Comment on: Rheumatoid factor positivity rather than anti-CCP positivity, a lower disability and a lower number of anti-TNF agents failed are associated with response to rituximab in rheumatoid arthritis

Sir, The recent article of Quartuccio et al. [1], ‘Rheumatoid factor positivity rather than anti-CCP positivity, a lower disability and a lower number of anti-TNF agents failed are associated with response to rituximab in rheumatoid arthritis’, draws the stated conclusion on the basis of a multivariate analysis in which RF status, but not anti-cyclic citrullinated peptide (anti-CCP) antibody status, remains significant in the model. However, this finding may be expected on the basis of multicollinearity of RF and anti-CCP. Only one of two variables that are significantly correlated will be significant in a multivariate model; this does not mean that the other variable is not significant, but rather that it is redundant. Furthermore, lower disability and a lower number of anti-TNF agents are significantly associated in a multivariate regression model analysing ACR50 responses, but not in a model for European League Against Rheumatism (EULAR) moderate-to-good responses. This observation also suggests to us that the title is somewhat misleading.

The authors note that ‘RF-negative cases showed a longer disease duration… and included a higher number of patients who failed more than one anti-TNF agent’. Conversely, no differences were seen in clinical variables for anti-CCP-positive vs anti-CCP-negative patients. This phenomenon may explain why RF-positive patients were more likely than RF-negative patients to achieve ACR50 responses, as longer disease duration and failure of more than one anti-TNF agent are associated with poorer outcomes, and further limit the conclusion that RF, but not anti-CCP positivity, is associated with response to rituximab in RA.

The proportions of ACR50 responders among RF-positive and anti-CCP-positive patients are almost identical, 75 vs 72% (Table 1) [assuming a typographical error in the sentence, ‘ACR response 50 was seen in 58/78 RF-positive/CCP-negative patients’, as the data appear to characterize RF-positive/CCP-positive patients]. To be sure, 82% of patients who are RF positive and anti-CCP negative have ACR50 response rates vs 43% of anti-CCP-positive-only subjects. However, only seven patients are anti-CCP positive/RF negative, and most anti-CCP-positive patients have response rates similar to those of RF-positive patients.

The reference of Carson et al. [2], cited to support the suggestion that treatment with rituximab can have a major effect on RF-producing B-cell clones and less so on anti-CCP-producing B-cell clones, was published in 1991, before reports of anti-CCP antibodies. Any slightly differential effect of rituximab on biological markers may be explained by an overall effect on inflammation rather than only on B-cells, as larger decreases in RF than anti-CCP titres have also been described after treatment with infliximab [3, 4] or adalimumab [5].

Finally, we have substantial concern about the value of prediction of responses to any therapy in groups of patients, according to any variable, to a physician caring for an individual patient. Of course, there are situations in which the prognosis of a poor response is clinically useful—most obviously for antibiotics with no (zero) antimicrobial activity against a given pathogen. But in this study, the group with the least likelihood of a response, patients who were negative for both RF and anti-CCP, had a response rate of 21%. A 1 in 5 likelihood of a response in a patient who has failed several other biological agents would appear a reasonable treatment option. We would treat such a patient, and would be concerned that reimbursement authorities would use data from groups to potentially deny treatment to individuals who really need it and might derive benefit.

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Miguel A. Belmonte Serrano1 and Theodore Pincus2

1Sección de Reumatología, Hospital General de Castellón, Castellón, Spain and 2Division of Rheumatology, New York University School of Medicine, NYU Hospital for Joint Diseases, New York, NY, USA

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Correspondence to: Theodore Pincus, Division of Rheumatology, NYU Hospital for Joint Diseases, 301 East 17th Street, Room 1608, New York, NY 10003, USA. E-mail: tedpincus@gmail.com

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3 Bruns A, Nicea-Roland P, Hayem G et al. Prospective cohort study of effects of infliximab on rheumatoid factor,

### Table 1 Rates of ACR50 responders to rituximab, according to RF and anti-CCP status

<table>
<thead>
<tr>
<th>ACR50+/Total</th>
<th>RF+</th>
<th>RF-</th>
<th>Subtotal anti-CCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CCP+</td>
<td>58/78 (74)</td>
<td>3/07 (43)</td>
<td>61/85 (72)</td>
</tr>
<tr>
<td>Anti-CCP-</td>
<td>09/11 (82)</td>
<td>3/14 (21)</td>
<td>12/25 (48)</td>
</tr>
<tr>
<td>Subtotal RF</td>
<td>67/89 (75)</td>
<td>6/21 (28)</td>
<td>73/110 (66)</td>
</tr>
</tbody>
</table>

Values are represented as n/N (%) and rates of responders are indicated as rounded percentages.
Significantly associated with both the ACR 50 response was the dependent variable in the models. RF was selected (P = 0.0003; odds ratio (OR) = 7.519; 95% CI 2.521, 22.426) and EULAR moderate/good response (P = 0.001; OR = 5.909; 95% CI 1.997, 17.483), whereas the anti-CCP antibodies were associated with the ACR 50 response, but with a low level of significance (P = 0.049; OR = 2.600; 95% CI 1.004, 6.736) and clearly not associated with the EULAR moderate/good response (P = 0.322). In addition, statistical analyses with two distinct stepwise regression models, where anti-CCP or RF was separately introduced, were also performed, and confirmed the absence of redundancy. In the first model, where anti-CCP was included and RF excluded in the pool of tested variables (the same as included in the paper) [1], anti-CCP was not selected. Conversely, in the second model where anti-CCP was excluded and RF included, RF was selected (P = 0.001) both for the ACR 50, and EULAR moderate/good response, thus reinforcing the concept that the presence of RF and not the presence of anti-CCP was associated with major response to rituximab in our RA cohort. Finally, this result was recently confirmed by other independent groups [5–8].

Although in our study the RF-negative RA subset included a higher number of patients who failed more than one anti-TNF agent, if compared with the RF-positive subset, no difference was observed as regards baseline disease activity or baseline disability between the two groups of patients, as stated [2]. The mechanism involved in a putative anti-TNF-mediated resistance to rituximab deserves further investigation, and we provided some preliminary support to the notion that the duration of the exposure to anti-TNF therapy may also be relevant [2].

The conclusion of our paper that “RF-positive patients with baseline lower disability may be best candidates for rituximab” [2] clarifies that the presence of the RF may be relevant for the choice of rituximab therapy after the failure of the first anti-TNF agent. RF-negative patients may as well respond to rituximab, but other biologicals may work better in such cases [9]. However, pharmacogenetic studies, also in course by our Group, might provide additional insights for the choice [10].

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Luca Quartuccio1 and Salvatore De Vita1

1Rheumatology Clinic, DPMSC, Azienda Ospedaliero-Universitaria ‘S. Maria della Misericordia’, University of Udine, Udine, Italy
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Correspondence to: Salvatore De Vita, Azienda Ospedaliero-Universitaria ‘S. Maria della Misericordia’, University of Udine, P.z.le S. Maria della Misericordia 15, 33100 Udine, Italy. E-mail: devita.salvatore@aoud.sanita.fvg.it

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