Factors Predicting 2 Years of Remission and Low Disease Activity in Rheumatoid Arthritis Patients Treated with TNF-inhibitors

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ABSTRACT: **Background:** The goals of treatment for rheumatoid arthritis (RA) are remission and low disease activity (LDA). However, many patients do not reach or maintain these targets with regard to disease control.

Objective: To identify predictive factors of remission/LDA in a cohort of RA patients who started treatment with first line tumor necrosis factor-inhibitors (TNF-i).

Methods: We included 308 RA patients treated with first line TNF-i for 2 years to evaluate remission/LDA based on the 28-joint disease activity score (DAS28). Predictive factors considered for achievement of remission/LDA were: gender, age at the time of TNF-i treatment, early arthritis, baseline C-reactive protein (CRP) and erythrocyte sedimentation rate levels, RF/anti-citrullinated protein antibody positivity, good/moderate European League Against Rheumatism response at 6 months, co-morbidities, and concomitant disease modifying antirheumatic drugs (DMARDs). Intention to treat, receiver operating characteristic curve, and univariate and multivariate analyses by logistic regression were performed.

Results: Positive predictors of remission/LDA in both the univariate and the multivariate analyses were: male gender, age at the time of TNF-i treatment ≤ 54 years, negative baseline CRP, and concomitant DMARDs. The presence of any co-morbidity resulted to be a negative predictor of remission/LDA in both the univariate and the multivariate analyses.

Conclusions: Demographic and clinical features were identified as reliable predictors of both the achievement and the maintenance of treatment targets in a cohort of RA patients treated for 2 years with first line TNF-i.

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KEY WORDS: low disease activity (LDA), remission, rheumatoid arthritis (RA), tumor necrosis factor-inhibitors (TNF-i), treatment targets

Rheumatoid arthritis (RA) is a chronic disease characterized by systemic and local inflammation leading to progressive joint damage [1]. Current treatment targets in RA are remission and low disease activity (LDA) [2]. With the advent of biologic treatment, as tumor necrosis factor (TNF)-α inhibitors (TNF-i), remission represents an achievable goal with a frequency that ranges between 10% and 40%, leading to a significant decrease of disease activity, structural damage and disability [3,4]. However, many patients do not reach or maintain these targets and report adverse events and discontinue the therapy with poor disease control [3]. Therefore, there is a real need to identify reliable predictors of response to biologic agents in order to gain therapy more specific and tailored for the patient. Several biomarkers have been proposed and are still under investigation to predict the pharmacological response to therapeutic interventions in RA patients [5-7]. Nevertheless, few biomarkers seem to represent reliable predictors of clinical response to certain biologic treatment such as rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) [8-10]. The aim of this study was to explore the potential role of several clinical and biochemical parameters as independent predictive factors of long-term remission and/or LDA in a cohort of Italian RA patients treated with first line TNF-i.

PATIENTS AND METHODS

We enrolled consecutive RA outpatients who started first-line TNF-i treatment at the Rheumatology Unit, Department of Medicina dei Sistemi, University of Rome Tor Vergata, Rome, Italy (January 2008–December 2014). Inclusion criteria were: RA diagnosis according to the 2010 European League Against Rheumatism response (EULAR)/ American College of Rheumarology (ACR) revised criteria [11], age ≥ 18 years old, a moderate-severe disease based on a 28-joint disease activity score (DAS28) with four variables and erythrocyte sedimentation rate (ESR) [12], and failure of treatment with at least one disease modifying antirheumatic drug (DMARD). Exclusion criteria were: previous courses of biologic therapy, recent infection (< 3 months), human immunodeficiency virus (HIV) infection, history of cancer, major organ dysfunction, or pregnancy. Patients

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were treated with etanercept, administered at 50 mg subcutaneously weekly, or adalimumab, administered at 40 mg subcutaneously every other week. Concomitant conventional synthetic (cs)DMARDs and steroids were permitted according to clinical efficacy and tolerance. Clinical data were collected at baseline, 6 months, 1 year, and 2 years from the beginning of TNF-i. A disease duration < 12 months was defined as early arthritis, whereas RA disease duration ≥ 12 months was defined as established arthritis [13]. Laboratory assays included: ESR (normal value < 20 mm/h), C-reactive protein (CRP; normal value < 3 mg/L, using nephelometric methods), RF (normal value < 20 IU/L), and ACPA (normal value < 20 IU/L). RF immunoglobulin A (IgA) and immunoglobulin M (IgM) were quantified by nephelometry using Immage 800® (Beckman Coulter, Fullerton, CA, USA) according to the manufacturer's guidelines. ACPA were quantified by second generation commercial enzyme-linked immunosorbent assay (ELISA) kit (QUANTA Lite® CCP IgG, Medical Technology Promedt Consulting, St. Ingbert, Germany). Patients were considered seropositive if they showed a positivity for either RF or ACPA. Patients were questioned through a face-to-face interview (yes/no) about co-morbidities including metabolic, cardiovascular, infectious, and pulmonary in accordance with the classification of diseases described by Charlson [14]. Moreover, the occurrence of thyroid disorders was defined as the presence of hyperthyroidism/hypothyroidism and/or goiter [15]. Metabolic syndrome (MetS) was assessed in accordance with international standard criteria [16]. Disease activity and response to treatment were measured by DAS28 (a score < 2.6 was considered as remission; < 3.2 was considered as LDA) and European League Against Rheumatism (EULAR) response criteria classifying patients as responders (good/moderate response) and no responders [17]. Maintenance of remission and LDA at two different time points of follow-up and sustained remission and LDA, defined as the achievement of these treatment targets for 2 years (at all the time points of evaluation) [18], were also evaluated. The study was performed in accordance with the Helsinki Declaration of 1975, as revised in 1983. All patients provided written informed consent and the ethics committee approved the study.

STATISTICAL ANALYSIS

All data were stored on a server and statistical analyses was performed using SPSS software version 18 for Windows (SPSS Inc., Chicago, IL, USA). To test normality of data sets the D'Agostino–Pearson omnibus test was used. Normal variables were expressed as mean ± standard deviation (SD). Univariate chi square test was used to analyze the influence of the predictive factors on the outcome of the patients at 6 months, 1 year, and 2 years from the beginning of the treatment. A multivariate binary logistic regression was performed using the predictive factors that showed as being most significant in the univariate analysis. Intention to treat analysis (ITT) was used to estimate treatment effect and includes every subject who is enrolled according to treatment assignment. Receiver operating characteristic (ROC) curves were performed to test a variable as a tool to discriminate patients on remission/LDA from patients who were not in remission/LDA at all the time points. Accuracy of the ROC analyses was measured by the area under the ROC curve (AUC). If the AUC value was greater than 0.5, the test was considered as a significant method to detect patients on remission/LDA. The optimal threshold value of the variable, which discriminates patients in remission/LDA, was the value for which sensitivity(c) + specificity(c) -1 is maximized. Pearson's correlation test was used to explore correlations between variables. All statistical tests were two-sided, and $P < 0.05$ was considered significant.

RESULTS

A total of 308 RA patients who started first line TNF-i were included in the study [Table 1]. At 1 year, 30.2% (93/308) of patients left the study and an additional 17.7% (38/215) of those dropped out after 2 years of treatment.

A good-moderate EULAR response was found in 54.9% (169/308) after 6 months, in 45% (133/215) after 1 year and in 54.8% (97/177) after 2 years of TNF-i treatment. The results are summarized in Table 2 (factors of remission), Table 3 (factors of low disease activity), and Table 4 (factors of maintenance of remission and low disease activity).

Table 1. Demographic and clinical data of rheumatoid arthritis patients

	RA Patients (N=308)
Female gender, n (%)	251 (81.5%)
Age (years)	55 ± 13
Disease duration (years)	7.6 ± 8.4
Early arthritis, n (%)	99 (32.1%)
Co-morbidities, n (%)	210 (68.2%)
Cardiovascular Thyroid disorders Infectious Metabolic syndrome Pulmonary	83 (26.9%) 64 (20.8%) 49 (15.9%) 26 (8.4%) 20 (6.5%)
RF positive, n (%)	220 (71.4%)
ACPA positive, n (%)	214 (69.5%)
DAS28 at baseline	5.4 ± 1.3
Adalimumab, n (%)	120 (35.4%)
Etanercept, n (%)	188 (57.5%)
csDMARDs at baseline, n Methotrexate Leflunomide Sulphasalazine	225 (73.1%) 156 (69.3%) 36 (16%) 33 (14.6%)
PDN at baseline, n (%)	160 (51.9%)

Continuous values are shown as mean ± standard deviation and categorical variables as absolute number and percentages

RA = rheumatoid arthritis; RF = rheumatoid factor, ACPA = anti-citrullinated peptide antibodies, DAS28 = 28 joint count disease activity score, csDMARDs = conventional synthetic disease-modifying antirheumatic drugs, PDN = prednisone

Table 2. Predicting factors of remission at 6 months, 1 year and 2 years of treatment with TNF inhibitors in patients with rheumatoid arthritis

	Remission 6 months (n=72)				Remission 1 year (n=70)				Remission 2 years (n=52)			
	Univariate		Multivariate*		Univariate		Multivariate*		Univariate		Multivariate*	
Variable	OR (CI95%)	*P*	OR (CI95%)	*P*	OR (CI95%)	*P*	OR (CI95%)	*P*	OR (CI95%)	*P*	OR (CI95%)	*P*
Male gender	2.1 (1.1–4)	0.02			2.7 (1.4–4.9)	0.002			NA	0.09		
Age at the start of TNF-i ≤ 54 years	2 (1.2–3.4)	0.01			2.1(1.2–3.6)	0.007	2.2 (1–5.3)	0.07	2 (1.1–3.7)	0.02		
Early arthritis	1.8 (1.02–3.3	0.04			2.5 (1.4–4.2)	0.001			2 (1.02–3.6)	0.04		
Baseline negative CRP	1.9 (1.1–3.3)	0.03	2.2 (1.1–4.4)	0.03	2.1 (1.2–3.6)	0.01	3.3 (1.5–7.2)	0.003	2.1 (1.1–4)	0.03	2.5 (1–6.1)	0.038
Baseline negative ESR	NA	0.1			2.2 (1.3–3.9)	0.004			NA	0.2		
Good-moderate EULAR response T22	NA	NA			2.9 (1.2–6.8)	0.01			NA	0.37		
Co-morbidities	0.5 (0.24–0.98)	0.04			NA	0.18			NA	0.2		
Cardiovascular	NA	0.08			NA	0.92			0.45 (0.2–1)	0.04		
Metabolic syndrome	NA	0.82			NA	0.25			NA	0.33		
Infectious	NA	0.42			NA	0.27			NA	0.96		
Pulmonary	ND	ND			ND	ND			ND	ND		
Thyroid disorders	NA	0.72			NA	0.22			NA	0.48		
csDMARDs baseline	NA	0.68			NA	0.66			2 (1.01–4.07)	0.04		
Steroids baseline	NA	1			NA	0.76			NA	0.69		
RF positive	NA	0.94			NA	0.89			NA	0.98		
ACPA positive	NA	0.83			NA	0.54			NA	0.46		
Seronegative	NA	0.86			NA	0.8			NA	0.87		

*Adjusted for gender, good/moderate EULAR response at 6 months, negative baseline CRP and ESR, age ≤ 54 years, early arthritis, cardiovascular co-morbidities, co-morbidities and csDMARDs baseline.

OR = odds ratio, CI = confidence interval, TNF-i = tumor necrosis factor inhibitors, CRP = C-reactive protein,; ESR = erythrocyte sedimentation rate, csDMARDs = conventional synthetic disease-modifying antirheumatic drugs, RF = rheumatoid factor, ACPA = anti-citrullinated peptide antibodies, NA = not applicable, ND = not determined

MALE GENDER

Male patients achieved remission in a higher proportion than did females at 6 months and 1 year from the beginning of the TNF-i treatment. Moreover, male patients showed a higher frequency of LDA after 1 year of therapy than did females. Male patients maintained remission at two time points of evaluation and sustained remission at three time points in a higher proportion than did females. Furthermore, male patients maintained LDA at two time points of evaluation and sustained LDA in a higher proportion than did females.

EARLY ARTHRITIS

Patients with early arthritis were more likely to achieve remission than those with established arthritis at 6 months, 1 year, and 2 years of treatment. Patients with early arthritis were more likely to achieve LDA than those with established arthritis at 1 year and 2 years of TNF-i treatment.

GOOD-MODERATE EULAR RESPONSE AT 6 MONTHS

Patients who achieved a good/moderate EULAR response at 6 months of TNF-i treatment (n=169) showed a higher prevalence of both remission and LDA at 1 year.

CSDMARDS AT BASELINE.

Patients taking csDMARDs at baseline achieved both remission and LDA at a higher proportion than patients on TNF-i monotherapy-only at 2 years.

AGE AT THE BEGINNING OF TNF-I TREATMENT

The age at the beginning of TNF-i resulted by using the ROC analysis as a marker to differentiate, with good accuracy, patients in remission at 6 months (AUC 0.625; 95% confidence interval [CI] 0.548–0.702; $P = 0.003$), 1 year (AUC 0.599; 95%CI 0.511–0.686; $P = 0.029$), and 2 years (AUC 0.642; 95%CI 0.546–0.737; $P = 0.006$), as well as patients on LDA at 6 months (AUC 0.617; 95%CI 0.548–0.691; $P = 0.003$) and 2 years (AUC 0.642; 95%CI 0.548–0.736; $P = 0.005$). In addition, the ROC curve was used as a method for determination of cut-off value of the age at the beginning of TNF-i, determining the age at which patients were in remission/LDA at all the time points. This threshold value showed patients ≤ 54 years old at all the time points with the following sensitivity and specificity: 61% and 52% at 6 months, and 61% and 57% at both 1 year and 2 years, for remission; 64% and 55% at 6 months, and 62% and 52% at both 1 year and 2 years, for LDA. Patients who started TNF-i at age ≤ 54 years (n=139) reached remission at a higher

Table 3. Predicting factors of low disease activity at 6 months, 1 year and 2 years of treatment with TNF inhibitors in patients with rheumatoid arthritis

	LDA 6 months (n=97)				LDA 1 year (n=94)				LDA 2 years (n=72)			
	Univariate		Multivariate*		Univariate		Multivariate*		Univariate		Multivariate*	
Variable	OR (CI95%)	P	OR (CI95%)	P	OR (CI95%)	P	OR (CI95%)	P	OR (CI95%)	P	OR (CI95%)	P
Male gender	NA	0.13			2.7 (1.5–4.8)	0.001			NA	0.2		
Age at the start of TNF-i ≤ 54 years	2.2 (1.2–3.3)	0.004			1.8 (1.1–2.9)	0.02			NA	0.08		
Early Arthritis	NA	0.07			1.9 (1.1–3.1)	0.02			1.9 (1.1–3.4)	0.02		
Baseline negative CRP	NA	0.19			1.8 (1.1–2.9)	0.03	3.9 (1.8–8.6)	0.001	1.9 (1.1–3.4)	0.02	3 (1.2–7.2)	0.016
Baseline negative ESR	NA	0.5			NA	0.2			NA	0.1		
Good-moderate EULAR response T22	NA	NA			2.8 (1.3–5.8)	0.005			NA	0.27		
Co-morbidities	0.45 (0.24–0.91)	0.02			NA	0.23			NA	0.13	0.29 (0.07–1)	0.06
Cardiovascular	0.56 (0.31–1)	0.04			NA	0.53			0.53 (0.28–1)	0.04		
Metabolic syndrome	NA	0.75			NA	0.42			0.34 (0.11–1)	0.04		
Infectious	NA	0.62			NA	0.58			NA	0.83		
Pulmonary	ND	ND			ND	ND			ND	ND		
Thyroid disorders	NA	0.88			NA	0.25			NA	0.63		
csDMARDs baseline	NA	0.64			NA	0.25	2.7 (1–6.8)	0.037	2.2 (1.2–4.1)	0.008	3.6 (1.2–10.6)	0.022
Steroids baseline	NA	0.43			NA	0.95			NA	0.46		
RF positive	NA	0.73			NA	0.87			NA	0.65		
ACPA positive	NA	0.53			NA	0.37			NA	0.23		
Seronegative	NA	0.84			NA	0.27			NA	0.87		

*Adjusted for gender, good/moderate EULAR response at 6 months, negative baseline CRP and ESR, age ≤ 54 years, early arthritis, cardiovascular co-morbidities, co-morbidities and csDMARDs baseline

OR = odds ratio, CI = confidence interval, TNF-i = tumor necrosis factor inhibitors, LDA = low disease activity, CR = C-reactive protein, ESR = erythrocyte sedimentation rate, csDMARDs = conventional synthetic disease-modifying antirheumatic drugs, RF = rheumatoid factor, ACPA = anti-citrullinated peptide antibodies, NA = not applicable, ND = not determined

Table 4. Predicting factors of maintenance of remission and low disease activity at two and three time points of follow-up in patients with rheumatoid arthritis

	Maintenance LDA (n=64) (2 time points)				Sustained LDA (n=23) (3 time points)				Maintenance remission (n=46) (2 time points)				Sustained emission (n=12) (3 time points)			
	Univariate		Multivariate*		Univariate		Multivariate*		Univariate		Multivariate*		Univariate		Multivariate*	
Variable	OR (CI95%)	P	OR (CI95%)	P	OR (CI95%)	P	OR (CI95%)	P	OR (CI95%)	P	OR (CI95%)	P	OR (CI95%)	P	OR (CI95%)	P
Male	2.5 (1.3–4.8)	0.003	3.2 (1.5–6.8)	0.02	4.8 (2–11.4)	0.001	6.3 (2.2–17.5)	0.001	2.9 (1.4–5.7)	0.002	3.5 (1.5–8.1)	0.003	3.4 (1–11)	0.04		
Age at the start of TNF-i ≤ 54 years	2.6 (1.5–4.7)	0.001	2.7 (1.4–5.3)	0.03	2.4 (1–5.9)	0.04			3.7 (1.9–7.4)	0.001	4.2 (1.9–9.6)	0.001	NA	0.13		
Baseline negative CRP	NA	0.15			3.5 (1.3–9.7)	0.01			2 (1.1–4)	0.03			4.7 (1–21.7)	0.03		
Baseline negative ESR	NA	0.15			2.8 (1.1–6.8)	0.02			2.8 (1.4–5.3)	0.002			4.4 (1.2–16.4)	0.02		
Co-morbidities	NA	0.08			0.25 (0.1–0.63)	0.002	0.23 (0.1–0.67)	0.007	NA	0.08			0.15 (0.04–0.5)	0.001	0.13 (0.07–0.5)	0.004

*Adjusted for gender, age at the start of TNF-i ≤ 54 years, baseline negative CRP, baseline negative ESR, co-morbidities

OR = odds ratio, CI = confidence interval, TNF-i = Tumor necrosis factor inhibitors, LDA = low disease activity, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate

proportion than those who started TNF-i at age > 54 years (n=169), at 6 months, 1 year, and 2 years of TNF-i treatment. Moreover, patients who started TNF-i at age ≤ 54 years maintained remission at two time points of evaluation in a higher proportion than older patients and also achieved LDA at a higher proportion at 6 months and 1 year of TNF-i than that

in older patients. Likewise, patients who started TNF-i at age ≤ 54 years maintained LDA at two time points of evaluation and sustained LDA at a higher proportion than those who started TNF-i at age > 54 years.

CO-MORBIDITIES

Patients with at least one co-morbidity (n=210) were less likely to achieve both remission and LDA at 6 months from the beginning of the treatment when compared to patients without these co-morbidities (n=98). Moreover, patients having at least one co-morbidity gained sustained remission and LDA at a lower proportion than patients without co-morbidities. In particular, patients suffering from cardiovascular co-morbidities (n=83) showed a lower rate of remission at 2 years and LDA at both 6 months and 2 years than patients without cardiovascular co-morbidities. Moreover, patients with MetS (n=26) achieved LDA in a lower percentage of cases than those without MetS at 2 years of treatment.

BASELINE INFLAMMATORY MARKERS

Patients with a negative baseline CRP value (n=162) achieved remission at a higher rate than patients with positive baseline CRP (n=146) at 6 months, 1 year, 2 years and LDA at 1 year, 2 years of TNF-i treatment. Patients with negative CRP at baseline maintained remission at two time points, and sustained remission and LDA with a higher frequency than those with positive baseline CRP.

Patients with a negative baseline ESR (n=119) achieved remission at a higher rate than patients with positive ESR (n=189) at 1 year of TNF-i treatment, maintenance of remission at two time points, as well as sustained remission and sustained LDA.

The multivariate analysis was adjusted for gender, early arthritis, EULAR response to treatment at 6 months, csDMARDs at baseline, age ≤ 54 years at the start of TNF-I, presence of any co-morbidities, cardiovascular co-morbidities, MetS, and baseline CRP and ESR levels. Male gender was confirmed to be a positive predictor of maintenance of remission and LDA at two time points, and of sustained LDA. The multivariate analysis showed that patients treated with concomitant csDMARDs achieved LDA at 1 year and 2 years at a higher frequency than patients on TNF-i in monotherapy. Moreover, patients who started TNF-i at ≤ 54 years of age showed a trend to reach a higher proportion of remission than older patients at 1 year of treatment, while a significant result was demonstrated in the maintenance of remission and LDA at two time points.

The presence of any co-morbidity was also a negative predictor of sustained remission and LDA in the multivariate analysis. Negative baseline CRP was confirmed to be a positive predicting factor of remission at all the time points. Patients with negative CRP levels achieved LDA at 1 year and 2 years at a higher rate than patients with positive baseline CRP.

DISCUSSION

Positive predictors of remission/LDA in the multivariate analysis were male gender, age ≤ 54 years old at the time of TNF-i treatment, negative baseline CRP and some extent of concurrent csDMARDs for LDA. The only negative predictor was the presence of any co-morbidity.

Women with RA have a more severe course of disease in terms of disease activity, loss of function, joint destruction and work disability [19]. Studies including TNF-i cohorts showed that male gender was an independent predictor of remission [5]. Our study reported that male patients achieved better outcomes in terms of remission/LDA than females at single time points of evaluation in the univariate analysis. Indeed, male gender was associated with maintenance of remission/LDA and sustained remission/LDA at 2 years of follow-up in the multivariate analysis. Overall this result conform to earlier findings [5], although caution should be used when a comparison is performed between males and females since the fulfillment of criteria to reach remission relies on patient-reported outcomes that may differ according to gender [20].

Among the clinical characteristics of RA patients, having early arthritis and/or reaching an early good/moderate response to the biologic treatment are the major factors that may influence the long-term response to therapy and therefore the disease outcome [5]. Our results show that both early arthritis patients and patients with early response achieved long-term remission/LDA with a higher frequency compared to those with established disease and those with no early response.

Treatment with concomitant csDMARDs resulted in a positive predicting factor of LDA at 1 and 2 years of TNF-i therapy even when the result was adjusted for the other variables. Patients at LDA were numerically more than those in remission; therefore, we hypothesize that studies on larger cohorts might confirm this result.

Both the univariate and multivariate analysis showed that a higher number of patients ≤ 54 years old achieved and maintained remission and LDA with the respect to older ones. Evidence reported that older RA patients were less likely to receive TNF-i within the same period of time compared with younger patients and the oldest patients had higher DAS28 levels prior to treatment than younger ones [21]. Overall, the relatively worse outcome that we observed in patients older than 54 years old may have several explanations, such as disease activity, disease duration or a restrained approach in the treatment combined with a delay in the initiation of biologics.

Co-morbidities may represent another limiting factor in the prescription of biological treatments and may also affect disease severity and treatment outcome [22]. Indeed, in our study population they were independent negative predictors of sustained remission and LDA when adjusted for other variables. Future studies should analyze more in depth their influences, taking

into account also their management in the context of polypharmacotherapy and multi-system involvement. In RA, although many biomarkers, especially pro-inflammatory cytokines, reflect the ongoing events in active synovitis and may mirror the disease process and response to treatment, they have not been shown to provide superior information to the traditional inflammatory markers [23]. ESR was not an independent predicting factor of remission/LDA when adjusted for confounding variables, while negative CRP at baseline was a significant independent predicting factor of remission at all time points and of LDA at one and two years of TNF-i treatment. Evidence from the literature reported that CRP was an independent predictor of radiographic progression in cohorts of patients with recent-onset inflammatory polyarthritis and RA [24]. Moreover, CRP concentration has been significantly associated with generalized bone loss in both healthy subjects and RA patients [25]. Based on our results, it is reasonable to hypothesize that negative CRP levels may identify a subpopulation of RA patients who may benefit from TNF-i regarding the possibility to achieve the treatment targets. It would be interesting in future studies to evaluate the possibility to include this parameter in the recommendations of RA treatment and not only in clinical practice.

Confounded by indication and observation, bias cannot be excluded from this study. We therefore chose to group all TNF-i treated patients rather than analyze them separately. Treatment targets were reached and maintained in a relatively low number of patients; therefore, studies on larger cohorts should confirm these findings. However, most of the predicting factors identified in the univariate and the multivariate analysis were associated with the disease outcome during the relatively long-term observation allowing us to hypothesize the consistency of our results.

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References

1. Scrivo R, Conigliaro P, Riccieri V, et al. Distribution of interleukin-10 family cytokines in serum and synovial fluid of patients with inflammatory arthritis reveals different contribution to systemic and joint inflammation. *Clin Exp Immunol* 2015; 179: 300-8.
2. Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; 73: 492-509.
3. Mierau M, Schoels M, Gonda G, Fuchs J, Aletaha D, Smolen JS. Assessing remission in clinical practice. *Rheumatology* 2007; 46: 975-9.
4. Conigliaro P, Chimenti MS, Triggianese P, et al. Remission and low disease activity in a cohort of real-life patients with rheumatoid arthritis treated with first-line antitumour necrosis factor. *J Int Med Res* 2016; 44 (1 Suppl): 90-4.
5. Katchamart W, Johnson S, Lin HJ, Phumethum V, Salliot C, Bombardier C. Predictors for remission in rheumatoid arthritis patients: A systematic review. *Arthritis Care Res* 2010; 62: 1128-43.
6. Ciccacci C, Conigliaro P, Perricone C, et al. Polymorphisms in STAT4, IL10, PSORS1C1, PTPN2 and MIR146A genes are differently associated with prognostic factors in Italian patients affected by rheumatoid arthritis. *Clin Exp Immunol* 2016; 186: 157-63.
7. Conigliaro P, Triggianese P, Perricone C, et al. Restoration of peripheral blood natural killer and B cell levels in patients affected by rheumatoid and psoriatic arthritis during etanercept treatment. *Clin Exp Immunol* 2014; 177: 234-43.
8. Martin-Mola E, Balsa A, García-Vicuna R, et al. Anti-citrullinated peptide antibodies and their value for predicting responses to biologic agents: a review. *Rheumatol Int* 2016; 36: 1043-63.
9. Conigliaro P, Chimenti MS, Triggianese P, et al. Autoantibodies in inflammatory arthritis. *Autoimmun Rev* 2016; 15: 673-83.
10. Isaacs JD, Cohen SB, Emery P, et al. Effect of baseline rheumatoid factor and anticitrullinated peptide antibody serotype on rituximab clinical response: a meta-analysis. *Ann Rheum Dis* 2013; 72: 329–36.
11. Aletaha D, Neogi T, Silman AJ, et al. Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; 62: 2569–81.
12. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 44-8.
13. Smolen JS, Collaud Basset S, et al. European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Clinical trials of new drugs for the treatment of rheumatoid arthritis: focus on early disease. *Ann Rheum Dis* 2016; 75: 1268-71.
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic co-morbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–83.
15. Temizkan S, Balaforlou B, Ozderya A, et al. Effects of thyrotrophin, thyroid hormones, and thyroid antibodies on metabolic parameters in a euthyroid population with obesity. *Clin Endocrinol* 2016; 85: 616-23.
16. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009; 120: 1640-5.
17. van Gestel AM, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum* 1996; 39: 34-40.
18. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016; 75: 3-15.
19. Tengstrand B, Ahlmén M, Hafström I. The influence of gender on rheumatoid arthritis: a prospective study of onset and outcome after 2 years. *J Rheumatol* 2004; 31: 214–22.
20. Sokka T, Toloza S, Cutolo M, et al. Women, men, and rheumatoid arthritis: analyses of disease activity, disease characteristics, and treatments in the QUEST-RA study. *Arthritis Res Ther* 2009; 11: R7.
21. Radovits BJ, Fransen J, Eljsbouts A, van Riel PL, Laan RF. Missed opportunities in the treatment of elderly patients with rheumatoid arthritis. *Rheumatology* 2009; 48: 906-10.
22. Chimenti MS, Triggianese P, Conigliaro P, Candi E, Melino G, Perricone R. The interplay between inflammation and metabolism in rheumatoid arthritis. *Cell Death Dis* 2015; 6: e1887.
23. McInnes IB, Buckley CD, Isaacs JD. Cytokines in rheumatoid arthritis–shaping the immunological landscape. *Nat Rev Rheumatol* 2016; 12: 63-8.
24. Carrier N, Marotta A, de Brum-Fernandes AJ, et al. Serum levels of 14-3-3η protein supplement C-reactive protein and rheumatoid arthritis-associated antibodies to predict clinical and radiographic outcomes in a prospective cohort of patients with recent-onset inflammatory polyarthritis. *Arthritis Res Ther* 2016; 18: 37.
25. De Pablo P, Cooper MS, Buckley CD. Association between bone mineral density and C-reactive protein in a large population-based sample. *Arthritis Rheum* 2012; 64: 2624-31.