

# The impact of anti-cyclic citrullinated peptide antibody status on the management of patients with early rheumatoid arthritis: observational study results from Lithuania

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**Background.** To provide data on the use of anti-cyclic citrullinated peptide antibody (anti-CCP) and other routinely used clinical parameters and to assess the impact of anti-CCP status on therapeutic decisions, an observational study was conducted in patients with rheumatoid arthritis (RA).

**Methods.** Sixty-seven adult patients with a recent diagnosis of RA were recruited from four rheumatology centres in Lithuania and were prospectively observed for 12 months. Data collection was based on the review of medical records and routine examination of patients. Patients completed the Health Assessment Questionnaire – Disability Index and Patient Global Assessment of disease activity using a visual analogue scale. Physicians were asked about the importance of the anti-CCP results and other factors important for therapeutic decisions.

**Results.** Of the 67 patients enrolled, 54 (80.6%) completed the study. At the beginning of the study, physicians considered anti-CCP results to be important for decision-making in 87.0% of patients. The perceived importance of anti-CCP results did not change significantly throughout the study. After one year of treatment, factors that were considered more important than the anti-CCP results included the presence of erosions, significantly increased C-reactive protein, duration of morning stiffness, multi-articular expanding, and rheumatoid factor status. For nearly half of the patients ( $n = 26$ ; 48.1%), physicians would not change the treatment strategy if the patient had the opposite anti-CCP results at baseline.

**Conclusions.** The study revealed that decision-making in the management of RA was based on multifactorial data. The role of anti-CCP as a single test in treatment decisions needs further investigation.

**Keywords:** rheumatoid arthritis, anti-CCP antibody, observational study

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## INTRODUCTION

Rheumatoid arthritis (RA), which affects 0.3% to 1% of the population (1), is an autoimmune disease characterised by chronic synovial inflammation. The inflammation from RA causes joint destruction and bone erosions that eventually lead to functional disability (2, 3). Joint damage occurs at the early stages of the disease. Approximately 75% of patients with early stage disease have joint erosions; the first erosions usually develop during the first two years of RA (4).

To prevent irreversible joint damage, early diagnosis and treatment initiation within the first three months of disease onset is essential (5). In patients with RA, early therapy with combinations of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) may delay the development of joint damage for several years (5–7).

The importance of early disease-modifying treatment is emphasized in the updated recommendations from the European League Against Rheumatism (EULAR) for the management of early arthritis. As first-line treatment, EULAR recommends the csDMARD methotrexate in combination with short-term glucocorticoids. If this strategy is unsuccessful, switching to or adding another csDMARD is suggested for patients without unfavourable prognostic markers. For patients with unfavourable prognostic markers, adding a biologic disease-modifying antirheumatic drug (bDMARD) or Janus Kinase (Jak) inhibitor is recommended (8). Unfavourable RA prognostic factors include a moderate to high disease activity state, high acute phase reactant levels, a high number of swollen joint counts, the presence of rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPAs), the presence of early erosions, and the failure of two or more csDMARDs (8).

In countries where patients have limited access to expensive innovative medicines (i.e., bDMARDs), new markers or combinations of existing laboratory and clinical tools are of special importance for the identification of patients with the worst prognosis who would benefit most from an individualised treatment. RF, an autoantibody that reacts with the Fc part of immunoglobulin G (IgG), has been used as a serological marker for the diagnosis and prognosis of RA for several dec-

ades (9). However, RF is not specific for RA; it is found in 5% of healthy individuals and in 10% to 20% of individuals older than 65 years. Besides, RFs are of low titre in the early stages of disease (10). Continuing the search for more specific RA markers, it has been discovered that patients with RA produce antibodies to peptides or proteins containing citrulline, a modified form of the amino acid arginine, referred to as ACPAs (11). Currently, the most well-known and established test is one that measures antibodies directed to anti-cyclic citrullinated peptides (anti-CCPs). Because the anti-CCP test is extremely specific for RA, is present early in disease, and predicts the erosive states of disease, it is considered to be a good serologic marker for RA (10). A large body of evidence shows that anti-CCP antibodies are more specific than RF for diagnosing RA, including in the early stages of the disease (12). Since 2010, the anti-CCP test has been established as an accepted RA diagnostic criterion (13). However, the utility of determining the anti-CCP antibody status of a patient over the course of the disease, as well as its role in the clinical decision-making process, has not yet been fully elucidated. A meta-analysis of 14 studies involving 5561 patients with RA concluded that neither the RF nor the anti-CCP status in patients with RA was associated with a clinical response to anti-tumour necrosis factor (TNF)- $\alpha$  treatment (14).

To provide data on the use of anti-CCP testing and other clinical parameters currently used in routine care and to assess the impact of known anti-CCP status on clinical decision-making and the management of patients with RA, a large observational study was conducted in Hungary, Romania, Estonia, Lithuania, and Croatia (15). Here we present the data collected in Lithuania.

## METHODS

This was a multi-centre, international, observational study conducted in Hungary, Romania, Estonia, Lithuania, and Croatia from 2008 to 2011. The protocol of the study was reviewed and approved by the national ethics committees. Participating physicians were selected based on their clinical practice and their ability to recruit a minimum of ten patients during the enrolment period. Random selection procedures were applied to

ensure appropriate regional representations. In Lithuania, four health care centres participated: Vilnius University Hospital Santaros Klinikos, Hospital of the Lithuanian University of Health Sciences Kauno klinikos, Klaipėda University Hospital, and Panevėžys State Hospital.

To be eligible for the study, subjects had to be adult patients ( $\geq 18$  years), diagnosed with RA within the previous six months, disease activity  $> 5.1$  on the Disease Activity Score 28 joints (DAS28) assessment, known anti-CCP status (positive or negative), and availability for up to 12 months for follow-up. All subjects signed written informed consent. Exclusion criteria included the following: unknown anti-CCP status; any condition preventing participation in the study and completion of the study procedures, including language limitation; and unwillingness to provide informed consent.

After enrolment, the patients were followed for 12 months. The study comprised five visits: a baseline visit (month 0) and four subsequent follow-up visits (months 3, 6, 9, and 12). Data collection was based on the review of medical records and routine examination of the subjects. Treatment was left to the discretion of the treating physician. No laboratory evaluations or diagnostic procedures specifically for the purposes of the study were performed. Medical records were reviewed to collect relevant demographic information, medical history, physical examination (weight, height, blood pressure, heart rate), and joint structure data as measured radiographically. The following information was also recorded: disease activity assessed by the DAS28 and its distinct items (i.e., tender joint count (TJC) and swollen joint counts (SJC)) and laboratory test results, such as RF, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and anti-CCP antibodies. Further, patients were asked to complete the Health Assessment Questionnaire – Disability Index (HAQ-DI) to assess physical function and health-related quality of life, and the Patient Global Assessment (PGA) of disease activity using a visual analogue scale (VAS). Antirheumatic drug therapy was also documented at each visit. Physicians recorded relevant data into standardized case report forms. At each visit, physicians were asked to rank the importance of the anti-CCP results on their therapeutic decisions.

At the end of the study, physicians again ranked the importance of the anti-CCP results and were also asked additional questions, including what other factors (possible answers were as follows: multi-articular expanding, general symptoms (fever), patients subjective complains, duration of morning stiffness, presence of rheumatoid nodules, significantly accelerated sedimentation rate, significantly increased CRP, presence of erosions, RF status, and presence of shared epitope) were more important than the anti-CCP status in their decision-making process and what their decisions would have been if the anti-CCP status had been the opposite of what was observed.

The primary study outcome variables were: (1) importance of anti-CCP results in the therapeutic decision-making process, (2) changes in the importance of anti-CCP, (3) factors considered more important than the importance of anti-CCP, and (4) decision if the anti-CCP status was opposite.

The descriptive statistics and statistical tests for group comparisons were applied for data analysis. The medians of two dependent samples were compared using a nonparametric Wilcoxon signed-rank test, whereas proportions were compared using McNemar's test. Statistical differences were interpreted at a 5% (two-sided) significance level. The statistical software package SPSS version 20 (IBM Corp, Armonk, NY, USA) was used for data analysis.

## RESULTS

A total of 942 patients were enrolled into this study in five participating countries. In Lithuania, 67 patients were enrolled; of these patients, 54 (80.6%) attended the follow-up visit 4 (Month 12).

There were 56 women (83.6%) in the study; the mean age of study participants was 52.4 years. Most of the patients (84.1%) had a prior medical history relating to at least one organ system, with musculoskeletal (i.e., other than RA; 22.1%) and cardiovascular (17.6%) diseases being the most frequently reported (Table 1). Of 67 patients, 62 (92.5%) had a positive anti-CCP result at baseline (median, 103.9 IU/mL) and 62 patients (92.5%) were RF positive (median, 60.2 IU/mL; Table 2).

Within the 12-month observation period, most of the objective laboratory and clinical parameters (anti-CCP, ESR, TJC, SJC), as well as subjective

**Table 1.** Baseline demographic and medical history characteristics

Characteristics	N = 67
Women, <i>n</i> (%)	56 (83.6)
Mean (SD) age, years	52.4 (13.4)
Prior medical history relating to at least one organ system, <i>n</i> (%)	57 (84.1)
Other musculoskeletal, <i>n</i> (%)	29 (22.1)
Cardiovascular, <i>n</i> (%)	23 (17.6)
Endocrine metabolism, <i>n</i> (%)	18 (13.7)
Renal/urinary/reproductive, <i>n</i> (%)	15 (11.5)
Gastrointestinal, <i>n</i> (%)	14 (10.7)
Ear, nose, throat, <i>n</i> (%)	12 (9.2)
Haematopoietic and lymph, <i>n</i> (%)	6 (4.6)
Respiratory, <i>n</i> (%)	6 (4.6)
Neurological, <i>n</i> (%)	3 (2.3)
Head, neck, <i>n</i> (%)	2 (1.5)
Psychiatric, <i>n</i> (%)	2 (1.5)
Skin, <i>n</i> (%)	1 (0.8)

SD – standard deviation.

**Table 2.** Clinical characteristics and laboratory parameters during the study period (12 months)

Characteristic*	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4
	<i>n</i> = 67	<i>n</i> = 66	<i>n</i> = 64	<i>n</i> = 59	<i>n</i> = 54
Anti-CCP					
Not performed, <i>n</i> (%)	0	44 (66.7)	46 (71.9)	31 (52.5)	17 (31.5)
Negative, <i>n</i> (%)	5 (7.5)	2 (3.0)	2 (3.1)	7 (11.9)	12 (22.2)
Positive, <i>n</i> (%)	62 (92.5)	20 (30.3)	16 (25.0)	21 (35.6)	25 (46.3)
Median (IU/mL)	103.9	103.9	84.6	21.9	71.4
Min; max	5.9; 1200.0	10.1; 890.2	5.9; 1200.0	9.0; 890.0	6.8; 710.1
RF					
Not performed, <i>n</i> (%)	2(3.0)	52 (78.8)	50 (78.1)	49 (83.0)	30 (55.6)
Negative, <i>n</i> (%)	3 (4.5)	2 (3.0)	4 (6.3)	3 (5.1)	4 (7.4)
Positive (RF ≥ 20 IU/mL), <i>n</i> (%)	62 (92.5)	12 (18.2)	10 (15.6)	7 (11.9)	20 (37.0)
Median(IU/mL)	60.2	47.8	99.1	40.3	78.7
min; max	20.0; 1325.0	20.0; 542.1	26.0; 690.3	25.4; 636.0	22.9; 338.2
CRP (mg/L)					
Not performed, <i>n</i> (%)	1 (1.5)	22 (33.3)	23 (35.9)	19 (32.2)	16 (29.6)
Median	12.4	8.4	10.2	10.2	8.0
Min; max	0.5; 276.8	0.6; 81.4	0.0; 53.1	0.4; 149.6	0.6; 101.2
ESR*(mm/h)					
Median	43.0	30.0	33.0	30.0	22.5
Min; max	11.0; 100.0	2.0; 85.0	5.0; 69.0	2.0; 56.0	2.0; 98.0
TJC*					
Median	11.0	6.0	4.0	2.0	2.0
Min; max	3.0; 28.0	0.0; 26.0	0.0; 24.0	0.0; 25.0	0.0; 28.0

Table 2. (Continued)

Characteristic*	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4
	n = 67	n = 66	n = 64	n = 59	n = 54
SJC*					
Median	8.0	3.0	1.5	2.0	1.0
Min; max	1.0; 28.0	0.0; 22.0	0.0; 20.0	0.0; 22.0	0.0; 22.0
Morning stiffness,* min					
Median	120.0	60.0	48.8	45.0	20.0
Min; max	20.0; 240.0	0; 240.0	0; 120.0	0; 240.0	0; 150.0
PGA VAS,* mm					
Median	80.0	45.5	34.5	29.0	22.5
min; max	21.0; 100.0	0.0; 93.0	0.0; 91.0	0; 87.0	0.0; 96.0
HAQ-DI score*					
Median	1.4	1.0	0.9	0.9	0.6
Min; max	0.0; 2.9	0.0; 2.8	0.0; 2.9	0.0; 2.5	0.0; 2.9
DAS28*					
Median	6.4	5.0	4.3	4.0	3.4
Min; max	5.2; 9.1	1.2; 8.2	1.8; 7.6	1.4; 7.6	1.5; 8.2
DAS28 <2.6, n (%)	0	6 (9.1)	8 (12.5)	7 (11.9)	15 (27.8)
DAS28 >2.6–3.1, n (%)	0	4 (6.1)	3 (4.7)	12 (20.3)	7 (13.0)
DAS28 >3.1–5.1, n (%)	0	28 (42.4)	29 (45.3)	21 (35.6)	20 (37.0)
DAS28 >5.1, n (%)	67 (100)	28 (42.4)	24 (37.5)	19 (32.2)	12 (22.2)
Treatment*					
csDMARD, n (%)	64 (95.5)	54 (81.8)	54 (84.3)	48 (81.3)	43 (79.6)
MTX (mono+comb), n (%)	53 (79.1)	48 (72.2)	47 (73.4)	43 (72.8)	39 (72.0)
MTX mono, n (%)	41 (61.2)	40 (60.6)	40 (62.5)	34 (57.6)	35 (64.8)
MTX comb, n (%)	12 (17.9)	8 (12.5)	4 (6.3)	9 (15.3)	4 (7.4)
SSL (mono+comb), n (%)	15 (22.3)	11 (16.7)	8 (12.5)	8 (13.6)	8 (14.8)
SSL mono, n (%) Other	6 (9.0)	5 (7.6)	4 (6.3)	5 (8.5)	5 (9.3)
csDMARD**mono, n (%)	4 (6.0)	2 (3.0)	3 (4.7)	2 (3.4)	1 (1.9)
bDMARD, n (%)	0	1 (1.5)	2 (3.1)	3 (5.0)	3 (5.5)
Other therapy, n (%)	67 (49.6)	58 (50.4)	53 (49.1)	49 (48.0)	44 (48.4)

Anti-CCP - anti-cyclic citrullinated peptide; bDMARD - biological disease-modifying anti-rheumatic drug; CRP - C-reactive protein; csDMARD - conventional synthetic disease-modifying anti-rheumatic drug; DAS28 - Disease Activity Score 28 joints; ESR - erythrocyte sedimentation rate; HAQ-DI - Health Assessment Questionnaire – Disability Index; MTX - methotrexate; PGA - Patient Global Assessment; RF, rheumatoid factor; SD - standard deviation; SJC - swollen joint count; SSL - sulfasalazine; TJC - tender joint count; VAS - visual analogue scale.

\* Performed for all patients attending the visit.

\*\* Leflunamid, hydrochloroquin, azathioprin.

patient self-assessment parameters (duration of morning stiffness, PGA VAS, and HAQ-DI scores) decreased. The median DAS28 value decreased from 6.4 at baseline to 3.4 at the end of the study observation. At the end of the study, 15 of 54 patients (27.8%) who attended the last study visit were in remission (DAS28 <2.6), but 12 patients (22.2%) still had high disease activity (DAS28

>5.1; Table 2). At the end of the study, anti-CCP was measured in 37 patients; 25 still had positive anti-CCP results. These patients had a tendency to have a higher RF and a higher TJC at baseline compared with patients with negative anti-CCP results (the demographic characteristics and disease activity parameters of these patients are presented in Table 3).

**Table 3.** Baseline demographic characteristics, disease activity parameters, and patient self-assessment parameters in subjects with positive or negative anti-CCP results at Visit 4

Characteristics	Subjects with positive anti-CCP results, <i>n</i> = 25	Subjects with negative anti-CCP results, <i>n</i> = 12
Women, <i>n</i> (%)	22 (88.0)	12 (100.0)
Mean (SD) age, years	54.0 (14.3)	55.1 (13.7)
Disease activity parameters		
CRP (mg/L)		
median	11.1	15.9
min; max	0.8; 276.8	0.5; 86.0
ESR (mm/h)		
Median	43.0	55.5
Min; max	18.0; 100.0	22.0; 100.0
RF (IU/mL)		
Median	69.3	58.5
Min; max	20.0; 1086	20.0; 378.4
TJC		
Median	13.0	9.5
Min; max	5.0; 28.0	5.0; 20.0
SJC		
Median	7.0	9.5
Min; max	1.0; 28.0	4.0; 20.0
DAS28 value		
Median	6.0	6.6
Min; max	5.3; 7.7	5.2; 8.0
Patients' subjective assessments		
Morning stiffness duration, min		
Median	120.0	120.0
Min; max	60.0; 240.0	60.0; 240.0
PGA VAS, mm		
Median	72.0	80.0
Min; max	21.0; 100.0	64.0; 100.0
HAQ-DI total score		
Median	1.1	1.3
Min; max	0.5; 2.8	0.0; 2.4

Anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; DAS28, Disease Activity Score 28 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire – Disability Index; PGA, Patient Global Assessment; RF, rheumatoid factor; SD, standard deviation; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue

There was a significant decrease in median values in most of the laboratory assessments (CRP, ESR), clinical assessments (TJC, SJC, DAS28), and patients' self-assessments (morning stiffness, PGA VAS, HAQ-DI) for the patients who had available data on disease activity for the comparative analysis. The median anti-CCP decreased from 123.0 to 71.4 IU/mL; however, this difference was not significant (Table 4).

At enrolment, 64 patients (95.5%) were treated with csDMARDs; 53 (79.1%) of them received methotrexate as monotherapy or as a part of a combination treatment. During the study, changes in csDMARD monotherapy and combination therapy were assessed. Only three patients received treatment with bDMARDs (infliximab). The proportions of the patients receiving oth-

er drugs (i.e., glucocorticoids, nonsteroidal anti-inflammatory drugs, etc.) remained similar throughout the study (Table 2).

At the beginning of the study, physicians considered anti-CCP results to be important in their decision-making process for the majority of patients (87.0%); it was ranked as of "highest possible importance" or of "significant importance." The importance of the anti-CCP results in the therapeutic decision-making process did not change significantly throughout the study (Table 5). Overall, the importance remained unchanged for the majority of patients ( $n = 30$ ; 55.6%), while most of the increases ( $n = 7$ ) or decreases ( $n = 13$ ) were one point on the 5-point scale ranging from "No importance at all" to "Highest possible importance."

**Table 4.** Comparison of disease activity parameters at baseline (Visit 0) and at the end of the study (Visit 4), median (min-max)

Disease activity characteristics (number of patients in the analysis)	Visit 0	Visit 4
Anti-CCP, IU/mL ( $n = 20$ )	123.0 (7.8–450.7)	71.4 (6.8–710.1)
CRP, mg/L ( $n = 37$ )	11.0 (0.8–279.8)	8.0 (0.6–29.0)***
ESR, mm/h ( $n = 54$ )	43.5 (11.0–100.0)	22.5 (2.0–98.0)*
RF, IU/mL ( $n = 23$ )	63.1 (8.0–1086.0)	71.5 (6.6–338.2)**
TJC ( $n = 54$ )	11.0 (5.0–28.0)	2.0 (0.0–28.0)*
SJC ( $n = 54$ )	8.0 (1.0–28.0)	1.0 (0.0–22.0)*
Morning stiffness, min ( $n = 54$ )	120.0 (60.0–240.0)	20.0 (0.0–150.0)*
DAS28 ( $n = 54$ )	6.3 (5.2–8.5)	3.4 (1.5–8.2)*
PGA VAS, mm ( $n = 54$ )	80.0 (21.0–100.0)	22.5 (0.0–96.0)*
HAQ-DI score ( $n = 51$ )	1.4 (0.0–2.9)	0.63 (0.0–2.9)*

Anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; DAS28, Disease Activity Score 28 joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire – Disability Index; PGA, Patient Global Assessment; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

\*  $p < 0.0001$ , \*\*  $p < 0.05$ , \*\*\*  $p < 0.01$  Wilcoxon signed-rank test.

**Table 5.** The importance of anti-CCP results in the therapeutic decision-making process,  $n$  (%)

Score	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4
	$n = 67$	$n = 66$	$n = 64$	$n = 59$	$n = 54$
No importance at all	0	0	0	0	0
Minor importance	0	1 (1.9)	2 (3.7)	2 (3.7)	2 (3.7)
Moderate importance	7 (13.0)	4 (7.4)	5 (9.3)	9 (16.7)	8 (14.8)
Significant importance	37 (68.5)	41 (75.9)	43 (79.6)	36 (66.7)	36 (66.7)
Highest possible importance	10 (18.5)	8 (14.8)	4 (7.4)	6 (11.1)	8 (14.8)

Anti-CCP, anti-cyclic citrullinated peptide.

No relationship between disease activity parameters and the physician's judgement of anti-CCP importance was observed at baseline. At the end of the study, the perceived importance of anti-CCP status tended to be higher in patients with more active disease. Namely, anti-CCP results were ranked as of the "highest possible importance" in eight patients that had a higher median number of tender and swollen joints and higher DAS28, PGA VAS, and HAQ-DI scores compared with patients for whom the anti-CCP result was ranked as less important (Table 6).

After one year of the study, rheumatologists indicated factors that were considered more impor-

tant than the anti-CCP results. For more than 50% of patients, the presence of erosions, significantly increased CRP, the duration of morning stiffness, multi-articular expanding, and RF status were considered more important (Table 7).

For nearly half of the patients who completed one year of observation ( $n = 26$ ; 48.1%), physicians would not have done anything different if the patient had an anti-CCP result opposite to what was observed at baseline. For four patients (7.4%), physicians would have changed their therapeutic approach, and for six patients (11.1%), physicians would have required further observations for decision-making.

**Table 6.** Disease activity parameters according to the physicians' judgement of anti-CCP importance at baseline (Visit 0) and the end of the study (Visit 4)

Disease activity	The importance of anti-CCP results in the therapeutic decision-making process									
	No importance at all		Minor importance		Moderate importance		Significant importance		Highest possible importance	
	Visit 0	Visit 4	Visit 0	Visit 4	Visit 0	Visit 4	Visit 0	Visit 4	Visit 0	Visit 4
Number of patients	2	0	3	2	10	8	42	36	10	8
Number of tender joints										
Median	7.0	–	7.0	2.0	12.5	1.5	12.5	1.0	7.5	20.0
Min; max	5; 9	–	3; 13	1; 3	9; 26	0; 11	5; 28	0; 28	5; 28	1; 26
Number of swollen joints										
Median	5.5	–	4.0	1.0	9.5	3.5	9.0	0.0	5.0	12.0
Min; max	4; 7	–	3; 4	0; 2	3; 20	0; 8	2; 28	0; 20	1; 24	0; 22
Morning joint stiffness duration, min										
Median	40.0	–	60.0	7.5	120.0	20.0	120.0	20.0	120.0	85.0
Min; max	20; 60	–	30; 180	0; 15	60; 240	0; 60	20; 240	0; 120	60; 180	0; 150
DAS28										
Median	5.7	–	5.8	3.2	6.8	3.3	6.4	3.3	6.0	6.9
Min; max	5.3; 6.1	–	5.4; 6.2	2.8; 3.6	5.2; 8.2	1.5; 5.7	5.2; 9.1	1.5; 7.9	5.3; 8.0	2.7; 8.2
PGA VAS, mm										
Median	83.5	–	85.0	19.5	80.0	28.0	80.5	17.0	76.0	82.0
Min; max	67; 100	–	80; 94	9; 30	21; 100	0; 90	37; 100	0; 93	50; 98	19; 96
HAQ-DI total score										
$n^*$	1	–	1	2	7	6	40	36	9	8
Median	1.1	–	1.4	0.3	1.4	0.6	1.6	0.6	1.0	2.4
Min; max	1; 1	–	1.4; 1.4	0.3; 0.4	0.0; 2.3	0.0; 1.6	0.0; 2.9	0.0; 2.9	0.5; 2.4	0.4; 2.7

Anti-CCP, anti-cyclic citrullinated peptide; DAS28, Disease Activity Score 28 joints; HAQ-DI, Health Assessment Questionnaire – Disability Index; PGA, Patient Global Assessment; SD, standard deviation; VAS, visual analogue scale.

\* Number of patients who completed the HAQ-DI.



**Table 7.** Factors important in the therapeutic decision-making process (Visit 4)

Factors important for therapeutic decision making	n (%)*
Anti-CCP result**	44 (81.5)
Factors considered more important than the anti-CCP result	
Presence of erosions	36 (66.7)
Significantly increased CRP	35 (64.8)
Multi-articular expanding	32 (59.3)
Duration of morning stiffness	32 (59.3)
RF status	30 (55.6)
Significantly accelerated sedimentation rate	26 (48.1)
Presence of rheumatoid nodules	24 (44.4)
Patient's subjective complaints	15 (27.8)
General symptoms (fever)	9 (16.7)
Presence of shared epitope	2 (3.7)

Anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; RF, rheumatoid factor.

\* Percentages were calculated based on the number of patients with available Visit 4 data ( $n = 54$ ).

\*\* Ranked by physicians of significant importance or highest possible importance.

## DISCUSSION

Anti-CCP has been shown to be an important serologic marker for the early diagnosis of RA, a differential diagnosis between RA and other rheumatic or immune diseases, as well as a prognosis of radiologic damage and progression (16). In addition to a role in the diagnosis, the measurement of serologic RA markers over the course of treatment may be used to assess treatment outcomes. Up until now, contradictory results have been reported regarding the response of the anti-CCP autoantibody system to RA treatment. Most of studies presented results in patients receiving treatment with bDMARDs (9, 14, 17), whereas studies regarding anti-CCP dynamics in patients with early RA receiving treatment with csDMARD therapy are still rare. This study assessed the impact of known anti-CCP status on clinical decision-making and the management of patients with RA in routine care. Patients in Lithuanian rheumatology centres were mostly treated with csDMARDs; only a few patients received bDMARD therapy. This approach is consistent with EULAR recommendations on the first-line treatment of patients with RA (8). Due to the strict biologic therapy reimbursement policy, which restricts the prescription of bDMARDs in the early stages of RA, the possibilities to control disease activity using these

medicines were limited. The Finnish Rheumatoid Arthritis Combination Therapy trial (FIN-RACo) indicated that csDMARD combination therapy is effective in patients with early RA (18). Thus, this treatment regimen could be used as an alternative treatment strategy to achieve remission in the early stages of RA. Throughout the 12 months of our study period, significant improvement was observed in CRP, ESR, joint swelling, and tenderness. The patients' subjective assessments improved as well. Anti-CCP levels were reduced during the course of treatment, but not significantly. According to the DAS28, 15 patients (27.8%) had remission (DAS28 <2.6) or decreased disease activity; however, 12 patients (22.2%) still had high disease activity. In selected rheumatology centres in Lithuania rheumatologists believed that anti-CCP results were "significant" or even of the "highest possible importance" for clinical decision-making for most patients (87%).

Clinical opinion about the importance of anti-CCP results did not significantly change over the duration of the study. Despite the perceived importance of the anti-CCP status, physicians stated that their clinical decisions would not be different if the anti-CCP status was opposite in nearly half of the study patients. The fact that the perceived importance of the anti-CCP status at the end of the study tended to be higher in

patients with more active disease, whereas no such tendency was observed at baseline is an interesting finding. In our study, after one year of patient treatment, the presence of erosions, significantly increased CRP, the duration of morning stiffness, multi-articular expanding, and RF status were considered more important factors than anti-CCP results. Since the importance of these factors was rated only at the end of the study, we were not able to investigate if there were any changes in their perceived importance over the course of treatment. It might be that physicians assessed all available examinations and tests only in the cases of unsuccessful disease control, whereas the assessment of the patients with controlled disease were restricted to clinical symptoms and standard disease activity parameters.

Similar results were reported from all five countries in which this study was conducted (Hungary, Romania, Estonia, Lithuania, and Croatia). Traditional inflammatory measures were more influential, whereas the anti-CCP status was considered as an important factor in treatment decisions for slightly more than half of the patients (58%) (15).

As the anti-CCP status was tested in only approximately half of the patients at the end of the study, the assessment of its importance in the decision-making process needs to be interpreted with caution. Due to the small number of participating sites and the small sample size, the trends observed in this study should be tested in a larger study to confirm these findings.

## CONCLUSIONS

Rheumatologists from selected study centres in Lithuania considered anti-CCP results of high importance for clinical decisions in the management of patients with RA. Nevertheless, after one year of treatment of RA, the presence of erosions, significantly increased CRP, the duration of morning stiffness, multi-articular expanding, and RF status were considered more important factors than anti-CCP results. The study revealed that decision-making process in the management of RA was based on multifactorial data. The role of anti-CCP as a single test in influencing decisions in the treatment of RA needs to be studied further.

## DISCLOSURES

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ANTI-KŪNŲ PRIEŠ CIKLINĮ CITRULINĮ  
PEPTIDĄ (ANTI-CCP) TYRIMO REZULTATŲ  
ĮTAKA ANKSTYVOJO REUMATOIDINIO  
ARTRITO PACIENTŲ GYDYMO TAKTIKAI:  
STEBĖJIMO TYRIMO REZULTATAI LIETUVOJE

*Santrauka*

**Įvadas.** Siekiant sukaupti duomenis apie antikūnų prieš ciklinį citrulinį peptidą (anti-CCP) ir kitų klinikinių rodiklių naudojimą klinikinėje praktikoje, taip pat įvertinti anti-CCP tyrimo rezultato reikšmę priimant klinikinius sprendimus, atliktas stebėjimo tyrimas, kuriame dalyvavo reumatoidiniu artritu (RA) sergantys pacientai.

**Metodai.** Keturiuose Lietuvos reumatologijos centruose tyrime dalyvavo ir 12 mėnesių prospektyviai stebėti 67 suaugę pacientai, kuriems neseniai buvo diagnozuotas RA. Duomenys buvo renkami iš ligos istorijų ir vertinant pacientą per įprastinį vizitą pas reumatologą. Pacientai pildė Sveikatos būklės įvertinimo klausimyną – negalios indeksą (angl. *Health Assessment Questionnaire – Disability Index*) ir nusa-

kė bendrą savo ligos aktyvumą vizualinėje analogijos skalėje (angl. *Visual Analogue Scale*). Gydytojai įvertino anti-CCP tyrimo rezultatų svarbą bei įvardijo kitus veiksnius, svarbius klinikiškaiems sprendimams.

**Rezultatai.** Iš 67 dalyvavusiųjų, tyrimą baigė 54 (80,6 %) pacientai. Iš pradžių gydytojai vertino, kad anti-CCP tyrimo rezultatai buvo svarbūs priimant klinikinius sprendimus 87,0 % pacientų. Anti-CCP svarbos vertinimas reikšmingai nesikeitė per visą tyrimą. Erozijos, reikšmingai padidėjęs C reaktyvusis baltymas (CRB), rytinio sustingimo trukmė, daugybiniai sąnarių pažeidimai ir reumatoidinio faktoriaus (RF) reikšmė buvo laikomi svarbesniais veiksniais nei anti-CCP tyrimo rezultatai po vienerių metų gydymo. Gydytojai nurodė, kad nebūtų keitę priimtų sprendimų beveik pusei tyrime dalyvavusių pacientų ( $n = 26, 48,1 \%$ ), net jei jų anti-CCP tyrimų rezultatai būtų buvę priešingi nei nustatyta tyrimo pradžioje.

**Išvados.** Tyrimo rezultatai atskleidė, kad sprendimai gydant RA buvo pagrįsti daugeliu veiksnių. Siekiant įvertinti anti-CCP, kaip vienintelio tyrimo, reikšmę priimant klinikinius sprendimus, reikalingi tolesni tyrimai.

**Raktažodžiai:** reumatoidinis artritas, anti-CCP antikūnai, stebėjimo tyrimas