Research article

Predictive factors for the progression of early inflammatory arthritis to rheumatoid arthritis

Rahal F[1], Chetouane R[1], Haid S[1], Bencheikh S[1], Ait Bellabes K[1], Megateli I[1], Azeli S[1], Teniou D[1], Gasmi A[1], Djidjik R[2], Allam I[2], Hannoun D[3], Brahimi N[1], Ladjouze-Rezig A[1], Hanni F[1]

[1]Rheumatology Department, EHS Ben Aknoun, Alger, Algeria
[2]Immunology Department, Beni Messous University Hospital Center
[3]National Public Health Institute

***Corresponding author**:*
Prof. Fadia Rahal, Professeur Agrégé en Rhumatologie
EHS Ben Aknoun,
Alger, Algérie. Email: ffadia_2007@yahoo.fr

Abstract

Objective: To identify factors predicting the progression of Early Inflammatory Arthritis (EIA) to Rheumatoid Arthritis (RA).

Design: This was a prospective longitudinal study.

Methods: Inflammatory rheumatism that could not be classified according to defined rheumatism criteria. Demographic, biological, immunological and radiographic data were collected at the time of inclusion in the study. Disease activity as determined by the Disease Activity Score 28-CPR (DAS28-CPR: 4 variables), functional handicap as calculated by Heath Assessment Score (HAQ), and bone and joint damage as evaluated by Sharp-Van der Heijde (SVDH) score. Ultrasound joint imaging were evaluated at the beginning of the study and then 1 year later. Logistic regression was performed to identify predictive factors for progression to RA.

Results: One hundred and seventy two patients were included (24 men, 148 women), with a mean age 43.13±14.07 years and a mean time to diagnosis 10.24±6.84 months. The mean ESR was 46.81±31.16 mm/1st hour, and the mean CRP level was 22.84±39.8 mg/l. Rheumatoid Factors (RFs) and Anti-Citrullinated Protein Antibodies (ACPAs) were present in 48.8% and 53% of patients, respectively. The erosion, joint space narrowing, and total SVDH scores were 3.38±3.48, 5.08±3.32, and 5.95±4.94, respectively. One hundred and sixty one patients were followed up for 12 months. Multivariate regression analysis showed that a DAS28-CRP level >5.2 (OR=28.6; CI 95% 8.7-94.5), an RF level >60 IU/L (OR=11.2; CI 95% 4.3-87.5), and an ACPA level >60 IU/L (OR=5.4; CI 95% 1.9-15.3) were predictive for progression to RA.

Conclusion: Our study suggests that clinical evaluation of EIA by DAS28-CRP from the time of diagnosis, as well as evaluating the presence of RA auto-antibodies, can predict progression to RA.

Key words: Early inflammatory arthritis, Rheumatoid arthritis, Predictive factors

Introduction

Early Inflammatory Arthritis (EIA) is a common reason for medical consultation. There is no single definition for EIA, and to date there are no tests or relevant diagnostic criteria that can predict progression to inflammatory arthritis. In addition, EIA can progress in very different ways from one patient to another, and disease progression therefore remains unpredictable. Some patients may experience transitory rheumatism that resolves spontaneously without treatment, while other patients develop chronic rheumatism with erosive or even destructive effects that can correspond to the beginning stages of Rheumatoid Arthritis (RA)[1]. Recent studies insist on the initiation of an early treatment of the RA as soon as it is diagnosed, giving more chance to its remission[2].

In Algeria, the estimated prevalence of RA is 0.13% to 0.15%[3]. The aim of this prospective study was to identify predictive factors for EIA progression to RA in an Algerian population.

Materials and methods

Patient selection: One hundred and seventy two consecutive patients with EIA who consulted a specialist over a period of 24 months were selected. EIA was defined by the presence of inflammatory polyarthralgia and/or

arthritis that had been developing for at least 6 weeks but less than 2 years. At the time of inclusion, none of these patients fulfiled the criteria for a defined inflammatory arthritis: RA, spondyloarthropathy, psoriatic arthritis, Sjogren's syndrome, polymyalgia rheumatica, lupus or other connective tissue disorders.

Clinical assessment: At the first visit, the rheumatologist completed a questionnaire regarding the presenting symptoms: demographic characteristics, detailed history and a complete clinical examination. The number of swollen and painful joints (out of 28 total joints) was determined, and the symmetric or asymmetric character of the arthritis, as well as the characteristics of the arthritis (progressive or sudden onset, affecting the upper and/or lower limbs, affecting the large and/or small joints) were noted. Visual Analogue Scales (VASs) were used for overall evaluation by the patient, as well as by the doctor. Grip strength and functional handicap were assessed using the Health Assessment Questionnaire (HAQ), and the duration of Morning Stiffness (MS) was recorded in units of minutes. Having a family history was defined as inflammatory arthritis in a first-degree relative. This study comprised patients who were referred from September 2014 to September 2016.

Biological assessment: The following blood tests were performed for all patients: blood count, hepatic and renal function tests, erythrocyte sedimentation rate (ESR: Westergren method), C- protein reactive level (CPR: by ELISA), markers of viral hepatitis, rheumatoid factors (ELISA), Anti-Nuclear Antibodies (ANA), and anti-CCP antibodies (ACPA: Inova Diagnostics, INC. United States).

Imaging: X-ray images of the hands and feet were taken for all patients at the time of inclusion, and then one year later in the same imaging facility. The Sharp method, as modified by van der Heijde (SVDH), was used to evaluate joint space narrowing and the number of erosions, as assessed by a single investigator[4]. X-rays of other joints were taken as needed based on clinical manifestations. In addition, thoracic and pelvic X-rays were taken for all patients, in search of pulmonary involvement and sacroiliitis. Ultrasound imaging of the metacarpophalangeal joints, the proximal interphalangeal joints, wrists, both hands, and both forefeet was performed for all patients at the time of inclusion and after one year, by a single experienced ultrasound technician (two years of practical experience). The ultrasound imaging of synovitis and erosion have been defined according to the OMERACT definition[5].

Follow-up: The patients were reviewed every three months up to one year. At each visit, all of the clinical variables described above were recorded.

Evaluation: After one year of follow-up, the patients were categorized based on the appropriate diagnostic criteria and/or classifications:

(i) RA as defined by the ACR/EULAR 2010 criteria for rheumatoid arthritis[6]
(ii) Gougerot-Sjörgen syndrome according to the SGS international diagnostic criteria established by the American European Consensus Group (AECG)[7]
(iii) Systemic lupus according to the American College of Rheumatology 1997 criteria[8]
(iv) Spondyloarthritis according to the ASAS criteria[9]
(v) Cutaneous sarcoidosis based on anatomo-histological analysis
(vi) Viral hepatitis based on positive viral serology
(vii) EIA was classified as persistent if, after one year of follow-up, it did not fulfil any of the defined criteria and still required symptomatic treatment (corticoids) and long-term treatment
(viii) EIA was classified as transitory if it did not fulfil any of the defined criteria but no longer required symptomatic and/or long-term treatment[6-9].

Statistical analysis: Statistical analyses were performed using SPSS version 18 software. Data are presented as mean±SD or percentage as appropriate. Comparisons between patients who developed or did not develop RA were performed by Student's *t*-test, Mann Whitney U-test, and Chi-square test for normally distributed, non-normally distributed and categorical variables, respectively. Variables found to associate with the development of RA were tested in a multivariate model using binary logistic regression analysis. Odds Ratios (ORs) and the corresponding 95% CI were calculated. $P < 0.05$ was considered to be statistically significant.

Results

This study included 172 patients. At the end of one year, 11 patients had been lost to follow-up; 161 completed the study. Of these 80 (49.6%) developed persistent inflammatory arthritis and of whom 68 (42.2%) progressed to RA, and 30 (18.6%) remained undifferentiated; 51 (42.2%) went into remission. Of 70 patients treated with methotrexate for EIA, 42 (60%) developed RA meeting the diagnostic criteria ACR-EULAR 2010[6].

The clinical, demographic and investigation results are shown in Table 1: The mean age at onset of EIA was 43.13±14 years, and the mean age at diagnosis was 10.24±6.84 months. There were 24 men and 148 women. For the majority of patients the onset of disease was under one year. More than half of the patients had one or more comorbidities. These were hypertension, 30 (17.4%); gastrointestinal events (epigastric pain or burning sensations) 15 (18.7%) patients; and type 2 diabetes 17 (10%) patients. The onset of symptoms was most often progressive (110 patients, 64%), with largely symmetric effects in 134 (77.9%) patients. At the time of inclusion in the study, the mean number of painful joints was six and the mean number of swollen joints was four, and arthritis of the ankle joint was found in a quarter of our patients [43 (25%) patients]. The mean DAS28-CPR score at the time of inclusion was 3.69, indicating moderate activity.

At the time of inclusion, the ESR for 159 patients was greater than 40 mm/h in half of the cases 84 (48.8%) patients, and out of 157 patients, 56 (32.5%) had a CRP level higher than 15 mg/l (cutoff value < 6 mg/l).

The presence of RFs was assessed in 161 patients and detected in 77 (44.76%) patients. ACPAs were found in 89 out of 166 (51.74%) patients.

Joint ultrasound was performed at the time of inclusion for 162 patients, and 38 (23.4%) had synovitis. The most frequently affected joints were the radiocarpal joint 63 (41%) patients and the radioulnar joint in 43 (28%) patients.

Ultrasound-detectable erosions were present from the beginning of the study in 30 (18.5%) patients. The most frequently affected joints were those of the hands, and interestingly, specifically the metacarpophalangeal joints, in 23 (76.6%) patients.

Bone and joint damage was noted in 67 (38.95%) patients at the time of their inclusion in the study. The SVDH at the inclusion for joint narrowing and bone erosion were respectively 3.38 ± 3.48 (1-18) and 5.08 ± 3.32 (1-14).

At the time of inclusion, from the 172 patients oriented by their treating physicians more than half 111 (64.5%) patients were immediately prescribed corticoids by the doctor at a mean dose of 4.86±2.8 mg/d, and 70 (41%) patients were prescribed methotrexate at a mean dose of 14.26±2.13 mg/d.

Table 1: Demographic, clinical, serological, radiographic and therapeutic characteristics of patients at inclusion (n=172)

Female patients, n (%)	148 (86)
Habitat, n (%)	
Urban habitat	133 (76.7)
Rural habitat	39 (22.7)
Start age (years), n (%)	
18-30	37 (21,51)
31-59	115 (66,86)
>60	20 (11,63
Time between symptom onset and diagnosis (months), n (%)	
< 6	65 (37,8)
6-12	82 (47,7)
> 12	25 (14,5)
Initial presentation[#], n = 171 (%)	
Monoarticular	26 (15,1)
Pauciarthritis	98 (56,9)
Polyarthritis	47 (27,3)
With professional activity, n (%)	59 (39.3)
Education[#], n = 171 (%)	36 (20.8)
High school	
Clinical presentation,	
NPJ, mean ± SD	5.96 ± 5.43 (0-28)
NSJ, mean ± SD	3.83 ± 3.83 (0-28)
MS (minutes), mean± SD	68.46 ± 55.47 (0-240)
Symmetric involvemment	134 (77.9%)
Localization initial joint symptoms	
Small articulation	69 (40.1%)
Large articulation	65 (32.6%)
Small and larg articulation	47 (27.3%)
Upper extremities	98 (57%)
Lower extremities	33 (19.2%)
Upper and lower extremities	41 (23.8%)
Unkle articulation	43 (25%)
VASs (millimetres), mean ± SD	
Patient	40.66 ± 20.61 (0-100)
Doctor	30.07 ± 20.03 (0-80)
DAS 28-CPR[##], mean ± SD	3.69 ±1.06 (1.36-7.74)
HAQ, mean ± SD	1.73 ± 0.82 (0-3)
Biological presentaion	
ESR [###]	46.81 ± 31.16 (3-148)
CPR [####]	22.84 ± 39.8 (0-348)
Auto immunity	
FRs positivity [#####]	77 (44,7)
ACPAs positivity [##]	89 (51)
Radiographic presentation	
Osteoaticular damage (erosion and/ or pincement) [######]	67 (38,9)
Therapy	
Corticoids	111 (64.5%)
Methotrexate	70 (40.7%)
Hydroxychloroquine	26 (15.1%)
Sulfasalazine	2 (1.2%)

ACPAs = Aanti-citrullinated protein antibodies; ESR = Erythrosedimentation rate; RFs = Rheumatoid factors; MS = Morning stifness ; NPJ = Number of painful joint; NSJ = number of swollen joint; VAS = Visual analogic scales; DAS 28-CPR = Disease activity score c protein reactive # data available for 171 patients; ## data invailable fore 166 patients; ### data invailable for 159patients; #### data available for 157patients;, ###### data available for 161 patients

Factors associated with the onset of RA after one year of evaluation (Table 2): In the 68 (42.23%) patients who developed RA at one year we looked for clinical, biological factors and radiological features present at the time of inclusion which might predict progression from EIA to RA.

Ankle involvement was present at onset in 41 patients and 25 (61%) developed RA (p=0.005). This risk was more than 2.7 times higher than in patients without ankle involvement (p=0.006). The VAS pain scores noted by the patient and the doctor were higher in patients who developed RA (p=0.011 and p=0.005, respectively). The number of painful and swollen joints present at the beginning of the disease was higher in RA+ patients, and this difference was significant (p <10^{-3}).

The mean HAQ score at the onset of symptoms was higher in patients who went on to develop RA (2.03±0.76 for RA+ patients versus 1.69±1.17 for RA- patients). The risk of developing RA increased 2.5 times with each unit increase in HAQ score.

There was a very significant association between the Disease Activity Score (DAS28) at the onset of symptoms and the risk of developing RA. It seems that the higher the score is, the greater the associated risk, as, out of 11 patients with a DAS28 score >5.2, 8 (72.7%) developed RA (p<10^{-3}). The risk of developing RA is also associated with the duration of Morning Stiffness (MS). The longer the duration, the higher the risk of developing RA. Out of 46 patients who had an MS duration <30 minutes, 12 (26.1%) developed RA, versus 10 (71.4%) of the 14 patients who had an MS duration >120 minutes (p=0.016).

According to our results, the ESR is not associated with the risk of developing RA; however, there was a significant association between the CRP level at the onset of symptoms and the risk of developing RA. Out of 56 patients who had a CRP level ≥15 mg/l at the time of inclusion, 32 (57.1%) developed RA (p=0.001). This risk was twice as high for all patients who had a CRP level >6 mg/l compared to patients with a CRP level <6 mg/l.

There was a very significant association between the RF level and the risk of developing RA. Out of 55 patients who had a level three times the normal value (>60 IU/l), 40 (72.7%) developed RA (p<10^{-3}). This risk was seven times higher in patients who had a level between 20 and 60 IU/L and 11 times higher in patients with levels greater than 60 IU/L compared to patients with levels <20 IU/L.

There was a similar association between the ACPA level and the risk of developing RA. A level 3 times the normal value (>60 IU/l) was observed in 73 patients, of whom 54 (74%) developed RA (p<10^{-3}). The risk was 18 times higher in patients with a level between 40 and 60 IU/L and 47 times higher in patients with a level higher than 60 IU/L compared to patients with levels <20 IU/L. Finally, the mean value of the SVDH score (erosion, joint space narrowing, total) was significantly higher at the time of inclusion in patients who developed RA .

Table 2: Characteristics of patients who developed or did not develop RA after one year (univariate analysis)

Baseline charactéristics (T0)		RA + (n=68)	RA - (n=93)	P value
VAS (Doctor) mm	(mean ± SD)	30.64 ± 20.23	20.72 ± 10.81	0.005*
VAS (patient) mm	(mean ± SD)	50.29 ± 20.89	40.23 ± 20.89	0.011*
Squeeze test hands+	(mean ± SD)	55 (48.2)	59 (51.8)	0.016**
Squeeze test foots +	(mean ± SD)	36 (51.4)	34 (48.6)	0.038**
Ankle + NPJ	n (%)	25 (61)	16(39)	0.005**
	(mean ± SD)	7.56 ± 5.74	4.58 ± 4.4	<10^{-3*}
NSG	(mean ± SD)	5.68 ± 4.56	2.69 ± 2.64	< 10^{-3*}
DAS 28-CPR > 5.2	n (%)	8 (72.7)	3 (27.3)	<10^{-3**}
MS > 60 minutes	n (%)	13 (46.4)	15 (53.6)	0.016**
HAQ	(mean ± SD)	2.03 ± 0.76	1.69 ± 1.17	0.005*
CPR > 15 mg/l.	n (%)	32 (57.1)	24 (42.9)	0.001**
FR > 60 UI/L	n (%)	40 (72.7)	15 (27.3)	<10^{-3**}
ACPA > 60UI/L.	n (%)	54 (74)	19 (26)	<10^{-3**}
OAD #	n (%)	34 (50.7)	33 (49.3)	0.05**
Erosion Score SVDH.	(mean ± SD)	1.94 ± 3.72	0.93 ± 2.11	0.034*
Pincement Score SVDH	(mean ± SD)	2.47±3.8	0.91 ± 2.16	0.001*
Total Score SVDH	(mean ± SD)	4.41 ± 6.25	1.85 ± 3.6	0.001*

* Student test; ** Chi-square test; SD = Standard deviation

ACPAs= Anti-citrullinated protein antibodies; CPR = C-Protéine reactive; RFs = Rheumatoid factors; VASs = Visual Analogue Scales; DAS28-CPR; disease activity score c-proteine réactive; HAQ = Health assesment questionnaire; NPS = Number of painful joint; NSJ = Number of swollen joint; MS = Morning stifness ; OAD = Osteoarticular damage; SD = Standard deviation; SVDH score = Sharp Van der Heidje score. mm = Milimetres

Table 3: Main variables associated with RA diagnosis (multiple logistic regression)

	Odds Ratio [CI 95%]	P value
DAS28-CPR > 5.2	28.6 [8.7 - 94.5]	$<10^{-3}$
ACPAs > 60 UI/L	5.4 [1.9 – 15.3]	0.01
RFs > 60 UI/L	11.2 [4.3 – 87.5]	$<10^{-3}$

ACPAs = Anti-citrullinated protein antibodies; CI = Confidence interval; DAS28-CPR = Disease activity score c proteine reactive; RFs = Rheumatoid factors

Multivariate analysis: At the end of the univariate analysis, the logistical regression (Table 3) showed that the predictive factors for EIA progression to RA are markers of activity, including a DAS28 score >5.2, and immunological markers: an elevated ACPA level (>60 IU/L), and an elevated RF level (> 60 IU/L).

Discussion

Studies of early arthritis evolving to RA have evaluated many different variables, notably arthritis persistence[10], functional capacity[11], and/or structural progression[12]. The primary difficulty that arises when comparing studies is the variety of definitions used for early arthritis. For example there is no agreed duration of symptoms used to define EIA: in most cohort studies it ranges from 16 weeks to 36 months[13,14].

In our study with an upper limit was 2 years, 75% of patients recorded a duration of one year or less. We therefore believe that this is an acceptable cohort to study the evolution of EIA.

Differences in the characteristics of our cohort include a younger age, 43 years mean compared to well over 50 years[11,15] and a longer time to diagnosis at 10 months compared to the 2-4 months in most other studies[14,15]. Concerning clinical presentation, involvement of the small joints during EIA was observed in more than 60% of our patients similar to the Leiden cohort[16] and symmetrical involvement was observed in two thirds of our patients, compared to 46.5% of the Rooy cohort[17].

At study entry the mean DAS28-CRP score was 3.69, indicating moderate activity, while Bedran *et al.*[18] observed a more intense disease activity with a DAS28 score of 5.2. This difference was almost certainly due to high proportion of patients (60%) on corticosteroid medication at the time of entry. The inflammatory marker readings (ESR CRP) tended to be higher than in other studies. RFs were present in 44.7% of our patients, which is similar to the results reported by van Aken e*t al*.[19], but lower than those reported for other series: 24.6% in the Rooy cohort.

Several observational cohorts of patients with EIA have shown that, depending on the inclusion criteria 13% to 59%[14,20] of patients progress to RA , while 21% to 87% remain as Undifferentiated Arthritis (UA)[14,21].

Our results were well within these limits. Of the 161 patients who completed the study 68 (42.2%) at one year had progressed to RA, and 30 (18.6%) remained undifferentiated. Since the new ACR-EULAR 2010 classification criteria for RA were introduced[6], UA seems to be more benign and occur less frequently, because the new criteria allow some forms of arthritis to be classified as RA that until now were considered to be UA. A new emphasis on early diagnosis and care for patients with RA has altered the natural progression of the disease.

Many predictive factors for EIA persistence have been identified, such as female sex[17,22], those with long disease duration[10,17,23], high disease activity with high number of involved joint[17,22], increased levels of acute phase reactants[17], high disability score[24,25] and the presence of erosions[12]. In addition, the presence of ACPA and RF are consistently found to be important determinants of persistent disease[10,17,23].

Many models have been developed to predict EIA progression to RA, and the Dutch developed a predictive score for RA development based on the Leiden cohort[10,26]. Using the same approach, the Egyptian study conducted by El Miedany *et al*[24] identified three independent variables associated with EIA progression to a chronic condition: duration of morning stiffness, change in HAQ score after three months of follow-up, and the presence of ACPA.

In our study, clinical variables such as the NPJ, the NSJ, the squeeze test and morning stiffness, were identified as predictive factors for developing RA in agreement with others[24,26,27]. However, unlike van der Helm-van Mil *et al.*[26] study we did not find any significant association between the risk of developing RA and the localisation of the affected joints at the onset of symptoms, notably the upper or lower extremities (p=0.53),

Markers of disease activity and severity, including a DAS28 score >5.2, an elevated level of ACPAs (>60 IU/L), and an elevated level of RFs (> 60 IU/L) and a high CRP (>6mg/l) were all predictive for developing RA .

Finally, similar to van der Helm-van Mil *et al.*[26] study, the presence of bone and joint damage from the time of onset doubled the risk of developing RA.

Study limitations and strengths

The main objective of this work was to identify patients who will develop proven RA and who, therefore, require rapid management. This work is the first in Algeria with different socio-cultural-and genetic backgrounds as well with probably differences in health systems.

One limitation of our study is the duration of follow-up which if extended might see more undifferetiated cases progressing to an identifiable entity such as RA. Another limitation is the inclusion of patients already undergoing treatment, with disease modifying agents such as corticosteroids and methotrexate can modify the inflammatory process and change the course of the disease. However, this is unavoidable in a setting where there is an urgency to implement early treatment of RA.

Conclusion

This study, similar to other international studies, identified predictive factors for EIA progression to RA, including markers of disease activity and severity such as a DAS28 score >5.2, elevated ACPA levels (>60 IU/L), and elevated RF levels (> 60 IU/L), which effectively predict this progression. Future studies with longer follow up are needed to identify more risk factors to develop RA in this population.

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