Anti-carbamylated protein antibodies are associated with early abatacept response in rheumatoid arthritis

Comment on:
Anti-carbamylated protein antibodies as a clinical response predictor in rheumatoid arthritis patients treated with abatacept

Sirs,
We read the article by Kumar et al., which is the first to address the association between anti-carbamylated protein antibodies (anti-CarP) and the response to abatacept (ABA) in rheumatoid arthritis (RA), with great interest. The most striking findings were the better response (a significant reduction in δ-DAS28-PCR) to ABA in anti-CarP positive patients and a reduction in anti-CarP levels. No differences in the therapeutic response were found when analyzed according to ACPA nor rheumatoid factor status (1).

This prompted us to assess whether we could reproduce their observations. The PACTABA study is a Spanish multicenter, observational sub-study of the ASCORE trial (NCT02905556) (2), including active RA patients who had previously failed with ≥1 conventional DMARD or ≥1 biologic therapy. Subcutaneous ABA was administered (125 mg weekly) and patients were followed prospectively. The therapeutic response was determined by δ-DAS28 (baseline to 3 months) and EULAR response criteria at 3 months of follow-up. Seventy-nine patients were included, of whom only the 65 who had sufficient information for data extraction were analysed. Anti-CarP were assessed at 0 and 3 months by a homemade ELISA test using fetal calf serum (cut-off ≥132.5 AU; 96% specificity vs. healthy population). The study is supported by Bristol Myers Squibb (BMS).

Fifty-two patients were female (80%), with mean age of 55.1(±13.9) years and a disease duration of 9.5(±7.2) years. Eighty percent were ACPA positive and 58.5% had previously failed with ≥1 biologic therapy. At baseline, 28(43.1%) patients were anti-CarP positive and no difference in DAS28 was observed according to anti-CarP status. At three months of follow up, a significant reduction in δ-DAS28 was observed in anti-CarP positive patients compared with anti-CarP negative patients (-4.8 AU vs. +3.4 AU; p<0.018) (Fig. 1b). In addition, responders showed a significant reduction in anti-CarP levels from 0 to 3 months on treatment with ABA, a finding not observed in non-responders (-4.8 AU vs. +3.4 AU; p<0.023). No differences were observed in δ-DAS28 according to ACPA status (Fig. 1c) or ACPA baseline levels between responders and non-responders (Fig. 1d).

Our findings reaffirm the report by Kumar et al. and posit a debate on whether anti-CarP are an ABA response biomarker in RA patients. This could be due to the similar chemical structure in the antigenic targets (homocitrulline and citrulline) of anti-CarP and ACPA or to the wide overlap between the two antibodies in RA patients. Nonetheless, the environmental and genetic backdrops of the two autoantibodies differ (3). Anti-CarP and ACPA are, independently, poor RA prognosis factors (4,5) and inhibition studies have shown that the overlap is merely a casual finding (6).

ACPAs have been shown to be a reliable ABA response biomarker in post hoc analyses from randomised controlled trials and large observational studies (7-9). However, neither we nor Kumar et al. (1) found differences in the treatment response according to ACPA status. This might be explained by the small sample size of the two studies.

The low sensitivity of anti-CarP (10), together with the overlap of anti-CarP with ACPA, casts doubt on the predictive value of anti-CarP in the treatment response to ABA. However, the findings of Kumar et al. and ourselves suggest that anti-CarP are an early response biomarker for ABA, which may be more specific but less sensitive than ACPA. Testing for anti-CarP could be especially useful in ACPA negative patients. These are exploratory analysis and the results should be interpreted with caution. Further studies should include larger populations and analyse long-term outcomes.

R. CASTELLANOS-MOREIRA1, MD, PhD
A. GOMEZ2, PhD
I. HARO2, MSc, PhD
V. RUIZ-ESQUEDE2, MD, PhD
S. MARSAL2, MD, PhD
R. SÀNCHAR2, MD, PhD

1Arthritis Unit, Rheumatology Department, Hospital Clinic of Barcelona, Barcelona;
2Rheumatology Research Group, Vall d’Hebron Research Institute, Barcelona;
3Unit of Synthesis and Biomedical Applications of Peptides, Institute of Advanced Chemistry of Catalonia (IQAC-CSIC), Consejo Superior de Investigaciones Científicas, Barcelona, Spain.
Letters to the Editors

Please address correspondence to:
Raimon Sanmarti,
Arthritis Unit - Rheumatology Department,
Hospital Clinic of Barcelona,
Villarroel 170,
08036 Barcelona, Spain.
E-mail: sanmarti@clinic.cat

Funding: this study was supported by
Bristol-Myers Squibb.

Competing interests: S. Marsal and R. Sanmarti
received grant support for this work; the other
authors have declared no competing interests.

References

1. KUMAR R, PIANTONI S, BOLDINI M et al.: Anti-
carbamylated protein antibodies as a clinical re-
sponse predictor in rheumatoid arthritis patients
with rheumatoid arthritis and their relationship
to genetic risk factors, cigarette smoking and
other autoantibodies. Ann Rheum Dis 2014; 73:
1761-8.

2. ALTEN R, MARIETTE X, BUCH M et al.: AB0361
ASCORE, a 2-year, observational, prospective
multicentre study of subcutaneous abatacept for the

3. JIANG X, TROUW LA, VAN WESEMAEL et al.: ANTI-CarP antibodies in two large cohorts of pa-
tients with rheumatoid arthritis: a study exploring replication and the added value to
ACPA and rheumatoid factor. Ann Rheum Dis 2017;
76: 112-8.

4. HUMPHREYS JH, VERHEUL MK, BARTON A et
al.: Anticarbamylated protein antibodies are associ-
ated with long-term disability and increased disease
activity in patients with early inflammatory arthri-
tis: results from the Norfolk Arthritis Register. Ann
Rheum Dis 2016; 75: 1139-44.

5. JUAREZ M, BANG H, HAMMAR F, REIMER U et
al.: Identification of novel antiactetylated vimen-
tin antibodies in patients with early inflammatory

6. ALTEN R, MARIETTE X, LORENZ HM et al.: Predicators of abatacept retention over 2 years in
patients with rheumatoid arthritis: results from the
real-world ACTION study. Clin Rheumatol 2019;

7. HARROLD LR, LITMAN HJ, CONNOLLY SE et al.: Comparative effectiveness of abatacept versus
rheumatoid arthritis who are anti-CCP positive in
the United States Corrona Registry. Rheumatol Ther

8. SOKOLOVE J, SCHIFF M, FLEISCHMANN R et
al.: Impact of baseline anti-cyclic citrullinated pep-
tide-2 antibody concentration on efficacy outcomes
following treatment with subcutaneous abatacept or
adalimumab: 2-year results from the AMPLE trial.

9. VERHEUL MK, BOHRINGER S, VAN DELFT MAM
et al.: Triple positivity for anti-citrullinated protein
autoantibodies, rheumatoid factor, and anti-carba-
mylated protein antibodies conferring high specific-
ity for rheumatoid arthritis: implications for very
early identification of at-risk individuals. Arthritis
Rheumatol 2018; 70: 1721-31.