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Letter to the Editor

Identification of cartilage oligomeric matrix protein as biomarker predicting abatacept response in rheumatoid arthritis patients with insufficient response to a first anti-TNFα treatment

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For unknown reasons, around 30%–50% of patients suffering from rheumatoid arthritis (RA) fail to respond to biologic disease-modifying anti-rheumatic drugs (bDMARDs) mainly TNFα inhibitors (TNFi). The recommended treatment strategy is to switch to another biologic [1]. However, the selection of the new therapeutic option among a plethora of available bDMARDs is not well-defined [2]. Identifying the right bDMARD is critical given that the likelihood of a response to subsequent biologic treatment declines as the number of previous TNFi treatments increases [3]. Our previous study identified predictive biomarkers of response for TNFi for RA bDMARD naïve patients [4]. In this study, we aimed at characterizing relevant blood biomarkers, which, when integrated into a multivariate model, could predict response to abatacept (ABA) as a second line bDMARD treatment.

To do so, 30 RA patients with an inadequate response to a 1st TNFi and who have received ABA treatment from the "ROC" study (NCT01000441) [5] were included in our study (Appendix A, Table S1; See the supplementary material associated with this article online). Good EULAR response was considered as responders (R) and moderate or lack of response as non-responders (NR) at 6 months [6]. To identify relevant predictive biomarkers, we compared the serum proteome before ABA treatment of the five best R to the five worst NR using mass spectrometry (LC-MS/MS) (Appendix A, Fig. S1). Six putative predictive biomarkers were selected: cartilage oligomeric matrix protein (COMP), neuropilin (NRP1), apolipoprotein M (APOM), C4 binding protein alpha (C4BPA), lipopolysaccharide-binding protein (LBP) and fibronectin (FN1) (Appendix A, Table S2).

Their concentration was determined in the whole 30-patients cohort by ELISA and only the baseline expression of COMP was significantly lower in serum from R patients (*P*-value = 0.018) (Fig. 1A and Appendix A, Fig. S2A). Univariate logistic regression analysis was performed to evaluate the predictive value of each biomarker independently and showed a significant *P*-value only for COMP (*P*-value = 0.03). Consistently, COMP exhibited a high predictive capability with an AUC–ROC value of 0.78 [75% sensitivity, 77% specificity, 55% of positive predictive values (PPV), and 89% of negative predictive values (NPV) (Table 1)].

As LBP (*P*-value = 0.18) and FN1 (*P*-value = 0.11) exhibited a relatively low *P*-value below 0.2 in univariate analysis and an inter-

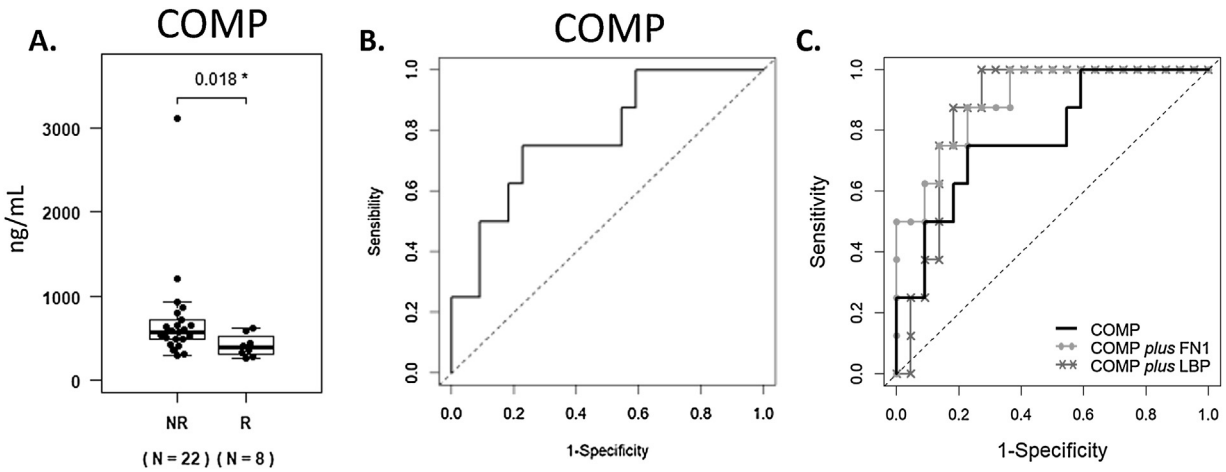

Fig. 1. A. Baseline COMP concentration for the whole cohort classed as patients for whom a good (R) or poor (NR) EULAR response was measured after 6 months' ABA treatment. A Mann–Whitney non-parametric test was used to assess the significance of differences of biomarkers. B. ROC curves analysis of COMP biomarker. C. Overlay of the ROC curves for the predictive COMP *plus* LBP and COMP *plus* FN1 multivariate combined models and the COMP univariate model. COMP: cartilage oligomeric matrix protein; LBP: lipopolysaccharide-binding protein; FN1: fibronectin.

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Table 1
Performance of the different predictive models.

Classifier	Predictive model	AUC	Sensitivity % (CI)	Specificity % (CI)	PPV % (CI)	NPV % (CI)
EULAR status	COMP	0.78	75 (0.35–0.97)	77 (0.55–0.92)	55 (0.23–0.83)	89 (0.67–0.99)
	COMP + FN1	0.90	88 (0.47–1)	77 (0.55–0.92)	58 (0.28–0.85)	94 (0.73–1)
	COMP + LBP	0.87	100 (0.52–1)	73 (0.5–0.89)	57 (0.29–0.82)	100 (0.71–1)
Remission	COMP	0.80	0.86 (0.42–1)	0.78 (0.56–0.93)	0.55 (0.23–0.83)	0.95 (0.74–1)
	COMP + FN1	0.89	0.71 (0.29–0.96)	0.91 (0.72–0.99)	0.71 (0.29–0.96)	0.91 (0.72–0.99)

AUC: area under the curve from the ROC analysis; PPV: positive predictive values; NPV: negative predictive values; CI: 95% confidence interval; COMP: cartilage oligomeric matrix protein; LBP: lipopolysaccharide-binding protein; FN1: fibronectin.

esting AUC–ROC values above 0.65 (Appendix A, Fig. S2B), their potential to strengthen the predictive potential of the model was tested using multivariate logistic regression analysis. Interestingly, the combination of COMP plus FN1 or COMP plus LBP improved notably the performance of the predictive model particularly in term of AUC, sensibility and NPV (Table 1). While using remission as classifier instead of EULAR response status COMP demonstrated similar predictive property as well as FN1 when combined with COMP (Table 1 and Appendix A, Fig. S3).

In conclusion, by applying a non-a priori stepwise approach (proteomics discovery, quantitative immunoassays, multivariate model generation) we identified COMP as strong predictive biomarker for response to ABA treatment for RA patients with a first TNFi failure. When validated in an independent and a larger population, it should be rapidly translated into daily clinical practice to assist clinicians to select the most appropriate bDMARD for the patient since IVD CE-accredited methods are available for COMP and FN1.

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Role of the funding source

Data collection, data analysis, data interpretation, manuscript preparation, decision to publish were independent from the study funding.

Authors' contributions

PG, AB participated in the study design and coordination, and critically revised the manuscript. MVCN participated in the study design and coordination of the samples dosages, analyzed the data and drafted the manuscript. AA coordinated and performed proteomic analysis and revised the manuscript. CT helped for the samples dosages, and critically revised the manuscript. JEG supplied patient samples, collected clinical data, and revised the manuscript.

Disclosure of interest

AB and PG are co-founders of Sinnovial Company. MVCN is employee of Sinnovial Company.

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Appendix A. Supplementary data

Supplementary data related to this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2018.09.005.

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