfilled the American College of Rheumatology 1987 criteria for RA. Once the diagnosis was confirmed by review of the clinical records, patients were contacted by telephone or letter, or both. If a patient could not be reached then that patient was replaced by another randomly selected from the same centre. All patients who entered the cohort gave written consent after being informed about the details of the study. The study protocol was reviewed and approved by the research ethics committee of the Hospital de la Princesa.

The data here presented were obtained from the cross sectional analysis of the baseline year (November 1999 to November 2000). Retrospective data were also collected from the clinical records and contrasted with the data obtained for the patients at this visit.

Rheumatologists were instructed in collecting the data and performing the joint counts and other measures. All patients were physically examined, laboratory tests were carried out, and hand *x* ray examinations performed. Additionally, chest and cervical spine *x* rays were performed if none were available within the year of the baseline visit. The definitions of all manifestations were based on commonly used criteria and were detailed in the study protocol by algorithms (table 1). The date of occurrence (or first episode) of a particular manifestation of RA was collected. The current prevalence included all patients in whom the EAM was present on the interview day. The two and 10 year cumulative prevalences considered all patients in whom the EAM had been present at any time since 1997 and 1989, respectively. The disease activity score (DAS) was obtained from 28 joint counts using the formula with three parameters, DAS28-3.[2] Remission was defined by using the preliminary criteria developed by Pinals and colleagues.[3] Radiological damage was assessed in hands and wrists by *x* ray examination, and the radiographs were read centrally by a trained radiologist, using the Larsen method

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Table 1 Cumulative 10 year prevalence and incidence within two and 10 years from diagnosis of extra-articular manifestations in a representative sample of Spanish patients with RA with a mean disease duration of 10 years

	Definition	Cumulative prevalence (95% CI)	Incidence within two years (95% CI)	Incidence within 10 years (95% CI)
Rheumatoid nodules	Subcutaneous nodules with a diameter ⩾5 mm in extensor face of extremities and fingers. Nodules in atypical locations must have a histological confirmation	24.5 (21.5 to 27.5)	5.2 (3.8 to 7.1)	15.7 (13.0 to 18.9)
Secondary Sjögren's syndrome	Presence of RA plus xerophthalmia and/or xerostomia, both objective and subjective (Vitali et al[15])	17.0 (14.4 to 19.6)	2.3 (1.4 to 3.7)	9.1 (6.9 to 11.8)
Anterior atlantoaxial subluxation	Distance between atlas and axis in a lateral x ray of the cervical column in forced flexion is >3 mm, regardless of the presence of symptoms	12.1 (9.8 to 14.4)	0.2 (0.02 to 1.0)	3.2 (1.9 to 5.3)
Carpal tunnel syndrome	Presence of symptoms (paraesthesia, pain or tiredness in the median nerve territory) plus one positive sign (Phalen or Tinel), or nerve conduction studies demonstrating median nerve entrapment, or previous treatment or surgery for carpal tunnel syndrome	10.7 (7.8 to 13.6)	3.5 (2.4 to 5.0)	8.0 (6.2 to 10.4)
Interstitial lung disease	Confirmed either by restrictive pattern or decrease in T_{LCO} or KCO in pulmonary function tests or by high resolution CT scan	3.7 (2.4 to 5.0)	0.5 (0.2 to 1.4)	1.9 (1.1 to 3.5)
Serositis	Pleuritis or pericarditis documented in the clinical record as related to RA or appearing as a new finding in chest x ray, with or without symptoms	2.5 (1.4 to 3.5)	0.1 (0.02 to 0.9)	0.4 (0.1 to 1.3)
Eye disease	Scleritis and/or episcleritis, confirmed by an ophthalmologist	2.5 (1.1 to 3.9)	–	1.5 (0.7 to 3.0)
Rheumatoid vasculitis	Presence in a patient with RA of one or more of the following: (a) Mononeuritis multiplex or acute peripheral neuropathy (b) Peripheral gangrene (c) Histological evidence of necrotising arteritis associated with systemic manifestations (d) Deep cutaneous ulcers or active extra-articular disease (pleuritis, pericarditis, scleritis) if associated with typical digital infarctions or histological evidence of vasculitis	1.3 (0.5 to 2.1)	–	0.4 (0.10 to 1.5)
Secondary clinical amyloidosis	Amyloid deposition confirmed by biopsy in a target organ or by fine needle aspiration of subcutaneous abdominal fat plus clinical and/or analytical repercussion	0.6 (0.1 to 1.2)	–	0.3 (0.4 to 11.8
Felty's syndrome	Neutropenia (<1.8×10⁹ neutrophils/l) plus splenomegaly (documented by ultrasound) without another cause in a patient with RA	0.3 (<0.6)	–	–

with the Scott modification (range 0–150).[4] All patients were assessed by the Spanish validated version of the Health Assessment Questionnaire (HAQ).[5]

Sample size was based on a pilot study, and calculated to estimate a mean (SD) HAQ score of 0.8 (0.8), with an error of ±0.1 (n=673), increased to account for failures in contacting patients and losses to follow up in the following five years, and rounded up. All estimates and confidence intervals are given adjusted to the cluster sampling design by using the *svy* commands of Stata (Stata 7.0, Stata corporation, Texas, 2001). Results are expressed as means (SD) or percentage (with corrected 95% confidence interval (CI) in parentheses), unless detailed otherwise. Time to occurrence of the first event is described by Kaplan-Meier curves and life tables.

RESULTS
A total of 1329 patients were randomly selected (eligible population 13 260). Of these, 135 patients did not have RA, 96 had died, 228 could not be located, and 82 refused to participate, which gave a final sample of 788 patients. In total, 562 (71.3%) of the patients included were women, with an average age of 61 (13) years and disease duration of 10 (8) years (112 (14.2%) patients had <2 years' disease duration). The

rheumatoid factor was positive in 574 (72.8%). The mean age at diagnosis was 48 (15) years, and 75% of the patients had been diagnosed before the age of 59. The patients who refused to participate were, on average, 10 years older and their disease had started 7 years later than the patients included (p<0.01), but their other sociodemographic and basic clinical characteristics were similar.

A total of 285 patients (36.2%) had at least one EAM of RA at present. An additional 6.6% had been referred for an EAM in the past, which was not present at the cohort baseline visit. Table 1 shows the cumulative prevalences of specific EAMs. The current prevalence of nodules was 14.3% (95% CI 10.9 to 17.8).

Figure 1 shows the time to the first occurrence of the more common EAMs. Table 1 gives the incidence of each manifestation within two and 10 years from diagnosis.

For measures of function and severity of disease, the median number of painful joints was 3 (25th-75th centile 0–7) and the median number of swollen joints 4 (25th-75th centile 1–8). Mean (SD) DAS28-3, HAQ, and Larsen scores were, respectively: 3.4 (1.2), 1.6 (0.4), and 54.7 (26.4). Only 32 patients were in remission at present, an estimated current prevalence of 4.1% (95% CI 2.8 to 5.7).
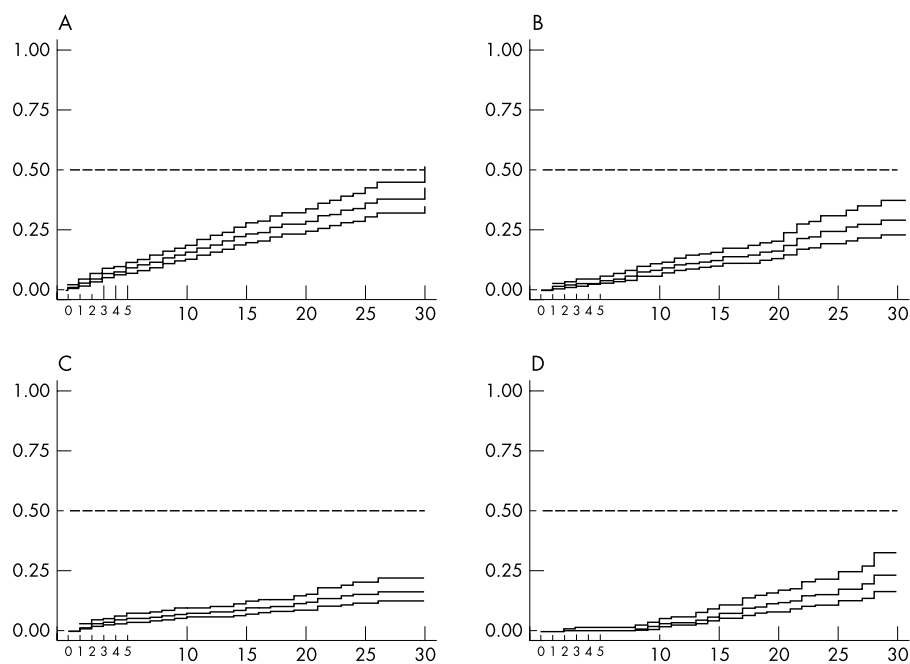
Figure 1 Probability (with 95% CI bands) of presenting with (A) rheumatoid nodules, (B) secondary Sjögren's syndrome, (C) carpal tunnel syndrome, and (D) anterior atlantoaxial subluxation by year after the diagnosis of RA (inverse Kaplan-Meier curves).

DISCUSSION

Several studies show varying patterns of RA in different populations, an issue which has been discussed previously.[1] [6] Some of this variability can be explained by the different methodological approaches of the studies—namely, the selection of patients and the criteria use to define extra-articular disease. Some general conclusions can be drawn from these studies: (*a*) RA seems to be more severe in Anglo Saxon populations, who seem to have more EAMs; (*b*) some EAMs are particularly common in some geographical areas; and (*c*) there is a need to standardise population studies of RA.

We used comprehensive and universally accepted criteria for definition of the EAMs of RA to facilitate comparisons with previous studies. The proportion of patients with extra-articular disease among Spanish patients with RA (36%) is similar to that described previously in Italian and Chilean studies—41% and 38%, respectively,[7] [8] and lower than that from Anglo Saxon countries—around 65%.[9] [10] In Spain, the prevalence of nodules in RA is similar to that found in Italian patients[7] and lower than found in Anglo Saxon countries.[9] [10] The second most common manifestation of extra-articular RA in Spanish patients is secondary Sjögren's syndrome (17%), which was actively looked for and thus was higher than previously reported in our country[11]; however, it did not reach the prevalence found in Greek patients[11] or even that found in Chilean patients.[8] The prevalence of atlantoaxial subluxation also varies between countries. A community based Finnish study found cervical complications in around one third of their patients, which is a prevalence almost three times greater than our estimate.[12] However, the Finnish patients were older and had a longer disease duration, and we have seen that the prevalence increases rapidly 10 years after diagnosis. The prevalence of atlantoaxial subluxation in Spanish patients with RA is actually closer to that of Malaysian and British patients.[9] All other manifestations are in the lower ranges of those reported, with the exception of eye disease, which is higher than expected, perhaps owing to the inclusion of cases of scleritis and not only episcleritis in our study.

It is difficult to compare the severity of RA between populations as the methods used vary.[13] On average, the Spanish patients with RA ever seen by a rheumatologist have moderately active disease, despite widespread use (currently 72%) of disease modifying antirheumatic drugs (DMARDs), and functional and structural progression which is similar to that found in other populations. Unfortunately, DMARD use cannot easily be controlled and it may be a source of variability. Another source of variability may be the genetic differences between RA populations.[14]

The EMECAR study provides national estimates of disease expression in RA. The major strength of the study is the random sampling of patients with RA from a large number of rheumatology centres throughout the country. All participating centres were public, but given the nature of the Spanish health system, with its universal coverage, the probability that any patient diagnosed with arthritis was seen at least once in a public centre is high. The sample includes patients who may not regularly be attending a rheumatologist at present, thus assuring a reasonably representative distribution of patients. Also, the use of a standard protocol to confirm criteria, instead of relying on clinical records only, guarantees a reliable picture of the disease. Moreover, prevalence estimates and confidence intervals account for the sampling scheme by adding a corrective factor, thus obtaining wider though more reliable estimates.

In conclusion, Spanish patients with RA have fewer EAMs than their Anglo Saxon counterparts and a similar number to those of other Mediterranean populations. The disease in Spanish patients seems less severe than in Anglo Saxon populations, although functional and structural outcomes are not benign. The use of standard measures, as well as random sampling of patients may help to unify methodology and to clarify the difference in expression of RA between populations.

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