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From undifferentiated arthritis to rheumatoid arthritis : epidemiology, immunology and early intervention

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CHAPTER 2

Undifferentiated arthritis - Disease course assessed in several inception cohorts

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Abstract

The prognosis of patients with undifferentiated arthritis (UA) may vary from self-limited to severe destructive rheumatoid arthritis (RA). Because early aggressive treatment might offer an effective means to slow disease progression in RA, it is important to identify UA patients who will develop RA and treat them as early as possible. At the same time, inappropriate treatment of patients with a more benign disease course should be avoided. Here, an overview is given of the characteristics and numbers of patients with UA who evolve into RA.

UA is defined as any arthritis that has the potential for a persistent course, without fulfilling the classification criteria for specific rheumatic disorders. To compare endpoints in the different databases, the 1987 ACR criteria for RA were used.

In the nine databases employing a similar definition for undifferentiated arthritis, the proportion of patients with UA that evolved into RA within 1 year varied from 6% to 55%. These differences arise in large part from differences in the inclusion criteria and in the definitions used for UA and RA. The data from the various cohorts support a hypothesis that a considerable proportion of UA patients are actually patients with RA in a very early stage. Controlled intervention studies with early antirheumatic treatment in these patients are mandatory in order to provide further insight into the natural course of UA and to define a treatment strategy that will successfully slow or prevent disease progression.

Introduction

Several studies have indicated a beneficial effect of the early treatment of rheumatoid arthritis (RA) to achieve a less severe disease course or even to induce remission (1-3). The possible extra therapeutic benefit attainable in this early period in the disease has been called the "window of opportunity". Since the presentation pattern of RA varies widely, it has been suggested that the treatment should be started as early as possible, even before patients fulfil the American College of Rheumatology (ACR) criteria for RA (4). Ideally, knowledge of prognostic factors in patients with undifferentiated arthritis (UA) will allow the identification of those patients who will develop RA, so that the inappropriate treatment of patients who will not develop RA can be avoided. For this it is also necessary to know the natural course of UA. The present review will attempt to describe the natural course of UA as reported in early arthritis cohorts.

The first problem encountered in the search for the percentage of patients presenting with UA who will develop RA is the fact that UA is a non-validated description of a phenotype. In clinical practice, all cases of arthritis that cannot be classified in one of the accepted categories are referred to as *e causa ignota* or "undifferentiated". For inclusion in early arthritis cohorts, various definitions and criteria have been used for the early phase of arthritis, which makes it difficult to compare the composition of the different study groups. 'Early arthritis', 'early RA', and 'undifferentiated arthritis' are terms that are currently in use to describe either arthritis that might evolve into RA or that has been diagnosed early after onset of arthritis or even early in the disease course of definite RA. Therefore, patients with UA are in general seen as those patients with the potential for development of persistent inflammatory arthritis, including RA, but in whom a recognized clinical pattern does not (yet) exist. In 1958 the American Rheumatism Association (ARA) identified criteria for 'probable rheumatoid arthritis' (5) as a distinction from classical RA, but these criteria only define a subgroup of patients generally referred to as having UA.

In this review, defining RA according to the classification criteria also has disadvantages from a scientific viewpoint. The ACR criteria for RA were developed to identify patients with established RA, and not for diagnostic purposes. In clinical practice, it is of great relevance to distinguish patients on prognostic items such as persistent arthritis or destructive arthritis. On the other hand, all intervention studies to date have been based on fulfilment of the ACR criteria, and evidence that adequate treatment changes the course of disease as well as the prognosis is available only in patients who meet the ACR criteria. Therefore, notwithstanding the imperfect definitions of the phenotype for clinical practice, it is important to assess what proportion of UAcases progress to RA, as defined by the ACR criteria.

Inception cohorts

Early RA databases and their inclusion criteria are listed in ***Table 1***. The databases marked by an asterisk have included and described patients with UA. Only the latter databases will be discussed. The other databases include 'early RA' patients who fulfilled the 1987 ACR criteria for established RA.

In Finland an early arthritis cohort was started in 1975 (6). Adults with one or more swollen joints and a symptom duration of less than 6 months were referred to the hospital in Heinola. Fortythree percent of the patients from this cohort had non-specific arthritis, defined as probable RA according to the 1958 ARA criteria or arthritis not falling within any

Table 1. Early RA databases

Study group	Inclusion criteria	Study strategy and characteristics	N	Reference
Heinola Cohort/ Rheumatism Foudation Hospital Cohort (Finland) *	≥ 1 swollen joints disease duration ≤ 6 months age ≥ 16 years	prospective cohort referred by phycisians of several health centres and hospitals follow-up after 1, 3, 8, 15, 20 and 25 years	442	(6)
Norfolk Arthritis Register (UK) *	early inflammatory polyarthritis age ≥ 16 years ≥ 2 swollen joints symptom duration ≥ 4 weeks onset after January 1989	referred from GP and local rheumatologists yearly follow-up for at least 5 yrs patient visited at home		(10;22)
Leeds (UK) *	undifferentiated arthritis of the hands symptom duration < 12 months	patients from the Leeds Early Arthritis Clinic (n=1877) pyramid treatment strategy	97	(12)
Duesseldorf (Germany)*	rheumatic symptoms duration ≤ 1 year age > 15 years	2-year prospective cohort study referred by GPs, internist, orthopaedic physicians	320	(13)
Austrian Early Arthritis Registry *	inflammatory arthritis with ≥ 2 clinical criteria and ≥ 1 laboratory criterion duration of symptoms < 12 weeks	referred by GPs and internists to participating rheumatologists multi-centre (country-wide) every 3 months questionnaires		(14;16)
Wichita Arthritis Centre (USA) *	undifferentiated polyarthritis syndrome or RA (ACR'87 criteria) disease duration ≤ 2 years	half of patients self-referred follow-up at least 13 months	506 (RA) 638 (UA)	(17)
ESPOIR Cohort Study (France) *	certain or probable clinical diagnosis of RA UA that may develop into RA duration of symptoms < 6 months age 18-70 years ≥ 2 inflammatory joints for the past 6 weeks no DMARD use prior to inclusion	800 patients from the community 10 yrs follow-up		(18)
Amsterdam (The Netherlands) *	≥ 2 swollen joints disease duration < 3 years	Patients from an early arthritis clinic	203	(19)

Study group	Inclusion criteria	Study strategy and characteristics	N	Reference
Leiden Early Arthritis Clinic (The Netherlands) *	any arthritis confirmed by rheumatologist symptom duration < 2 years no DMARD use prior to inclusion	referred by GPs follow-up at 2 weeks, 3 months and yearly		(20)
EURIDISS-Oslo (Norway)	RA (ACR'87 criteria) age 20-70 years disease duration ≤ 4 yrs	Norwegian part of international collaborative research effort follow-up at 1, 2 and 5 years	238	(23)
French Early Arthritis Cohort	RA (ACR'87 criteria) RA diagnosis < 1 year no DMARD use prior to inclusion	multi-centre referred from primary care follow-up 10 year		(18)
GIARA Registry Study Group (Italy)	RA (ACR'87 criteria)	aggressive RA registry	706	(24)
Jyäskylä Cohort (1983-1985) (Finland)	newly diagnosed RA (ARA'58 criteria)	follow-up 18-24 months	58	(6;25)
Jyäskylä Cohort (1988-1989) (Finland)	definite RA (ARA'58 criteria) and ≥ 2 criteria (ESR>20mm/hour, ≥ 6 joints with active RA, duration morning stiffness > 45 minutes) age 18-80 years symptom duration < 1 year	randomised, double blind, placebo controlled study on treatment with sulfasalazine follow-up at 4, 8, 12, 24 and 48 weeks	80	(6;26)
Central Finland RA database	(newly) diagnosed RA according to physician	all new patients with RA are referred to Jyäskylä Central Hospital	>2000	(6)
Helsinki Cohort (Finland)	RA (ACR'87 or revised ACR'87 criteria) symptom duration < 2 year no DMARD use prior to inclusion	prospective study on early aggressive therapy referred from primary care or private outpatients clinics	150	(6;27)
FIN-RACo study (Finland)	RA (ACR'87 criteria) symptom duration < 2 year age 18-65 year, ≥ 3 swollen joints and three of: ESR>28, CRP>19, morning stiffness.>29min, >5 swollen joints, >10 tender joints	multi-centre randomised trial on treatment strategies	199	(28)
CLEAR Registry (USA)	early RA disease duration < 2 years African-American		500	(29)
German early RA inception cohort	RA (ACR'87 criteria) age 21-75 years disease duration < 1 year	prospective, multi-centre study referred by GP, rheumatologist, arthritis care units follow-up at least 3 years		(30;31)

specific diagnostic group (7). The percentage of UA patients who developed RA was not mentioned. After 3 years 58% of the UA patients had no symptoms. Twenty-eight percent of the patients in this cohort met the 1987 ACR classification criteria for RA at inclusion.

From the same cohort, 32 patients were described with the diagnosis of non-classified monoarthritis, defined as swelling of a peripheral joint not due to trauma, degenerative

joint diseases or any other specific joint disease (8). Of those 32 patients, 2 (6%) had rheumatoid factor (RF)-positive definite RA after a 3-9 year follow-up. In 29 patients the diagnosis remained "non-classified" arthritis during follow-up.

In the Finnish cohort a group of 47 patients with recent onset RF-negative oligoarthritis was also described (9). After 23 years of follow-up, reclassification of the diagnoses revealed 1 patient with RA, 7 patients with erosions in the hands or feet, 1 patient with systemic lupus erythematosus (SLE), 1 patient with ankylosing spondylitis, 2 patients with "post-traumatic arthritis", 4 patients with osteoarthritis, and 6 patients with reactive arthritis. The other 25 patients presumably still did not fulfil the criteria for a rheumatic disease.

In the UK the Norfolk Arthritis Registry (NOAR) has been following patients with early inflammatory polyarthritis who had been referred by general practitioners (GPs) and local rheumatologists since January 1990, as described by Symmons *et al*. (10). All adults with two or more swollen joints, lasting for at least 4 weeks, could be included. The proportion of UA patients who developed RA was not mentioned in the published data. However, Wiles *et al*. (11) described a study in which the ACR criteria were applied cumulatively, meaning that once a criterion was fulfilled, this criterion was regarded as positive in all subsequent assessments. In this study, 55% of the patients with a symptom duration of less than 2 years satisfied the criteria for RA at inclusion as described above. Sixty-seven percent fulfilled these criteria after one year.

Also from the UK, Quinn *et al*. (12) recently described a cohort of 97 patients with early undifferentiated arthritis of the hands and a disease duration of less than 12 months who were followed for 12 months. RA developed in 14% of the 97 UA patients. Thirty-six percent had persistent synovitis (defined as the presence of 2 or more of the following: joint swelling, joint tenderness or decreased range of motion) after 12 months, whereas 13% were in clinical remission. Only 54% of the patients could be diagnosed with a specific rheumatic disease after a 12-month follow-up.

Initially these patients were included in a cohort of 1877 patients in the Leeds early arthritis clinic of whom 56% had an inflammatory arthritis at inclusion; 50% of these patients had RA and 23% had UA. Patients with UA were classified as having an inflammatory disorder where a specific rheumatic disease could not be diagnosed. It should be noted that patients were eligible for inclusion in the study if they had a history suggestive of inflammatory arthritis, but clinically detectable synovitis was not required. This resulted in the observation that 47% of patients with UA had no synovitis at the time of inclusion.

In Germany Huelsemann *et al*. (13) described a two-year prospective cohort study of patients with "rheumatic symptoms" for less than 1 year's duration who were investigated in an early arthritis clinic in Duesseldorf. The patients were sent to the tertiary referral centre by general practitioners, internists and orthopaedic physicians. Of 320

patients who were investigated, 217 were classified as having inflammatory rheumatic diseases. Of these 217 patients, 117 (54%) could not be diagnosed definitely and were thus considered undifferentiated, and 39 (19%) were diagnosed as having RA. Sixty-eight percent of the patients with UA presented with oligoarticular joint manifestations, while 14% had a monoarticular and 18% had a polyarticular disease (5 or more joints). Follow-up data 4 to 38 months after the initial symptoms were available for 28 patients with UA. Fifteen (54%) of them had a complete remission, 8 patients had unchanged or progressive unclassified disease and 2 (7%) were diagnosed with RA according to the ACR 1987 criteria.

The Austrian early arthritis registry (Austrian Early Arthritis Action, EAA) (14) follows patients with inflammatory arthritis whose symptoms began less than 12 weeks before presentation and who fulfil at least 2 clinical criteria (absence of trauma, joint swelling in at least 1 joint, joint pain in at least 1 joint, morning stiffness > 60 minutes) and at least 1 laboratory criterion (positive RF, ESR > 20 mm/hour, CRP > 5 mg/L, leucocytes > upper limit of normal). Approximately 15% of the patients after 1 year still had no established diagnosis and were classified as having UA. Sixty-five percent of the patients had RA after 1 year, using the ACR 1987 criteria cumulatively as described in the NOAR (15).

In another paper, Machold *et al*. (16) describe 108 patients who had been followed for at least 1 year. At inclusion, 31 patients (29%) had undifferentiated arthritis and 50 patients (46%) were diagnosed with RA. After 1 year, 17 of the UA patients (55%) were diagnosed with RA. The diagnosis of RA was made if patients fulfilled the ACR 1987 criteria, or if clinical examination revealed a polyarthritis of at least 6 weeks duration without evidence of other inflammatory rheumatic diseases. In cases in which the diagnosis could not be ascertained by the rheumatologist, the disease was classified as UA.

Wolfe *et al*. (17) followed 532 patients with undifferentiated arthritis at the Wichita Arthritis Center who at presentation had a symptom duration of at least 2 years. Synovitis was not required if the patient had other clinically suspected characteristics of RA in the history, at physical examination or in laboratory results. 100% were followed up for $\geq$13 months, 93% for $\geq$2 years and 87% for $\geq$ 3 years. 22% of the patients had no joint swelling, and 6% had questionable swelling at the time of inclusion. Fifty-four percent of the cases resolved, while 17% evolved into RA.

A French multi-centre cohort study (18) that includes patients with early arthritis with a maximum duration of 6 months has recently been started. No data on this ESPOIR cohort have been published yet. The study includes RA patients, probable RA patients and patients with a clinical diagnosis of UA that may potentially develop into RA and with at least two inflammatory joints for the past 6 weeks. UA patients with "no potential to develop into RA" are excluded.

In a Dutch study by Jansen *et al*. (19), a group of patients from the Amsterdam early arthritis clinic with peripheral arthritis involving at least 2 joints and a disease duration

of less than 3 years was followed in order to identify variables that could predict an outcome of progressive disease after 1 year. In this study 27% (n=77) of the patients were clinically diagnosed as having UA at inclusion and 72% (n=203) as RA. 42% of the UA patients had oligoarthritis and 58% had polyarthritis. After one year 42% of the patients with UA were categorized as progressive and 58% as mild, using radiographic parameters and the HAQ score as criteria. Thirtyone percent of the progressive UA group (n=10) fulfilled the ACR criteria for RA after one year. From the total UA group, 17% were classified as having RA at 1 year.

The other Dutch cohort is the Leiden Early Arthritis Clinic, which includes patients with any form of arthritis confirmed by a rheumatologist except gout, and a symptom duration of 2 years or less (20). Out of 936 patients at inclusion, 346 (37%) were categorized as having UA and 22% were diagnosed with RA. After one year of follow-up 32% of the UA patients fulfilled the ACR 1987 criteria for RA. The percentage had increased to 40% at 3 years of follow-up (21).

Discussion

We have reviewed inception cohorts with monoarthritis and polyarthritis to evaluate what proportion of patients with UA progress to RA. In the various cohorts these proportions varied considerably. This may be explained by the differences in referral and recruitment procedures, inclusion criteria and, most notably, disease criteria between the various cohorts. The reported proportion of patients with UA who progressed to RA one year after inclusion range between 6% and 55%. However, in the cohorts that required arthritis to be present at inclusion and that defined RAaccording to the ACR 1987 criteria, the proportions range from 17% to 32%.

The part of the Finnish early RA cohort in which only 6% of the patients with UA progressed to RA after a follow-up period of 3 to 9 years (8) probably represents a subgroup of UA, defined as non-classified monoarthritis and RF negative oligoarthritis, and consequently, a small group of patients is concerned (n = 32). Huelsemann *et al*. reported that 7% of his patients with UA developed RA (13). However, at inclusion patients were diagnosed based on clinical expertise and were not classified according to ACR criteria. As only 18% of the UA patients at inclusion had a polyarticular disease, it is possible that a certain proportion of the patients with polyarthritis at inclusion were prematurely diagnosed as having RA. Therefore the proportion of UA patients who progressed to RA might have been underestimated. Also, only 24% of the 117 patients with UA at inclusion were followed. This suggests that these patients represent a subgroup of UA that more often than not has a mild or self-limiting disease course.

Wolfe *et al*. reported that 17% of their UA patients progressed to RA after 3 years (17). The inclusion of patients without synovitis in this cohort could have led to an underestimation of this value however. The same is true for the cohort described by Quinn *et al*. (12). Jansen *et al*. (19) described a cohort of oligo- or polyarthritis patients, and found a 17% progression from UA to RA. In a mixed population of monoand polyarthritis patients, Van Gaalen *et al*. (21) reported that 32% progressed from UA to RA (diagnosis according to the ACR 1987 criteria) within one year. An even higher rate of 55% was described by Machold *et al*. (16). However, in that study not only patients who fulfilled the ACR criteria were diagnosed as having RA, but also patients with polyarthritis for more than 6 weeks without evidence of other inflammatory rheumatic diseases upon investigation. Therefore, the value of 55% could be an overestimation of RA in comparison with other studies that focused only on the ACR criteria for diagnosing RA.

The findings of these cohort studies support the hypothesis that many patients with UA are actually in the first stages of RA. Unpublished observations in the Leiden EAC cohort indicate that patients whose UA evolved into RA within one year have, on average, the same prognosis as patients who presented with RA at baseline, as measured by the rate of joint destruction, disease activity and functional status. Early treatment may moderate the disease progression, possibly to the point that fewer patients develop RA as defined by the ACR 1987 criteria. Ideally, patients with UA who will progress to RA should be identified at presentation in order to receive early aggressive treatment.

Decisions to treat UA patients will depend on the likelihood that a patient will develop RA. When this is high, it is worthwhile to start disease modifying anti-rheumatic drug (DMARD) therapy immediately. Our review shows there is a 17-32% pre-test probability that a patient with UA actually has RA. The question is what tests are available to obtain a substantially higher post-test probability.

A great deal of research has already been carried out to try to identify predictors that could be used for such a test. At present the most promising diagnostic tool appears to be a test for anti-cyclic citrullinated peptide (CCP) autoantibodies. Van Gaalen *et al*. (21) reported that in the Leiden EAC 93% of the patients with UA who were anti- CCP positive fulfilled the ACR 1987 criteria for RA within 3 years. The negative predictive value was 75%. Furthermore, anti-CCP antibody testing was of little value in UA patients who fulfilled none of the ACR 1987 criteria for RA, but had a significant additional value in predicting the progression to RA in UA patients fulfilling one or more of these criteria at presentation. As anti-CCP antibodies can be detected several years before the onset of disease, Holers and Majka (32) proposed a model in which the development of anti-CCP antibodies in genetically predisposed individuals initiates the autoimmune process in a preclinical phase. The presence of anti-CCP antibodies could therefore be used as prediction criteria for the development of RA in patients with UA.

Another more intuitive approach rather than an analytical one is to treat all UA patients with a relatively safe drug regardless of their post-test probability in the event of new predictive tests. This would prevent that "false-negative" patients would not receive aggressive therapy. It is however not (yet) clear how aggressive such a – at the same time safe – therapy could be. It is unclear if such a therapy should be, for example, MTX, corticosteroids or NSAIDs.

Current research is focusing on these treatments and on whether patients with UA will benefit from early treatment with DMARDs to a similar extent as RA patients. In Leiden a doubleblind placebo-controlled randomised trial (Probaat) with 110 patients who fulfill the ACR 1958 criteria for probable RA and with a symptom duration of less then 2 years is now underway. The aim of the study is to determine whether early treatment can prevent progression into RA or even induce remission. The patients are being treated with either placebo or MTX. After one year the medication will be tapered and then stopped.

The study 'Stop Arthritis Very Early' (SAVE) is another placebo-controlled study that has just started and will try to modify the disease course of UA patients whose complaints began less than 16 weeks earlier, with a single injection of methylprednisolone i.m. Subgroup analyses may reveal whether all UA patients need to be treated or if only a proportion of these patients will benefit from early treatment.

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