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LETTER

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Serum IL-33 level is associated with auto-antibodies but not with clinical response to biologic agents in rheumatoid arthritis

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Trial registration: Rotation or Change of Biotherapy After First Anti-TNF Treatment Failure for Rheumatoid Arthritis (ROC), registered 22 October 2009, NCT01000441

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Interleukin (IL)-33 may play a role in rheumatoid arthritis (RA) pathophysiology as shown by human studies and murine models [1]. Previously, we demonstrated that detectable serum IL-33 predicts clinical response to rituximab independently of auto-antibody status [2].

Here, we aimed to investigate whether the prediction of therapeutic response using serum IL-33 level is generalizable to all biologic agents, including TNF inhibitors (TNFi) and non-TNFi in RA.

We set up an ancillary study of the ROC (Rotation or Change of Biotherapy After First Anti-TNF Treatment Failure for RA) trial (NCT01000441) which compared the efficacy of TNFi vs non-TNFi in patients with insufficient response to a first TNFi [3]. Three hundred patients were randomized, and treatment efficacy was evaluated at 24 weeks according to EULAR response, showing that a non-TNFi was more effective in achieving EULAR response than a TNFi. Serum IL-33 level was assessed before treatment using an accurate enzyme-linked immunosorbent assay (ELISA IL-33, Quantikine, R&D Systems) [4]. Statistical analyses used Prism (Mann-Whitney and Fisher tests for quantitative and qualitative values, respectively). Serum IL-33 level was defined as detectable when > 6.25 pg/mL (lower threshold).

Results were analyzed for 267 patients with available serum and clinical data (Table 1). Serum IL-33 level was detectable for 109/267 (40.8%) patients (mean ± standard deviation serum level was 49.7 ± 61.0 pg/mL when detectable) (Table 2). IL-33 detection was associated with auto-antibody positivity: rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide antibody (anti-CCP), either combined or analyzed separately (Table 3). Auto-antibody positivity was not associated with response to the different treatment: TNFi (N = 132, odds ratio (OR) = 1.1, 95% confidence interval (CI) = 0.39–3.16), non-TNFi (N = 130, OR = 1.5, 95% CI = 0.40–5.62), or different sub-groups of non-TNFi (data not shown). There was no association between IL-33 detection and response to TNFi as well as to non-TNFi drugs overall or analyzed separately (Table 2). Likewise, there was no difference when comparing the levels of serum IL-33 between responders and non-responders in TNFi and non-TNFi groups (data not shown).

Thus, this new study confirms the association between serum IL-33 detection and seropositivity in RA patients. However, it did not replicate the association between IL-33 detection and response to rituximab.

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Table 1 Characteristics of the patients included in the ancillary study of the ROC trial

Characteristics	TNFi	Non-TNFi biologic	Total
Number of women (%)	114 (85.7)	110 (82.1)	224 (83.9)
Mean age (SD)	55.9 (13.0)	58.4 (11.2)	57.2 (12.1)
Number rheumatoid factor-positive (%)	108 (82.4)	101 (76.5)	209 (79.8)
Number anti-CCP-positive (%)	102 (79.7)	105 (82.7)	207 (81.2)
Mean DAS28-CRP (SD)	4.7 (0.9)	4.8 (1.1)	4.8 (1.0)

Table 2 EULAR response, IL-33 detectability rates and association between IL-33 detection and response to tumor necrosis factor inhibitor (TNFi; including adalimumab, certolizumab, etanercept and infliximab) and non-TNFi (including abatacept, rituximab, and tocilizumab) in patients from the ROC study

	Treatment	Number of patients	Number of EULAR responders (%)	Number of detectable IL-33 among all patients (%)	Number of detectable IL-33 among EULAR responders (%)	Association between IL-33 detectability and EULAR response (OR [95% CI])
TNFi	Adalimumab	53	30 (56.6)	23 (43.4)	14 (46.7)	1.4 [0.5–4.1]
	Etanercept	49	29 (59.2)	20 (40.8)	13 (44.8)	1.5 [0.5–5.0]
	Certolizumab	23	10 (43.5)	10 (43.5)	5 (50.0)	1.6 [0.3–8.5]
	Infliximab	8	1 (12.5)	3 (37.5)	1 (100)	6.6 [0.2–226]
	Total TNFi	133	70 (52.6)	56 (42.1)	33 (47.1)	1.6 [0.8–3.1]
Non-TNFi	Rituximab	37	20 (54.0)	10 (27.0)	6 (30.0)	1.4 [0.3–6.1]
	Abatacept	30	18 (60.0)	11 (36.6)	8 (44.4)	2.4 [0.5–11.9]
	Tocilizumab	67	53 (79.1)	32 (47.8)	25 (47.2)	0.9 [0.3–2.9]
	Total non-TNFi	134	91 (67.9)	53 (39.6)	39 (42.9)	1.6 [0.7–3.3]

Results are presented as odds ratios (OR) [95% confidence intervals (CI)]

Table 3 Association between IL-33 detection and auto-antibody positivity

Auto-antibody status	Number of patients	OR	95% CI
RF+ and/or anti-CCP+ vs RF− and anti-CCP−	262	21.1	2.8-158.3
RF+ vs RF−	263	9.7	3.7-25.3
Anti-CCP+ vs anti-CCP−	255	2.7	1.3- 5.7

Results are presented as odds ratios (OR), 95% confidence intervals (CI) for each factor
RF rheumatoid factor, *Anti-CCP* anti-cyclic citrullinated peptide antibody

This may be due to a lack of power related to the number of patients who received this treatment ($N = 37$), but it may also reflect the difficulty of studying IL-33 as a possible predictor of response given its association with seropositivity, which is a well-known factor associated with response to some biologics such as rituximab or abatacept [5].

In conclusion, we confirm that serum IL-33 detection is associated with auto-antibody positivity but is not a predictive marker for response to TNFi and non-TNFi in RA.

Abbreviations

Anti-CCP: Anti-cyclic citrullinated peptide; CI: Confidence interval; ELISA: Enzyme-linked immunosorbent assay; EULAR: European League Against Rheumatism; Ig: Immunoglobulin; IL: Interleukin; OR: Odds ratio; RA: Rheumatoid arthritis; RF: Rheumatoid factor; TNFi: Tumor necrosis factor inhibitor

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

ER participated in conception and design of the study, performed acquisition of the data, performed the statistical analysis and interpretation of the results, and wrote the manuscript. JS participated in conception and design of the study, participated in the statistical analysis and interpretation of the results, and wrote the manuscript. JP participated in the design of the study and the acquisition of the data. PR participated in interpretation of the data. JEG is the principal investigator of the main ROC. He participated in the conception and design of the study and in interpretation of the data. XM participated in conception and design of the study, statistical analysis and interpretation of the results, and wrote the manuscript. All authors reviewed and approved the final manuscript.

Ethics approval and consent to participate

The trial (Clinicaltrials.gov identifier NCT01000441) was approved by the institutional review board of the Comité de Protection des Personnes-Est 1, Strasbourg, France. The study was conducted according to the current regulations of the International Conference on Harmonization guidelines and the principles of the Declaration of Helsinki. All patients gave written informed consent after receiving oral and written information about the trial.

Consent for publication

We confirm that all authors approved the manuscript for submission.

Competing interests

Dr. Rivière reported receiving a PhD grant from Fondation Arhtirits Courtin.
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