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Intitulé

Response to biological therapies based on anti-cyclic citrullinated peptide antibodies status in rheumatoid arthritis patients from the RBSMR registry after one year of follow-up.

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A notre maître,

Monsieur le professeur BEZZA Ahmed,

Vous nous avez confié ce travail sans aucune réserve.

Nous souhaitons être digne de cet honneur.

Vous nous avez guidés tout au long de notre travail
en nous apportant
vos précieux et pertinents conseils.

Nous vous remercions pour votre patience
et votre soutien lors de la réalisation de ce mémoire.

Veuillez trouver ici l'expression de notre respectueuse considération
et notre profonde admiration pour toutes vos qualités
scientifiques et humaines.

SUMMARY

ABSTRACT

Résumé

Objectifs *:* Les études sur l'efficacité des bDMARD (biological Disease-Modifying Anti-Rheumatic Drugs) en fonction du statut des anticorps anti-peptides cycliques citrullinés (ACPA) dans la polyarthrite rhumatoïde (PR) trouvent de nombreuses discordances. Dans le but de contribuer à lever l'équivoque, notre étude visait à évaluer l'association entre le statut des ACPA et la réponse thérapeutique aux biomédicaments chez les patients PR issus d'un registre national de vraie vie.

Méthodes *:* Il s'agissait d'une étude de cohorte historico-prospective multicentrique ayant inclus des patients PR traités par bDMARD. Après leur inclusion, les patients étaient suivis tous les 6 mois et les données d'efficacité et de tolérance étaient recueillies. Dans notre étude, nous avons évalué la réponse thérapeutique aux bDMARD à 12 mois (M12) de suivi en fonction du statut des ACPA avec comme critère de jugement principal un DAS28-CRP $\leq 3,2$ à M12.

Résultats : 225 patients dont 28 hommes ont été inclus. Les ACPA étaient positifs dans 67,1 % des cas. Les bDMARD utilisés étaient le rituximab (60%), le tocilizumab (23,6%) et les anti TNF α (Tumor Necrosis Factor alpha) (16,4%). Le DAS28-CRP avait significativement diminué de $4,8 \pm 1$ à $2,8 \pm 1,2$ chez les patients de l'inclusion à M12 ($p < 0,001$). Le DAS28-CRP à M12 était plus élevé chez les patients ACPA positifs ($2,9 \pm 1,2$) que chez les patients ACPA négatifs ($2,4 \pm 1$), mais la différence n'était pas statistiquement significative. Les pourcentages de bons répondeurs étaient de 87 % et 68 % respectivement chez les patients ACPA négatifs et ACPA positifs (p non significatif). La réponse thérapeutique n'était pas significativement associée à la présence d'ACPA et était comparable quel que soit le bDMARD.

Conclusions : L'association entre l'efficacité des bDMARD et le statut des ACPA chez les patients PR n'a pas été retrouvée dans notre étude.

Mots clés : Polyarthrite rhumatoïde, statut ACPA, réponse biologique, anti TNF alpha, rituximab, tocilizumab.

الملخص

الأهداف :تتناقض نتائج الدراسات حول فعالية الأدوية البيولوجية المضادة للروماتيزم حسب حالة مضادات الأجسام للببتيد الستروليني عند مرضى التهاب المفاصل الروماتويدي، من أجل المساعدة في الحصول على جواب هدفت دراستنا إلى تقييم هذه العلاقة من خلال معطيات السجل الوطني للأدوية البيولوجية.

الطريقة :يعتبر السجل الوطني للأدوية البيولويجية سجلا تاريخيا مستقبليا، هذا السجل تم بمشاركة عدة مراكزبحثية حيث تم تضمين مرضى التهاب المفاصل الروماتويدي المعالجين بالأدوية البيولوجية و تتبع حالاتهم لمدة 12 شهرا . بعد التضمين ، تمت متابعة المرضى كل 6 أشهر وتم جمع بيانات الفعالية والسلامة .في دراستنا ، قمنا بتقييم الاستجابة العلاجية في الشهر الثاني عشر مع اعتبارضإ ص أقل من 3،2 كنقطة نهاية أولية .

النتائج :تم تضمين 225 مريضا من بينهم 28 رجلا .كانت مضادات الأجسام للببتيد الستروليني إيجابية لدى 67 %من الحالات، الأدوية البيولوجية التي تم استعمالها هي ريتوكسيماب)٪60 (وتوسيليزوماب)٪23.6 (ومضاد عامل نخر الورم ألفا)٪16.4.(تم تخفيض نشاط المرض بشكل كبير، كانت النسب المئوية للمستجيبين الجيدين 87٪ و 68٪ على التوالي في المرضى السلبيين و الموجبين لمضادات الأجسام للببتيد الستروليني .لم تكن الاستجابة العلاجية مرتبطة بشكل كبير بوجود مضادات الأجسام للببتيد الستروليني وكانت قابلة للمقارنة بغض النظر عن نقطة النهاية الأولية.

لاستنتاجات :لم يتم العثور على العلاقة بين فعالية الأدوية البيولوجية وحالة مضادات الأجسام للببتيد الستروليني عند مرضى التهاب المفاصل الروماتويدي في دراستنا.

الكلمات المفتاحية :التهاب المفاصل الروماتويدي ، حالة مضادات الأجسام للببتيد الستروليني ، الاستجابة البيولوجية ، مضاد ألفا عامل نخر الورم ، ريتوكسيماب ، التوسيليزوماب.

Abstract

Objectives: Studies on the efficacy of biotherapies according to the status of anti-cyclic citrullinated peptides (ACCP) antibodies in rheumatoid arthritis (RA) find many discrepancies. In order to contribute to resolving this ambiguity, our study aimed to assess the association between ACCP status and the therapeutic response to bDMARD (biological Disease-Modifying Anti-Rheumatic Drugs) in RA patients from a national real-life registry.

Methods: This was a multicentric, historical-prospective cohort study that included RA patients treated with bDMARD. After inclusion, patients were followed up every 6 months and efficacy and tolerance data were collected. In our study, we assessed the therapeutic response to biotherapy at 12 months (M12) of follow-up according to the status of ACCP. The main endpoint was a DAS28-CRP ≤ 3.2 at M12.

Results: 225 patients including 28 men were included. ACCPs were positive in 67.1% of cases. The bDMARDs used were rituximab (60.0%), tocilizumab (23.6%) and anti TNF α (Tumor Necrosis Factor alpha) (16.4%). DAS28-CRP was significantly decreased from 4.8 ± 1.0 to 2.8 ± 1.2 in patients from inclusion to M12 ($p < 0.001$). DAS28-CRP at M12 was higher in ACCP positive patients (2.9 ± 1.2) than in ACCP negative patients (2.4 ± 1.0), but the difference was not significant (p: 0.127). The percentages of good responders were 87% and 68% respectively in ACCP negative and ACCP positive patients (p: 0.228). The therapeutic response was not significantly associated with the presence of ACCP and was comparable regardless of the bDMARD.

Conclusions: An association between the efficacy of biotherapy and ACPA status in RA patients was not found in our study.

Keywords: Rheumatoid arthritis, ACCP status, efficacy of biotherapy, anti TNF alpha, rituximab, tocilizumab.

INTRODUCTION

Rheumatoid arthritis (RA) is the most common chronic inflammatory rheumatism. In a recent meta-analysis, its global prevalence was 0.46% (95% CI 0.39-0.54) [1]. Its immunological diagnosis is based on the positivity of rheumatoid factors (RF) and / or anti-cyclic citrullinated peptides (ACCP) antibodies. However, the most specific autoantibodies for RA remain ACCP. These are the prognostic markers of the structural severity of RA [2,3]. Indeed, ACCPs are responsible for the early onset of bone erosions and joint destruction [4–8]. Their presence and especially their high rate are associated with the occurrence of extra-articular manifestations [9,10]. Thus, ACCPs define two clinical phenotypes of RA namely ACCP positive RA and ACCP negative RA. Depending on each phenotype, the therapeutic response may vary. Since biotherapy has revolutionized the management of RA, rituximab and abatacept have been shown to be particularly more effective in ACCP positive patients than in ACCP negative patients [11–13]. In 2014, a meta-analysis showed that there was no association between ACCP status and clinical response to TNF α (Tumor Necrosis Factor alpha) inhibitors in RA patients [14]. However, studies on this association are conflicting [15–20]. This discrepancy requires further studies in order to resolve the ambiguity. This is why our study aimed to assess the association between ACCP status and the therapeutic response to bDMARD (biological Disease-Modifying Anti-Rheumatic Drugs) in RA patients from a national real-life registry (RBSMR) after 12 months of follow-up.

METHODS

The RBSMR and the current study

The RBSMR (Registre des Biothérapies de la Société Marocaine de Rhumatologie) is the first Moroccan register to have included patients with RA or spondyloarthritis (SA) treated with bDMARD and followed for 3 years. The main objective of this register was to assess the tolerance of biotherapies in rheumatology. Thus, it was a multicentric historical-prospective cohort study that included patients from the 10 rheumatology departments of Moroccan university hospitals: Agadir, Casablanca, Fès, Marrakech, Meknes, Rabat, Salé and Oujda. The inclusion period was from May 2017 to January 2019.

The patients included in the register were aged at least 18 years, followed in rheumatology for RA fulfilling the ACR-EULAR 2010 (American College of Rheumatology - European League Against Rheumatism 2010) criteria or SA fulfilling the ASAS (Assessment of SpondylArthritis international Society) criteria, treated with bDMARD, and had given their written informed consent. Patients treated with bDMARD indicated for diseases other than RA or SA as well as patients with juvenile idiopathic arthritis were not included. Using an electronic questionnaire, we recorded efficacy and tolerance data every six months as well as adverse events and treatment changes. The questionnaire included the characteristics of the patients (age, disease duration and the main characteristics of the disease); comorbidities (diabetes, high blood pressure, tobacco smoking, cardiovascular events, osteoporosis, depression, infections, cancer); as well as the therapeutic history of patients in the context of RA or SA before the initiation of biotherapy (current use of analgesics, non-steroidal anti-inflammatory drugs, corticosteroids, cDMARD (conventional Disease-Modifying Anti-Rheumatic Drugs)). For patients with RA, indexes of activity and severity were collected: the DAS28 (Disease Activity Score 28) and its components, the HAQ (Health Assessment Questionnaire Disability Index),

history of joint surgeries. In January 2019, a total of 419 patients including 225 with RA and 194 with SA were included in the study.

The current study was based on the 225 RA patients of the RBSMR and assessed the therapeutic response of these patients to biotherapy according to their ACCP status after 12 months of follow-up. For this reason, we used the DAS28 response criteria of the EULAR [21]. Thus, the biological response was considered to be good at 12 months for values of DAS28 less than or equal to 3.2 at M12. For didactic reasons, we preferred to work with DAS28-CRP (DAS28 calculated with the C-reactive protein). To achieve our objective, we first compared DAS28 and its components between patients at inclusion (M0) and at one year of follow-up (M12): this was intended to shed light on the evolution of DAS28 between these two periods. Then, in order to see if there was a difference in the values of DAS28 and its components between patients according to their ACCP status, we compared the same parameters between ACCP negative and ACCP positive patients at M0 on the one hand and at M12 on the other hand. Then, we compared the percentage of good EULAR responders (patients with DAS28-CRP $\leq$ 3.2) between ACCP negative and ACCP positive patients at M12 overall and per bDMARD. Finally, we determined the factors associated with the therapeutic response at M12.

The statistical analysis

The statistical study was done using the frozen database from January 2019 at baseline (M0) and from January 2020 at one year follow-up (M12). For data analysis, we used Excel and IBM SPSS Statistics version 21. Comparisons of the components of DAS28 between patients at M0 and M12 were performed using the Wilcoxon test. The paired sample t-test was used to compare DAS28-CRP between patients at M0 and M12. The Mann-Whitney test made it possible to compare the components of DAS28 between ACCP negative and ACCP

positive patients at M0 and M12. The independent samples t-test was used for comparison of DAS28-CRP between ACCP negative and ACCP positive patients at M0 and M12. To compare the percentage of good responders between ACCP negative and ACCP positive patients at M12, Fisher's exact test was used. To determine the factors associated with the therapeutic response at M12, we used logistic regression. P-values of less than 0.05 were considered statistically significant.

RESULTS

Table 1 provides information about the characteristics of the patients at inclusion (M0). The total number of patients was 225 including 28 men (12.4%). Their mean age was 51.9 ± 11.3 years and the median duration of the course of RA was 12 years. ACCPs were positive in 67.1% of cases. The mean value of DAS28-CRP was 4.8 ± 1.0. As for the comorbidities, 27.5% were obese (body mass index ≥ 30 Kg / m2), 39.3% were sedentary, 20.4% were diabetic, 16.4% suffered from arterial hypertension, 1.8 % were tobacco smokers, 12.5% and 2.8% had hypercholesterolemia and hypertriglyceridemia respectively. 74.6% of patients were still receiving corticosteroid therapy at the mean dose of 7.2 ± 4.2 mg per day. 92% had not stopped their cDMARD (including methotrexate: 78.2%). 50% of patients had started biologic therapy before 6.5 years of disease progression and 9.3% had received at least their third bDMARD. The biologic drugs used were rituximab (60.0%), tocilizumab (23.6%) and TNF α inhibitors (16.4%).

Table 2 presents comparisons of DAS28 and its components between patients at M0 and M12. There was a very significant decrease in the tender joint count, the swollen joint count, the visual analogue scale (VAS) of the disease, CRP and erythrocyte sedimentation rate (ESR) in patients from M0 to M12 ($p < 0.001$). Likewise, DAS28-CRP very significantly decreased from 4.8 ± 1.0 to 2.8 ± 1.2 in patients from M0 to M12 ($p < 0.001$).

In Table 3, we compare DAS28 and its components between ACCP negative and ACCP positive patients at M0 on the one hand and M12 on the other. Thus, we can notice that at inclusion the ESR of ACCP positive patients was significantly higher than that of ACCP negative patients ($p = 0.032$). Even if the CRP decreased at M12 in the two categories of patients, it is nevertheless observed that the CRP at M12 was higher in the ACCP positive patients than in the ACCP negative patients ($p = 0.006$). The DAS28-CRP at M12 was higher in

ACCP positive patients (2.9 ± 1.2) than in ACCP negative patients (2.4 ± 1.0), but the difference was not significant (p: 0.127).

Table 3 also shows information about the comparison of the percentages of good EULAR responders between ACCP positive and ACCP negative patients. Thus, 87% of ACCP negative patients were good responders while in ACCP positive patients, good responders represented 68%, but this difference was not statistically significant (p: 0.228). There was also no significant difference between the percentages of good responders in ACCP negative and ACCP positive patients when compared per bDMARD.

Table 4 highlights the factors associated with the therapeutic response at M12 in RA patients. In univariate analysis, the biological response was not significantly associated with the presence of ACCP (OR: 3, 95% CI [0.7-14.2], p: 0.157). Moreover, there was no association between therapeutic efficacy and the type of bDMARD in the population of ACCP positive RA patients. The biological response was significantly associated with a disease duration of less than 10 years (OR: 2.5, 95% CI [1.2-5.1], p: 0.018).

DISCUSSION

The efficacy of biotherapies based on ACCP status in RA patients has been the subject of several studies over the past two decades. Thus, rituximab and abatacept have been shown to be more effective in PR ACPA positive patients than in ACCP positive RA. In our study, there was no association between the efficacy of biotherapies and the presence of ACCP (OR: 3, 95% CI [0.7-14.2], p: 0.157). In ACCP positive RA patients, therapeutic efficacy was not associated with the type of bDMARD. Furthermore, there was no significant difference between the percentages of good responders in ACCP negative and ACCP positive patients.

Sellam et al. reported that the presence of ACCP or RF was associated with a good EULAR response at 24 weeks (OR: 3.5, 95% CI: 1.6-7.6) [22]. In another study about rituximab, an association was reported between the positivity of ACCP and a good EULAR response at 6 months of treatment (OR: 2.86, p: 0.003) [23]. In the study by Couderc et al., ACCP positivity was associated with a good to moderate response to rituximab (OR: 4, 95% CI: 1.04-15.5, p: 0.04) [24]. Other studies reported that very high titers of ACCP were associated with a better response to rituximab. Thus, in one study it was shown that not only positivity of ACCP was associated with a good EULAR response to rituximab, but also high titers of ACCP > 300 U / mL were 3 to 4 times more likely to obtain a better EULAR response (OR: 3.38, 95% CI: 1.025-11.17) [25]. For Anaïs et al., it was ACCP titers ≥ 1000 U / mL that were associated with a good EULAR response (OR: 4.26, 95% CI: 1.52-11.95, p: 0.0059) [26].

In the ORA registry, ACCP positivity was significantly associated with the EULAR response (OR: 1.9, 95% CI: 1.2-2.9, p: 0.007) with a higher abatacept retention rate at 6 months [27]. This association of ACCP with a high retention rate of abatacept was confirmed by the ACTION study [28,29]. The results of the pan-European registry analysis suggested that the positivity of ACCP was strongly associated with better efficacy of abatacept treatment [30]. In the

AMPLE trial, initial positivity for ACCP2 was associated with a better response for abatacept and adalimumab, but the high level of ACCP2 was associated with better efficacy of abatacept compared to the low level, which has not been observed with adalimumab [31].

As for TNF α inhibitors, studies were contradictory and a meta-analysis ended up showing that there was no association between these bDMARDs and the status of ACCP [14]. However, a post hoc analysis of the RISING study showed that high initial titers of RF and ACCP were significantly associated with initially high TNF levels, low infliximab levels and reduced clinical response [32]. Another study had previously shown that initial TNF was significantly associated with clinical response to infliximab and suggested baseline TNF may be a useful measure to personalize RA treatment with infliximab [33]. It emerges from these two studies that ACCPs could influence the therapeutic response to TNF α inhibitors, given the positive correlation existing between ACCP and TNF.

Concerning tocilizumab, in the study by Pers et al., the therapeutic response was not associated with the status of ACCP [34]. According to another study on the predictors of an early response to tocilizumab in RA patients, no relationship was found with the positivity of ACCP [35].

In our study, ACCP positive patients kept significantly (p: 0.006) low inflammatory activity with a median CRP of 6.3 mg / L (3.0 mg / L-14.7 mg / L) at M12 in comparison with ACCP negative patients with a median CRP of 2.2 mg / L (0.6 mg / L-6.7 mg / L). Moreover, low RA activity persisted in ACCP positive patients (DAS28-CRP 2.9 ± 1.2) at M12, while ACCP negative patients were in remission (DAS28-CRP 2.4 ± 1.0), but this difference was not significant (p: 0.127). The study by Chatzidionysiou et al. reported greater improvement in DAS28 at 6 months in ACCP positive patients compared to ACCP negative patients [23]. In our study, there was no significant difference in

DAS28 response between ACCP positive and ACCP negative patients after 12 months of biotherapy. In another study about the persistence of subclinical local inflammation after 6 months of biotherapy in RA patients, 83% of patients with doppler positive erosions were ACCP positive patients [36].

Our study has its strengths and limitations. One of the limitations of our study was the very low number of ACCP negative patients. This is a real-life study and the bias in the choice of biotherapy by prescribers based on ACCP status cannot be excluded. Furthermore, abatacept has not been used as a treatment in RBSMR. The strength of our study is that it is multicentric and is based on the data collected on patients from the 10 rheumatology departments of Moroccan university hospitals. Thus, the results of this study can be generalized.

CONCLUSION

An association between the efficacy of biotherapy and ACCP status in RA patients was not found in our study. An analysis at M36 is planned to verify this assertion over a longer term.

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TABLES

Table 1: Characteristics of RA patients at inclusion (M0) in the RBSMR register.

Characteristics	Values (N = 225)
Age (years	51.9 ± 11.3
Sex	
Male	28 (12.4)
Female	197 (87.6)
Comorbidities	
Obesity (Body mass index ≥30 Kg/m^2)	52 (27.5)
Arterial hypertension	37 (16.4)
Diabetes mellitus	46 (20.4)
High blood Cholesteriol	28 (12.5)
High blood triglycerid	6 (2.8)
Physical inactivity	88 (39.3)
Tobacco smoking	4 (1.8)
Disease characteristics	
Disease duration (years)	12.0 (8.0 – 18.1)
Disease duration before the first biological drug (years)	6,5 (3.0 – 11.0)
DAS28-CRP	4.8 ± 1.0
RF status	
Negative	20 (8.9)
Positive	192 (85.3)
ACCP status	
Negative	19 (5.0)
Positive	151 (67.1)
Corticosteroid therapy	168 (74.6)
Dose of corticosteroid (mg/day)	7.2 ± 4.2
cDMARD	207 (92)
Type of bDMARD	
TNF α inhibitors	37 (16.4)
Etanercept	17 (7.6)
Adalimumab	14 (6.2)
Infiliximab	4 (1.8)
Golimumab	2 (0.9)
Rituximab	135 (60.0)
Tocilizumab	53 (23.6)
Biotherapy lines	
1st	163 (72.4)
2nt	41 (18.2)
≥3rd	21 (9.3)

Data are presented as: number (%), mean ± standard deviation, median (1st quartile - 3rd quartile)

DAS28-CRP: Disease activity calculated with C-reactive protein, RF: rheumatoid factors, ACCP: anti-citrullinated cyclic peptide antibodies, cDMARD: conventional Disease-Modifying Anti-Rheumatic Drugs, bDMARD (biological Disease-Modifying Anti-Rheumatic Drugs), TNF α: Tumor Necrosis Factor alpha.

Table 2: Comparisons of DAS 28 and its components between RA patients from the RBSMR register at M0 and M12.

Variables	M0 (N = 225)	M12 (N = 225)	P
TJC	14 (8 – 20)	2 (0 – 6)	<0.001
SJC	7 (4 - 11)	0 (0 – 2)	<0.001
VAS patient	7 (6 – 8)	5 (3 – 6)	<0.001
ESR (mm)	39.0 (23 – 58)	20 (9.8 – 36.5)	<0.001
CRP (mg/L)	17.1 (7.0 – 34.8)	6,0 (2.3 – 15.8)	<0.001
DAS28-CRP	4.8 ± 1.0	2.8 ± 1.2	<0.001

Data are presented as: median (1st quartile - 3rd quartile), mean ± standard deviation.

TJC: tender joint count out of 28, SJC: swollen joint count out of 28, VAS: visual analogue scale, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, DAS28-CRP: Disease activity calculated with the C reactive protein

Table 3: Comparisons of the therapeutic response between ACCP negative and ACCP positive RA patients from the RBSMR register at M12.

Variables	ACCP negative (N = 19)	ACPA positive (N = 151)	P
TJC M0	10 (7-19)	14 (8-20)	0.52
TJC M12	2 (0-5)	2 (0-5)	0.73
SJC M0	5 (4-10)	7 (4-11)	0.34
SJC M12	0 (0-0)	0 (0-2)	0.06
VAS Patient M0	7 (5-8)	7 (6-8)	0.55
VAS Patient M12	4 (2-5)	5 (3-7)	0.11
CRP M0	14.5 (6.0-32.5)	17.1 (6.1-37.6)	0.49
CRP M12	2.2 (0.6-6.7)	6.3 (3,0-14.7)	0.006*
ESR M0	25 (9-45)	40 (24-59)	0.03*
ESR M12	15 (4-26)	21 (10-39)	0.08
DAS28-CRP M0	4.6 ± 0.9	4.8 ± 1.0	0.48
DAS28-CRP M12	2.4 ± 1.0	2.9 ± 1.2	0.13
Good responders at M12 (N = 128)	13 (87)	77 (68)	0,23
Good responders with TNF α inhibitors at M12 (N = 22)	2 (100)	14 (74)	1.000
Good responders with rituximab at M12 (N = 83)	7 (78)	46 (62)	0.48
Good responders with tocilizumab at M12 (N = 23)	4 (100)	17 (85)	1.000

Data are presented as: median (1st quartile - 3rd quartile), mean ± standard deviation, number (%).

TJC: tender joint count out of 28, SJC: swollen joint count out of 28, VAS: visual analogue scale, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, DAS28-CRP: Disease activity calculated with the C reactive protein

Table 4: Factors associated with the therapeutic response at M12 in RA patients from the RBSMR register

Variables	Univariate analysis		
	OR	**95%CI**	**P**
ACCP status			
Negative	1		
Positive	3.0	[0.7-14.2]	0.16
RF			
Negative	1		
Positive	1.4	[0.4-4.7]	0.56
Disease duration			
≥ 10 years	1		
< 10 years	2.5	[1.2-5.1]	0.02*
Corticosteroid therapy			
No	1		
Yes	0.8	[0.4-2.0]	0.67
cDMARD			
No	1		
Yes	0.3	[0.1-1.5]	0.16
Type of bDMARD§			
TNF α inhibitors§	0.7	[0.2-2.2]	0.57
Rituximab§	2.3	[0.95-5.8]	0.06
Tocilizumab§	0.3	[0.1-1.2]	0.09
Biotherapy lines			
1st	1		
2nd	0.3	[0.1-0.9]	0.03*
≥3rd	0.8	[0.3-2.5]	0.7
Obesity			
No	1		
Yes	0.8	[0.3-1.6]	0.47

§ Given the primary objective of the study, the association between therapeutic response and type of bDMARD has only been investigated in ACCP positive patients.

ACCP: anti-cyclic citrullinated peptides, RF: rheumatoid factors, cDMARD: conventional Disease-Modifying Anti-Rheumatic Drugs, bDMRAD: biological Disease-Modifying Anti-Rheumatic Drugs, TNF α: Tumor Necrosis Factor alpha.