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Original Article

What are patients with early rheumatoid arthritis like in Spain? Description of the PROAR cohort

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ABSTRACT

Objective: To identify factors present in recent onset arthritis that may help to predict rheumatoid arthritis (RA), and to describe a cohort of recent onset RA.
Patients and method: A 5 year prospective cohort of patients with early oligo and polyarthritis (<1 year of evolution) from 34 rheumatology units, was performed. Sociodemographic, clinical features, and RA risk factors were recorded. Rheumatoid factor (RF), anti-CCP determinations, and radiographs of hands and feet were analyzed too. After 3 years, a diagnosis of certainty and the variables that determined the evolution to RA, were evaluated.
Results: One hundred and seventy one patients were included; 161 (94.2%) fulfilled RA diagnostic criteria; most of them (157; 97.5%) in the first visit. Factors associated with RA diagnosis were: positive RF, anti-CCP, and DAS-28; 65% of the patients had radiological erosions in the first visit.
Conclusions: Positive RF, anti-CCP, and the disease activity are predictive factors of RA. Radiological damage exists very early in most of patients, that's why it is more important to treat the disease aggressively instead than achieving an RA diagnosis of certainty

¿Comó son los pacientes con artritis reumatoide de reciente comienzo en España? descripción de la cohorte PROAR?

Palabras clave:
Artritis
Estudios de cohortes
Diagnóstico precoz
Enfermedades autoinmunitarias

RESUMEN

Fundamento y objetivo: Identificación de factores presentes en la artritis de reciente comienzo que puedan ayudar a predecir el desarrollo o no de artritis reumatoide (AR). Descripción de las características clínicas de una cohorte de AR de inicio.
Pacientes y método: Cohorte de inicio prospectiva de 5 años de duración en 34 servicios de reumatología españoles formada por pacientes con oligoartritis y poliartritis de menos de un año de evolución no tratados previamente. A todos los pacientes se les realizó al inicio una valoración de la actividad inflamatoria, capacidad funcional y factores de riesgo de AR. Además se realizaron radiografías de manos y pies y determinaciones de factor reumatoide (FR) y de anticuerpos anti-CCP. Tras 3 años, se evaluó el diagnóstico definitivo y las variables que determinaron la evolución hacia AR.
Resultados: Se incluyó a 171 pacientes, de los que 161 (94,2%) acabaron cumpliendo criterios diagnósticos de AR, la mayoría (157; 97,5%) en la visita inicial. Los factores relacionados con el diagnóstico de AR fueron: el FR positivo (odds ratio [OR]= 8,5; intervalo de confianza [IC] del 95%, 1–69,8), los anti-CCP (OR = 8,5; IC del 95%, 0,96–75,7) y el DAS28 (OR = 1,9; IC del 95%, 1,1–3,3). El 65% de los pacientes presentaban erosiones en la visita basal.
Conclusiones: Tanto la extensión de la afección articular como tener un FR positivo y anticuerpos anti-CCP permiten predecir la evolución a AR. El daño radiológico, en muchos pacientes, ya está al inicio, por lo que es más importante un tratamiento contundente precoz que esperar a tener un diagnóstico de AR.

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Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory disease that mainly affects joints and produces deterioration of the patient's functional capacity, a reduction in the quality of life and an increase in mortality.[1] Clinically, RA is very heterogeneous, with important differences not only between patients but also during the different phases of disease progression in the same person, making the natural course of the disease difficult to describe and, therefore, making its progression difficult to predict, an aspect of great importance if its course is to be altered effectively.[1–3]

Early intervention during the course of RA and the therapeutic strategy currently seem to have substantially influenced the long term history of the disease.[4,5] However, it is difficult to determine which patients with RA will respond adequately to different therapeutic strategies. This circumstance has motivated a growing interest in the search and identification of factors that are present at the beginning of the process, which may predict a more severe disease, in order to treat it more aggressive and effectively.[6] The decision to employ or not to employ these strategies, potentially toxic and more expensive, must be concretely based on the prognosis of each patient.

Most of the prognosis studies regarding RA or early arthritis have been performed in American or Northern European populations.[4–7] It has been noted that in countries bordering the Mediterranean, RA can be more benign,[8,9] making it necessary to have studies on prognostic factors in early arthritis, with the end of establishing diagnostic and treatment guidelines that will lead to better attention of the patient and an improvement in their quality of life.

The study of the prognostic factors of severe disease in early rheumatoid arthritis (PROAR), promoted by the Spanish Society of Rheumatology, is a unique opportunity to know the relationship between sociodemographic, clinical, and serological factors and disease progression: the appearance or not of remission and its duration, alterations in the functional capacity, appearance and progression of radiological lesions and the need for joint surgery. In this study, the baseline characteristics of early arthritis in our country are shown and the factors that are useful in the prediction of RA in patients with recent onset arthritis are evaluated.

Patients and methods

The PROAR project is a longitudinal, multicentric study lasting 5 years with a cohort of short time since onset of disease RA patients, whose objective is to identify the effect of independent variables on disease activity, functional capacity and radiological deterioration.

All of the centers with specialized rheumatology departments in our country were invited to participate through a letter addressed to the head of the department, of which 34 accepted. In each one of the participating centers, a rheumatologist responsible for the project was named.

The study was approved by the Ethics committee of the hospital in which the principal investigator was based and the included patients gave their consent to participate in the study approved the study protocol. The protocol adhered to the principles of the Declaration of Helsinki of 1975 and its later modifications.

Patients with oligo or polyarthritis of less than 1 year since disease onset were included, independent of whether they complied with the American College of Rheumatology (ACR) 1987 RA criteria,[10] who had not been previously treated with disease-modifying antirheumatic drugsand who were not undergoing steroid treatment at the moment of inclusion. Patients with crystal arthritis or infectious arthritis diagnoses were excluded from the analysis.

Patient recruitment, which took place during one year, was based on the consecutive sampling of the first 5 new patients who came to the clinics of the participating rheumatologists ad who complied with the inclusion criteria. Because it is a low incidence process and because it involved first time patients, the type of sampling was considered probabilistic.

Variables and study groups

Data from the patients was acquired through specialized questionnaires during semestral visits. In the baseline visit, patients' characteristics which could influence the analysis of the main variables were gathered: gender, age, time since onset of disease, past or current medical treatment, concomitant disease, study level, social class (the last profession and that of the partner were gathered and crossed referenced with tables prepared by the Spanish Society of Epidemiology for their categorization of the social class, on the basis of the last professional occupation[11]), work situation upon data gathering, smoking habit (at the moment of data gathering and prior history, as well as duration), gynecological history (number of pregnancies, abortions and live-born products, age at menarche and menopause and the use and duration of hormonal replacement therapy and contraception) and history of transfusions (number, motive, and year it occurred in).

At the baseline visit and every 6 months afterward, joint pain and the general evaluation of the disease by both the patient and the physician was carried out using a visual analog scale (VAS), a tender joint (52 and 28 joints), and swollen joint (44 and 28 joints) counts were performed, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were determined through the usual method in each center and then converted to common units in mg/dL, and rheumatoid factor (RF) was reported in U/mL. RA was defined as seropositive based on a single RF determination, while it was deemed seronegative if all other determinations were negative. Inflammatory activity was quantified using DAS28, a grouped measure based on joint counts, the patient health evaluation and the ESR (Disease Activity Score).[12,13] The measurement of functional capacity was carried out based on the patients' self application of the Health Assessment Questionnaire (HAQ) in its Spanish validated version,[14] which give points to the patients functionality in a scale of 0 to 3 (total capacity to absolute lack of capacity) and the functional class of the ACR[15] (I to IV, best to worst).

To quantify the joint damage, the radiological method proposed by Sharp was used, as modified by van der Heijde et al.[16] Maximal score of erosions on all of the joints of both hands is 160 and of both feet, 120. Maximal score for joint space narrowing is 120 and in both feet, 48. Hand and feet x-rays of all of the patients were evaluated in a centralized manner by an expert, taken at baseline and every year afterward.

Blood samples from the patients were collected on every visit in order to determine anti-citrullinated peptide antibodies (anti-CCP). The determination was carried out centrally in the Immunology laboratory of the Hospital La Paz using a mark 2 CCP-kit by Eurodiagnóstica, a second-generation ELISA (maximal detection, 1600 U/mL; minimal detection, 25 U/mL).

RA extraarticular manifestations were also looked for on each visit (atlanto axial dislocation, rheumatoid nodules, vasculitis, pleuritis or pericarditis, Felty's syndrome, interstitial pneumopathy, eye affection, Sjögren's syndrome, amyloidosis, carpal tunnel syndrome, and peripheral neuropathy).

To insure quality of the data collection, a standardization course in data collection was carried out anteceded by a pilot study with the questionnaires, with the objective of unifying criteria regarding joint examination. In addition, a follow-up of quality and trustworthiness of the data collection was performed by a monitor for the whole follow-up

The definition of RA is based on the accumulation of ACR 1987 criteria from the onset of symptoms, independently of the physicians judgement. The "development of RA during follow-up" variable was initially considered to be the analysis variable, allowing for the

differentiation between RA and non-RA, but when observing patients who developed RA according to the criteria, but in relation to other autoimmune diseases, a group known as *"AR-overlap"* was considered as conceptually differentiated enough.

Statistical analysis

Central tendency measurements adapted to the distribution of the variables for the description of the sample were employed. That included a prior Kolmogorov test of normality to prove the adjustment of discrete or normally continuous variables. To contrast the hypothesis of differences between groups: RA, no RA, and RA overlap; both parametric and non-parametric tests were used, according to the distribution of the variable. Fisher's test was used to contrast hypothesis when in a group there was less than 5 patients with compared categorical characteristics. Data analysis was done with Stata and SPSS statistical software.

Results

During the year of inclusion the 34 participating centers recruited 171 patients with oligo or polyarthritis of less than 1 year since onset of disease, of whom 161 (94.2%) complied with the ACR RA criteria during follow-up. The mean (standard deviation) of follow-up of patients was 3.6 (1.6) (interval, 0–5.6) years. Figure shows the flow of patients, with follow up losses, throughout their visits.

The diagnosis of arthritis that did not comply with RA criteria were: undifferentiated arthritis (n=8), sarcoidosis (n=1), and spondyloarthritis (n=1); 11 patient complied with RA criteria and other joint inflammatory diseases: psoriatic arthritis (n=2), undifferentiated connective tissue disease (n=1), systemic lupus erythematosus (n=1), and peripheral spondyloarthritis (n=7). In this way, 150 patients were included into the RA group, 10 in the group with no RA, and 11 in the RA overlap group.

The mean time since onset of disease before the first visit was 5 months (median, 4.5; P_{25-75}, 2.5–7.3). Patients who finally did comply with RA criteria, in their majority (157; 97.5%) happened by the initial visit. Two patients complied with criteria at the 6 month visit and the other 2 in the visit at 1 year.

Tables 1 and 2 show the baseline sociodemographic characteristics and the RA risk factors in the PROAR included patients, both those with RA as well as those that did not develop the disease.

Sociodemographic characteristics

No significant differences were observed between the patients diagnosed with RA, no RA, and RA-overlap regarding age, gender, time since onset of symptoms, concomitant illnesses, schooling, social class, work situation, smoking, gynecological history, and number of transfusions (Table 1 and 2).

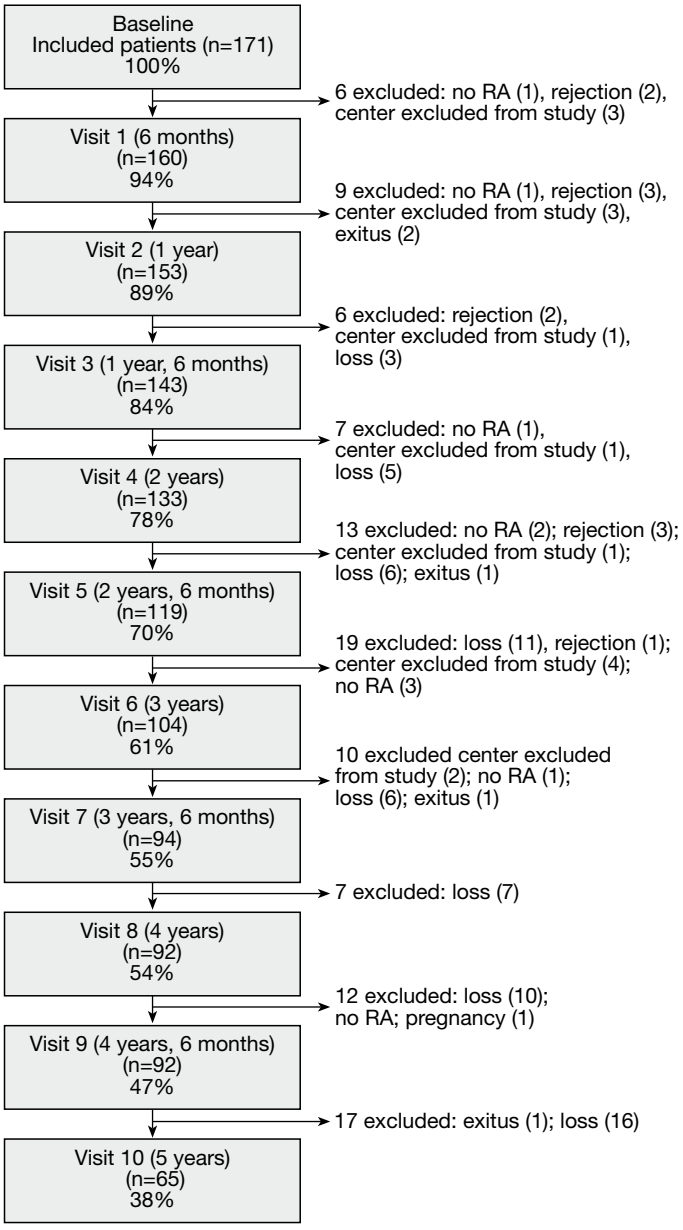

Figure. PROAR study flow chart. The visits carried out in each of the periods and patients abandoning the cohort after each visit are shown. In a given visit, patients that remained in the cohort could be more than the visits made by the patients because they did not come to some of their visits.

Clinical characteristics

Table 3 describes the baseline characteristics of the patients regarding activity and the functional affection of the disease. During the first visit 5 patients were identified with onset symptoms similar to polymyalgia and 1 with extraarticular manifestations who developed RA (4% of RA). Most of them began as polyartritis and one third were oligoarticular. The most common onset of disease was subacute (69%). Twenty-one point five percent of the patients who developed RA criteria had some form of extraarticlular manifestations in their baseline visit; the most frequent was the affection of the median nerve which led to carpal tunnel syndrome symptoms, followed by rheumatoid nodules. RF was more frequently positive in patients diagnosed with RA (53%) than among those who developed another disease (11.1%), with a statistically significant difference, in spite of a low number of patients without RA (P=.03). Patients included in the RA overlap group presented positivity for RF and higher titles than patients without the diagnosis of RA. The odds ratio (OR) of the relationship between positive RF and a diagnosis of RA is 8.5 (95% confidence interval [CI], 1–69.8). There were also significant differences regarding the RF titles which were higher in the group of patients diagnosed with RA. Anti-CCP also showed a relationship to the diagnosis of RA (OR=8.5; 95% CI, 0.96–75.7) and, therefore, are positive with greater frequency in patients with early RA and in those that initially complied with the criteria of another disease but that ended up being diagnosed as RA: RA-overlap (χ^2, P=.071). Sensitivity and specificity of anti-CCP and RF as predictive factors of RA were 63% and 83% and 52% and 88%, respectively, while

Table 1
Sociodemographic characteristics of patients at baseline

	RA	No RA	RA overlap	*P*
Current age, mean (SD), y	54 (15)	48 (19)	52 (12)	.369 [a]
Women	107 (71)	7 (70)	6 (55)	.502 [b]
Time since onset, mean (SD), mo	5 (3)	6 (3)	6 (3)	.935 [a]
Schooling				.831 [b]
No schooling	6 (4)	0	0	
Elemental or primary	83 (56)	5 (50)	7 (64)	
Secondary or professional non university	48 (32)	5 (50)	3 (27)	
University	11 (7)	0	1 (9)	
Social class				.579 [b]
Low	57 /42)	2 (22)	6 (55)	
Middle	68 (50)	6 (67)	4 (36)	
High	12 (9)	1 (11)	1 (9)	
Work situation [c]				.720 [b]
Working	55 (37)	4 (40)	6 (55)	
Retired	31 (21)	1 (10)	3 (27)	
Homemaker	39 (26)	3 (30)	0	
Unemployed	7 (5)	1 (10)	0	
Transitory work incapacity	13 (9)	1 (10)	2 (18)	
Permanent work incapacity	3 (2)	0	0	

Results are expressed as n (%) unless otherwise specified.
Abbreviations: RA, rheumatoid arthritis; SD, standard deviation.
[a] ANOVA test.
[b] χ^2 test.
[c] No students were found in the cohort.

Table 2
Risk factors for rheumatoid arthritis (RA) in the PROAR baseline visit and their distribution among patients who finally developed RA criteria or not

	RA	No RA	RA overlap	*P*
Smokers	56 (37)	4 (40)	6 (55)	.525 [a]
Past transfusions	12 (8)	1 (10)	0	.6 [a]
Family history of arthritis	21 (14)	1 (10)	2 (18)	.864 [a]
Only women				
Any pregnancy	88 (91)	5 (71)	6 (100)	.182 [a]
Number of pregnancies, mean (SD)	3 (2)	1 (1)	3 (1)	.368 [b]
Menarche, mean (SD), y	13 (2)	12 (2)	14 (2)	.929 [b]
Menopause, mean (SD), y	47 (8)	47 (4)	46 (7)	.256 [b]
Hormone replacement therapy	12 (18)	0	1 (20)	.646 [a]
Oral contraception	45 (45)	2 (33)	1 (17)	.352 [a]

Results are expressed as n (%) unless otherwise specified.
Abbreviations: RA, rheumatoid arthritis; SD, standard deviation.
[a] χ^2 test.
[b] ANOVA test.

the sensitivity and specificity of their combination (positive anti-CCP and positive RF) were 37.4% and 100%.

The number of swollen joints on the first visit, as well as DAS28 is also related with the diagnosis of RA. For every point on the DAS, the relationship clearly increases (OR=1.9; 95% CI, 1.1–3.3).

Most of the patients diagnosed as RA were initially found to be in functional class II (34%), followed in frequency by I and III (33% and 24%, respectively). Nine percent of patients with recent onset RA had functional class IV. The functional class was not statistically different between patients from the 3 groups.

Hand and feet x-rays were obtained in 111 patients during the baseline visit. Of those, 72 (65% of those with x-rays) presented at least 1 erosion. Patients with RA had a larger maximal erosion score in all of the joints of both hands and feet than those that did not develop RA, with a statistically significant difference in the case of the hands (*P*=.04). Regarding joint space narrowing of the hands and feet, it was also higher in patients with RA (*P*=.009 and *P*=.1, respectively). Patients in the RA overlap group presented more erosions than patients not diagnosed with RA, as well as a higher total radiological score, with a significant difference in the case of the erosions.

Discussion

Patients in PROAR form a representative sample of early onset arthritis in specialized rheumatology departments in Spain. This study considered recent onset arthritis as that which presents oligo or polyarthritis of less than 1 year since onset. It probably represents a slightly late onset of arthritis. Given the characteristics of the Spanish health system, known from the conclusions of the emAR study (variability in the management of RA study in Spain); only half of the patients that came to the rheumatologist through the emergency department had less than 5 months since onset of disease; the usual time is around 14 months since onset of RA before the patient is attended by a rheumatologist.[17] The effect of time since onset is reflected, on the other hand, by the high percentage of patients that comply with the RA criteria during the first visit or before one year. However, this percentage could be explained by the inclusion criteria used for this study, taking into account they were selected to include patients with the highest probability of progressing into RA; therefore, the number of patients classified in the group without RA and in the RA overlap group was small, a limitation of this study.

Other interesting data provided by PROAR regards the follow up of this type of patients. We have been able to prove how difficult it is to maintain a cohort for more than 2 years. Due to the elevated number of physicians implicated, it could not only be the influence of empathy between patients and physicians what achieves the goal of keeping the patient in the cohort, but the fact that it is probably related to the fact that the patients are still unaccustomed to the chronic nature of their disease.[18,19]

Tree variables have been observed which, after 1 year of symptom progression, allow for the discrimination or prediction of progression into RA, and these are activity at onset, as measured by DAS28, RF, and anti-CCP. These variables are precisely the ones that are being evaluated for their use in the new criteria by the European League Against Rheumatism (EULAR) for recent onset RA. These criteria, currently under development, originated from the recommendations for the early treatment of RA.[20] Although it is noticeable that in this series of patients, the specificity of anti-CCP, as a predictive factor of RA, was less than that of RF, in contrast to what has been described in the literature, it must be taken into account that several of the participating hospitals could not send the sample for determination of anti-CCP to the central laboratory, and therefore this could not be analyzed in all of the patients.

The description of the PROAR cohort allows us to describe the situation of early RA in Spain in a manner which is very similar to cohorts of patients with the same disease in other countries[21], which indicates that RA in our country is not more benign, as pointed out by other studies.[8] Single center, early RA studies in Spain do not support this impression of benignity of RA in our country.[22,23]

A relevant result of this description are the erosions observed during the first visit in up to two-thirds of patients. Even when the frequency of erosions varies a lot between the series, this data is in accordance with the time since onset of disease in our patients and with the frequency described in studies performed in other countries, which demonstrate the rapid radiological progression in patients with recent onset RA.[5,24–26]

In conclusion, both the extension of joint damage as well as a positive rheumatoid factor and anti-CCP antibodies, in our clinical context, are factors that allow us to predict that the progression of an oligo or polyarthritis of less than 1 year but more than 3 months progression, will result in RA. However, the radiological damage is found in almost two thirds of the patients by this time, making it evident that the most important element is a firm early treatment

Table 3
Clinical characteristics of the disease at baseline

	RA	No AR	RA overlap	*P*
Subacute onset of disease, n (%)	102 (68)	7 (70)	9 (82)	.631 [a]
Polyarticular onset, n (%)	104 (70)	5 (50)	7 (64)	.709 [a]
Positive rheumatoid factor, n (%)	77 (53)	1 (11)	4 (36)	.035 [a]
Rheumatoid factor, U/mL	178 (279)	31 (33)	146 (210)	.001 [b]
Positive anti-CCP (>25 U/mL), n (%)	58 (62)	1 (17)	5 (71)	.071 [a]
Pain (VAS, 0–100 mm from less to more)	55 (24)	52 (19)	57 (26)	.604 [b]
General activity through VAS 0–100 (patient)	55 (25)	49 (20)	54 (25)	.714 [b]
General activity through VAS 0–100 (physician)	50 (21)	44 (23)	54 (22)	.882 [b]
Number of swollen joints (of 28)	10 (5)	4 (3)	13 (8)	.017 [b]
Number of painful joints (of 28)	12 (6)	7 (5)	17 (10)	.073 [b]
Erythrocyte sedimentation rate, mm/first h	39 (27)	35 (23)	36 (31)	.722 [b]
C-reactive protein, mg/dL	4 (7)	4 (3)	1 (1)	<.001 [b]
DAS28	5.8 (1.1	4.9 (1)	6.1 (1.9)	.016 [b]
HAQ (0-3, from less to more)	1.4 (0.7)	1.2 (0.8)	1.1 (0.5)	.514 [b]
Functional class, n (%)				.63 [a]
I–II	101 (67)	6 (60)	6 (55)	
III–IV	49 (33)	4 (40)	5 (45)	
Joint space narrowing on the hands (0–120)	8 (6)	5 (5)	5 (2)	.009 [b]
Hand erosions (0–160)	2 (4)	1 (1)	2 (3)	.042 [b]
Joint space narrowing of the feet (0–48)	3 (3)	1 (1)	4 (2)	.116 [b]
Feet erosions (0–120)	0.7 (2)	0.4 (3)	0.4 (2)	.599 [b]
Total score (0–448)	14 (10)	9 (6)	12 (6)	.087 [b]

Results are expressed as mean (standard deviation) unless otherwise specified.
Abbreviations: DAS, disease activity score; HAQ, Health Assessment Questionnaire; RA, rheumatoid arthritis; VAS, visual analog scale.
[a] χ^2 test.
[b] ANOVA test.

than waiting to have a diagnosis of RA, at least with the data that we usually have in our clinics.

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References

1. Laffon Roca A. Artritis reumatoide. Epidemiología, etiopatogenia y manifestaciones clínicas. In: Manual SER de las Enfermedades Reumáticas. 4th ed. Madrid: Panamericana; 2004. p. 169.
2. Porter DR, Capell HA. The "natural! history of active rheumatoid arthritis over 3-6 months – an analysis of patients enrolled into trials of potential disease-modifying anti-rheumatic drugs, and treated with placebo. Br J Rheumatol. 1993; 32:463–6.
3. Abdel-Nasser AM, Rasker JJ, Valkenburg HA. Epidemiological and clinical aspects relating to the variability of rheumatoid arthritis. Semin Arthritis Rheum. 1997;27:123–40.
4. Emery P, Breedveld FC, Dougados M, Kalden JR, Schiff MH, Smolen JS. Early referral recommendation for newly diagnosed rheumatoid arthritis: evidence based development of a clinical guide. Ann Rheum Dis. 2002;61:290–7.
5. van Aken J, Lard LR, Le Cessie S, Hazes JM, Breedveld FC, Huizinga TW. Radiological outcome after four years of early versus delayed treatment strategy in patients with recent onset rheumatoid arthritis. Ann Rheum Dis. 2004;63:274–9.
6. Goronzy JJ, Matteson EL, Fulbright JW, Warrington KJ, Chang-Miller A, Hunder GG, et al. Prognostic markers of radiographic progression in early rheumatoid arthritis. Arthritis Rheum. 2004;50:43–54.
7. Pensec VD, Saraux A, Berthelot JM, Alapetite S, Jousse S, Chales G, et al. Ability of foot radiographs to predict rheumatoid arthritis in patients with early arthritis. J Rheumatol. 2004;31:66–70.
8. Ronda E, Ruiz MT, Pascual E, Gibson T. Differences between Spanish and British patients in the severity of rheumatoid arthritis: comment on the article by Drosos et al. Arthritis Rheum. 1994;37:147–8.
9. Drosos AA, Lanchbury JS, Panayi GS, Moutsopoulos HM. Rheumatoid arthritis in Greek and British patients. A comparative clinical, radiologic, and serologic study. Arthritis Rheum. 1992;35:745–8.
10. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31:315–24.

11. Alonso J, Pérez S, Saez M, Murillo C. Validez de la ocupación como indicador de la clase social, según la clasificación del British Registrar General. Gac Sanit. 1997;11:205–13.
12. van der Heijde DM, van 't Hof M, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumato- logists. J Rheumatol. 1993;20:579–81.
13. Balsa A, Carmona L, Gonzalez-Alvaro I, Belmonte MA, Tena X, Sanmarti R. Value of Disease Activity Score 28 (DAS28) and DAS28-3 compared to American College of Rheumatology-defined remission in rheumatoid arthritis. J Rheumatol. 2004;31: 40–6.
14. Esteve-Vives J, Batlle-Gualda E, Reig A. Spanish version of the Health Assessment Questionnaire: reliability, validity and transcultural equivalency. Grupo para la Adaptacion del HAQ a la Poblacion Española. J Rheumatol. 1993;20:2116–22.
15. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis Rheum. 1992;35: 498–502.
16. van der Heijde D, Dankert T, Nieman F, Rau R, Boers M. Reliability and sensitivity to change of a simplification of the Sharp/van der Heijde radiological assessment in rheumatoid arthritis. Rheumatology (Oxford). 1999; 38:941–7.
17. Hernández-García C, González-Álvaro I, Villaverde V, Vargas E, Morado IC, Pato E, et al. El estudio sobre el manejo de la artritis reumatoide en España (emAR) (II). Características de los pacientes. Rev Esp Reumatol. 2002;29:130–41.
18. Fernández Dapica MP, Herrero Manso M, Jiménez Muro M, González Crespo M, Valiente M, Méndez A, et al. Implantación y gestión de un programa de educación para la salud dirigido a pacientes y sus familiares con artritis reumatoide de inicio. Rev Esp Reumatol. 2004;31:320 [abstract 222].
19. Zeidler H, Merkesdal S, Hulsemann JL. Early arthritis and rheumatoid arthritis in Germany. Clin Exp Rheumatol. 2003;21:S106–12.
20. Combe B, Landewe R, Lukas C, Bolosiu HD, Breedveld F, Dougados M, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2007;66: 34–45.
21. Verpoort KN, van Dongen H, Allaart CF, Toes RE, Breedveld FC, Huizinga TW. Undifferentiated arthritis-disease course assessed in several inception cohorts. Clin Exp Rheumatol. 2004;22:S12–7.
22. Sanmarti R, Gomez A, Ercilla G, Gratacos J, Larrosa M, Suris X, et al. Radiological progression in early rheumatoid arthritis after DMARDS: a one- year follow-up study in a clinical setting. Rheumatology (Oxford). 2003;42:1044–9.
23. Richi P, Balsa A, Munoz-Fernandez S, Villaverde V, Fernandez-Prada M, Vicario JL, et al. Factors related to radiological damage in 61 Spaniards with early rheumatoid arthritis. Ann Rheum Dis. 2002;61:270–2.
24. Caruso I, Santandrea S, Sarzi Puttini P, Boccassini L, Montrone F, Cazzola M, et al. Clinical, laboratory and radiographic features in early rheumatoid arthritis. J Rheumatol. 1990;17:1263–7.
25. Brook A, Corbett M. Radiographic changes in early rheumatoid disease. Ann Rheum Dis. 1977;36:71–3.
26. van der Heijde DM, van Leeuwen MA, van Riel PL, Koster AM, Van't Hof MA, van Rijswijk MH, et al. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum. 1992;35:26–34.