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ORIGINAL ARTICLES

Impact of ACPA and RF titers and their reduction on therapeutic response after one year in rheumatoid arthritis patients

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ABSTRACT

Background: Rheumatoid arthritis (RA) is an autoimmune disease where autoantibodies, such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), are associated with disease severity and clinical outcomes. This study aimed to evaluate the reduction in RF and ACPA levels at one year in RA patients treated with bDMARDs or tsDMARDs and identify baseline factors associated with these reductions and their relationship with disease activity.

Methods: This prospective, longitudinal study included RA patients from the Reuma-check program who initiated bDMARDs or tsDMARDs. Clinical, laboratory, and imaging evaluations were conducted at baseline and one year, including RF and ACPA levels, SDAI, and CDAI.

The reduction was defined as the difference between the title at year and the baseline.

Results: Of 183 enrolled patients, 110 completed one-year follow-up. ACPA and/or RF reductions were observed in 38–50%, with median decreases of 38.7 IU/mL for ACPA and 12.5 IU/mL for RF. In logistic regression the predictive factor for decrease were: diagnosis less than 12 months (p = 0.007; OR = 9), smoking (p = 0.04; OR = 3). TNF blockers independently predicted reductions in both antibodies (OR=5, p=0.022). Patients with RF or ACPA reductions had significantly lower CDAI and SDAI scores at one year. For RF, median CDAI was 6 (IQR 3–19) vs. 11 (IQR 5–22) in those without reduction (p=0.03). ACPA reductions similarly correlated with improved disease activity scores.

Conclusions: Reductions in RF and ACPA occurred in nearly half of patients, correlating with improved clinical outcomes. Shorter disease duration, use of TNFb were key predictors of antibody reduction.

Keywords: Rheumatoid arthritis; Rheumatoid factor; Anti-citrullinated protein antibodies.

KEY MESSAGES

- Antibody Reduction (%): 38–50% of patients experienced a reduction in ACPA and RF after one year of treatment.
- Factors Associated with Reduction were, early disease (<12 months), high antibody levels, and positive ultrasound findings predicted antibody reduction.
- Impact on Disease Activity: Antibody reductions were linked to lower disease activity scores (CDAI, SDAI) at one year.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent inflammation of synovial joints, leading to progressive joint damage and functional disability[1]. Two key autoantibodies are essential for the diagnosis and classification of RA: rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA)[2].

The ACPAs and RF antibodies were considered a product of the immune response in RA and mainly helped in the diagnosis and classification of patients[2,3]. However, current research has clarified that ACPAs and RF play a critical role in the pathophysiology of RA. These autoantibodies are now recognized for their involvement in the disease process, including interactions with both environmental and genetic factors, their impact on T cell function, and their role in osteoclast differentiation, among others[4].

Understanding the concentration dynamics, isotypes and modifications of ACPAs, particularly in the preclinical phase of RA, has provided new insights into the

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mechanisms of the disease. Especially in predicting the development of the disease in patients with early symptoms such as arthralgia[5,6].

Some subanalysis of clinical trials and real-life data have shown that baseline antibody titers can predict therapeutic response; for example, patients treated with therapies targeting T or B cells have a better response when ACPA titers are high at the beginning of treatment, the inverse has been observed for RF and anti-TNF[7,8]. On the other hand, it has also been seen that decrease in these antibodies and very few cases of their negativity was also associated with better clinical results; some authors have called this phenomenon: immunological remission[9,10]. These data underline the potential of ACPAs and RF not only as specific markers of diagnosis and severity but also as guides for therapeutic decision-making[11].

The main aim of this study was to estimate the decrease in RF and/or ACPA titers at one year in a cohort of patients who start treatment with bDMARDs or tsDMARDs and to analyze baseline features associated with this decrease. Additionally, to evaluate the association between the therapeutic response and the baseline status of FR and ACPA, as well as their changes in titres

METHODS

Study design and patient population

We conducted a prospective, longitudinal cohort study of adult patients (≥18 years) diagnosed with rheumatoid arthritis (RA) according to the 2010 ACR/EULAR criteria. All patients initiated biologic or targeted synthetic DMARDs (bDMARDs or tsDMARDs) between August 2017 and March 2023 and were evaluated within the Reuma-Check® program at treatment initiation and again after one year. Reuma-Check® is a structured, standardized circuit established in 2017 for the early diagnosis and comprehensive management of inflammatory arthritis at our institution.

Reuma-check protocol

This program uses a station-based structure involving separate laboratory, imaging, and clinical assessments conducted on the same day. Operators are blinded to other findings to ensure unbiased evaluation. The clinical evaluation includes validated measures such as tender and swollen joint counts (TJC28, SJC28), visual analogue scales for global disease assessment (VAS-patient and VAS-physician), and the Health Assessment Questionnaire Disability Index (HAQ-DI) [12].

Clinical and demographic data

Demographic and baseline clinical characteristics were recorded, including age, sex, disease duration (months since RA diagnosis), smoking status, body weight, comorbidities, and current treatments. Disease activity was assessed using three validated composite indices: the Disease Activity Score with 28 joints using erythrocyte sedimentation rate (DAS28-ESR), the Clinical Disease Activity Index (CDAI), and the Simplified Disease Activity Index (SDAI). These indices incorporate tender and swollen joint counts (TJC28 and SJC28), patient and physician global assessments (VAS), and acute-phase reactants (for SDAI and DAS28-ESR). Disease activity categories were defined as remission, low, moderate, or high activity according to established thresholds.[13,14]

Laboratory assessments

Laboratory tests included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP, reported in mg/L), rheumatoid factor (RF) measured by immunoturbidimetry, and anti-citrullinated protein antibodies (ACPA) measured by chemiluminescence. ACPA titers were categorized into quartiles: Q1 (0–5 IU/mL), Q2 (5–50 IU/mL), Q3 (50–200 IU/mL), Q4 (>200 IU/mL). Antibody reduction analyses were limited to patients who were seropositive for RF or ACPA at baseline.

Baseline ultrasound evaluation

All US examinations were performed by the same rheumatologist with extensive experience on this imaging technique, on the same day of the clinical and laboratory evaluation. Patients were asked not to talk with the medical operator during the US examination. A MyLab 25 Gold (Esaote) machine with a multifrequency linear transducer (6-18 MHz) was used. A standardized hand US scanning method recommended by European League Against Rheumatism (EULAR)[15] was used. The following joints were assessed bilaterally: wrist, 2nd to 5th metacarpophalangeals and 2nd to 5th proximal interphalangeals, giving a total of 18 assessed joints per patient. Joint cavity widening, due to the presence of synovial fluid and/or synovial hypertrophy (grayscale synovitis) according to the "Outcomes measures in Rheumatology" (OMERACT) definitions[16], was evaluated at each joint. All joints were evaluated with PD technique to assess the presence of increased abnormal synovial vascularization. Intraarticular PD signal was scored on a semiquantitative scale 0-3 (Grade 0 = no intraarticular PD signal; G1 = presence of a single PD signal; G2 = more than two confluent foci of PD signal but occupying less than 50% of intraarticular area; G3= PD signal in more than 50% of the intraarticular area). In order to maximize PD sensitivity and minimize the presence of artifacts, the settings of PD were adjusted as follow: low pulse frequency repetition (PRF) (500 and

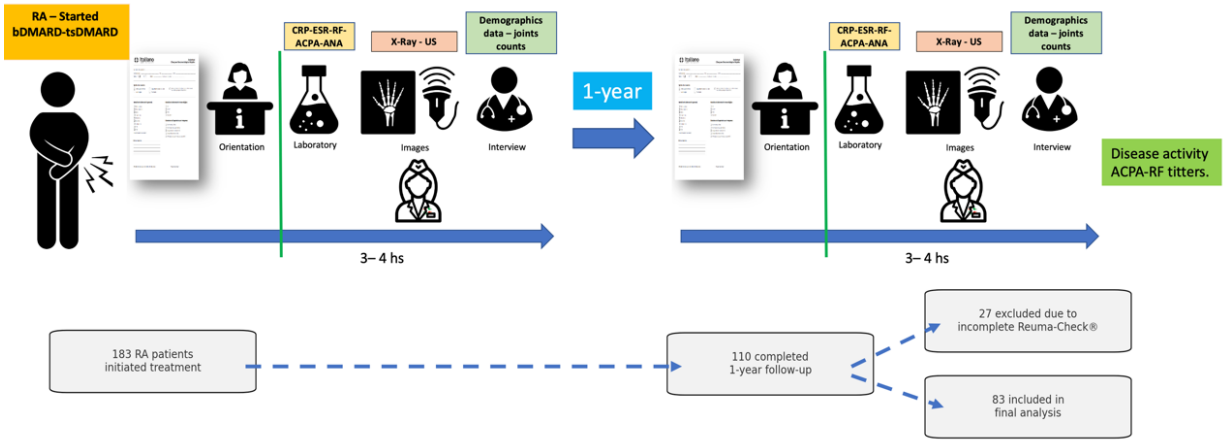

Figure 1. Rheuma-check circuit, procedures and patients´ flowcharts.

1000 Hz), dynamic range 20-40 dB, low wall filters and PD gain below the level at which color noise appeared in the underlying bone[17].

Radiographic evaluation

Standardized radiographs of hands and feet were performed at baseline and interpreted by a rheumatologist blinded to clinical and serologic results. The presence or absence of bone erosions was determined by an experienced medical rheumatologist at any joint included on the Sharp/van der Heijde score[18].

Follow-up and definition of antibody reduction

After one year of treatment, patients underwent a second Reuma-Check® evaluation including repeat RF and ACPA measurements and disease activity scoring. Antibody reduction was defined as any numerical decrease in RF or ACPA titer at 1 year compared with baseline, consistent with previous clinical practice studies that have used similar operational definitions to capture early serologic changes. Given the lack of established biological thresholds for a significant reduction outside of seroconversion, this approach allowed us to explore predictive factors within a hypothesis-generating framework. Ethical approval for the study was obtained from the Hospital Italiano de La Plata and informed consent was obtained from all patients (number evaluation 25328).

Statistical analysis

Descriptive statistics are presented as means with standard deviations (SD) or medians with interquartile ranges (IQR) for continuous variables, and as frequencies and percentages for categorical variables. Group comparisons were performed using the Student's t-test or Mann–Whitney U test for continuous variables, and the chi-squared or Fisher's exact test for categorical variables, as appropriate.

Univariate associations between categorical predictors and antibody reduction (RF and ACPA) were evaluated using contingency tables. Given the prospective design of the study and the time-forward nature of the antibody reduction outcome, relative risks (RRs) with 95% confidence intervals (CIs) were calculated to estimate the strength of associations. Multivariable analysis was conducted using logistic regression models to identify independent predictors of antibody reduction. Variables with $p < 0.10$ in univariate analysis or strong biological plausibility were included. Results are presented as odds ratios (ORs) with 95% confidence intervals.

Disease activity indices (CDAI, SDAI) were analyzed both as continuous variables and as categorical outcomes (remission and low disease activity), using established thresholds. Statistical significance was defined as $p < 0.05$.

RESULTS

Of the 183 RA patients who initiated treatment, 110 completed the one-year follow-up visit. However, 27 patients lacked one or more components of the full Reuma-Check® protocol (e.g., antibody testing or imaging data) and were therefore excluded from the final analysis. This selection reflects the variability inherent in routine clinical practice, where not all patients undergo comprehensive re-evaluation at fixed intervals.

Baseline features are shown in Table I. A decrease in ACPAs and RF levels was observed in 38–50% of the patients (Figure 2), with median reductions in titers of 38.7 (IQR 1–190) for ACPAs and 12.5 (IQR 3.6-77) for RF.

TABLE I. Baseline features

RA baseline Characteristic	N 83
Female (%)	81
Diagnosis < 12 months (%)	23.8
Age (Med-IQR)	57 (44-64)
Education (Med-IQR)	12 (8.5-15)
Disease duration (month) (Med-IQR)	48 (12-78)
Weight - Kg (SD)	77 (17.8)
Years of study (Med-IQR)	12 (10-15)
Smoking (%)	32.5
RF+ (%)	71
ACPA+ (%)	60
RF (Med-IQR)	37.5 (13.5-140)
ACPA (Med-IQR)	29 (0.5-185)
ACPA quartile 1 (%)	40
ACPA quartile 2 (%)	15
ACPA quartile 3 (%)	22
ACPA quartile 4 (%)	21
High titers RF (%)	52
High titers ACPA (%)	55
ESR (Med-IQR)	25 (10-41)
CRP mg/L (Med-IQR)	3 (1-8)
Double-seropositive (%)	55
Seronegative (%)	26.3
CRP+ (>5 mg/L)(%)	29
Comorbidities (%)	60
Lung disease (%)	11
csDMARDs (%)	89.5
Prednisone ≤ 10 (%)	24
Prednisone > 10 (%)	5
TNF-blockers (%)	75
CDAI (SD)	14.5 (8.9)
SDAI (SD)	15.3 (9.3)
DAS28 (SD)	3.9 (1.2)
HAQ (IQR)	0.5 (0.3-1)
MTX dose (SD)	15. (4)

RA: Rheumatoid arthritis, Med-IQR: Median and interquartile range, SD: Standard deviation, Kg: Kilogram, RF: Rheumatoid factor, ACPA: Anti-citrullinated protein antibodies, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, CRP: C-reactive protein, csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs, CDAI: Clinical Disease Activity Index, SDAI: Simplified Disease Activity Index, DAS28: Disease Activity Score with 28 joints, HAQ: Health Assessment Questionnaire, MTX: Methotrexate.

Baseline features and reduction of ACPAs and RF at one year

Baseline features were analyzed using univariate analysis for reduction of ACPAs, RF, and both at one year. Significant findings included: in early RA (≥12 months), 35% of patients with ACPAs reduction vs. 14% without (p=0.03; RR=3.2; 95% CI: 1.1-9). No significant decrease in ACPAs was observed in the first quartile (55% vs. 24.4%, p=0.005; 95% CI: 0.1-0.7), while the third quartile showed 34% reduction vs. 12% (p=0.016; RR=4; 95% CI: 1.2-9). US findings were significantly associated with ACPAs reduction: greyscale synovitis in 56% vs. 24% (p=0.003; RR=4; 95% CI: 1.5-10) and PD positivity in 42.5% vs. 10% (p=0.001; RR=7; 95% CI: 2-23). Baseline ACPAs titers were higher in the reduction group (88.3 vs. 0.8, p=0.004). Disease duration was shorter in those with ACPAs reduction (60 vs. 24, p=0.046). For RF reduction in early RA, 32% vs. 17% (not significant; p=0.09; RR=2.4; 95% CI: 0.8-7). PD-positive US showed a trend towards RF reduction (35% vs. 17%, p=0.06; RR=2.6; 95% CI: 0.9-8). Disease duration was shorter in the RF reduction group (60 vs. 24, p=0.023). Smoking prevalence was higher in RF reduction (44% vs. 21%, p=0.03; RR=2.8; 95% CI: 1.1-7.5). Reduction in both ACPA and RF was associated with early RA (41% vs. 15%, p=0.008; RR=4; 95% CI: 1.3-11), ACPAs in the third quartile (37% vs. 15%, p=0.02; RR=3.2; 95% CI: 1.1-9.3), and positive US (GS: 57% vs. 31%, p=0.02; RR=3; 95% CI: 1.1-7.4; PD: 45% vs. 15%, p=0.004; RR=4.4; 95% CI: 1.5-13). TNF blocker use was also associated with reduction in both antibodies (37% vs. 17%, p=0.04; RR=2.8; 95% CI: 1.1-8). (Figure 3).

Three logistic regression models were created, including predictor variables: for ACPA decrease, it was associated with diagnosis less than 12 months (p = 0.007; OR = 9), for RF smoking (p = 0.04; OR = 3). The decrease in both antibodies was associated with diagnosis less than 12 months (p = 0.002; OR = 10.7) and the use of TNF blockers (p = 0.022; OR = 5).

Baseline ACPAs and RF results regarding disease activity at one year

This analysis assessed remission and LDA as categorical outcomes using a univariate model based on baseline RF and ACPA titers, as presented in Table II. Baseline RF titers demonstrated no significant association with either remission or LDA at one year. Median RF titers were comparable between patients who achieved remission and those who did not (CDAI, p = 0.9; SDAI, p = 0.9) and between patients who achieved LDA and those who did not (CDAI, p = 0.8; SDAI, p = 0.4). Similarly, baseline ACPA titers showed no significant differences between remission groups (CDAI, p = 0.6; SDAI, p = 0.4). However, with respect to LDA, statistically significant associations were observed: patients in the fourth quartile of ACPA titers had a greater likelihood of achieving LDA, both in the CDAI model (p = 0.02; RR = 4 [1.1-12]) and in the SDAI model (p = 0.03; RR = 3 [1.1-7]).

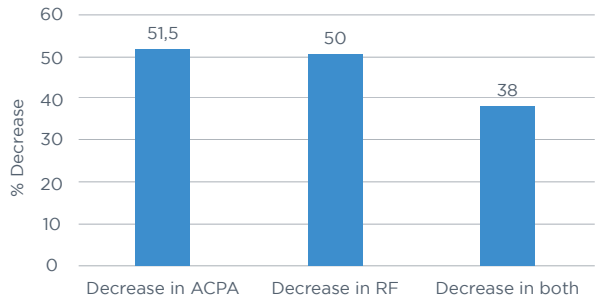

Figure 2. Frequency of decrease in antibody titer at one year

Antibody reduction at one year in relation to disease activity

The analysis evaluated the relationship between reductions in RF and ACPA titers at one year and disease activity status. CDAI and SDAI were assessed as both categorical variables (remission and LDA) (Table II) and continuous numerical variables (Figure 4). A reduction in RF was observed in 67% of patients in remission by CDAI, compared to 45% without remission (p = 0.09; RR = 2.5 [0.8-7]). Similarly, 63% of patients with LDA based on SDAI experienced RF reduction compared to 45% without LDA (p = 0.09; RR = 2.5 [0.8-7]). Median CDAI and SDAI values were significantly lower in patients with RF reduction, with values of 6 [IQR 3-19] versus 11 [IQR 5-22] for CDAI (p = 0.03) and 7 [IQR 3-20] versus 11 [IQR 6-24] for SDAI (p = 0.02). Patient-reported VAS scores were also significantly lower in patients with RF reduction (25 mm [IQR 10-60] vs. 50 mm [IQR 20-70], p = 0.04).

Regarding ACPAs, 61% of patients in remission according to CDAI showed a reduction in ACPA titers compared to 46% without remission (p = 0.2; RR = 2 [0.6-4]). For patients in LDA according to SDAI, 63% experienced a reduction in ACPA compared to 46% without LDA (p = 0.2; RR = 2 [0.6-4]). CDAI and SDAI scores were also significantly lower among patients with reduced ACPA titers (CDAI: 9 [IQR 4-18] vs. 11 [IQR 5-22], p = 0.04; SDAI: 9 [IQR 3-18] vs. 11 [IQR 6-25], p = 0.03), while VAS scores showed a trend towards being lower (35 mm [IQR 10-60] vs. 50 mm [IQR 20-70], p = 0.06).

The reduction of both RF and ACPAs was analyzed, with 39% of patients in CDAI-defined remission showing reductions in both antibodies, compared to 32% without remission (p = 0.6; RR = 1.3 [0.4-4]). Similarly, in SDAI-defined LDA, 42% of patients experienced reductions in both antibodies compared to 32% without LDA (p = 0.6; RR = 1.3 [0.4-4]). Median CDAI and SDAI values were also lower in patients with reductions in both RF and ACPA, although these differences were not statistically significant (CDAI: 6 [IQR 2-20] vs. 11 [IQR 5-18], p = 0.1; SDAI: 8 [IQR 3-21] vs. 11 [IQR 5-20], p = 0.09).

DISCUSSION

In our study, RA patients who initiated biological treatment and that were follow-up after one year, a decrease in ACPA and RF levels was observed in nearly 50%. Early RA was the most important factor associated with ACPAs reductions. US findings were also significantly associated with ACPAs reduction, while early RA was

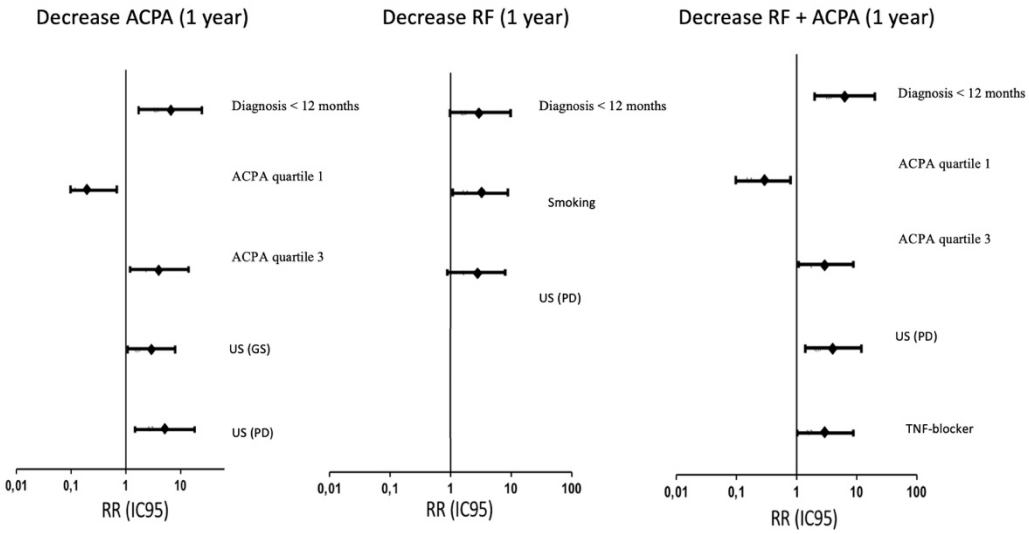

Figure 3. Baseline characteristics associated with antibody decrease at 1 year (univariate).

TABLE II. Basal and 1-year Antibody Status vs Disease Activity at Year (Categorical Yes/No)

n 83	Remission (1 year)								LDA (1 year)							
Basal Antibody status	CDAI yes (18)	CDAI no (65)	p	RR (95% IC)	SDAI yes (19)	SDAI no (64)	p	RR (95% IC)	CDAI yes (47)	CDAI no (36)	p	RR (95% IC)	SDAI yes (47)	SDAI no (36)	p	RR (95% IC)
RF + (%)	72	72	0.9	0.9 (0.3-3.2)	74	72	0.9	11 (0.3-3)	77	67	0.3	1.6 (0.6-4.3)	77	67	0.3	1.6 (0.6-4.3)
RF titter UI/ml (IQR)	34 (16-168)	32 (12-168)	0.9		45 (19-137)	31 (12-160)	0.8		45 (15-192)	31 (8-140)	0.4		45 (15-192)	31 (8-140)	0.4	
ACPA + (%)	61	60	0.9	1 (0.3-3)	68	58	0.4	1.5 (0.5-5)	68	50	0.09	2.1 (0.9-5)	68	50	0.09	2.1 (0.9-5.2)
ACPA titter U/ml (IQR)	168 (0.7-647)	15 (0.5-169)	0.6		168 (2-423)	15 (0.5-170)	0.6		83 (0.6-200)	6.4 (0.5-132)	0.08		83 (0.6-200)	6.4 (0.5-132)	0.08	
ACPA quartil 1 (%)	39	40	0.9	0.9 (0.3-2.3)	32	42	0.4	0.6 (0.2-1.8)	32	50	0.09	0.4 (0.2-.1)	32	50	0.9	0.5 (0.2-1.1)
ACPA quartil 2 (%)	11	17	0.5	0.6 (0.1-3)	16	16	0.9	1 (0.2-4)	13	19	0.4	0.6 (0.2-2)	13	19	0.4	0.6 (0.2-2)
ACPA quartil 3 (%)	22	23	0.9	0.9 (0.3-3)	26	22	0.7	1.2 (0.4-4)	32	11	**0.02**	**4 (1.1-12)**	32	11	**0.02**	**3.7 (1.1-12)**
ACPA quartil 4 (%)	28	20	0.5	1.5 (0.5-5)	26	20	0.6	1.4 (0.4-5)	23	19	0.6	1.2 (0.4-4)	23	19	0.6	1.3 (0.4-4)
Doble + (%)	56	57	0.9	0.9 (0.3-3)	63	55	0.5	1.4 (0.5-5)	64	47	0.1	2 (0.8-5)	64	47	0.1	2 (0.8-5)
high titers RF (%)	56	52	0.8	1.1 (0.4-3)	58	52	0.6	1.3 (0.4-4)	57	47	0.3	1.5 (0.6-4)	57	47	0.3	1.5 (0.6-4)
high titers ACPA (%)	56	55	1	1 (0.3-3)	58	55	0.8	1.1 (0.4-3)	66	42	**0.03**	**3 (1.1-7)**	66	42	**0.03**	**3 (1.1-7)**
Seronegative (%)	22	25	0.8	0.9 (0.2-3)	21	25	0.7	0.8 (0.2-3)	19	31	0.2	0.5 (0.2-1.4)	19	31	0.2	0.5 (0.2-1.4)
1 year Antibody status																
Decrease RF (%)	67	45	0.09	2.5 (0.8-7)	63	45	0.2	2 (0.7-6)	53	44	0.4	1.4 (0.6-3.3)	53	44	0.4	1.4 (0.6-3)
Decrease ACPA (%)	61	46	0.2	2 (0.6-4)	63	45	0.2	2 (0.7-6)	53	44	0.4	1.4 (0.6-3)	53	44	0.4	1.4 (0.6-3)
Decrease RF+ACPA (%)	39	32	0.6	1.3 (0.4-4)	42	31	0.3	1.6 (0.6-5)	33	33	1	1 (0.4-2.5)	33	33	1	1 (0.4-2.5)
RF titter UI/ml (IQR)	25 (14-290)	31 (11-200)	0.7		40 (15-244)	31 (10-230)	0.9		32 (16-295)	31 (10-162)	0.1		32 (16-295)	31 (10-162)	0.1	
ACPA titter U/ml (IQR)	121 (2-416)	18 (0.6-165)	0.3		121 (2-308)	18 (0.6-160)	0.3		47 (0.8-200)	7 (0.5-145)	0.1		48 (0.8-200)	7 (0.5-145)	0.1	

Med-IQR: Median and interquartile range, RF: Rheumatoid factor, ACPA: Anti-citrullinated protein antibodies, ESR: Erythrocyte sedimentation rate, CDAI: Clinical Disease Activity Index, SDAI: Simplified Disease Activity Index.

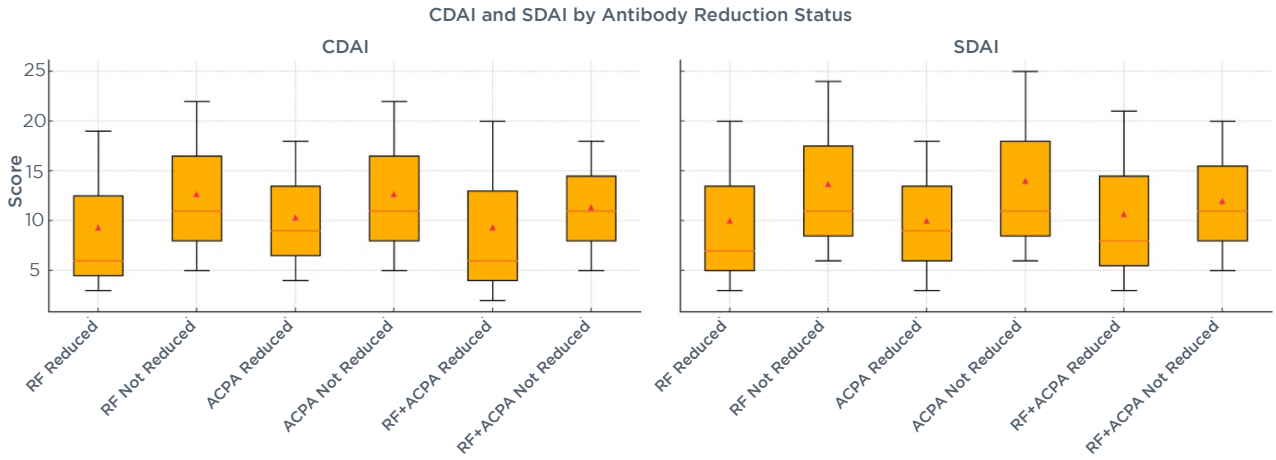

Figure 4. Reductions in RF and ACPA titers at one year and disease activity status.

linked to reductions in both ACPAs and RF. The use of TNF blockers was also associated with a reduction in both antibodies. Baseline levels of RF and ACPAs were analyzed in relation to disease activity at one year. No significant associations were found between baseline RF or ACPA levels and remission or LDA. However, patients with higher baseline ACPA levels had an increased likelihood of achieving LDA. The reduction in RF and ACPA levels after one year was also evaluated in relation to disease activity. Patients with reduced RF or ACPA titers generally had lower disease activity, as measured by CDAI and SDAI, compared to those without reductions.

One of the most relevant findings was the association of anti-TNF therapy with the reduction of autoantibodies after one year. Multiple studies and meta-analyses have not demonstrated a clear correlation between biomarkers and the response to advanced therapies in RA, and this remains an area of ongoing investigation[19]. Although studies like the ANSWER cohort have explored the differential effects of TNF inhibitors based on molecular structure (e.g., presence or absence of Fc region), our study was not designed to assess differential responses by agent. Therefore, while mechanistic insights may be relevant, our findings more broadly support the association between TNF inhibitor use and antibody reduction. [20]

Regarding the association between US findings and the reduction of ACPA and RF, data are limited. However, it is known that antibody status is linked to US activity findings[21]. Lastly, evidence on the relationship between early disease and antibody reduction is scarce. Nonetheless, it is plausible that early and timely treatment may lead to a reduction in autoantibodies, emphasizing the importance of early intervention in RA[22].

Regarding antibodies and response to treatments, the studies on abatacept relevant evidence. In the sub-analyses of the AMPLE and AVERT trials, baseline ACPA seropositivity was associated with better clinical response in patients treated with abatacept. This was particularly evident in patients with high ACPA titers, who showed a greater reduction in these antibodies during follow-up[7], [23]. These findings were also found in real-life studies such as OPAL[24,25].

Several studies have explored RF levels and their influence on the response to anti-TNF therapies. A post hoc analysis of the EXXELERATE study demonstrated that CZP, (Fc-free) was more effective than ADA (Fc-containing) in patients with high RF levels (>204 IU/mL), showing greater reductions in DAS28-CRP, a significantly higher proportion of patients achieving low disease activity (LDA) after 104 weeks, and more consistent drug concentrations, confirming the impact of the Fc fragment on treatment efficacy[26]. In a Spanish multicenter study, CZP also demonstrated higher retention rates compared to ADA and etanercept (ETA) in patients with elevated RF levels, likely due to the absence of the Fc fragment, which prevents interference with RF[8]. Finally, Ridha et al, highlighted that RF and ACPA seropositivity were associated with greater improvements in CDAI after one year of treatment with etanercept, although no differences were observed in DAS28 response. These findings emphasize the critical role of serological biomarkers in the selection and optimization of therapies in RA[27].

Delving into the reduction of antibodies during follow-up. In the AGREE study, treatment with abatacept plus methotrexate (MTX) resulted in a significant reduction in ACPA and RF levels, with higher rates of seronegative conversion compared to MTX alone. This seronegative conversion was associated with improved clinical outcomes, including higher remission rates, re-

duced radiographic progression, and more sustained remission[28]. Furthermore, the AVERT study reported a decrease in the number of epitopes recognized by ACPAs, with this reduction being more pronounced in the abatacept-MTX combination[23]. Additionally, recent findings by Konsett et al. highlighted that early changes in RF levels are predictive of long-term clinical outcomes, showing that patients with an early decrease of more than 50% in RF levels tend to achieve better clinical responses over time. These findings emphasize the importance of monitoring antibody levels early in the treatment process as a tool to optimize outcomes in patients with early RA[29].

Our study has several limitations. First, the relatively small sample size may affect the generalizability of the findings. Second, the absence of a control group not receiving biological treatment limits the ability to directly attribute changes in antibody levels to the therapies administered. Third, the binary definition of antibody reduction (yes/no) may oversimplify the continuous nature of serologic responses, potentially masking dose–response relationships and introducing misclassification bias—particularly in cases of minor fluctuations. Although a ≥50% reduction threshold might better reflect a clinically meaningful change, we did not apply this stricter definition due to the low number of patients achieving such a decrease, which would have compromised statistical power. Lastly, although 183 patients initiated treatment, only 83 were ultimately included in the final analysis due to incomplete evaluations in the Reuma-Check® protocol at the one-year follow-up. This reflects the realities of routine clinical care, where not all patients undergo comprehensive re-evaluation, and does not represent true loss to follow-up. Nonetheless, this may introduce a degree of selection bias. Future studies with larger cohorts are needed to validate more stringent thresholds and continuous modeling approaches for serologic change.

One of the main strengths of our study is the detailed analysis of ACPAs and RF reduction in RA patients, which allowed us to evaluate their relationship with clinical response and disease activity using multiple tools (CDAI, SDAI, and ultrasound). Another significant strength is the Reuma-Check® is a validated tool in various studies, which provides a comprehensive evaluation of the patient. Additionally, Reuma-Check® offers complete data obtained by the same operators following a standardized[6,30,31].

While reductions in RF and ACPA titers have been previously reported, our study contributes novel insights by identifying clinical, serological, and ultrasound-based predictors of such reductions in a prospective cohort using a standardized and blinded evaluation protocol (Reuma-Check®). Moreover, we assessed the relationship between these serologic changes and disease activity using validated composite indices in real-world clinical practice. To our knowledge, this is among the first studies to explore these associations in a Latin American population, where data on biomarker dynamics and their clinical implications remain scarce.

In conclusion, our study showed that reductions in ACPA and RF titers occurred in a substantial proportion of RA patients treated with bDMARDs or tsDMARDs, particularly those with early disease and those receiving TNF inhibitors. These reductions were modestly associated with lower disease activity scores at one year. However, given the limited effect sizes and the absence of statistically significant differences in remission rates, the clinical utility of autoantibody reduction as a reliable biomarker of treatment response remains uncertain. Further prospective studies are warranted to clarify their prognostic role.

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