Does early seronegative arthritis develop into rheumatoid arthritis? A 10-year observational study

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Abstract

Objective

To investigate the 10-year clinical course of patients with seronegative arthritis with the emphasis of reclassification of diagnoses when applicable.

Methods

A total of 1030 patients including 435 seronegative cases were classified as early RA in 1997-2005 at Jyväskylä Rheumatology Centre and prospectively scheduled for a ten-year follow-up. Clinical data from the follow-up visits and the case-reports until and including the 10-year visit or death, whichever happened earlier, were retrospectively collected and reviewed with re-classification of the cases when applicable. Descriptive statistics were used.

Results

Among the 435 seronegative cases (69 % women, baseline mean age was 59 years), 13 (13/435 [3%]) could be reclassified as seropositive or erosive RA: 4 turned seropositive (2 for ACPA and 2 for RF [> 2x reference level]) and 9 developed erosions typical for RA. Reclassification revealed 68 (16%) cases of polymyalgia rheumatica, 46 (11%) psoriatic arthritis, 45 (10%) osteoarthritis, 38 (8.7%) spondyloarthritis, 15 (3.4%) plausible reactive arthritis, 10 (2.3%) gout, 17 (3.9%) pseudogout, 6 (1.4%) paraneoplastic arthritis, 6 (1.4%) juvenile arthritis, 2 (0.5%) haemochromatosis, 3 (0.7%) ankylosing spondylitis, 2 (0.5%) giant cell arteritis, and 8 miscellaneous diagnoses. The other 140 patients (32%) could not be reclassified in any clear-cut diagnosis and had features of transient arthritis (n=41), seronegative spondyloarthritis (n=47), while 49 remained unspecified.

Conclusion

Over a 10-year follow-up period, reclassification revealed significant heterogeneity in the diagnosis of seronegative RA. Therefore, seronegative arthritis should not be studied as a homogenous entity.

Key words

rheumatoid arthritis, seronegative, outcome

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Introduction

Rheumatoid factor (RF) and especially anticitrullinated protein antibodies (ACPA) have become specific early serological markers of rheumatoid arthritis (RA) and crucial for patient classification (1, 2). The autoantibodies have been hypothesised to have a role in the pathogenesis of RA. Further, positive serology is associated with more aggressive disease and radiographic joint damage (3, 4).

Disparities between seronegative and seropositive arthritis have been noticed in hereditability, associations with known major genetic and environmental risk factors for RA, as HLA-DRB SE alleles and smoking (5, 6). Some studies have noted differences also in the age, showing that seronegativity is more common in elderly onset RA (>60 years) (7). In studies focusing on prognosis, clinical progression and treatment response, seronegative arthritis behaves differently compared to seropositive RA, showing better response to treatment and more favourable radiographic outcomes (8, 9). The more benign radiographic course of seronegative RA patients has also been shown in a long-term follow-up studies of over 15 to 20 years (10, 11). Furthermore, the incidence of extra-articular manifestations differ between seropositive and seronegative patients (12).

Nevertheless, RA clinical trials and cohorts have included up to one third of seronegative patients (13). It is evident that the pathogenesis and clinical course of seronegative arthritis need to be elucidated more profoundly (14, 15). Long-term follow-up studies can provide useful information about the clinical course of arthritides, but the studies are scarce (11). With the opportunity of having a prospectively followed cohort of incident patients with clinical early RA, we aimed to study 10-year outcomes of those with seronegative disease and perform reclassification of diagnoses when applicable.

Patients and methods

Setting

Jyväskylä Central Hospital is the largest non-university hospital in Finland covering a population of 250.000 people. Since 1997, the rheumatology clinic has employed a standard management protocol for patients with RA to ensure early, intensive and uniform care to all patients, delivered by a multidisciplinary team including rheumatologists, rheumatology nurses, physical and occupational therapists. A common clinical protocol has been employed in all patients concerning therapies, patient education, and follow-up procedures (16). Clinical data are available from the hospital records and primary health care, integrated in the common electronic medical records.

Patients

All adult patients with incident inflammatory arthritis who did not meet criteria or show clinical signs of any other specific arthritis were made a clinical diagnosis of early RA. Data of all 1030 incident cases who were seen in Jyväskylä Rheumatology Clinic between 1997 and 2005 were prospectively collected, including demography, clinical characteristics, medications, patient-reported outcomes, measures reflecting disease activity and progression of radiographic joint damage. All 435 seronegative patients were included into the present analyses.

Visits

A structured treatment path includes 4–5 multidisciplinary visits during the first two years after diagnosis [described in detail elsewhere (16)] and follow-up visits at five and ten years.

Monitoring

Clinical monitoring included a complete clinical examination, radiographs of hands and feet and patient reported outcomes such as Health Assessment Questionnaire (HAQ, range 0-3).

Laboratory tests

The following laboratory data were recorded: haemoglobin (Hb, g/l), C reactive protein (CRP, mg/l) and erythrocyte sedimentation rate (ESR, mm/h) and rheumatoid factor (IgM RF). After 2005, anticitrullinated protein antibodies (ACPAs) were tested at follow-up visits. A negative result of RF or ACPA was defined as <2x normal level for RF

and as any value <8 IU/ml for ACPA. At follow-up visits, if other rheumatic disease than RA was suspected, additional serological tests (*e.g.* HLAB27, antinuclear antibodies (ANA), antibodies against double stranded deoxyribonucleic acid (DNA), antineutrophil cytoplasmic antibodies (ANCA), myositis associated antibodies or serology for infectious agents) were tested according to treating specialist's decisions.

Radiographs

Radiographs of hands and feet were taken at baseline and during follow-up at 2, 5 and 10 years. Radiographs of seronegative patients were evaluated by JA and KP, and on demand, radiographs were assessed also by KR, an experienced radiologist.

Methods

The clinical diagnosis of RA at the initial rheumatology visit was based on clinical features, routine laboratory tests and radiographs, and exclusion of other rheumatic diseases, *e.g.* gout and OA. Clinical data from the follow-up visits and the case-reports until and including the 10-year visit or death, whichever happened earlier, were retrospectively collected and reviewed, with reclassification of the cases when applicable.

Reclassification

All patients were reclassified according to accumulated clinical information collected during a 10-year follow-up period, and with adherence to effectual classification criteria.

• *Spondyloarthritis group*

A diagnosis of spondyloarthritis (SPA) or ankylosing spondylitis (AS) was made if patient had features of SPA (*e.g.* dactylitis, uveitis, family history of SPA, history of inflammatory back pain, signs of persistent enthesitis, HLAB27 positivity, radiographic evidence of sacroiliitis) during the follow-up and the ASAS classification criteria for peripheral or axial SPA were fulfilled (17, 18). The diagnosis of psoriatic arthritis (PsA) was made if the patient had psoriatic nail or skin lesions or typical findings in joint radiographs during follow-up and CASPAR criteria for PsA were fulfilled (19). Patients with preceeding genitourinary or gastrointestinal infection, or infection with known micro-organism associated with reactive arthritis, was categorised as having reactive arthritis. Inflammatory bowel disease (IBD) related arthritis was diagnosed if a patient was diagnosed with IBD during follow-up.

• *Polymyalgia rheumatica and giant cell arteritis group*

Polymyalgia rheumatica (PMR) was considered to be the diagnosis if a patient had typical polymyalgic symptoms and did not develop persistent arthritis similar to RA during follow-up. PMR patients also remained non-erosive and fulfilled the ACR/EULAR classification criteria for polymyalgia rheumatica (20). Giant cell arteritis (GCA) was discovered if patient had in addition to peripheral synovitis and polymyalgic symptoms either positive temporal artery biopsy or identical clinical course and response to treatment of GCA.

• *Crystal arthritis group*

Gout was reclassified during follow-up based on typical clinical pattern and synovial fluid findings of sodium urate crystals. Pseudogout or calcium pyrophosphate deposition disease (CPPD) was suspected if a patient had typical chondrocalcinosis in radiographs of symptomatic joints, had suitable clinical pattern of pseudogout/CPPD or positive calcium pyrophosphate crystal finding in synovial fluid. If patient had positive synovial fluid finding the diagnosis was definite, otherwise the reclassification was probable CPPD.

• *Vasculitis group*

A diagnosis of granulomatous polyangiitis (GPA) was made if the ANCAs directed to proteinase 3 (PR3) were positive and patient had other organ manifestation typical for GPA (*e.g.* lung involvement). Microscopic polyangiitis (MPA) diagnosis was made if the patient developed renal failure, had positive antimyeloperoxidase antibodies and typical renal biopsy for microscopic polyangiitis.

• *Other disease entities*

Osteoarthritis (OA) diagnosis was made if patient developed typical findings of OA in the radiographs of hands or feet or other symptomatic joints and did not have evidence of inflammatory condition during follow-up. If review discovered that initial inflammatory joint symptoms had begun during adolescence (before the age of 16), and with appropriate clinical course, the diagnosis of juvenile arthritis was made. The diagnoses of reflex symphatetic dystrophy, hemochromatosis, posttraumatic arthritis, Nasu Hakola disease or meniscal injury were made based on typical clinical and radiographic findings during follow-up. Arthritis was reclassified as paraneoplastic if the patient was diagnosed with malignancy within 6–12 months after RA onset. A patient with positive anti-Jo-1 antibodies and interstitial lung disease (ILD) was reclassified to suffer from antisyntetase syndrome.

Treatment

Disease-modifying anti-rheumatic drugs were started at the time of diagnosis by the treating rheumatologist. The target of treatment was clinical remission.

Ethics approval

All data were obtained as part of routine clinical care in accordance with the national regulations regarding ethical issues (21) and the study was conducted as a register based study.

Results

The study population involved 435 seronegative patients (69% women, baseline mean age 59 years) (Table I). A total of 427 and 423 patients returned for the 2 and 5 year visits. Altogether, 272 subjects returned for the10 year visit with the mean HAQ of 0.5 (SD 0.6) and mean disease activity DAS28 of 2.2 (SD 0.9). Out of the remaining 163 patients, 102 had died and 56 did not attend the 10-year visit due to altered diagnosis (19 cases), refusal (17 cases) or comorbidity (20 cases). Five patients had dropped out. Case- reports of 16 patients were missing. Among the 435 patients, 218 (50.1%) patients fulfilled the revised 1987 ACR criteria

for RA (22) at baseline. All subsequent demographic characteristics refer to the baseline if not otherwise defined.

Possible rheumatoid arthritis group
During the follow-up 13 (2.9%) patients could be classified as seropositive or erosive RA: 4 turned seropositive (2 for ACPA and 2 for RF [> 2x reference level]) and 9 patients developed erosions typical for RA.

Polymyalgia rheumatica and giant cell arteritis group
A total of 68 (15.6%) patients (68% female) were reclassified as PMR, with the mean age (SD) of 73 (7.7). All 68 PMR patients remained non-erosive. The GCA patients were both women, aged 65 and 56, one had GCA based on temporal arteritis PAD finding and a other diagnosis was based on clinical course and response to treatment of GCA. At the 10-year visit both were asymptomatic and had no evidence of RA on their radiographs of hand or feet.

Spondyloarthritis and ankylosing spondylitis group
A total of 38 (8.7%) patients (76% female) were reclassified as SPA, with the mean (SD) age of 44 (14.4). All SPA cases fulfilled the ASAS criteria for peripheral spondyloarthritis. Out of the 25 patients tested for HLA B27, 19 were positive for this antigen. The clinical characteristics of the SPA patients are illustrated in Table II.
Three (0.7%) patients (one female) were reclassified either AS or axial SPA with the mean (SD) age of 32.7 (0.5) at the baseline. All patients had positive HLAB27 and bilateral sacroiliitis in conventional radiographs or in MRI. At baseline, joint symptoms were oligoarticular in all three patients.

Psoriatic arthritis group
A total of 46 (10.6%) patients (50% female) were reclassified as PsA, with the mean (SD) age of 51 (15.5). Among these 46 patients, 44 fulfilled the CASPAR criteria for PsA (19) and two patients developed pencil-in-cup deformities in PIP or MTP joints. The characteristics of PsA patients are illustrated in Table III.

Table I. Baseline and 10-year follow-up characteristics of the seronegative RA study population.

	Number available for analyses	
Age at baseline (years) mean (SD)	435	59.2 (16.9)
Female, n (%)		301 (69.2)
Symptom duration at baseline (months) median (IQR)	431	4.9 (7.5)
ACR 1987 criteria for RA fulfilled at baseline, n (%)		218 (50.1)
Baseline laboratory and clinical characteristics		
CRP, mg/l, mean (SD)	409	28.4 (46.5)
ESR, mm/h, mean (SD)	407	34.2 (25.8)
Hb, g/l, mean (SD)	415	128.9 (13.5)
HAQ, mean (SD)	323	0.9 (0.7)
SJC, mean (range)	261	5.8 (0-22)
TJC, mean (range)	252	5.3 (0-28)
10-year laboratory and clinical characteristics		
CRP, mg/l, mean (SD)	272	4.46 (8.0)
ESR, mm/h, mean (SD)	272	13.3 (13.2)
Hb, g/l, mean (SD)	269	137 (12.7)
HAQ, mean (SD)	244	0.5 (0.6)
SJC, mean (range)	269	0.85 (0-15)
TJC, mean (range)	269	1.5 (0-40)
DAS28, mean (range)	261	2.2 (0.7-6.3)
Baseline DMARD treatment	413	
SSZ, n (%)		253 (58.2)
MTX, n (%)		82 (18.9)
HCQ, n (%)		37 (8.5)
MTX based combination therapy, n (%)		33 (7.5)
SSZ + HCQ, n (%)		3 (0.7)
GOLD, n (%)		3 (0.7)
AZA, n (%)		1 (0.2)
None		6 (1.3)
Data missing, n (%)		17 (3.9)
GC use at baseline or during first year, n (%)		273 (62.8)

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: haemoglobin; HAQ: Health Assessment Questionnaire; SJC: swollen joint count; TJC: tender joint count; DAS28: Disease Activity Score; DMARD: disease-modifying anti-rheumatic drug; SSZ: sulphasalazine; MTX: methotrexate; HCQ: hydroxychloroquine; AZA: azathioprine; GOLD: i.m. gold injection; GC: glucocorticoid.

Reactive arthritis group
A total of 15 (3.4%) patients (73% women) were reclassified as plausible reactive arthritis, with the mean (SD) age of 41.7 (14.4). At 10 years 5 (33.3%) patients were on DMARDs. Among these 15 patients, reactive arthritis associated pathogens were tracked for 9 patients (illustrated in Table IV). The causative pathogens of the other 6 patients (40%) were not known and the cases were reclassified based on clinical data: 4 cases had gastrointestinal infection prior joint symptoms and 2 cases were classified as chronic reactive arthritis based on clinical review of the case reports.

Colitis ulcerosa related arthritis
One 45-year-old male patient was reclassified as colitis ulcerosa related arthritis during follow-up.

Crystal arthritis group
A total of 10 (2.3%) patients (all male) were reclassified as gout, with the mean (SD) age of 61.1 ± (13). Among these 10 patients, 8 patients had typical clinical symptoms and findings and monosodium urate crystals (MSU) in synovial fluid. Two other patients suffered from chronic gout (tophi, erosions in joint radiographs, persistent high urate levels in plasma, typical joint attacks).
A total of 17 (3.9%) patients (82.4% female), were reclassified as CPPD, with the mean (SD) age of 71.3 (7.4). During follow-up CPPD patients had a typical clinical presentation and x-ray findings of CPPD in symptomatic joints (14 patients) or positive synovial fluid for calcium pyrophosphate crystals (3 patients).

Paraneoplastic arthritis group
A total of 6 (1.4%) patients (66.7% female), were reclassified as paraneoplastic arthritis, with the mean (SD) age of 74 (8.8). The malignancies of

Table II. The clinical characteristics of the spondyloarthritis patients.

Characteristic	n=38
HLAB27 positive arthritis with predilection for lower extremity, n (%)	11 (28.9)
Radiographic sacroiliitis, n (%)	6 (15.8)
Recent GI or GU infection or past history of reactive arthritis, n (%)	5 (13.1)
with positive HLAB27	2 (5.2)
with other SPA features (dactylitis, enthesitis, psoriasis)	3 (7.9)
Uveitis, n (%)	6 (15.8)
with positive HLAB27	3 (7.9)
with enthesitis (achilles or plantar)	3 (7.9)
Enthesitis and family history of SPA, n (%)	3 (7.9)
Dactylitis, persistent enthesitis, n (%)	2 (5.2)
HLAB27 and dactylitis/enthesitis, n (%)	2 (5.2)
Psoriatic nail changes, n (%)	1 (2.6)
Inflammatory bowel disease (non specific), n (%)	1 (2.6)
Dactylitis and family history of SPA, n (%)	1 (2.6)
Baseline joint symptoms, n (%)	
monoarticular	7 (18.4)
oligoarticular	20 (52.6)
polyarticular	11 (28.9)

Table III. The clinical characteristics of psoriatic arthritis patients.

Characteristic	n=46
Dactylitis, n (%)	11 (23.9)
Asymmetric oligoarticular or spinal disease, n (%)	12 (26.1)
Juxta-articular new bone formation, n (%)	9 (19.6)
Pencil-in-cup deformities, n (%)	2 (4.3)
Other typical radiographical and clinical findings (dactylitis or enthesitis+ DIP affision) of PsA, n (%)	6 (13.0)
Psoriasis skin involvement, n (%)	37 (80.4)

Table IV. Reactive arthritis associated pathogens among reactive arthritis patients.

Pathogen	n=15
Chlamydia trachomatis, n (%)	3 (20)
Chlamydia pneumoniae, n (%)	2 (13.3)
Campylobacter jejuni, n (%)	1 (6.7)
Neisseria gonorrhoeae, n (%)	1 (6.7)
Yersinia enterocolita, n (%)	2 (13.3)

these 6 patients were: lymphoma (1 patient), corpus cancer (1 patient), ovarian cancer (2 patients) and lung cancer (2 patients).

Osteoarthritis group

A total of 45 (10.3%) patients (91% female) were reclassified as OA, with the mean (SD) age of 63 (11.4). All patients had clinical course of OA in the absence of inflammatory features and with typical OA findings in the radiographs of hands or feet radiographs. None of them developed RA resembling erosions.

Juvenile arthritis group

A total of 6 (1.4%) patients (all female) were reclassified as juvenile arthritis, with the mean (SD) age 40.2 (23.5). The initial inflammatory joint symptoms had started during adolescence, which was only revealed during the follow-up. The delay from initial inflammatory symptoms to diagnosis varied from 3 months to over three decades. Among these 6 patients, the baseline joint manifestations of five patients were oligoarticular and radiographic destruction was present in joints of four patients.

Vasculitis group

One 70-year-old female patient was reclassified as GPA. She initially presented PIP joint synovitis and GPA diagnosis was based on positive ANCA PR3 antibodies and an infiltrate in HRCT. Further, another (0.2%) 58-year-old female patient was reclassified to have MPA. She had transient MCP and wrist synovitis and ANA-negative Raynaud at baseline. Seven years later the patient`s joint symptoms recurred with progressive renal failure and haematuria, and she was eventually diagnosed MPA confirmed by renal biopsy.

Other disease entities

Two (0.4%) male patients, aged 46 and 43 years, were reclassified to have haemochromatosis. Both developed hook-like osteophytes in radial ends of MCP joints characteristics of haemochromatosis, and were homozygotes to HFE gene mutation. One 36-year-old female patient was during review reclassified to have trauma-induced arthritis. Further, one female patient aged 63 years, was reclassified as amyopatic antisyntetase syndrome. She developed progressive interstitial lung disease and positive anti-JO1-antibodies. Further, two female patients (aged 45 and 35 years) were reclassified as reflex symphatetic dystrophy and meniscal injury. Finally, one 19-year-old female was reclassified as Nasu Hakola disease (polycystic lipomembranous osteodysplasia with sclerosing leucoencephalopathy).

Unspecified arthritis (UA) group

The remaining 140 patients (32.2%) could not be reclassified in any clear-cut diagnostic group. A total of 41 of these undifferentiated cases had transient arthritis, 47 cases had features of seronegative spondyloarthritis and 49 cases remained totally unspecified, while three patients had features of inflammatory connective tissue disease (SLE and Sjögren's syndrome), but they did not meet available classification criteria.

• *Transient UA group*

A total of 41 (9.4%) patients (61% female), with the mean age (SD) of 63.6 (15.9) were reclassified as transient UA. The mean time (SD) for clinical remission assessed by the treating specialist was 3.6 months (SD 1.5). Nine of these patients were on DMARDs at the 10-year visit. None of the patients had any relapse of synovitis during follow-up.

• *UA with SPA features group*

A total of 47 (10.8%) patients (74,5% female), with the mean age (SD) of 47.6 (15), were reclassified as unspecified arthritis with SPA features. Altogether 17 patients were on drugfree remission at 10-year visit. All of these patients had some features of SPA but

did not meet ASAS criteria for SPA during follow-up.

• *UA with connective disease features group*

A total of three (0.7%) patients (two female) with the mean age (SD) of 51.3 (24.6), were reclassified as unspecified arthritis with connective disease features. These patients' connective tissue disease features were: positive DNA antibodies (2 patients), positive ANA antibodies (1 patient), Raynaud's phenomenon (2 patients) and thromboembolism with positive cardiolipin antibodies (1 patient).

• *UA group*

A total of 49 (11.2%) patients with the mean age (SD) of 58.1 (13.8) (69.4% female), remained totally unspecified during follow-up. At baseline only 26 patients (53,1%) fulfilled revised ACR1987 criteria for RA. Among these 49 unspecified patients 3 patients initially diagnosed as RA resolved without DMARDs during follow-up, and RA diagnosis was discarded during reviews. This group included patients with clinical features of polymyalgia rheumatica at baseline, patients with radiographic and clinical features of crystal arthritis during follow-up and also patients with clinical features of juvenile, oligoarticular, destructive arthritis. However, during the follow-up, these diagnoses or RA could not be confirmed and the cases remained as unclassified arthritis.

Discussion

The main observation of the current study is the heterogeneity of the diagnoses revealed over a 10-year observation period among patients initially diagnosed as seronegative RA. Our findings are somewhat controversial to some earlier studies, which did not find distinguishable subphenotypes in seronegative patients over a mean follow-up of 5 years (23). However, short-term follow-up period may not be sufficient enough to show neither the genuine nature and course nor definite diagnosis of seronegative patients. So far, seronegative RA has been in focus of only a few cohorts, and long-term follow-up studies of seronegative RA patients are rare. An exception is from the Heinola group, which reported 23-year outcomes of 64 non-specific seronegative oligoarthritis patients (11). Most of these patients (40/64 patients) were classified as possible spondyloarthritis (PsA, ReA, HLAB27 related arthritis) during follow-up. They also reclassified one case each of RA, SLE and ankylosing spondylitis, two cases of post-traumatic arthritis and four cases of OA in this long-term follow-up cohort. Their findings in heterogeneity of diagnoses in seronegative oligoarthritis patients are compatible to ours.

In early disease, clinical characteristics between seronegative and seropositive patients can not be distinguishable from each other (9). Additional biomarkers might be a solution, although a common biomarker for the entire heterogenous seronegative group can not exist. As we demonstrated, various inflammatory and non-inflammatory conditions, for example PMR, SPA, PsA and erosive OA, can mimic seronegative RA at early phase.

Long-term follow-up of seronegative patients can reveal the differences in their outcome and clarify the true nature of the disease. For example, several earlier longitudinal observational studies involving patients with RA indicated that the radiographic outcome is remarkably different between seronegative and seropositive cases. Patients with seronegative RA did not develop rheumatoid-like of erosions – or the extent of radiographic scores was minimal compared to the group of seropositive patients over an observation period of up to 15 to 20 years (10, 24, 25). In retrospect, those observations are not surprising, knowing the heterogeneity of diagnoses among patients with seronegative RA and rarity of seronegative cases with rheumatoid-like erosions.

Interestingly, Nordberg *et al*. reported similar radiographic scores in seronegative and seropositive patients at the baseline in the ARCTIC study (26). The total median van-der-Heijde-modified Sharp scores were low, 5.5/448 in seronegative and 4.0/448 in seropositive patients, and only longitudinal follow-up will reveal the course of the disease in the ARCTIC cohort, in terms of radiographic progression. There is an option that some of the seronegative patients will turn seropositive over time, such as 4/435 patients in our cohort. Some patients show rheumatoid-like erosions and stay seronegative at least for the first 10 years such as 9/435 patients in our cohort. Furthermore, as far as joint space narrowing is considered, one needs to keep in mind that it is also seen in many other conditions such as PsA, OA and CPPD, in addition to RA.

A rarely seen form of aggressive and destructive seronegative RA has been described in a case report of four seronegative patients with disease duration of 20 to 35 years, showing destructions in wrists, sub-talar and ankle joints (27). In these patients, small joints of fingers and toes were spared, which is atypical for RA radiographic outcome and more typical for advanced seronegative juvenile polyarthritis. Such patients were not identified in the current cohort.

Early and aggressive treatment for early RA has gained a lot of attention over the past two decades. This practice may need to be re-evaluated based on our results. If seronegative patients are treated according to the treatment guidelines of progressive RA, a substantial proportion of patients is exposed to unnecessary long-term medication.

Our study has some limitations. The initial diagnosis of our study patients was based on clinical observations and all patients did not fulfil revised ACR1987 criteria for RA at baseline, allowing inclusion of a proportion of undifferentiated early arthritis patients. The predominant "treat to target"-concept of early intensive therapeutic intervention in patients with early RA lead clinicians to start RA therapy also to patients with undifferentiated arthritis without definite RA diagnosis. This may partly explain the heterogenicity our study population. One must also pay attention to the fact that a majority of our patients were diagnosed as seronegative RA prior to the era of ACPA analyses and serology was based on RF-negativity only. However, only two

initially seronegative (RF-negative) patients were revealed as ACPA-positive during the follow-up. On the other hand, it is not excluded that a proportion of our study patients, whose diagnosis was seronegative RA, could have been seropositive for ACPA at the beginning, and later turned seronegative during the anti-rheumatic treatment period. Finally, diagnostic procedures and classification criteria for SPA, PsA and partly also in PMR have improved during our study follow-up period. This fact can partly explain a rather big portion of these diagnoses in our study population. However, our study population includes all seronegative RA patients diagnosed and treated in the central hospital district between years 1997 and 2005 and so gives a remarkable real-world follow-up data of seronegative patients.

In conclusion, our study sheds light into the long-term course of patients with seronegative RA. Our observations may have considerable implications in real-world setting encouraging rheumatologists to invest in differential diagnosis of seronegative arthritis not only at baseline but also during follow-up. Furthermore, our results suggest that it may not be reasonable to study seronegative arthritis patients as a homogenous entity in RA studies.

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