Evolution of undifferentiated arthritis: a ten-year experience from the early arthritis clinic of a tertiary care hospital

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Abstract

Objective

Undifferentiated arthritis (UA) is an inflammatory oligo/polyarthritis where no definite diagnosis can be reached. Patients with UA may progress towards a chronic inflammatory disease, however, in some cases arthritis may completely resolve. To date, a universally accepted diagnostic and therapeutic algorithm for UA is not available.

Methods

We retrospectively studied 192 patients with UA followed by us over the last 10 years in the early arthritis clinic of our institution.

Results

A total of 192 patients, 91 men (47.4%) and 101 women (52.6%), with mean age 57.9±17.8 years, were included in the study. Eighty-four patients (43.7%) presented with acute/subacute mono-/pauci-arthritis, 56 patients (29.2%) with chronic mono-/pauci arthritis, 42 patients (21.9%) with acute polyarthritis and 10 (5.2%) with chronic polyarthritis. From the total of 192 patients, 102 are currently followed. Current diagnosis at the time of this report included: rheumatoid arthritis in 18 (17.6%) patients, self-limiting arthritis in 35 (34.4%), undifferentiated/unclassified arthritis in 45 (44.1%), spondyloarthropathy in 3 (2.9%), and crystal-induced arthritis in one (1%). The time between the initial evaluation and the definitive diagnosis of RA ranged between 6 and 15 months. Seropositivity (RF and/or ACPA) and disease duration were strong predictors of developing RA in our cohort.

Conclusion

Our data indicate that serepositive patients with chronic symptoms carry an increased risk of developing RA, and that these patients may be candidates for a more aggressive treatment.

Key words

undifferentiated arthritis, unclassified arthritis, rheumatoid arthritis, early arthritis, treatment

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Introduction

Undifferentiated arthritis (UA) is an inflammatory oligo/polyarthritis where no definite diagnosis can be reached (1). Patients with UA may progress towards a chronic inflammatory disease, however, in some cases arthritis may completely resolve. In rheumatoid arthritis (RA), the most common form of inflammatory arthritis, therapeutic algorithms are established and favour implementation of therapy as early as possible in order to prevent joint destruction and functional impairment (2). For patients with UA, however, it is not known which patients will eventually evolve to RA and therefore may benefit from an early and intense therapeutic intervention. Recently, classification criteria for early RA have been proposed something that may help in the early identification of these patients (3). There have been several efforts to define prognostic factors for patients with UA and stratify them according to the risk of developing RA, however, there is no universally accepted prognostic model (4-6).

The purpose of this study was the description of the evolution and clinical course of those patients, attending the early arthritis clinic of Patras University Hospital during the ten years of its existence (2003–2013), whose clinical and laboratory picture did not allow a definitive diagnosis at the initial visit. Up to now, a universally accepted diagnostic and therapeutic algorithm for these cases of arthritis has not been available (7-9). In this context, our experience on a large cohort may contribute to a better approach of these patients in the future.

Patients and methods

Patients

We retrospectively studied 192 patients followed by us over the last 10 years in the early arthritis clinic of our institution, who were characterised as suffering from undifferentiated/unclassified arthritis. This term was used for every case in which established classification criteria for a specific clinical entity were not fulfilled and a definitive diagnosis could not be made during the first six weeks of follow-up. In 2010, the revised at that time classification criteria for rheumatoid arthritis (RA) (10) and spondyloarthropathy (SpA) (11) were retrospectively applied to our patients. If retrospectively a patient was found that fulfilled these revised criteria during the initial six week period of his observation in the clinic, he/she was excluded from the study. From 2010 and on, only the revised criteria were applied to the newly recruited patients as well as to those already attending the clinic. Patients were referred to the early arthritis clinic by primary care physicians working in the wider area of Patras (Achaia, Greece) as well as by Emergency Departments of Hospitals in the same area. Patients could be referred to the early arthritis clinic if they met the following criteria i) at least one joint sensitive to squeezing and/or swollen, for at least one week and ii) no prior history of trauma and iii) no obvious diagnosis of gout. The local Ethics Committee (Patras University Hospital) approved the study.

Initial studies during the first visit included: a) complete history and physical examination, b) complete haematologic and biochemical profile, c) serologic tests for autoimmune diseases including rheumatoid factor (RF), anti-cyclic citroulinated peptide antibodies (available from 2008 and onwards), anti-nuclear antibodies, d) serologic tests for viruses or other infectious agents that may associate with arthritis, e) x-rays of affected joints which were repeated every year, f) ultrasound/power Doppler examination of specific joints in cases of questionable clinical findings, and g) synovial fluid examination when an effusion was detected in a large joint. Follow-up visits, with clinical evaluation and appropriate laboratory, were scheduled regularly according to the severity of the clinical picture and the treatment applied, usually but not exclusively at three month intervals. The patients with undifferentiated arthritis were further classified according to:

1) Age and gender,

2) Initial clinical presentation of the arthritis: a) acute/subacute mono- or pauci-arthritis of ≤3 month duration, b) chronic mono- or pauci-arthritis of >3 months, c) acute/subacute polyarthritis,

and d) chronic polyarthritis, as well as according to the predominant involvement of the upper or lower extremities.
3) Duration of follow-up (≤6 months, ≤2 years, ≤5 years and >5 years),
4) Treatment applied in order to control the arthritis. As a rule, initial treatment consisted of NSAIDs (for mild mono- / pauci-arthritis of small joints) and if not adequate response was observed after 15 days, p.o. glucocorticoids were administered. In cases with more serious presentation, intra-muscular steroid injection or prednisone p.o. 10–25mg/day with quick tapering (so that after 3 months the dose to be ≤5mg/d), addition of a conventional DMARD if the arthritis persisted for more than three months or recurred after a short remission. Administered DMARDs included methotrexate or sulfasalazine. In case of no response to a conventional DMARD, a second was given. Finally, if the arthritis persisted, a biologic agent was given, even if the diagnosis of RA had not been established. In case of a favourable response to steroids, these drugs were continued for 6–24 months at doses of ≤5mg/d, usually 1–2.5mg/d.
5) Final working diagnosis: a) Undifferentiated arthritis, b) Rheumatoid arthritis, c) Spondyloarthropathy, d) Crystal induced arthritis, e) Non rheumatic pathology, for example paraneoplastic syndrome, and f) "self-limiting arthritis", in cases of long term remission (≥2 years) off treatment or on minimal corticosteroid treatment. Patients whose initial diagnosis had been revised according to the newly applied classification criteria were excluded.
6) Disease activity: active disease was defined the persistence of arthritis or the recurrence of arthritis after a remission period of ≤6 consecutive months. On the other hand, remission was defined the absence of arthritis for ≥6 months, whereas long-term remission (self limiting disease) the absence of arthritis for ≥2 years.

Statistical analysis

Statistical analysis was performed using the SPSS software (SPSS Inc, Chicago, Illinois), version 20. Data are presented as mean±SD or percentages 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.

Results

Demographic characteristics and clinical presentation of study subjects

A total of 192 patients, 91 men (47.4%) and 101 women (52.6%), with mean age 57.9±17.8 years, were included in the study. Eighty-four patients (43.7%) presented with acute/subacute mono-/pauci-arthritis, 56 patients (29.2%) with chronic mono-/pauci arthritis, 42 patients (21.9%) with acute polyarthritis and 10 (5.2%) with chronic polyarthritis. These are diagrammatically depicted in Figure 1A. From the total of the 192 patients, 102 are currently followed. Out of the 90 not followed any more (last visit >2 years ago), 52 (57.8%) stopped coming to the clinic on their own, after having been in remission. Thirty-one (34.4%) stopped coming on their own without having experienced remission. In another 7 patients (7.8%) a non-rheumatic primary condition was diagnosed (myelodysplastic syndrome in 6 and a solid abdominal tumour in one), and these patients were referred to the appropriate specialists. These are diagrammatically depicted in Figure 2. Out of the 102 patients currently being followed, 17.6% have been followed for ≤6 months, 41.2% for >6 months to 2 years, 16.7% for 2–5 years and 24.5% for more than 5 years. Clinical and demographic characteristics of these patients are presented in Table I. The clinical picture at the initial visit or during the initial 6 week period included acute/subacute mono- pauci- arthritis in 47 patients (46.1%), chronic mono- pauci- arthritis in 31 (30.4%), acute polyarthritis in 21 (20.6%) and chronic polyarthritis in 3 (2.9%) as shown in Figure 1B. This distribution was similar to that observed among our initial total cohort of 192 patients. Fifty-eight patients (56.9%) had arthritis predominately in the upper extremities, 33 (32.3%) had arthritis predominately in the lower extremities and in 11 patients (10.8%) a predominance of upper or lower extremities was not evident. Seventy one (69.6%) of the currently followed 102 patients were in remission, whereas 31 (30.4%) had active disease. The latter consisted of those being followed for less than 3 months after the initial visit to the early arthritis clinic (8 patients) and a group within 6 months after modification of treatment because of recurrence of the arthritis or no response to therapy (23 patients).

Current diagnosis of study subjects

Current diagnosis at the time of this report included: Rheumatoid arthritis in 18 (17.6%) patients (those with their initial diagnosis revised based on the 2010 criteria excluded, as already mentioned, included only those with initial picture of undifferentiated arthritis that subsequently evolved to RA), self-limiting arthritis in 35 (34.3%),

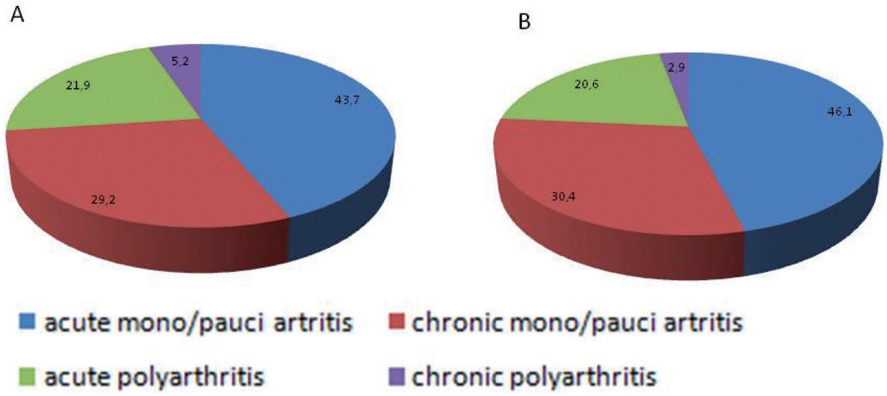

Fig. 1. Clinical presentation of the initial cohort of 192 patients (**A**) and of the cohort of 102 patients currently being followed (**B**). A similar pattern of presentation can be seen.

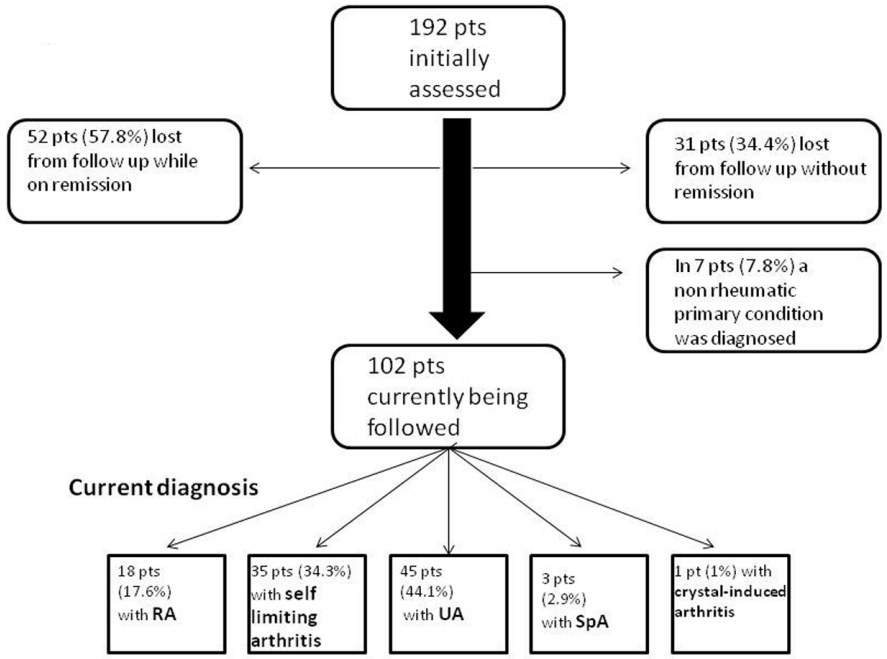

Fig. 2. Flowchart of the study.

Table I. Clinical and demographic characteristics of study subjects currently being followed (n=102).

Age (yrs)		
Mean (SD)	58.85	(17.12)
Gender n (%)		
Male	41	(40.2%)
Female	61	(59.8%)
Follow-up duration n (%)		
<6 months	18	(17.6%)
6 months - 2 years	42	(41.2%)
2 years - 5 years	17	(16.7%)
>5 years	25	(24.5%)
Mean follow-up duration months (SD)	31.46	(26.16)
Initial presentation		
Acute mono/pauci arthritis	47	(46.1%)
Acute polyarthritis	31	(30.4%)
Chronic mono/pauci arthritis	21	(20.6%)
Chronic polyarthritis	3	(2.9%)
Seropositivity at initial presentation (RF and/or ACPA) n (%)	10	(9.8%)

undifferentiated /unclassified arthritis in 45 (44.1%), spondyloarthropathy in 3 (2.9%), and crystal induced arthritis in one (1%) as shown in Figure 2. The time between the initial evaluation and the definitive diagnosis of RA ranged between 6 and 15 months. The majority of the individuals classified as suffering from RA had arthritis predominantly of the upper extremities.

Treatment and radiographic progression

Treatment during the last evaluation of our cohort consisted of NSAIDs or colchicine in 5 patients (4.9%), corticosteroids alone in 60 (58.8%), conventional DMARDs with or without concomitant glucocorticoids in 32 (31.4%) and biologics in 5 patients (4.9%). For those patients achieving remission a median time of 5 months was needed.

The majority of the individuals classified as suffering from RA were receiving DMARDs, whereas three of them and a biologic agent as well. Out of the 35 patients with self-limiting arthritis, thirty one (88.6%) came into remission within 3 months after initiation of treatment. This was achieved with glucocorticoids in 29 patients and NSAIDs in two. DMARDs were necessary in four patients for remission to occur and the latter was achieved after 6–12 months.

From the 102 patients currently being followed, 42 have more than 2 years follow-up. Interestingly, only in 2 (4.7%) of these patients there was clear evidence of radiographic progression as depicted in x-rays. No patient had evidence of erosive disease at baseline.

Factors associated with development of RA

We further explored which factors associated with the development of RA in the cohort currently being followed. We compared patients who developed RA *vs*. those who did not. As shown in Table II, the strongest predictive factor was seropositivity; all seropositive patients were finally classified as having RA ($p<0.001$). In sharp contrast, all patients who did not develop RA were seronegative. Moreover, patients who developed RA had a longer disease duration compared to patients who did not develop RA ($p=0.018$) and presented more frequently as polyarthritis ($p=0.037$). We next used binary logistic regression analysis to evaluate the independence of the factors associated with development of RA. All factors that contributed significantly in the univariate assessment were included in the model: disease duration as a linear variable, clinical presentation (mono/pauciarthritis *vs*. polyarthritis as a categorical variable) and seropositivity (yes/no) alongside with age and gender. The R^2 of the model was 0.7 and seropositivity remained the strongest independent predictive factor ($p<0.001$) followed by disease duration ($p=0.018$). The type of clinical presentation (mono/pauci-arthritis *vs*. polyarthritis) lost its significant association with RA development in the multivariate model ($p=0.12$) whereas age and gender did not associate with RA development as in the univariate analysis. Similar results were obtained when disease duration was entered as a categorical variable (acute/chronic).

Discussion

According to the results of this 10-year observational study of patients attending the early arthritis clinic of our institution, the outcome regarding the final/current diagnosis at the time of this report appears similar to that reported in the literature. A recent systemic review of the relevant literature showed that 17–32% of the total number of patients with undifferentiated arthritis evolves to RA within a year, whereas 40–55% remits permanently (self-limiting arthritis) (1). Similarly, the percentage of our patients that remained under the diagnosis of undifferentiated arthritis after a 12 month observation (44.1%) did not differ from that reported in the

Table II. Demographic, clinical and serological characteristics of patients who developed or did not develop RA.

	Patients who developed RA (n=18)	Patients who did not develop RA (n=84)	*p*-value
Age (years) mean (SD)	59.44 (18.46)	58.73 (16.93)	NS
Gender (female) n (%)	10 (55.55)	51 (60.71)	NS
Disease duration (months) mean (SD)	45.37 (29.41)	28.48 (24.66)	0.018
Clinical presentation n(%)			
Acute arthritis /	6 (33.33)/	56 (54.9)/	0.01
Chronic arthritis n (%)	12 (66.66)	28 (45.1)	
Mono or pauci-arthritis /	9 (50)/	63 (61.76)/	0.037
Polyarthritis n (%)	9 (50)	21 (38.23)	
Seropositivity at initial presentation (RF and/or ACPA) n (%)	10 (55.55)	0 (0)	<0.001

literature, ranging from 22% to 31% (12, 13). Most of the available studies on the outcome of undifferentiated arthritis are prospective observational of 12-month duration. However, a consensus on a definite time duration, adequate for a reliable conclusion regarding the evolution of undifferentiated arthritis to either RA or permanent remission, does not exist. In our cohort, the observed time duration elapsed before undifferentiated arthritis was diagnosed as RA ranged between 6 and 15 months. Similarly, there is no consensus about the time span required in order to characterise a remitted arthritis to a permanently remitted one (self-limiting arthritis). In our study we had the opportunity to observe the clinical course of our patients for longer time periods and we were allowed to classify under the term "self-limiting arthritis" only those cases with remission lasting for ≥2 years, whereas those cases with remission duration between 6–24 months were classified as "undifferentiated arthritis in remission". According to Quinn *et al*., a case of undifferentiated arthritis which does not go into remission after IM glucocorticoid administration within the first 3 months, has a very high possibility (85%) to evolve within 12 months to "persistent arthritis" necessitating a DMARD or to RA (12). From our data as well, it was shown that the vast majority (29 out of 35 patients: 82.8%) finally classified as self-limiting had favourably responded, within a few weeks after the initial visit, to glucocorticoid administration. Another observation from our study was that more than one third of the patients necessitated a DMARD for disease control, irrespective of evolution to RA. Our therapeutic approach differs from that of Quinn *et al*. and that of two similar studies (14, 15) because, besides cases of mild mono-/pauci-articular disease of small joints in which we administered NSAIDs, in the vast majority of undifferentiated arthritis patients, after completion of the appropriate laboratory studies, we gave from the beginning p.o. glucocorticoids for 3 months with gradual tapering, in order to control disease activity within these 3 months. In those cases that this goal was achieved, we would continue glucocorticoids in very small doses for 6-24 months and if recurrence did not occur. In 3 cases of large joint monoarticular arthritis where intra-articular steroid injection was applied, recurrence was observed in all three and the patients were placed on p.o. glucocorticoids and methotrexate.

In this study we had the chance to compare clinical and demographic characteristics in patients with UA who eventually developed RA *vs*. those who did not. We found that simple clinical characteristics such as disease duration and type of clinical presentation (mono/pauci-arthritis *vs*. polyarthrtis) alongside with seropositivity are powerful predictors of RA development. In the multivariate model, disease duration and seropositivity were found to be strong, independent predictors of RA development. Our data indicate that patients with UA with chronic symptoms and seropositivity carry a very high risk of developing RA. Therefore, chronicity of symptoms and seropositivity could serve as reliable and easy to use predictors of RA development in patients with UA and guide treatment decisions; these patients may be candidates for a more aggressive therapeutic approach. The predictive value of seropositivity for RA development, is well known (16, 17) even though this was not a consistent finding in all studies (18). Our study has potential limitations such as the retrospective design and the fact that many patients were lost from follow-up. However, taking into account the paucity of data regarding the long term outcome of patients with UA, our study could provide useful information about the evolution of UA.

To date, a consensus on the therapeutic approach of the patients with undifferentiated arthritis, such as a therapeutic algorithm used in RA, does not exist. Although immediate treatment is a common practice in cases of undifferentiated arthritis, it is not clear at all whether such an approach will prevent evolution to RA or a persistent arthritis which will cause articular destruction. For this to be clarified, studies involving early treatment should be compared to ones not using such early therapeutic intervention. What appears though from the review of the available studies is that the immediate steroid administration may postpone the need for DMARDs and that early DMARD use may postpone evolution to RA (1, 19, 20) even though these are not supported by all studies (21). The small percentage of patients with radiographic progression in our study supports the view that early implementation of therapy may favourably affect outcome in these patients. However, definite conclusions can only be drawn from large scale randomised controlled studies which are currently lacking. Furthermore, there is no consensus on the duration of pharmaceutical treatment after remission has been achieved. In conclusion, it appears critical for the rheumatology community to end up, through well designed studies in larger cohorts, with an evidence based therapeutic algorithm for undifferentiated arthritis, with a goal to prevent its evolution to RA or to achieve permanent remission.

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