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Original article

High anti-CCP antibody titres predict good response to rituximab in patients with active rheumatoid arthritis

Anaïs Gardette[a], Sébastien Ottaviani[a,*], Florence Tubach[b,c,d], Carine Roy[b,c,d], Pascale Nicaise-Roland[e], Elisabeth Palazzo[a], Ghislaine Gill[a], Olivier Meyer[a], Philippe Dieudé[a,f]

[a] Université Paris Diderot, Service de Rhumatologie, Hôpital Bichat, AP–HP, Paris, France
[b] AP–HP, Hôpital Bichat-Claude-Bernard, Département d'Épidémiologie Biostatistique et Recherche Clinique, Paris, France
[c] Université Paris Diderot, Sorbonne Paris Cité, Paris, France
[d] INSERM, CIE801, Paris, France
[e] Université Paris Diderot, Service d'Immunologie, Hôpital Bichat, AP–HP, Paris, France
[f] Université Paris Diderot, INSERM U699, Paris, France

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ABSTRACT

Objective: Previous studies reported that anti-CCP antibody positivity predicts good response to rituximab (RTX) in rheumatoid arthritis (RA). A quantitative approach to such possibility could be a good way to detect the subset of patients most likely to respond. We investigated whether serum anti-CCP antibody titres could predict response to RTX in RA patients.
Methods: We retrospectively investigated RA patients who received RTX. The primary criterion was decrease in DAS28 > 1.2 at 6 months (M6). Secondary efficacy criteria included a good response and remission according to EULAR. Predictors of response were investigated by multivariate logistic regression analysis.
Results: We included 114 RA patients (81.6% female, median age 53.5 [IQR 45.7–61.2] years, median disease duration 8.5 [4.0–16.0] years). Anti-CCP antibodies were present in 93 patients (81.6%), with median anti-CCP antibody titres 583 [195–1509] U/mL. In all, 44 patients (38.6%) showed decreased DAS28 > 1.2 at M6. On univariate analysis, high anti-CCP titres were associated with response rather than non-response to RTX (median 1122 [355–1755] vs. 386 [149–800] U/mL, $P = 0.0191$) at M6. On multivariate regression analysis, with a cut-off of 1000 U/mL, anti-CCP antibody titres $\geq$ 1000 was associated with a decrease in DAS28 > 1.2 (OR 5.10 [1.97–13.2], $P = 0.0002$); a EULAR good response (4.26 [1.52–11.95], $P = 0.0059$); and a trend for EULAR remission (2.52 [0.78–8.12], $P = 0.1207$).
Conclusion: High anti-CCP antibody titres predict response to RTX in RA. This factor, easily assessed in clinical practice, can help with personalized medicine and selecting the best candidates for RTX treatment.

1. Introduction

In rheumatoid arthritis (RA), a variable clinical response to targeted therapies, including biologics, strongly highlights the variability in disease. To date, the data support that different pathogenetic processes may lead to common final pathways and shared clinical signs and symptoms associated with the syndrome termed RA. In the current era, with a rapid increase in number of new biologic targets and related therapies for RA, understanding why patients respond or do not respond to a given treatment is crucial. The next step may be to select subgroups of patients who are more likely to exhibit a favourable response to a specific mechanism of action.

Rituximab (RTX), a monoclonal antibody targeting B cells has shown efficiency in treating active established RA resistant to disease modifying anti-rheumatic drugs (DMARDs) or anti-tumour necrosis factor (TNF) agents [1,2]. Evidence is emerging that anti-cyclic citrullinated peptide (anti-CCP) antibody status can further characterize the heterogeneous RA phenotype, including the

Abbreviations: RA, rheumatoid arthritis; RTX, rituximab; DMARDs, disease modifying anti-rheumatic drugs; TNF, tumour necrosis factor; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide; SJC, swollen joint count; TJC, tender joint count; VAS, visual analog scale; DAS28, disease activity score of 28 joints; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

* Corresponding author at: Université Paris Diderot, Service de Rhumatologie, Hôpital Bichat, AP–HP, 46, rue Henri-Huchard, 75018 Paris, France.
E-mail address: sebastien.ottaviani@bch.aphp.fr (S. Ottaviani).

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response to methotrexate (MTX) in undifferentiated arthritis [3] or in early RA [4]. Because B cells, the target of RTX, play pivotal roles in RA pathogenesis [5], serum biomarkers of B cell activation, such as the presence of rheumatoid factor (RF), or anti-CCP antibodies and elevated IgG level, were recently identified as potential predictors of response to RTX [6]. Thus, RTX might have a greater role in anti-CCP+ than anti-CCP− RA. Several retrospective and prospective studies reported that both RF and anti-CCP antibody status can predict the response to RTX in RA [6–13], but only one study focused on quantitative anti-CCP antibody production and found a strong association of high anti-CCP titres and response to RTX [12]. Regarding anti-CCP+ RA, a quantitative approach to anti-CCP antibody titres could be a good way to detect the subset of patients most likely to respond to RTX. Therefore, we aimed to test serum titres of anti-CCP antibodies in predicting the response to RTX among patients with active RA.

2. Methods

2.1. Study population

We performed a retrospective study of 114 RA patients who had received RTX in the rheumatology department of Bichat hospital, Paris. All patients fulfilled the 1987 American College of Rheumatology criteria [14] and had active disease defined by disease activity score in 28 joints (DAS28) [15] with erythrocyte sedimentation rate (ESR) (DAS28-ESR) > 2.6. As recommended, RTX treatment consisted of 2 intravenous infusions of 1000 mg per treatment cycle separated by a 2-week interval, with repeated courses of therapy at least 6 months afterward [2]. Data collected at baseline (M0) included age, gender, disease duration, use of corticosteroids, details of past and present anti-rheumatic therapy, and assessment of disease activity, including swollen joint count (SJC) and tender joint count (TJC) in 28 joints, pain on a visual analog scale (VAS pain), ESR, C-reactive protein (CRP) level, DAS28-ESR, and rheumatoid factor (RF) and anti-CCP status. Local institutional review board (No. 12-081) approved the study, and written informed consent was obtained from all subjects in the study.

2.2. Study protocol

The primary criteria was decrease in DAS28 > 1.2 at month 6 (M6). Secondary efficacy criteria included a EULAR good response (decrease in DAS28 > 1.2 and final DAS28 ≤ 3.2), EULAR remission (DAS28 < 2.6) and change in DAS28 (ΔDAS), SJC (ΔSJC) and TJC (ΔTJC), VAS pain (ΔVAS), ESR (ΔESR), CRP level (ΔCRP) and use of corticosteroids (ΔCTC). Predictors of good response were investigated by age, gender, disease duration, CRP level at M0, DAS28 at M0, treatment with DMARDs or previous treatment with an anti-TNFα agent, RF positivity and titres, and anti-CCP positivity and titres.

2.3. Autoantibody analysis

Anti-CCP and RF were identified and quantified with the Immunoscan-CCPlus ELISA test (Eurodiagnostica, Malmö, Sweden) and nephelometry (BNII, Siemens, Marburg, Germany), respectively. Levels above 25 U/mL and 30 UI/mL, respectively, were regarded as positive. A cut-off of 1000 U/mL was defined to qualify anti-CCP levels as high. This cut-off was previously demonstrated to be associated with pulmonary involvement [16].

Table 1
Baseline characteristics of RA patients.

	Rituximab (n = 114)
Age (years), median [IQR]	53.5 [45.7–61.2]
Female gender, n (%)	93 (81.6)
Disease duration (years), median [IQR]	8.5 [4.0–16.0]
BMI (kg/m^2), median [IQR]	26.8 [23.8–31.1]
Tobacco smoking, n (%)	23 (20.2)
DAS28, median [IQR]	5.1 [4.1–6.0]
RF status (% positivity)	75.2
RF titres (U/mL)[a], median [IQR]	172.0 [67.0–510.0]
Anti-CCP status (% positivity)	81.6
Anti-CCP titres (U/mL)[a], median [IQR]	583.0 [195.0–1509.0]
Anti-CCP titres ≥ 1000 U/mL[a], n (%)	36 (31.6)
ESR (mm), median [IQR]	28 [16–42]
CRP (mg/L), median [IQR]	11.0 [5.0–19.7]
DMARDs, n (%)	85 (74.6)
Previous anti-TNFα, n (%)	72 (63.2)
Corticosteroids (mg/day), median [IQR]	9 [5–10]

RA: rituximab; IQR: interquartile range; BMI: body mass index; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DMARDs: disease modifying anti-rheumatic drugs; TNF: tumor necrosis factor; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide.
[a] For positive status.

2.4. Statistical analysis

Categorical variables are expressed as frequencies and percentages. Comparisons between categorical variables involved the Pearson Chi^2 test. Student's t-test (two-tailed) was used to compare normally distributed continuous variables and Wilcoxon rank-sum test to compare continuous variables not normally distributed. We used logistic regression to determine predictors of response to RTX according to analysed criteria (EULAR DAS28 response, ΔDAS28, ΔTJC, ΔSJC, ΔVAS pain, ΔCRP, ΔESR). The model included variables significantly associated with each dependant variable on univariate analyses (P = 0.20). Multivariate analysis includes the following variables: age, gender, disease duration, DAS28 at baseline, DMARDs use, previous anti-TNFα therapies, tobacco smoking, anti-CCP and FR status. Anti-CCP antibody titres were considered a categorical variable on multivariate analysis. Statistical analysis involved use of SAS v9.2 (SAS Inst., Cary, NC). P < 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of RA patients at baseline

We included 114 RA patients who had received RTX (93 [81.6%] female, median [IQR] age 53.5 [45.7–61.2] years and median disease duration 8.5 [4.0–16.0] years [Table 1]). The median baseline DAS28 was 5.1 [4.1–6.0] and CRP level 11.0 [5.0–19.7] mg/L. A total of 93 (81.6%) and 85 (75.2%) patients were positive for anti-CCP antibodies and RF, respectively (median titres 583.0 [195.0–1509.0] and 172.0 [67.0–510.0] U/mL). The median dose of corticosteroids was 9 [5.0–10.0] mg/day. In all, 85 patients (74.6%) had received DMARDs (77.5% MTX) and 72 (63.2%) were previously treated with anti-TNFα biologics. Tobacco smoking was noted in 20.2% of all