CONCISE REPORT

Patients with seronegative RA have more inflammatory activity compared with patients with seropositive RA in an inception cohort of DMARD-naïve patients classified according to the 2010 ACR/EULAR criteria

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ABSTRACT

Objectives To compare the presentation of seropositive and seronegative early rheumatoid arthritis (RA) in disease-modifying antirheumatic drug (DMARD)-naïve patients classified according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria.

Methods All patients had symptom duration from first swollen joint <2 years and were DMARD naïve with an indication for DMARD treatment. Patients were stratified as seropositive (positive rheumatoid factor (RF)+ and/or anticitrullinated peptide antibody (ACPA)+) or seronegative (RF− and ACPA−), and disease characteristics were compared between groups.

Results A total of 234 patients were included, and 36 (15.4%) were seronegative. Ultrasonography (US) scores for joints (median 55 vs 25, p<0.001) and tendons (median 3 vs 0, p<0.001), number of swollen joints (median 17 vs 8, p<0.001), disease activity score (DAS; mean 3.9 vs 3.4, p=0.03) and physician global assessment (mean 49.1 vs 38.9, p=0.006) were significantly higher in seronegative patients compared with seropositive. Total van der Heijde-modified Sharp score, Richie Articular Index and patient-reported outcome measures were similar between groups.

Conclusions Seronegative patients had higher levels of inflammation, assessed both clinically and by US, than seropositive patients. These differences may reflect the high number of involved joints required for seronegative patients to fulfil the 2010 ACR/EULAR classification criteria for RA.

Trial registration number NCT01205854; Pre-results.

INTRODUCTION

The identification of rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPAs) has led to the recognition of the subgroups of seropositive and seronegative rheumatoid arthritis (RA).[1] Serological status has become an important factor in diagnosis and prognostication of the disease. Patients with seropositive RA share certain genetic and environmental risk factors and have been shown to have a more severe disease course.[2 3] Less is known about seronegative RA, but evidence of genetic associations for ACPA-negative RA has been found.[4] The clinical presentation and disease course of seronegative RA are usually reported as less severe than for seropositive RA, although studies are conflicting.[5]

The 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA have led to the redefinition of the patient population by increased weighting of serology.[6] Compared with the 1987 criteria,[7] the new criteria appear to result in an increased prevalence of classifiable RA with a milder disease course.[8] In previous studies, the new criteria do not seem to alter the ratio of patients with seronegative RA to patients with seropositive RA,[9 10] but it is unknown how they affect the presentation of the two subgroups.

Our aim was to compare the clinical presentation of seronegative and seropositive RA in disease-modifying antirheumatic drug (DMARD)-naïve patients classified according to the 2010 criteria, with a focus on inflammatory activity assessed clinically and by ultrasonography (US).

METHODS

Patients

Patients with RA who fulfilled the 2010 ACR/EULAR classification criteria were recruited at 11 Norwegian rheumatology centres between 2010 and 2013 and included in the Aiming for Remission in Rheumatoid Arthritis: a Randomized Trial Examining the Benefit of Ultrasonography in a Clinical Tight Control Regiment (ARCTIC) trial (ClinicalTrials.gov identifier NCT01205854). All patients provided written informed consent. All patients had symptom duration of less than 2 years and were DMARD naïve with an indication for DMARD treatment. Patients were stratified as seropositive (RF (IgM or IgA)+, ACPA+ or both) or seronegative (both RF− and ACPA−).

Data collection

The data collection included demographic data, ACPA, RF, erythrocyte sedimentation rate (ESR,

mm/h), C reactive protein (CRP, mg/L), Ritchie Articular Index, 44 swollen joint count (SJC) and the patient's and physician's assessment of disease activity on 0–100 mm Visual Analogue Scales (VASs). The original disease activity score (DAS) was calculated.[11]

RF and ACPA were analysed centrally by ELISA and fluorescence enzyme immunoassay, respectively. A positive result was defined as any value ≥10 IU/mL for ACPA and 25 IU/mL for RF. A low antibody level was defined as any value > the defined upper limit of normal (ULN) and ≤3× ULN, and a high antibody level as a value >3× ULN.[6]

The impact of disease was assessed by the Rheumatoid Arthritis Impact of Disease (RAID) score, Patient-Reported Outcome Measurement Information System (PROMIS), 36-item Short Form Health Survey (SF-36), EuroQol-5 Dimensions (EQ-5D), fatigue VAS and pain VAS.

US examinations were performed by experienced ultrasonographers using a validated 0–3 semiquantitative scoring system for grey scale (GS) and power Doppler (PD).[12] The 36 joints were as follows: metacarpophalangeal (MCP) 1–5, proximal interphalangeal (PIP) 2–3, radiocarpal (RCJ), intercarpal (ICJ), distal radioulnar (DRUJ), elbow, knee, talocrural and metatarsophalangeal (MTP) 1–5. Tenosynovitis of the tibialis posterior tendon and the extensor carpi ulnaris tendon was also evaluated. An atlas was available as reference during scorings. For dichotomisation of ultrasonographic synovitis, we used a definition of GS score ≥2 and/or a PD score ≥1 based on previous publications.[13] For the wrist, ultrasonographic synovitis was defined as present if RCJ, DRUJ or ICJ had ultrasonographic synovitis.

Radiographs of hands and feet were acquired and scored according to the van der Heijde-modified Sharp score (vdHSS).[14] Two experienced readers blinded for patient identity and clinical information scored all radiographs.

Statistical analyses

Statistical analyses were performed using Stata 14. Continuous variables are presented as means (SD) or medians (25th, 75th centiles) according to distribution, and dichotomous variables are presented as frequencies and percentages. Disease characteristics were compared between subgroups using independent samples t test, Mann–Whitney U test or χ^2 test as appropriate. Statistical tests were two-sided and p values less than 0.05 were considered statistically significant. For all variables, less than 5% of data were missing, thus no imputation of data was done.

RESULTS

A total of 234 patients with mean age (SD) 51.5 (13.7) years and median disease duration (25, 75 centiles) 5.6 (2.8, 10.2) months were included. Overall, 145 patients (62.0%) were women, and 36 patients (15.4%) were seronegative.

Seronegative patients were older than seropositive patients (55.8 years vs 50.7 years, p=0.04), while the gender distribution was similar. Similar percentages of patients fulfilled the 1987 ACR criteria (61.1% seronegative vs 68.7% seropositive patients, p=0.37). In patients who did not fulfil the 1987 criteria, few statistically significant differences between seronegative and seropositive patients were found with regard to which of the 1987 criteria items were fulfilled. Seronegative patients more often had arthritis of three or more areas (71% vs 26%, p=0.001) and arthritis of hand joints (79% vs 48%, p=0.04).

US scores, SJC, DAS and physician global were significantly higher in seronegative compared with seropositive patients (table 1). Limiting analyses to patients meeting the 1987 criteria for RA revealed similar results; however, the differences were numerically smaller (data not shown) and interpretation is difficult as patients fulfilling the 1987 criteria only were not included.

SJC was significantly higher in seronegative patients compared with patients with high levels of RF/ACPA (p<0.001), but did not differ substantially compared with patients with low antibody levels (p=0.18). There was a statistically significant difference between patients with high and low antibody levels for SJC (p=0.02) (figure 1A). Seronegative patients differed compared with patients with both low and high

Table 1 Disease characteristics compared across serology status

Variable	Seronegative RA (n=36)	Seropositive RA (n=198)	p Value
Age, years	55.8 (15.4)	50.7 (13.3)	**0.04**
Female, n (%)	21 (58.3)	124 (62.6)	0.63
Disease duration, months	4.8 [2.5–11.7]	5.9 [2.9–9.9]	0.89
Positive for ACPA, n (%)	NA	187 (94.4)	
Positive for RF IgM	NA	154 (77.8)	
Positive for RF IgA	NA	110 (55.6)	
DAS*	3.9 (1.2)	3.4 (1.2)	**0.03**
44 SJC	17 [11–25]	8 [4–13]	**<0.001**
CRP, mg/L	7.3 [3.0–27.0]	7.0 [3.0–18.0]	0.48
ESR, mm/h	14.0 [10.0–29.0]	20.5 [12.0–33.0]	0.21
Ritchie Articular Index	7.5 [3.5–14.0]	7.0 [4.0–13.0]	0.73
Physician global VAS 0–100 mm	49.1 (21.1)	38.9 (20.2)	**0.006**
Patient global VAS 0–100 mm	50.0 (26.6)	49.6 (23.9)	0.92
Total US joint score†	55 [31–82]	25 [15–40]	**<0.001**
US PD joint score	16 [7–27]	7 [3–14]	**<0.001**
US GS joint score	37 [23–58]	18.5 [10–27]	**<0.001**
Joints with US synovitis	16 [9–20]	6 [3–10]	**<0.001**
Total US tendon score	3 [0–7]	0 [0–3]	**<0.001**
US PD tendon score	1 [0–4]	0 [0–2]	**0.008**
US GS tendon score	2 [0–3]	0 [0–2]	**<0.001**
Total van der Heijde-modified Sharp score	5.5 [2.0–13.0]	4.0 [1.5–8.0]	0.20
Joint space narrowing	1.5 [0.0–6.0]	1.0 [0.0–3.0]	0.06
Erosion score	3.0 [1.0–6.5]	3.0 [1.0–4.5]	0.43
EQ-5D	0.66 [0.11–0.76]	0.66 [0.23–0.73]	0.84
Pain VAS 0–100 mm	45.5 (26.3)	48.1 (23.5)	0.55
Fatigue VAS 0–100 mm	41.5 (29.8)	40.0 (28.4)	0.78
RAID score	4.7 (2.3)	4.4 (2.1)	0.53
PROMIS HAQ	36.3 [13.8–58.8]	29.5 [17.5–48.8]	0.78
SF-36 PCS	32.5 (7.9)	36.6 (9.7)	0.37
SF-36 MCS	48.6 (11.9)	49.3 (10.3)	0.75

Bold indicates p-values less than 0.05.
Values are median [25th–75th centiles] or mean (SD), unless otherwise indicated.
*Original disease activity score based on ESR, patient global, 44 SJC and Ritchie Articular Index.
†Ultrasonography (US) semiquantitative scoring system with ranges 0–3 for grey scale (GS) and power Doppler (PD) in 36 joints and 4 tendons. (Total US joint score, range: 0–216. Total US tendon score, range: 0–24.)
ACPA, anticitrullinated peptide antibody; CRP, C reactive protein; DAS, disease activity score; EQ-5D, EuroQol-5 Dimensions (UK weighted); ESR, erythrocyte sedimentation rate; MCS, Mental Components Summary; PCS, Physical Components Summary; PROMIS HAQ, Patient-Reported Outcome Measurement Information System Health Assessment Questionnaire; RA, rheumatoid arthritis; RAID, Rheumatoid Arthritis Impact of Disease (range from 0 to 10, with higher scores indicating greater impact of disease); RF, rheumatoid factor; SF-36, 36-item Short Form Health Survey; SJC, swollen joint count; VAS, Visual Analogue Scale.

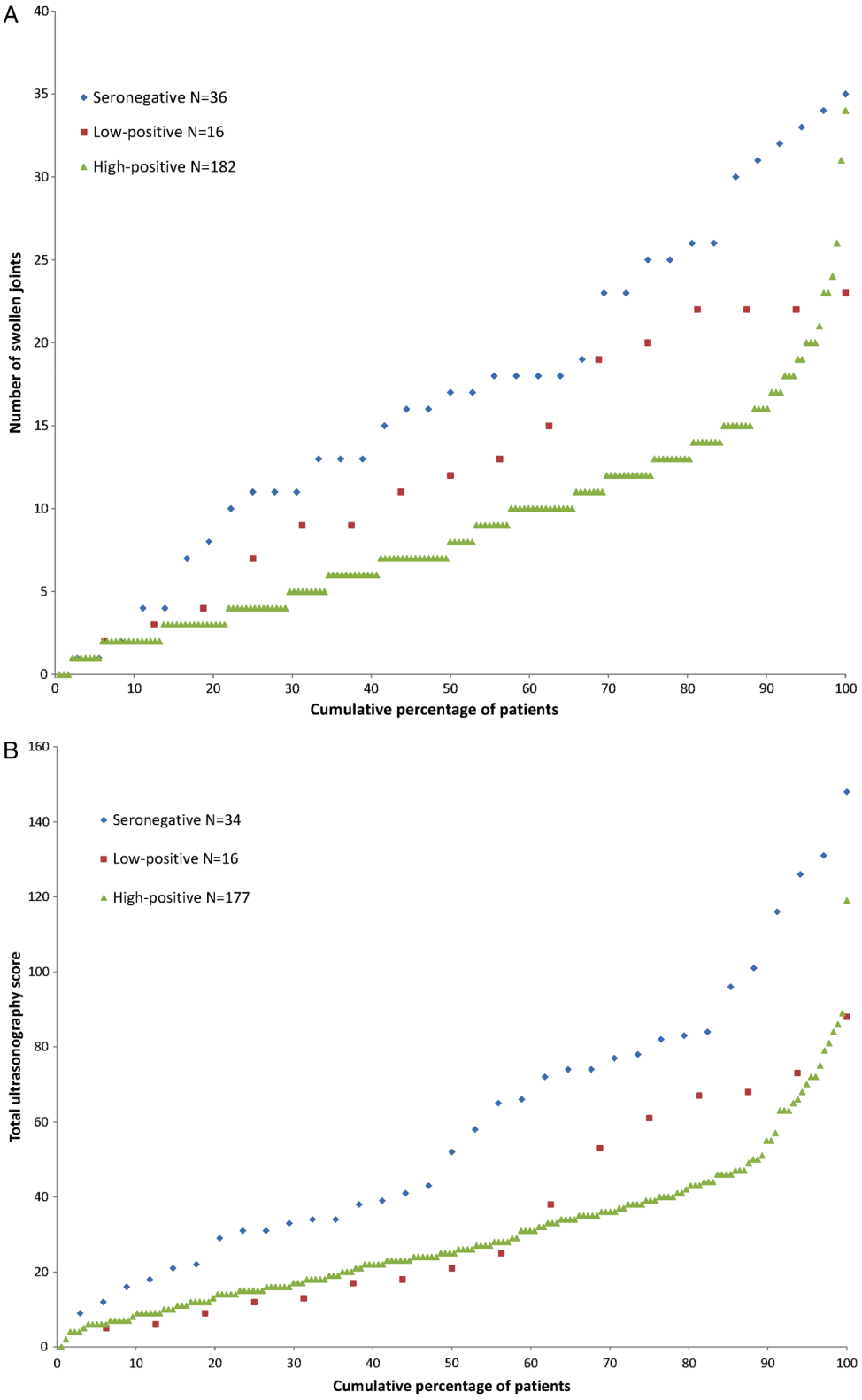

Figure 1 Cumulative probability plots of (A) 44 swollen joint count (SJC) and (B) total ultrasonography (US) score. Groups according to antibody levels: seronegative (<ULN), low positive (ULN to ≤3×ULN) and high positive (>3×ULN). (A) 44 SJC. (B) Total US score. ULN, upper limit of normal.

antibody levels with regard to US scores (p=0.017 and <0.001, respectively), whereas no significant differences were found between patients with low and high antibody levels (p=0.73, figure 1B).

Joint tenderness, patient-reported outcome measures and radiography scores were similar between groups (table 1). In seronegative patients, the MCP joints were more often swollen and positive for ultrasonographic synovitis than in seropositive

Table 2 Distribution of most common clinically swollen joints and joints with ultrasonographic inflammation

Clinically swollen joints				Joints with ultrasonographic synovitis			
Seronegative patients N=36 patients, 72 joints		Seropositive patients N=198 patients, 396 joints		Seronegative patients N=34 patients, 68 joints		Seropositive patients N=194 patients, 388 joints	
Joint	Percentage affected (ordered according to frequency) (%)	Joint	Percentage affected (ordered according to frequency) (%)	Joint	Percentage affected (ordered according to frequency) (%)	Joint	Percentage affected (ordered according to frequency) (%)
Wrist	75.0	MTP3	43.2	Wrist	82.4	MTP3	38.1
MCP3	66.7	MTP2	41.7	MCP2	73.5	Wrist	37.9
MCP2	65.3	PIP2	40.9	MCP3	63.2	MTP2	37.9
PIP3	61.1	MCP2	40.4	MCP1	55.9	MCP2	33.3
MCP1	59.7	PIP3	38.1	MCP4	48.5	MTP1	30.8
PIP2	56.9	Wrist	32.8	MTP2	45.6	MCP1	26.8
MTP3	54.2	MCP3	30.3	PIP2	45.6	MTP4	26.5
PIP4	51.4	MCP1	29.8	PIP3	44.1	MCP3	22.9
MTP2	51.4	MTP4	28.3	MCP5	44.1	PIP2	22.7
MCP5	48.6	PIP4	20.5	MTP1	41.2	MTP5	21.9

The 10 most frequently affected joints are presented. Joints were assessed bilaterally and analysed on an aggregated level.
MCP, meatacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

patients, while seropositive patients had relatively more frequent involvement of MTP joints (table 2).

DISCUSSION

We found patients with seronegative RA to have higher disease activity, assessed both clinically and by US, than seropositive patients, despite similar disease duration. This is in contrast with most previous studies, which have shown either no difference between the subgroups or more severe disease in seropositive patients.[15–18]

The 2010 criteria put great emphasis on RF and ACPA status. While seropositive patients can fulfil the criteria with only one affected joint, more than 10 involved joints are required for seronegative patients to fulfil the criteria.[6] Consequently, it was not unexpected that seronegative patients had more joint involvement compared with seropositive patients. However, we find the differences to be larger than expected. Seronegative patients had a median of 17 swollen joints (the criteria require 11 swollen and/or tender joints to get a maximum score), compared with a median number of swollen joints of 8 in the seropositive group. In our cohort, 38.9% of the seronegative patients did not fulfil the 1987 criteria, indicating that the new criteria do capture seronegative patients excluded by the old criteria. In line with our findings, more severe disease was seen in seronegative than in seropositive patients with early arthritis in the Canadian Early Arthritis Cohort (CATCH).[19] The majority of these patients had already received DMARD treatment, hampering the interpretation of the results.

It has been suggested that seropositive patients are referred to a rheumatologist regardless of disease severity, while seronegative patients with mild disease are less frequently referred than seronegative patients with severe disease.[19] Similarly, the rheumatologist may more often apply the RA criteria in seronegative patients with severe disease, while a diagnosis of RA is considered regardless of disease severity in seropositive patients. Such mechanisms may have affected recruitment of patients to the current study and contributed to the relatively low proportion of seronegative patients (15.4%). Higher numbers of seronegative patients in a previous Norwegian RA cohort based on 1987 ACR criteria (34.5% seronegative) indicate that the introduction of the 2010 criteria changed the ratio of patients with seronegative RA to patients with seropositive RA, although we cannot know for sure how different mechanisms contributed to this.[20]

As the seronegative patients had markedly higher disease activity, it is surprising that assessments of pain and quality of life were similar between the groups. Although seronegative patients had more inflammatory activity, radiographic joint damage was not statistically significantly different between groups. These findings may reflect different pathophysiological mechanisms in the subgroups.

A limitation of this study is that only patients classified as having RA according to the 2010 ACR/EULAR criteria were included, thus it was not possible to assess patients only fulfilling the 1987 criteria for RA. Strengths of our study are the extensive data collection aiming to include all newly diagnosed patients with RA at the participating centres, with radiographic and ultrasonographic examinations of all patients. Questions regarding the performance of the 2010 ACR/EULAR criteria in seronegative patients have previously been partly addressed, but with limiting supporting data.[21] To our knowledge, this is the first study to specifically examine the presentation of DMARD-naïve seronegative RA in patients classified according to the new criteria.

In summary, we found seronegative patients to have higher disease activity, assessed both clinically and by US, than seropositive patients. This finding may reflect a limitation in the performance of the 2010 ACR/EULAR classification criteria. Our results suggest that the new criteria capture a different subset of patients with seronegative RA, with more inflammatory activity, compared with the 1987 criteria.

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Contributors All authors were involved in drafting the article or revising it critically for important intellectual content and approved the final manuscript to be submitted and agreed to be accountable for all aspects of the work. Conception and design of the study: EAH, SL, LBN, A-BA, EL, ICO, HBH, TU, DvdH and TKK. Acquisition of data: EAH, A-BA, HBH, TU, JMK and the ARCTIC study group. Analysis and interpretation of data: LBN, ICO, EAH, SL, EL, A-BA, DvdH and TKK.

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Competing interests HBH has received speakers's fees from BMS, UCB, Roche, Abbvie and Pfizer, v TKK has received grants from Abbvie, BMS, MSD/Schering-Plough, Pfizer/Wyeth, Roche, UCB and payment for lectures from Abbvie, Astra Zeneka, MSD/Schering-Plough, Pfizer/Wyeth, Roche, UCB, Celltrion and Eli Lily. EAH has received personal fees for consultancy, payment for lectures or development of educational material from UCB Pharma, Roche, Abbvie and Pfizer.

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Seronegative patients have higher disease activity

The 2010 ACR/EULAR classification criteria for rheumatoid arthritis may not be appropriate for people with seronegative disease

INTRODUCTION

Rheumatoid arthritis is a chronic inflammatory disease that affects a person's joints, causing pain and disability. It can also affect internal organs. It is more common in older people, but there is also a high prevalence in young adults, adolescents and even children and affects both men and women.

An antibody is a protein that the immune system makes to attack foreign substances in the body, such as viruses or bacteria. In autoimmune disease, the body makes antibodies that attack its own tissues. Antibodies can be detected in a person's blood. Certain antibodies can be used as a marker to classify people with rheumatoid arthritis. The two most common are called rheumatoid factor (or RF) and anticitrullinated protein antibodies (often shortened to ACPA). People with rheumatoid factor or ACPA are said to have seropositive rheumatoid arthritis, which is often thought to be more severe. Not as much is known about seronegative rheumatoid arthritis.

WHAT DID THE AUTHORS HOPE TO FIND?

The authors hoped to learn about seronegative rheumatoid arthritis in people who had been classified according to some well-accepted criteria published in 2010 by the ACR (American College of Rheumatology) and EULAR (European League Against Rheumatism). In the 2010 criteria, quite a lot of emphasis is put on seropositivity. This means that doctors have been unsure about whether the criteria are able to identify seronegative disease equally well.

WHO WAS STUDIED?

The study looked at 234 people from 11 clinics in Norway. Almost two-thirds of the people included were women. These people had been diagnosed with rheumatoid arthritis according to the 2010 ACR/EULAR classification criteria. Everyone included had symptoms of rheumatoid arthritis that had lasted for less than 2 years. In that time, the people had not received any treatment with disease-modifying antirheumatic drugs (often called DMARDs – for example, methotrexate), but they were eligible for such treatment. In total, 36 people in the study had seronegative disease.

HOW WAS THE STUDY CONDUCTED?

This study used data from a trial that was set up to look at the benefit of ultrasound in people with rheumatoid arthritis (the ARCTIC trial). In the original trial, people were grouped as either seropositive or seronegative. For this study, the authors compared the disease characteristics between these two groups.

WHAT WERE THE MAIN FINDINGS?

The authors found that people with seronegative rheumatoid arthritis have higher levels of inflammation, assessed both clinically and by ultrasound, compared to people with seropositive rheumatoid arthritis. People with seronegative disease also had more swollen joints than people with seropositive disease. This is in contrast with most previous studies, which have shown either no difference between the subgroups or more severe disease in seropositive patients. The authors suggest that people with seropositive disease are referred to a rheumatologist regardless of disease severity, while those who are seronegative with mild disease are less frequently referred.

ARE THESE FINDINGS NEW?

Yes. It was thought that people with seronegative rheumatoid arthritis classified according to the 2010 criteria would have more joint involvement compared to those with seropositive disease, but the differences found were much larger than expected. The authors are not aware of other studies comparing the clinical presentation of seronegative and seropositive rheumatoid arthritis in people classified according to the new criteria who have not taken DMARDs.

ARE THERE ANY LIMITATIONS?

A limitation of this study is that only people who had been classified as having rheumatoid arthritis according to the 2010 ACR/EULAR criteria were included. This means that it was not possible to assess people who fulfilled only the older criteria (1987), and impossible to compare between the two.

WHAT DO THE AUTHORS PLAN ON DOING WITH THIS INFORMATION?

The authors are working on analysing 2-year follow-up data to assess differences between seropositive and seronegative rheumatoid arthritis.

WHAT DOES THIS MEAN FOR ME?

These results may indicate that the 2010 criteria perform less well in the early identification of seronegative rheumatoid arthritis. If you have rheumatoid arthritis, you may want to talk to your doctor about your serological (antibody) status, and the impact it may have on your disease, as well as the best treatment choices for you.

FURTHER READING

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