10-year experience of early arthritis clinic at a tertiary rheumatology center: achievements and challenges

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ABSTRACT

Objectives: To characterize patients evaluated in our Early Arthritis Clinic (EAC) in the first ten years; to assess diagnostic delay and its underlying causes; and to evaluate the level of agreement between the referring physician and the rheumatologist regarding the presence of referral criteria.

Methods: Cross-sectional study including patients attending EAC between 2012 and 2021. Demographic data, provenience, final diagnosis, referral criteria and time related to diagnosis delay were retrieved from clinical files and the Portuguese Registry of Rheumatic Patients (reuma.pt). Characteristics of the patients and the time variables were analysed with descriptive statistical analysis. The agreement between the referring physician and rheumatologist regarding the referral criteria was evaluated using Cohen's Kappa.

Results: A total of 440 patients (68.9% females, mean age of 54.0±16.7 years) were referred, mostly from primary care (71.6%). Inflammatory Rheumatic Disease was diagnosed in 65.7% of the patients, with 58.9% classified as early arthritis. The median time from onset of symptoms to referral for EAC was 76 days (IQR 33.5-144.0); the median time from referral to the first EAC was 34 (IQR 19.0-46.0) days, and the median time from onset of symptoms to first EAC was 114.5 (IQR 66.8-190.3) days (16.3 weeks). Only about 10% were observed by a rheumatologist within the first six weeks following the onset of symptoms. The level of agreement between the referring physician and the rheumatologist was slight to fair to clinical criteria (Cohen´s Kappa 0.09-0.29) and moderate to substantial to laboratory criteria (Cohen´s Kappa 0.43-0.62).

Conclusions: Patients with suspected early arthritis experience significant diagnostic delay, with the time elapsed between symptom onset and referral identified as a major contributor. A low agreement between referral and rheumatologists suggests that non-rheumatologists education/training is needed. Identifying the barriers that prevent the adequate referral of patients is necessary to define strategies to improve it.

Keywords: Early arthritis; Early arthritis clinic; Referral criteria; Diagnostic delay; Medical education

INTRODUCTION

Inflammatory arthritis is a distinctive feature of rheumatic diseases, such as rheumatoid arthritis (RA), spondylarthritis and connective tissue diseases[1], all of them leading to high impact in several domains of patients´ lives, resulting in poor quality of life, high social and individual costs and increased mortality.

There is strong evidence, particularly in RA, that the early commencement of disease-modifying antirheumatic drugs can reduce or suppress the inflammatory process, minimize joint destruction and improve overall quality of life. This supports the concept that there is a critical "window of opportunity" in the early phases of these diseases, if we aim to effectively change their natural history and prevent disability in the long term[2]. Therefore, the early recognition of patients with suspected inflammatory arthritis and their referral to rheumatologists plays a crucial role in optimizing patient outcomes.

The European League Against Rheumatism (EULAR) recommendations for the management of early arthritis (EA), advocate that these patients should be "referred and seen" by a rheumatologist within six weeks after symptom onset[3]. However, several studies have shown a wide range of delays since symptom onset and demonstrate that only a minority of these patients is treated in less than 12 weeks, wasting the optimal "window of opportunity"[4–7]. Several factors contributing to this delay at different levels have been identified and different strategies have been implemented[8,9].

In the early 90´s, Early Arthritis Clinics (EACs) were established in leading Rheumatology Departments, promoting faster appointments for patients with suspected early synovitis. EACs facilitate interaction with Primary Care, establish referral guidance and protocols and promote educational programs for General Practitioners (GPs). EACs have strongly contributed to earlier diagnosis and improved outcomes in these patients[10,11].

In 2012, the EAC of the Rheumatology Department at Centro Hospitalar e Universitário de Coimbra was implemented to pursue these objectives with dedicated rheumatologists and nurses. Specific referral criteria were defined and widely disseminated among primary care physicians.

In this publication, we characterize the patients referred to the EAC in the first ten years and assess diagnostic delay and its underlying causes. The level of agreement between the referring physician and the rheumatologist, regarding the presence of referral criteria, was also evaluated, as a means to ascertain the need for further education in patient evaluation.

METHODS

Study design and population

Cross-sectional study including consecutive patients referred and observed in the EAC at the Rheumatology Department of Centro Hospitalar e Universitário de Coimbra, in the first ten years of its existence, between 2012 and 2021. This study was conducted in agreement with the principles of the Declaration of Helsinki. All patients signed the Portuguese Registry of Rheumatic Patients (Reuma.pt) informed consent before inclusion.

Referral criteria and Early Arthritis Clinic characterization

The referral criteria comprise a combination of clinical and laboratory parameters with less than 12 months duration (Figure 1): criteria A (arthritis); or ≥ 2 Criteria B (clinically suspected arthralgia); or ≥ 1 Criteria B and ≥ 1 Criteria C (suspicious laboratory alterations); and Criteria D (onset of symptoms < 12 months ago). All patients are observed following a structured protocol that includes rigorous clinical assessment, patient-reported outcomes and ultrasound assessment.

Data source, outcomes, and patient assessments

Individual medical records and the electronic database of the cohort were reviewed. Individual patient characteristics assessed included demographic data (gender, age), referral source (primary care, other hospital specialities or other rheumatologists), final diagnosis and referral criteria (clinical and laboratory parameters described in Figure 1 - inflammatory arthralgias, arthritis, morning stiffness > 30 minutes, positive squeeze test, C-reactive Protein [CRP] >0.5mg/dL, Erythrocyte Sedimentation Rate [ESR] >20mm/h, Rheumatoid Factor [RF] ≥ 60UI/mL and anti-citrullinated peptide antibody [ACPA] ≥10U/mL). Inflammatory arthralgia was defined as a joint pain that exhibits inflammatory characteristics (improves with movement, worsens with rest, is more intense in the morning, and is associated with morning stiffness lasting more than 30 minutes). On the other hand, arthritis is defined by one or more joints with elastic swelling during clinical examination[12]. If there is uncertainty regarding the presence of arthritis after clinical examination, a musculoskeletal ultrasound was performed. Other autoimmunity lab tests requested by the rheumatologist, based on the clinical manifestations, were also collected, e.g. leukocyte antigen [HLA] B27, antinuclear antibodies [ANAs], anti-double-stranded DNA [anti-dsDNA] and/or extractable nuclear antigens [ENAs]. These last lab tests were not

routinely requested for all patients attended at EAC; only when considered clinically indicated by the attending rheumatologist.

According to the definitive diagnosis, patients were split into two groups: inflammatory rheumatic disease (IRD) and non-inflammatory rheumatic disease (NIRD). Patients with IRD and symptoms for less than 12 months were classified as having early arthritis (EA).

The time from symptom onset to diagnosis was assessed in the subgroup of patients with early arthritis, considering the following time-intervals: (1) Time from the onset of symptoms to the referral for EAC; (2) The time from referral to the first visit to EAC; (3) The time from the onset of symptoms to the first visit to EAC and (4) Time between onset of symptoms and final diagnosis. Patients were excluded if the referral request or the medical records from the first visit to the EAC were not available or if they had a previous IRD diagnosis.

Statistical analysis

Descriptive statistical analysis was conducted to characterize patients referred to EAC and evaluate time intervals related to diagnosis delay. Continuous variables were described as mean and standard deviation (SD) or median and interquartile range (IQR), according to distribution. Categorical variables were expressed as absolute frequencies and percentages. The agreement between the referring physician and the rheumatologist in the first EAC visit regarding the presence/absence of the referral criteria was assessed using Cohen's Kappa[13]: values ≤ 0 were interpreted as indicating no agreement, 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41– 0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement. All analyses were performed using IBM SPSS Statistics, version 26.0.

RESULTS

The total number of patients observed in EAC

In total, 440 patients (68.9% females, with a mean age of 54.0±16.7 years) were included. Most of them were referred from primary care (71.6%), the remaining ones being split between other hospital specialities (13.6%) and other rheumatologists (14.8%).

Clinical and Analytical Characteristics

At the first assessment in the EAC, according to the evaluation by the rheumatologist, most of these patients presented inflammatory arthralgias (N=363/440; 82.5%), arthritis (N=233/440; 53.0%) and/or morning stiffness > 30 minutes (N=266/402; 66.2%). A positive squeeze test was present in 40.3% (N=136/337) of patients. Regarding laboratory criteria, CRP>0.5mg/dL and ESR >20mm/h were observed in 53.9% (N=237/440) and 50.2% (N=221/440) of the cases, respectively. Concerning autoimmunity, RF was identified in 25.2% (N=108/429) and ACPA in 21.6% (N=90/416). Other autoimmunity lab test requests, when clinically indicated, include HLA-B27 (N=10/57; 17.5%), ANAs (N=207/383; 54.0%), Anti-dsDNA (N=9/355; 2.5%) and ENAs (N=19/382; 5.0%) (Supplement).

Final Diagnoses

The most common final diagnoses of patients referred to the EAC (Table I) include RA (N=138/440; 31.4%), Osteoarthritis (N=46/440; 10.5%), Spondylarthritis (N=45/440; 10.2%) and Fibromyalgia (N=45/440; 10.2%). IRD with arthritis was diagnosed in 289 (65.7%) of all referred patients, of whom 259 (58.9%) had the disease for less than 12 months (Figure 2).

Diagnostic delay for EA patients

Considering the subgroup of patients with EA, the median time from onset of symptoms to referral for EAC was 76 (IQR 33.5-144.0) days; the median time from referral to the first EAC was 34 (IQR 19.0-46.0) days, and the median time from onset of symptoms to first EAC was 114.5 (IQR 66.8-190.3) days (~16.3 weeks). Only 10% (N=26/259) of EA patients satisfied the EULAR recommendations to visit a rheumatologist within 6 weeks after symptom onset. The median time from onset of symptoms to diagnosis was 137 (IQR 74-258) days (Figure 2).

Level of agreement regarding the presence of referral criteria of patients observed in EAC

The level of agreement between the referring physician and the rheumatologist regarding the presence of referral criteria (Table II) was slight to fair regarding clinical criteria (Cohen´s Kappa 0.09 – 0.29) and moderate to substantial with laboratory criteria (Cohen´s Kappa 0.43 – 0.62).

DISCUSSION

Our study shows that about two-thirds of patients (66%) referred to EAC had IRD, and 59% were confirmed to have EA. In these patients, the median time elapsed between symptom onset and diagnosis was 137 (IQR 74-258) days. Most of this delay was from the onset of symptoms to the referral. This period includes (1) patient delay, the time from the onset of symptoms till reporting to a physician, and (2) physician delay, i.e. from consulting a physician to referral to a rheumatologist[14,15]. Several studies show that these two levels are, commonly, the most relevant to the overall delay in EA diagnosis[5,7,14–18]. The date of presentation to primary care was unavailable; therefore, we cannot evaluate these two components separately. The Hospital delay, defined as the time from referral to rheumatology appointment, was 34 (IQR 19-46) days. This is a relatively shorter delay compared to other similar studies. Specifically, a Canadian cohort had a Hospital delay of 66 (IQR 18-84) days[19], while a Spanish cohort had a delay of 3.6±5.8 months[7].

Among patients with EA, the time from symptoms onset to the first EAC visit was 16.4 weeks, with 90% being referred after 6 weeks of symptoms onset. The average time between symptom onset to the first visit to a rheumatologist varied significantly in different European studies, being higher than the 6 weeks in all of them[21]/01/2024 17:15:00 A study across 10 European centers[5] found a median delay of 24 weeks; and in a UK cohort[15], the median delay was 27.2 (IQR 14.1-66) weeks. A French cohort[16] had a mean delay of 76 days (~10.6 weeks), and a Spanish cohort[7] of 10.2±12.7 months (~40.8 weeks). In the same French cohort, 46.2% of patients were seen by a rheumatologist within the EULAR-recommended time frame. The most significant contributor to the overall delay (the patien[5,7,18] vs. the physician[14,15]) varies among different studies. Studies designed to identify the underlying reasons and implement adequate corrective measures are needed.

Unfortunately, we are unable to separately assess the patient's and the GP's contribution to the delay in referring to the EAC, and the reasons underlying each. In our cohort, 76% of patients were referred from primary health care. GPs play a key role in identifying patients with inflammatory arthritis, as they typically serve as "gatekeepers" for rheumatologists, being the first contact with the health system for about 90% of patients[9]. Several reasons have been

reported to justify the delay in referral to rheumatology[20–26]. The most common reason is the low confidence in identifying inflammatory arthritis, particularly if the presentation is rather atypical or there is no clear evidence of swollen joints. Additionally, GPs tend to value laboratory tests more than their clinical view, preferring to wait for blood tests before referring patients or leading to no referral if negative[19,21,25]. The poor agreement observed in our study, particularly regarding clinical referral criteria, reflects such difficulties.

Furthermore, 34.6% of patients referred to EAC do not have an IRD. This is consistent with results from other EACs[11,27] and probably reflects the uncertainty in the evaluation by the GP. This could lead to an overload in EAC and impair the timely observation of patients with EA, but probably this is not far from the ideal: a percentage of IRD close to 100% would certainly mean that many patients with a reasonable probability of inflammatory disease had not been referred to a rheumatologist.

There are several strengths to this study. To our knowledge, it is the first Portuguese study that characterizes the experience of an EAC and analyzes diagnosis delay in EA patients. Additionally, it is based on a formalized cohort that covers a period of 10 years and involves the training of GPs, presenting real-world cases found in clinical practice.

Nevertheless, our results should be interpreted in light of some limitations. First, although the sample after 10 years is substantial, it is not a large cohort. The information regarding the description of the initial clinical presentation (in particular, the date of onset of symptoms) depended on patient recall. Several referral requests only highlighted positive parameters, but it was not clear whether the unreported parameters were negative or had not been evaluated. In these cases, the parameters were treated as missing. This factor may have influenced the results regarding the agreement between the rheumatologist and the referring physician. Lastly, the date of presentation to primary care was not available. Consequently, it was not possible to separately assess the patient delay and the physician delay and explore their major determinant. This knowledge would be crucial to guide education strategies (GPs vs. population) and must be included in future studies.

Our study has important implications for clinical practice. Despite the strategies implemented over the last 10 years to raise awareness of the importance of timely referrals and remove some of the bureaucratic obstacles, we still observe a long delay before the first assessment of patients with EA by a rheumatologist. The implementation of other strategies such as continuous medical education through workshops, training in rheumatology (particularly training courses for specialized GPs), joint consultation, tele-clinic and distribution of educational material, and improvement the communication between EAC and GPs may contribute to the quality of referral and in appropriate time of patients with EA. Even more,

continuous application and the regular evaluation of the efficacy of such strategies can contribute to a better referral of patients with EA. Although GPs are the main target of such measures, other non-rheumatologist health professionals, with common contact with patients with musculoskeletal symptoms should be made aware of the importance of early referral of patients with arthritis.

Various public awareness programs were proposed to promote education on rheumatic diseases, particularly inflammatory diseases, through various means such as public websites, television advertising campaigns, and mobile units[28–30]. However, there is insufficient data to evaluate the efficacy of these strategies in reducing patient delay[9,31]. A community active health-fair screening approach, combining the Connective Tissue Disease Screening Questionnaire and antibodies testing (RF and ACPA), was developed in Colorado (USA), demonstrating clinically useful diagnostic accuracy for detecting inflammatory arthritis/RA[32]. Further research is necessary to validate these findings and determine their applicability and effectiveness in diverse populations and healthcare settings.

Given the significant number of patients referred to the EAC without IRD, potential modifications to our referral protocol may be considered to optimize the referral process, ensuring timely and appropriate care for patients with inflammatory arthritis. Firstly, in light of the results of this study, we will review the referral protocol considering the elimination of the items with the lowest agreement. Additionally, we recognize the need for increased efforts to strengthen educational initiatives for GPs. The implementation of a feedback mechanism could provide GPs with insights into referral outcomes, pinpointing aspects for improvement. For complex cases, the integration of a telemedicine triage system, enabling rheumatologists to remotely assess referred cases, could prove advantageous in assessing the likelihood of inflammatory arthritis before scheduling in-person appointments. Furthermore, providing GPs with decision support tools, such as algorithms or online platforms, could assist them in systematically evaluating patients with joint complaints and making more informed referrals.

CONCLUSION

In conclusion, this assessment of our EAC activity over 10 years highlighted some constraints and problems in the adequate and timely referral of patients with EA. It constitutes an important tool for defining and implementing strategies to allow the evaluation of these patients and implementation of appropriate treatment within the "window of opportunity", contributing to a better prognosis.

Tables and Figures

Table I. Final diagnoses of patients observed in the Early Arthritis Clinic

Final Diagnosis	N (%)
Inflammatory rheumatic disease	**289 (65.7)**
Rheumatoid arthritis	138 (31.4)
Spondylarthritis	45 (10.2)
Connective tissue disease	33 (7.5)
Microcrystalline arthritis	29 (6.6)
Unclassified arthritis	20 (4.5)
Polymyalgia rheumatica	15 (3.4)
Sarcoidosis	4 (0.9)
Palindromic rheumatism	3 (0.7)
Paraneoplastic arthritis	2 (0.5)
Non-inflammatory rheumatic disease	**151 (34.3)**
Osteoarthritis	46 (10.5%)
Fibromyalgia	45 (10.2%)
Unspecific arthralgias	24 (5.5%)
Periarticular Condition	22 (5.0%)
Carpal Tunnel Syndrome	7 (1.6%)
Other diagnoses	7 (1.6%)
Total	**440 (100%)**

Table II. Agreement between the referring physician and the rheumatologist regarding the presence of each of the seven criteria.

	Cohen´s Kappa (CI 95%)	Strength of agreement
Inflammatory arthralgias (n=381)	**0.09 (0.09-0.10)**	**Slight**
Arthritis (n=354)	**0.29 (0.00-0.00)**	**Fair**
Morning stiffness >30min (n=291)	**0.22 (0.00-0.00)**	**Fair**
Squeeze test (n=211)	**0.07 (0.33-0.34)**	**Slight**
Elevated C-reactive Protein (n=335)	**0.46 (0.00-0.00)**	**Moderate**
Elevated Erythrocyte Sedimentation Rate (n=339)	**0.43 (0.00-0.00)**	**Moderate**
Positive Rheumatoid Factor (n=275)	**0.62 (0.00-0.00)**	**Substantial**

The analysis included 440 patients (total number of referred patients). Parameters not mentioned in the referral request, were treated as missing. This explains the n<440 in all parameters.

REFERRAL CRITERIA

(A) ≥1 joint with elastic swelling

Yes □ No □

(B1) Morning stiffness >30 minutes

Yes □ No □

(B2) Inflammatory arthralgias of the hands and/or feet

Yes □ No □

(B3) Squeeze test MCF positive

Yes □ No □

(B4) Squeeze test MTF positive

Yes □ No □

(C1) ESR >20 mm/h

Yes □ No □

(C2) CRP >0.5mg/dl

Yes □ No □

(C3) RF ≥ 60UI/ml

Yes □ No □

(C4) ACPA ≥10U/ml

Yes □ No □

(D) Onset of symptoms < 12 months ago

Yes □ No □

WHO TO REFER?

Patients who have

• CRITERIA A (Arthritis)

or

• ≥ 2 CRITERIA B (Clinically suspected arthralgia)

or

• ≥ 1 CRITERIA B and ≥ 1 CRITERIA C (Suspicious laboratory alterations)

AND

• CRITERIA D

Figure 1. Referral criteria for Early Arthritis Clinic in the Department of Rheumatology of Centro Hospitalar e Universitário de Coimbra

ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive Protein; FR: Rheumatoid Factor; ACPA: anti-citrullinated peptide antibody

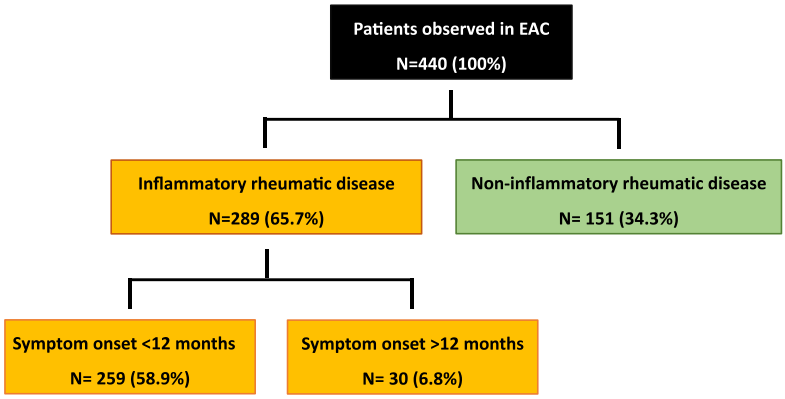

Figure 2. Overview of patients observed in Early Arthritis Clinic regarding the correct identification of Inflammatory Rheumatic Disease and time from onset.

EAC: early arthritis Clinic

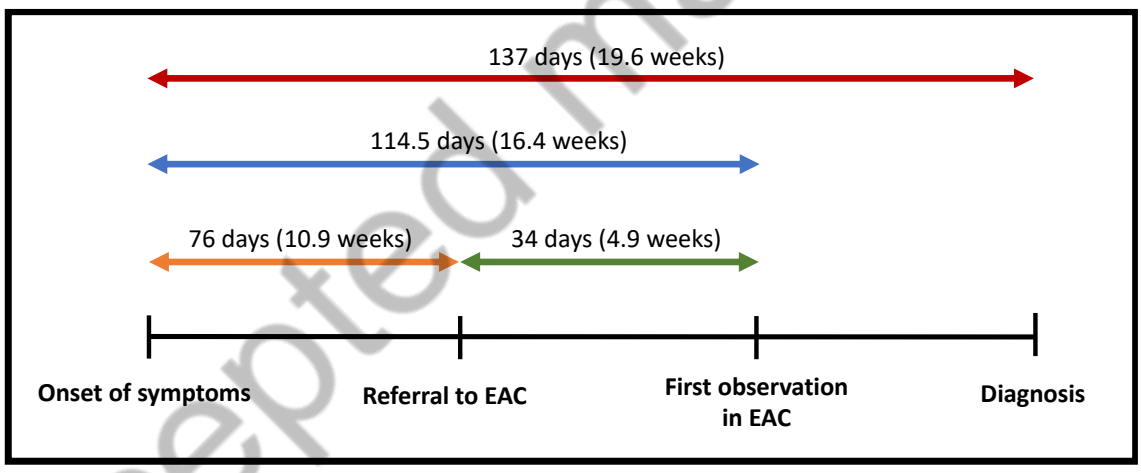

Figure 3. Time elapsed between the onset of symptoms and referral for Early Arthritis Clinic, from referral to the first observation in Early Arthritis Clinic and from the onset of symptoms to diagnosis.

EAC: Early Arthritis Clinic

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Supplementary material

Table III. Autoimmunity features of patients observed in Early Arthritis Clinic

Autoimmunity pattern	N = 440 (100%)
RF	
Positive	108 (24.5%)
Negative	321 (73.0%)
Unsolicited	11 (2.5%)
ACPA	
Positive	90 (20.5%)
Negative	326 (74.1%)
Unsolicited	24 (5.4%)
HLA-B27	
Positive	10 (2.3%)
Negative	47 (10.7%)
Unsolicited	383 (87.0%)
ANAs	
Positive	207 (47.0%)
Negative	176 (40.0%)
Unsolicited	57 (13.0%)
Titre	
>1/1280	1 (0.2%)
1/1280	7 (1.6%)
1/640	12 (2.7%)
1/320	33 (7.4%)
1/160	101 (23.0%)
1/80	53 (12.0%)
ANAs Pattern	
Nuclear Homogeneous (AC-1)	11 (2.5%)
Nuclear Dense Fine Speckled (AC-2)	170 (38.6%)
Nuclear Centromere (AC-3)	2 (0.5%)
Nuclear Fine Speckled (AC-4)	18 (4.1%)
Nuclear Large Speckled (AC-5)	2 (0.5%)
Other	4 (0.9%)
Anti-dsDNA	
Positive	9 (2.0%)
Negative	346 (78.6%)
Unsolicited	85 (19.3%)
ENAs	
Positive	19 (4.3%)
Negative	363 (82.5%)
Unsolicited	58 (13.2%)
Specificity	
SS-A/Ro and/or SS-B/La	12 (2.7%)
Centromere	1 (0.2%)
U1RNP	1 (0.2%)
Anti-SSA52+	1 (0.2%)
PL-7	1 (0.2%)
Mi-2	1 (0.2%)

RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibody; HLA-B27: leukocyte antigen B-27; ANAs: antinuclear antibodies; Anti-dsDNA: Anti-double stranded DNA; ENAs: Extractable Nuclear Antigens