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 seropositive 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 citrullinated 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, ≤3 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 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%),...
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/pauci-arthritis vs. polyarthritis as a categorical variable) and seropositivity (yes/no) alongside with age and gender. The R² 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.

<table>
<thead>
<tr>
<th>Clinical presentation n(%)</th>
<th>Patients who developed RA (n=18)</th>
<th>Patients who did not develop RA (n=84)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute arthritis /</td>
<td>6 (33.33%)</td>
<td>56 (54.9%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Chronic arthritis n (%)</td>
<td>12 (66.66%)</td>
<td>28 (45.1%)</td>
<td></td>
</tr>
<tr>
<td>Mono or pauci-arthritis /</td>
<td>9 (50%)</td>
<td>63 (61.76%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Polyarthritis n (%)</td>
<td>9 (50%)</td>
<td>21 (38.23%)</td>
<td></td>
</tr>
<tr>
<td>Seropositivity at initial presentation (RF and/or ACPA) n (%)</td>
<td>10 (55.55%)</td>
<td>0 (0%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

A study of 35 patients: 82.8% eventually developed RA, whereas those with remission lasting for ≥2 years, were allowed to classify under the term “self-limiting arthritis” only 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 mono-articular 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. polyarthritis) 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 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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References