Methods: The CareRA trial included 379 patients with early RA (≤ 1 year) fulfilling 1987 or 2010 ACR criteria and naïve to disease modifying anti-rheumatic drugs (DMARDs). Patients were randomized to one of four different intensive treatment strategies based on methotrexate (MTX) monotherapy or synthetic (cs)DMARD combinations with or without glucocorticoid (GC) bridging. Before randomization, stratification into a high- or low-risk group according to classical poor prognostic markers (presence of erosions, positivity to rheumatoid factor (RF) and/or anti-citrullinated protein antibody (ACPA), and elevated disease activity) was conducted. One of these strategies, COBRA Slim, a combination of MTX and a prednisone remission induction scheme stepping-down from 30 mg QD, was initiated in 141 patients from both risk strata, of which 38 were negative for both RF and ACPA (seronegative). Following the treat-to-target principle, using the disease activity score in 28 joints with C-reactive protein (DAS28CRP), treatment adaptations were steered at low disease activity (≤ 3.2), while aiming for remission (< 2.6) as final outcome.

The "as observed" population was analysed for differences in disease activity and radiographic progression between seronegative and seropositive patients at several time points during the 2-year study using independent sample t-test, Man Whitney-U or adjusted X^2 (Yate's correction for small samples). Survival analysis using Kaplan Meier was employed for time to first response to treatment. First response to treatment was defined as achieving first remission (DAS28CRP < 2.6) or first relevant improvement (Δ DAS28CRP > 1.2) after screening. Sensitivity analyses were applied on the complete CareRA cohort.

Results: Seronegative patients starting COBRA Slim ($n=38$), had similar age (53 vs 51 years, $p=0.52$), body mass index (25.5 vs 26.7, $p=0.08$), symptom duration (7.9 vs 7.2 months, $p=0.23$), presence of erosions (24% vs 23%, $p=0.99$) and gender distribution (82% vs 63%, $p=0.06$), compared to seropositive patients ($n=103$). However, parameters of disease activity were higher in seronegative patients at screening: DAS28CRP (5.1 vs 4.5, $p=0.01$), 28 swollen joint count (8.2 vs 5.7, $p=0.02$) and 28 tender joint count (10.3 vs 6.9, $p=0.006$). These results were corroborated when analysing the entire CareRA cohort.

The mean disease activity was significantly higher in seronegative patients at the first stages (week 8 and 16), but became comparable by year 1 and 2 (Table 1). There was a significant difference in time to first treatment response between seronegative and seropositive patients, despite being treated with the same strategy, as depicted in the inverted Kaplan Meier plot (Figure 1).

Conclusion: In conclusion, CareRA participants with seronegative RA had a higher initial disease activity, longer time to experience a first treatment response, but achieve comparable remission status as seropositive patients with COBRA Slim, a combination of MTX with moderate dose GC bridging. This provides further evidence that, seronegative RA can no longer be considered a milder form of disease and requires an equally intensive initial treat-to-target therapy as seropositive RA.

Abstract THU0094 –Table 1. demographics

Table 1: Disease activity and radiographic progression throughout the 2-year trial.

DAS28CRP at	SERONEGATIVE	SEROPOSITIVE	p-value
W8	2.9 $\pm$ 1.2 (35)	2.3 $\pm$ 1.0 (100)	0.006
W16	2.6 $\pm$ 1.1 (35)	2.2 $\pm$ 0.9 (100)	0.023
Y1	2.3 $\pm$ 1.0 (33)	2.3 $\pm$ 1.0 (93)	0.929
Y2	2.0 $\pm$ 0.9 (27)	2.1 $\pm$ 0.8 (87)	0.162
SHARP VAN DER HEIJDEN SCORE	SERONEGATIVE	SEROPOSITIVE	p-value
W0	1.3 $\pm$ 2.2 (33)	1.1 $\pm$ 2.2 (78)	0.156
W28	1.4 $\pm$ 2.3 (31)	1.2 $\pm$ 2.5 (77)	0.107
Y1	1.7 $\pm$ 2.4 (29)	1.3 $\pm$ 2.8 (79)	0.026
Y2	1.5 $\pm$ 2.2 (22)	1.8 $\pm$ 3.4 (70)	0.384
Δ Y1-W0	0.3 $\pm$ 0.5 (28)	0.3 $\pm$ 0.9 (71)	0.345
Δ Y2-W0	0.3 $\pm$ 0.8 (21)	0.8 $\pm$ 1.6 (62)	0.724

Data is presented as mean $\pm$ standard deviation, ( ) number of patients, w=week, y=year, Δ =change/delta

Abstract THU0094 – Figure 1

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THU0095

CIGARETTE SMOKING AS PREDICTOR OF INADEQUATE RESPONSE TO METHOTREXATE IN RHEUMATOID ARTHRITIS PATIENTS NAÏVE TO DMARDS

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Background: Methotrexate (MTX) is the gold standard as first line treatment in rheumatoid arthritis (RA). Identifying predictors of response to MTX should be crucial in the view of a personalized therapy.

Objectives: To identify prevalence and potential clinical baseline predictors of inadequate response (IR) to MTX in RA patients naïve to disease modifying anti-rheumatic drugs (DMARDs)*.

Methods: Data of 233 consecutive RA patients (according to ACR/EULAR 2010 criteria) naïve to traditional and biologic DMARDs, attending the AOU University Clinic, Rheumatology Unit, Monserrato (Cagliari), Italy, were analyzed. Table 1 shows baseline demographic, clinical and serological characteristics of the cohort. Patients failing to reach low disease activity state (DAS 28 > 3.2) at 6 months (T1) since the beginning of MTX (T0) or patients undergoing therapeutic modification for persistently high disease activity (switch or addition of other traditional or biological DMARDs) before T1 were considered as IR. By univariate analysis, demographic, clinical and serological factors recorded at T0 were evaluated as potential predictors of IR at T1. Afterwards, factors with $p < 0.10$ were included in a logistic regression model, to identify independently associated factors to IR ($p < 0.05$). Odd-Ratio (OR) with 95% confidence interval (CI) was calculated.

Results: At T1, 104 patients (44.6%) were classified as IR to MTX. In univariate analysis, factors significantly associated with IR were: female

gender (69.2% vs. 54.3%; $p=0.02$), condition of "current smoker" (22.1% vs. 10.9%; $p=0.012$), ESR [median (IQR): 30.0 (19.0-48.0) vs. 40.0 (25-62); $p=0.035$] and DAS28 (mean $\pm$ standard deviation: 5.5 ± 1.1 vs. 5.2 ± 1.3 ; $p=0.037$). High-titre positivity for RF and/or ACPA (57.3% vs. 45.9%; $p=0.095$) and high cumulative steroids dose [852 mg (300-1200) vs. 691 mg (0-150); $p=0.071$] were numerically higher in IR.

In multivariate analysis, the "current smoker" condition was confirmed as the only independent factor associated with IR to MTX after 6 months of treatment (OR: 2.333, 95% CI: 1.132-4.805; $p=0.022$).

No significant association between ex-smoker status and IR to MTX was demonstrated. This result was confirmed even after stratification of ex-smokers over the time since smoking stop. Finally, for both current smokers and ex-smokers, the duration of exposure to cigarette smoking did not show any significant association with IR.

Conclusion: In this RA cohort, the condition of "current smoker" was the only predictor of IR to MTX. This observation, together with the lack of association between previous smoking habit and IR to MTX, further prompt to recommend cessation of cigarette smoking in patients with RA who begin treatment with MTX.

Table 1. Baseline demographic, clinical and serological features.

Gender, n (%) Female	142 (60.9%)
Age at enrollment, mean ($\pm$ SD), yrs	54.2 ($\pm$ 14.5)
RF/ACPA positivity, n (%)	132 (60.5%)
BMI, mean ($\pm$ SD) Kg/m ²	24.9 ($\pm$ 4.1)
Current smoker, n (%)	27 (15.9%)
Ex smoker, n (%)	89 (38.2%)
DAS28, mean ($\pm$ SD)	5.3 ($\pm$ 1.2)
TJC28, median (IQR)	9 (5-15)
SJC28, median (IQR)	5 (2-10)
ESR, mean ($\pm$ SD)	39.9 ($\pm$ 24.9)
X-ray Erosion, n (%)	36 (22.3%)
Rheumatoid Nodules, n (%)	8 (3.4%)

DS: standard deviation; RF: factor rheumatoid factor; ACPA: anti-citrullinated peptide antibodies; BMI: body mass index; DAS-28: disease activity score; TJC: tender joint count; SJC: swollen joint count; ESR: erythrocytes sedimentation rate.

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THU0096

PERSISTENT HIGH DISEASE ACTIVITY IN THE ANTI-CARBAMYLATED PROTEIN ANTIBODY POSITIVE EARLY ARTHRITIS PATIENTS INDEPENDENTLY OF TREATMENT

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Background: There is great interest in the identification of prognostic biomarkers informing early therapeutic decisions for the improvement of rheumatoid arthritis (RA) evolution. Promising results in early arthritis (EA) patients indicate the anti-carbamylated protein antibodies (ACarPA) may serve this function. In effect, they are associated with high baseline disease activity and, in our patients, with less improvement in the first 6-months of follow-up. This association was independent of sex, age at diagnosis, time since symptoms onset, smoking and the year of onset. However, the influence of the treatment has not been explored yet.

Objectives: We aimed to explore the influence of the initial treatment on the persistent high disease activity associated with the presence of ACarPA in EA patients.

Methods: Samples were obtained at the first visit of two EA cohorts from Hospital Universitario La Paz and Hospital Universitario La Princesa, which recruit patients within one year from the clinical onset. Information on the initial treatment and the disease activity at the baseline and at 6-months of follow-up was available from 546 patients. Treatment was categorized according to the use of corticosteroids, methotrexate (MTX) and other DMARDs, and considering changes in the first 6 months. In addition, MTX dose was considered either quantitatively or as a dichotomous

variable (≥ 12.5 mg and < 12.5 mg). Main effects general linear regression was used for analysis, including the treatment and the other confounders as covariates.

Results: A large fraction (83%) of the EA patients received specific treatment from the initial visit. It comprised DMARD (50.1%), corticosteroids (10.6%), or a combination of both (39.3%). The most common DMARD was MTX (82.2%), whereas less frequently used medications included sulfasalazine (5.4%), leflunomide (3.2%), hydroxychloroquine (8.1%) and other (1.0%). The 35.5% of the treated patients maintained the treatment during the 6-month follow-up. The presence of ACarPA was associated with a 0.45 higher mean baseline DAS28 and with less decrease of DAS28 (Δ DAS28) from the baseline to 6 months of follow-up ($\beta = 0.08$, $p = 0.016$), as already communicated. This latter association persisted without modification after accounting for the initial treatment (DMARD, corticosteroids, and changes in treatment). In addition, it was independent of the consideration of all DMARDs in a single group, or separated into two categories: MTX and the other. Similarly, the association was independent on MTX dose, defined both as a categorical or a quantitative variable.

Conclusion: The association of ACarPA with a persistently increased disease activity in EA patients is independent of the initial treatment. These results reinforce the possibility that ACarPA can be useful as prognostic biomarkers for the first 6 months of evolution and indicate the need for personalized management of the patients carrying ACarPA.

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THU0097

VALUE OF ANTIBODIES AGAINST ACETYLATED PEPTIDES FOR THE CLASSIFICATION OF PATIENTS WITH EARLY ARTHRITIS

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Background: Patients with rheumatoid arthritis (RA) achieve the best response when they receive adequate treatment as soon as possible. This fact motivated the modification of the classification criteria by the ACR and the EULAR in 2010 to enable early detection. One of the changes is the increased weight conferred to the autoantibodies: rheumatoid factor and anti-citrullinated protein antibodies. As these antibodies are not present in all patients, other antibodies could provide similar information. In this regard, the antibodies that recognize an acetylated peptide from mutated vimentin (Anti-Acetylated Peptide Antibodies or AAPA) stand out (1).

Objectives: We aimed to evaluate the AAPA predictive value at the baseline visit for the classification of early arthritis patients.

Methods: A total of 438 patients with available samples and information were randomly selected from two early arthritis clinics. The AAPA were determined in baseline sera as previously described (1). Two peptides were included, one acetylated at a lysine (anti-AcLys) and the other at an ornithine (anti-AcOrn) and considered either individually or combined. The sensitivity, specificity, predictive positive (PPV) and negative (PNV) values and the AUC of the ROC curve were assessed. Logistic regression was also applied adjusting for age, sex, the centre of origin, anti-CCP, and RF. The study was approved by the ethics committee of the Hospital Universitario La Paz, the Hospital Universitario La Princesa, and Autonomo de Galicia.

Results: The AAPA at baseline were sensitive and specific for the classification of the patients fulfilling RA criteria (46.8%) at the end of the 2-year follow-up (table 1). Specifically, the anti-AcOrn antibodies were slightly