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 (NCT02090556) (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 (-1.904 *vs*. -0.212; $p<0.005$) (Fig. 1a). According to anti-CarP status, a similar proportion achieved a EULAR response (13/32(41%) *vs*. 8/21(38%); p=NS). However, EULAR responders had higher baseline anti-CarP levels than non-responders (451.3±675.4 *vs*. 152.6±158.3; p=0.018) (Fig. 1b). In addition, responders showed a significant reduction in anti-CarP levels after 3 months on treatment with ABA, a finding not observed in non-responders (-84.8 AU *vs*. +34.92 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).

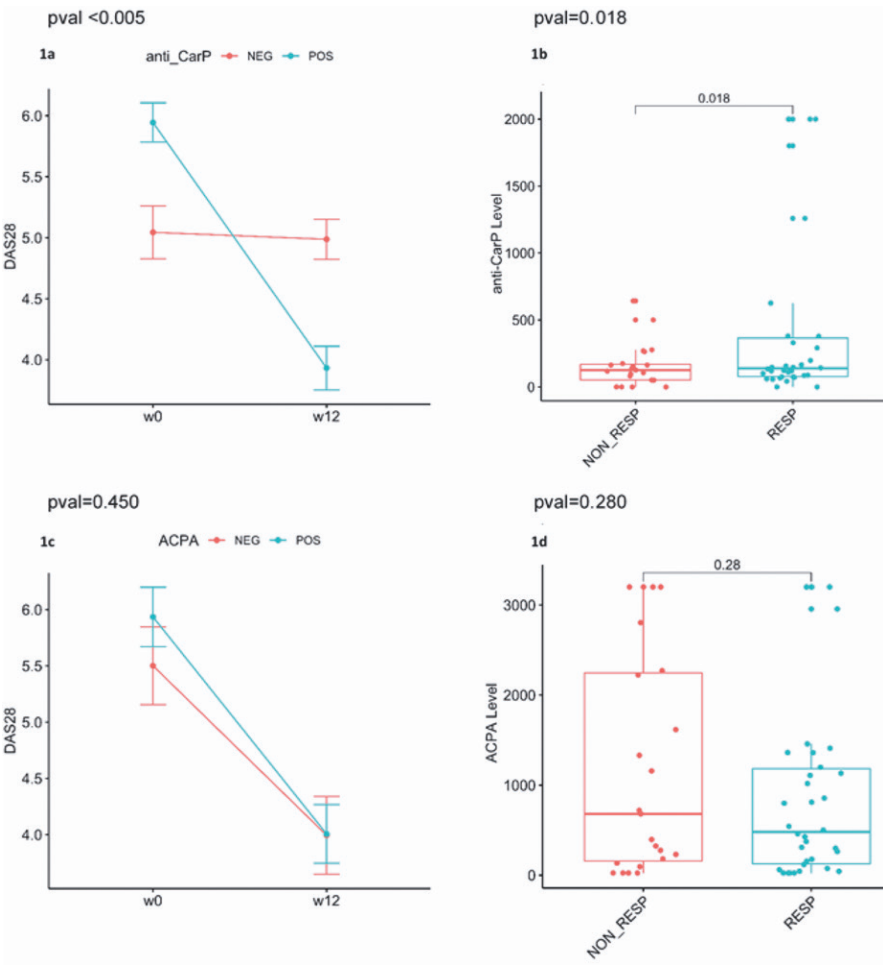

Fig. 1. **a**: δ-DAS28 according to anti-CarP status; **b**: anti-CarP levels according to EULAR response critieria; **c**: δ-DAS28 according to ACPA status; **d**: ACPA levels according to EULAR response critieria.

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 backgrounds 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).

ACPA 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.

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