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

by Castellanos-Moreira *et al*.

Sirs,

We read with interest the letter of Castellanos-Moreira *et al*. (1), a comment on our original study on the potential role of anti-carbamylated protein antibodies (anti-carP) as response predictor in rheumatoid arthritis (RA) patients treated with abatacept (ABA), a soluble fusion protein (CTLA4-Ig) acting as lymphocyte co-stimulation blocker (2). The main observation of our study was that the patients with the anti-carP positivity had a greater reduction of disease activity after therapy, if compared with negative ones. This was reinforced by our colleagues who demonstrated that anti-carP positive RA patients treated for 3 months with ABA had a greater significant reduction in disease activity if compared with negative ones, adding that EULAR responders had higher baseline levels than non-responders (1). The reduction of disease activity was also accompanied by a significant decrease of the titers which was found only in responders (1). In both studies, the decrease of antibodies titers after therapy, in parallel with the reduction of DAS28-CRP, supports the clinical association between anti-carP titres and disease activity, as demonstrated by previous observations (3). In our cohort, in which more than the 50% of patients was responders, we could not demonstrate a relation between anti-carP titres and the major responsiveness to the drug, as in the Spanish one, in which a balanced number of patients were in the responder and in the non-responder groups (1, 2). Taken together, our findings suggested that the determination of anti-carP serum levels could be useful in predicting clinical response to ABA (1, 2). The potential effects of ABA in reducing immunoglobulins and the number of post- switched memory B-cells, was previously demonstrated by us (4), reinforcing the evidence that the co-stimulation blockade induced by the drug could have effects on B-cell polyclonal activation during the course of the disease (5, 6). Further investigations are necessary to better clarify if the reduction of anti-carP after ABA therapy was related to the improvement of clinical status or if the peculiarity of ABA mechanism of action makes them suitable to be specific drug-related biomarkers, such as anti-CCP, as demonstrated by registry data and *post-hoc* analysis of clinical trials (7, 8). The same results in response prediction were not observed if dividing the cohorts according with RF or anti-CCP positivity in ours and in Spanish cohort, probably because the number of seropositive patients (*i.e*. RF and/or anti-CCP positive subjects) was greater than that of seronegative ones. In fact, the selection of patients was done according with clinical practice (9), that reflects the demonstration of a better response to ABA in seropositive patients (8). The small sample size of seronegative patient group, which were anti-carP positive in the 25% of our seronegative patients (2), limits the considerations on this subset of RA subjects. In fact, anti-carP showed modest sensitivity in seropositive patients but good specificity for RA with an association with bone erosions, disease activity, decrease of bone mineral density, disability and mortality in arthritis patients regardless of anti-CCP antibodies (10-12). Furthermore, when looking for clinical relations between these antibodies and RA specific clinical manifestations, an association with interstitial lung disease in RA was found (13). In this specific subset of patients at high-risk of mortality, ABA seems to be safe (14). Additional basic studies on the genesis of anti-carP in individuals are needed, and a better knowledge of the mechanisms underlying their potential pathogenetic function are required to clarify their role in RA. Further studies on larger cohorts are necessary to confirm the role of anti-carP as biomarkers for specific subsets of RA patients, especially if seronegative and as a potential response predictor to target therapies.

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