Association between seropositivity and remission in rheumatoid arthritis patients receiving disease-modifying antirheumatic drugs: a retrospective analysis of 5 phase III randomized clinical trials of tocilizumab

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Introduction

- Rheumatoid arthritis (RA) is an auto-immune inflammatory disease that is associated with progressive disability.
- RA is often classified according to the presence of anti-cyclic citrullinated peptide antibodies (ACPA) and/or rheumatoid factor (RF) into seropositive and seronegative.
- RF and/or ACPA can be found in about 75% of RA patients and are used as a diagnostic and prognostic tool.
- Seropositivity amongst RA patients may indicate higher disease activity and poorer disease prognosis.
- There is growing evidence towards using RF and ACPA in combination as a more effective diagnostic tool rather than using each one separately because of their moderate sensitivity when used individually.
- It has been suggested that combination seropositivity can be used as a more accurate early predictor of structural damage than using them individually.

The hypothesis

RF and/or ACPA status may influence RA treatment outcomes

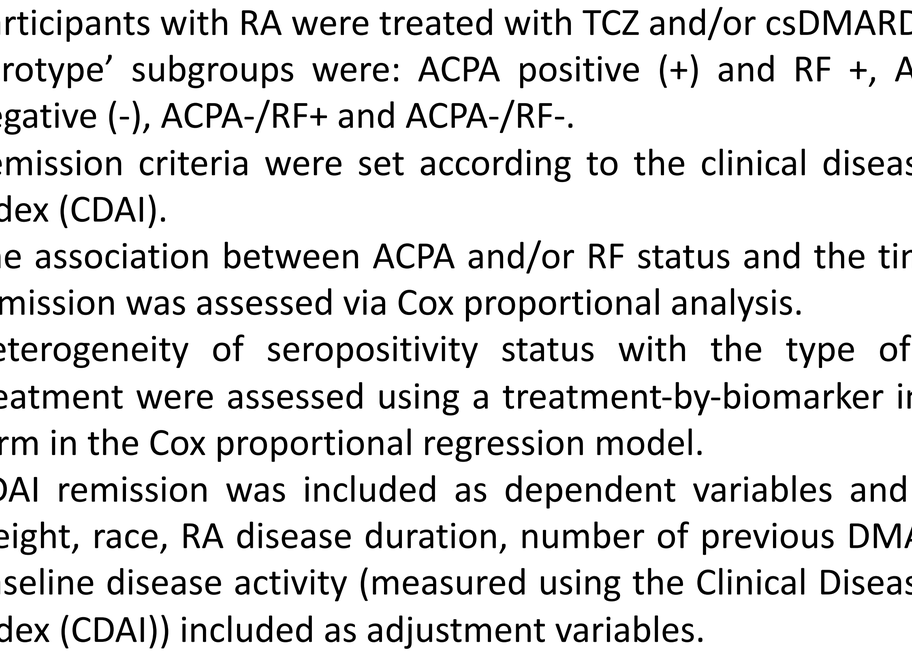
Aims

To examine the association between RF and/or ACPA seropositivity and remission in RA patients treated with tocilizumab (TCZ) and/or conventional synthetic disease-modifying antirheumatic drugs (csDMARDs)

Methods

- Available data were pooled from 5 phase III clinical trials where participants with RA were treated with TCZ and/or csDMARD.
- Serotype' subgroups were: ACPA positive (+) and RF +, ACPA +/RF negative (-), ACPA-/RF+ and ACPA-/RF-.
- Remission criteria were set according to the clinical disease activity index (CDAI).
- The association between ACPA and/or RF status and the time of first remission was assessed via Cox proportional analysis.
- Heterogeneity of seropositivity status with the type of received treatment were assessed using a treatment-by-biomarker interaction term in the Cox proportional regression model.
- CDAI remission was included as dependent variables and age, sex, weight, race, RA disease duration, number of previous DMARDs, and baseline disease activity (measured using the Clinical Disease Activity Index (CDAI)) included as adjustment variables.
- Kaplan-Meier analysis was used for plotting and estimating remission probabilities.

Figure 1. Patients included in the analysis, RA: rheumatoid arthritis, ACPA: anti-cyclic citrullinated peptide antibodies, RF: rheumatoid factor



References

Smolen, J.S., D. Aletaha, and I.B. McInnes, *Rheumatoid arthritis.* Lancet, 2016. **388**(10055): p. 2023-2038.

Results

- The analysis included data from a total of 5502 RA patients treated with TCZ and/or csDMARDs, of which 4108 (74.6%) were ACPA+/RF+, 816 (14.8%) were ACPA+/RF-, 219 (4%) were ACPA-/RF+, and 298 (5.4%) were ACPA-/RF- (Figure 1).
- In the pooled analysis, RF and ACPA status were associated with significantly higher remission rate using both univariable (Table 1) and adjusted (Table 2) analyses.
- Patients who were ACPA+/RF+ were more likely to achieve CDAI remission compared with ACPA-/RF- on univariable (Table 1) and adjusted (Table 2) analyses.
- There was no difference in remission rates between either ACPA-/RF+ and ACPA+/RF- groups compared to the ACPA-/RF- and ACPA-/RF+ groups.
- The association of the seropositivity status of ACPA and/or RF with remission was independent of the type of RA therapy used (interaction P>0.05).

Figure 2: Kaplan-Meier estimates of the proportion of RA patients achieving CDAI remission at least once by A) rheumatoid factor B) anti-cyclic citrullinated peptide antibodies. The numbers underneath Kaplan- Meier plots indicate the absolute number of patients at risk by time.

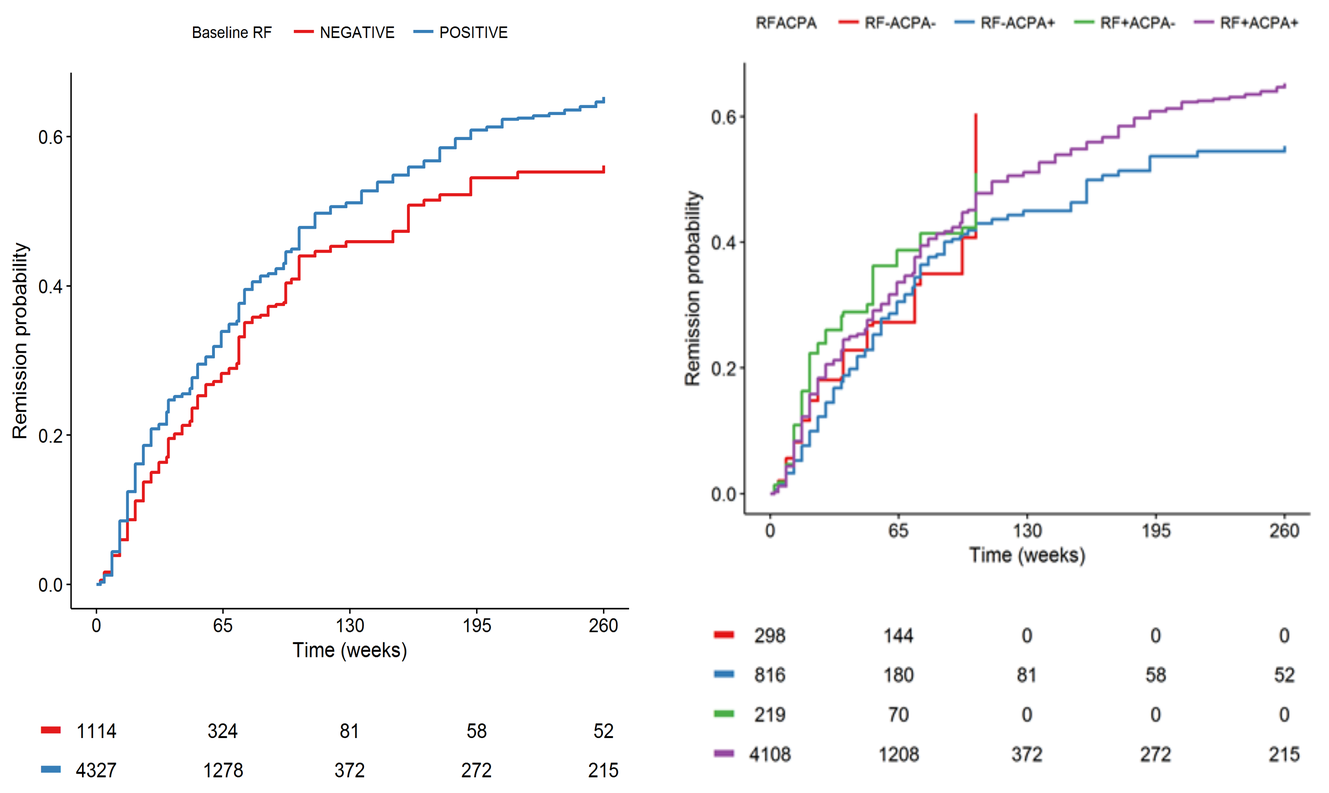


Table 1. Univariable pooled cohort analysis of the association between RF and/or ACPA status and remission

	CDAI-defined remission		
		HR (95%CI)	P
Rheumatoid factor			
Negative	295/1114	1	
Positive	1479/4327	1.15(1.01-1.30)	0.035
Anti-cyclic citrullinated peptide antibodies			
Negative		1	
Positive		1.27(1.08-1.49)	0.004
Anti-cyclic citrullinated peptide antibodies / Rheumatoid factor			
ACPA-/RF-	98/298 (33%)	1	
ACPA-/RF+	80/219 (37%)	0.97(0.72-1.31)	
ACPA+/RF-	197/816 (24%)	1.12(0.87-1.45)	
ACPA+/RF+	1399/4108 (34%)	1.25(1.01-1.55)	0.016

Table 2: Adjusted analysis: Adjustment variables: age, sex, weight, race, RA disease duration, number of previous DMARDs, and baseline disease activity.

	CDAI-defined remission	
Rheumatoid factor		
Negative	1	
Positive	1.17(1.03-1.33)	0.015
Anti-cyclic citrullinated peptide antibodies		
Negative	1	
Positive	1.28(1.09-1.51)	0.003
Anti-cyclic citrullinated peptide antibodies / Rheumatoid factor		
ACPA-/RF-	1	
ACPA-/RF+	0.99(0.73-1.34)	
ACPA+/RF-	1.08(0.83-1.40)	
ACPA+/RF+	1.30(1.04-1.61)	0.002

Conclusion

Seropositivity of both RF and ACPA was independently associated with more frequent remission in RA patients regardless of the type of DMARD used. Seropositivity of both RF and ACPA in combination may increase the ability to predict RA treatment outcome.