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Anti-cyclic-citrullinated-protein-antibodies in psoriatic arthritis patients: how autoimmune dysregulation could affect clinical characteristics, retention rate of methotrexate monotherapy and first line biotechnological drug survival. A single center retrospective study.

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Abstract

Aim: Occasional findings of anti-cyclic-citrullinated-protein-antibodies (anti-CCP) were rarely observed in psoriatic arthritis (PsA). The aim of our study is to evaluate whether the presence of anti-CCP can determine different clinical subsets and influence methotrexate monotherapy survival, and biotechnological drug retention rate.

Methods: We conducted a retrospective study on PsA patients. All patients were required to fulfill the CASPAR criteria for PsA, and to present juxta-articular osteo-proliferative signs at X-ray. The exclusion criteria were age less than 18 years old, satisfaction of rheumatoid arthritis classification criteria, and seropositivity for rheumatoid factor. Clinical characteristics, anti-CCP titer, drug survival and comorbidities information were recorded for each patient. Statistical significance was set at $p \leqslant 0.05$.

Results: Of 407 patients with PsA screened 113 were recruited. Twelve patients were anti-CCP positive. Methotrexate monotherapy survival was shorter in patients with anti-CCP (150 ± 48.3 weeks *versus* 535.3 ± 65.3 weeks; $p = 0.026$) [discontinuation risk hazard ratio (HR) = 2.389, 95% confidence interval (CI) 1.043, 5.473; $p = 0.039$] than those without. Significant shorter survival of first-line biotechnological drugs (b-DMARDs) was observed in the anti-CCP positive group than in that without (102.05 ± 24.4 weeks *versus* 271.6 ± 41.7 weeks; $p = 0.005$) with higher discontinuation risk (HR = 3.230, 95% CI 1.299, 8.028; $p = 0.012$). A significant higher rate of multi-failure (more than second-line b-DMARDs) was found in anti-CCP positive patients than in those without (50% *versus* 14%, $p = 0.035$).

Conclusion: Anti-CCP in PsA could be suggestive of more severe disease, with worse drug survival of both methotrexate monotherapy and first-line b-DMARDs, and higher chance to be b-DMARDs multi-failure. So, they can be considered for more intensive clinical management of these patients.

Keywords: ACPA, anti-CCP, biologic drugs, DMARDs, methotrexate, psoriatic arthritis

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Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease characterized by a wide spectrum of articular and periarticular involvements with heterogeneous courses. Typical signs of PsA are distal inter-phalangeal joint involvement, enthesitis, dactylitis, axial

involvement, inflammatory back pain, and new bone apposition at X-rays. Spreading evidences on wide heterogeneity of clinical presentation, characterized by extra-cutaneous and extra-articular manifestation, and several new pathogenetic hypotheses strengthen the concept of "Systemic Psoriatic Disease".[1–5] Recently, the presence of autoreactive T cell in synovia of PsA patients, and findings of specific autoantibodies directed against peptide epitopes expressed in skin and in entheses in PsA patients[6] support the hypothesis of autoimmune pathogenesis of PsA.[7–9] Even though a negative test result for the presence of rheumatoid factor (RF) is an item of both Moll and Wright[10] and CASPAR PsA classification criteria,[11] the clinical importance of anti-cyclic-citrullinated-protein-antibodies (anti-CCP) in PsA is not yet well known. The presence of anti-CCP in PsA is rarely described and ranged between 1% and 20%.[12] It is evidenced that anti-CCP in PsA patients are associated with more severe arthritis characterized by bone erosion at X-ray, polyarticular involvement, dactylitis, and female sex prevalence.[13–17]

Despite the growing interest in the role of anti-CCP in PsA, how this autoimmune dysregulation can affect the course of the disease is not yet understood. The aim of this study is to evaluate in clinical practice setting whether the presence of anti-CCP can determine different PsA clinical subsets, and influence methotrexate monotherapy survival, first line biotechnological drugs (b-DMARDs) survival, and eventual failure of first, second, or other lines of b-DMARDs.

Patients and methods

We performed a retrospective analysis, examining the medical records of a longitudinal cohort of 407 patients, regularly admitted to our clinic, and then followed at our outpatient clinic, from 2009 to 2019. All patients were required to fulfill the CASPAR classification criteria for PsA.[11]

To avoid including rheumatoid arthritis (RA) patients, in addition to inflammatory arthritis, the patients must have psoriasis or family history of psoriasis with nail psoriasis (in order to satisfy a CASPAR score of 3) and at least one additional clinical characteristic among asymmetrical arthritis or dactylitis. All patients had to present at hands or feet X-rays juxta-articular osteo-proliferative signs, and/or pencil-in-cup phenomenon and/or distal interphalangeal involvement. The exclusion criteria were age less than 18 years old, satisfaction of RA classification criteria (at the time of PsA diagnosis and during the time span of the study) and the presence of rheumatoid factor seropositivity. This study utilized baseline data of patients at the time of the PsA diagnosis.

Clinical manifestations, laboratory data [erythrocytes sedimentation rate (ESR), C-reactive protein (CRP), titer of anti-CCP, instrumental data (joints X-ray), type of joint involvement (oligoarticular or polyarticular), presence of enthesitis, axial involvement (defined by the presence of inflammatory back pain and by radiographic evidence of sacroiliitis or spondylitis), and the disease activity scores (DAS 28[18] and DAPSA[19]) were collected at baseline (time of PsA diagnosis). The comorbidities were evaluated at the time of the PsA diagnosis and were summarized as Charlson Comorbidity Index.[20] Patients' treatments were recorded at baseline and at follow-up visits. Serological tests were performed at local laboratories and anti-CCP seropositivity was determined at the time of the PsA diagnosis based on local guidelines and the cut-off values recommended by commercially available assays.

The study was approved by the local ethics committee (Ethics Review Board of Policlinico Riuniti of Foggia, protocol number EUR-BIO-18-11391) and all patients were informed about the nature and aim of the study and gave and signed their consent to participate in this study.

Statistical analysis

The results are expressed as mean ± SD and as percentage. The normal distribution was assessed using the Shapiro–Wilk test. Comparisons between study groups of PsA patients were evaluated by the Student's *t*-test or Mann–Whitney *U*-test as appropriate. The differences between categorical variables were assessed by Pearson chi-square or Fisher's exact test, as opportune. The estimation of the drug survival was realized by Kaplan–Meier estimate, followed by log-rank (Mantel–Cox) test in the case of comparison between different groups of patients. The risks for drug discontinuation have been evaluated using Cox regression model and are presented as the hazard ratio (HR) and 95% confidence interval (CI).

Statistical significance was set at $p \leq 0.05$. All statistical analysis was assessed using IBM SPSS Statistics 23.

Results

One hundred and thirteen out of 407 PsA Caucasian patients examined satisfied the inclusion criteria of the study; 63 were women and 50 were men. The mean age was 57.2 ± 13.9 years, with symptoms duration of 162.81 ± 218.8 weeks at the diagnosis time. Twelve patients (11%) were anti-CCP positive (mean titer 64.1 ± 23.7 U/ml). The comparisons of clinical characteristics between PsA patients with anti-CCP and those without anti-CCP at baseline are shown in Table 1. The anti-CCP+ group was characterized by significant greater number of tender joints ($p = 0.012$), higher value of ESR ($p = 0.013$), higher score of both DAS 28 ($p = 0.009$) and DAPSA ($p = 0.021$), and higher mean dose of steroids (prednisone equivalent) ($p = 0.004$) (Table 1). No significative differences were found in the rate of steroid or methotrexate (MTX) use, the score of Charlson Comorbidity Index, the frequency of hepatitis B or hepatitis C virus infection, the rate of articular subsets (oligoarticular, polyarticular), enthesitis and axial involvement, and the rate of smokers between anti-CCP+ and anti-CCP− groups (Table 1).

Ninety-four patients (83%) started monotherapy with MTX (15 mg/week) at the time of the diagnosis or during the time span of the study. MTX monotherapy survival was estimated at 525 ± 59.6 weeks, in whole group of patients. We underline that MTX failure was recorded in 60% of patients with enthesitis and in 46% of patients with polyarticular subset. Considering PsA patients with anti-CCP and those without anti-CCP, overall MTX monotherapy survival was significantly shorter in patients with anti-CCP than in those without (150.8 ± 48.3 weeks *versus* 535.3 ± 65.3 weeks; $p = 0.026$) (Figure 1). The probability of MTX treatment discontinuation in the anti-CCP+ group was significantly higher (HR = 2.389, 95% CI 1.043, 5.473; $p = 0.039$) compared with the anti-CCP− group.

Considering specifically the reason for drug discontinuation as failure of MTX monotherapy, we found that MTX monotherapy survival was significantly lower in the anti-CCP+ group (163.8 ± 51.3 weeks *versus* 593.1 ± 69.3 weeks; $p = 0.016$) with higher risk of discontinuation (HR = 2.852, 95% CI 1.138, 7.148; $p = 0.025$) compared with the anti-CCP− group (Figure 1). MTX failure was recorded in 56% of patients with anti-CCP and in 26% of those without anti-CCP ($p = 0.071$) (Table 2). All these MTX-failure patients required the addition of b-DMARDs (anti-TNF α 60% and anti-IL17 40% as first line b-DMARDs). We recorded that all anti-CCP+ patients were treated with anti-TNF α as first line b-DMARD. No significative differences in MTX monotherapy survival, discontinued for adverse events, were observed in anti-CCP+ patients and those without (293.6 ± 62.9 weeks *versus* 691.6 ± 58.9; $p = 0.721$) (Figure 1).

Fifty patients started b-DMARDs; the details of treatments at follow-up visits are shown in Table 2. Of note two patients anti-CCP− and one patient anti-CCP+ directly started b-DMARDs without previous treatment with MTX due to the presence of axial involvement other than polyarticular involvement.

As regards the b-DMARDs, a shorter survival time of first line b-DMARDs was observed in the anti-CCP+ group than in the anti-CCP− group (102.05 ± 24.4 weeks *versus* 271.6 ± 41.7 weeks; $p = 0.005$) (Figure 2). By Cox regression analysis, the risk of first line b-DMARDs' discontinuation was higher in the anti-CCP+ patients (HR = 3.230, 95% CI 1.299, 8.028; $p = 0.012$) compared with those without. Failure of first line b-DMARDs was recorded in 16 patients without anti-CCP and in six patients with anti-CCP. All patients that discontinued the first line b-DMARDs were treated with anti-TNF α. Stratifying for different anti-TNF α agents, we observed a significant higher rate of adalimumab failure in PsA patients with anti-CCP compared with those without anti-CCP (86% *versus* 35%; $p = 0.05$). We found a significant higher percentage of multi-failure (more than II line) to b-DMARDs in PsA patients with anti-CCP than in those without anti-CCP (50% *versus* 14%, $p = 0.035$) (Table 2).

Discussion

The presence of anti-CCP in PsA patients is proven and ranged between 1% and 20%.[12] It is hypothesized that the anti-CCP production in PsA patients could be an epiphenomenon of autoimmune response triggered by inflammatory event or genetic background or cellular injury with the citrullination of arginine, leading to amplification of inflammatory cascade and inducing a chronic inflammatory disease. An association between anti-CCP and the shared epitope in PsA has been previously demonstrated. It is supposed that the shared epitope

Table 1. Comparison of demographic and clinical characteristics at the time of diagnosis of PsA between patients with anti-cyclic-citrullinated-protein-antibodies (anti-CCP+) and those without anti-cyclic-citrullinated-protein-antibodies (anti-CCP–).

	Anti-CCP–	Anti-CCP+	*p*-value
	101	12	
Sex f/m	58 (57.4%)/43 (42.6%)	5 (41.7%)/7 (58.3%)	0.299
Age at the diagnosis, $M \pm SD$	56.57 ± 13.7	64.5 ± 13.3	0.610
Smokers	15 (15%)	2 (17%)	0.193
BMI	27.1 ± 5.1	30.2 ± 3	0.310
Symptoms duration at the diagnosis, weeks	164.7 ± 218.6	172 ± 243.3	0.919
Oligoarticular involvement	25 (25%)	2 (17%)	0.575
Polyarticular involvement	76 (75%)	10 (83%)	0.749
Enthesitis	57 (56%)	7 (58%)	0.900
Axial involvement	21 (21%)	2 (17%)	0.542
Cutaneous psoriasis	41 (41%)	6 (50%)	0.532
Erosion at baseline	10 (10%)	2 (17%)	0.123
No. of tender joints	5.8 ± 6	11.5 ± 8.1	**0.012***
No. of swollen joints	0.98 ± 2.7	2.5 ± 4.9	0.157
ESR, mm/h	4.3 ± 1.4	5.6 ± 1.4	**0.013**
CRP, mg/l	8.2 ± 12.3	11.2 ± 14.4	0.615
DAS 28	2.8 ± 1	3.7 ± 1.1	**0.009***
DAPSA	19.6 ± 112.7	30.2 ± 16.0	**0.021***
Treated with steroid	42 (42%)	5 (42%)	0.614
Prednisone equivalent mean dose, mg	7.86 ± 5.3	18.75 ± 17	**0.004***
Time of steroid treatment, weeks	77.7 ± 71.7	117.2 ± 107.3	0.318
Start MTX monotherapy	83 (82%)	11 (92%)	0.369
Charlson Comorbidity Index	2.42 ± 1.5	1.72 ± 1.4	0.117
HBV infection	2 (2%)	0 (0%)	0.833
HCV infection	1 (1%)	0 (0%)	0.711

Data are shown as mean ± SD or *n* (%).
*Statistical significance was set at $p \leqslant 0.05$.
BMI, body mass index; CRP, C-reactive protein; ESR, erythrocytes sedimentation rate; f/m, female/male; HBV, hepatitis B virus; HCV, hepatitis C virus; MTX, methotrexate.

alleles (HLA-DRB1 × 0401 molecules) could bind peptides containing citrulline, inducing their presentation to T cells,[21,22] although some contradictions are described.[23,24] In RA patients, the hapten-carrier mechanism could represent a new alternative model of the development of anti-CCP, in which peptidylarginine deiminases are the carrier and the citrullinated proteins are the haptens, all supported by T-cells response and amplified by B-cells activity.[25,26] The

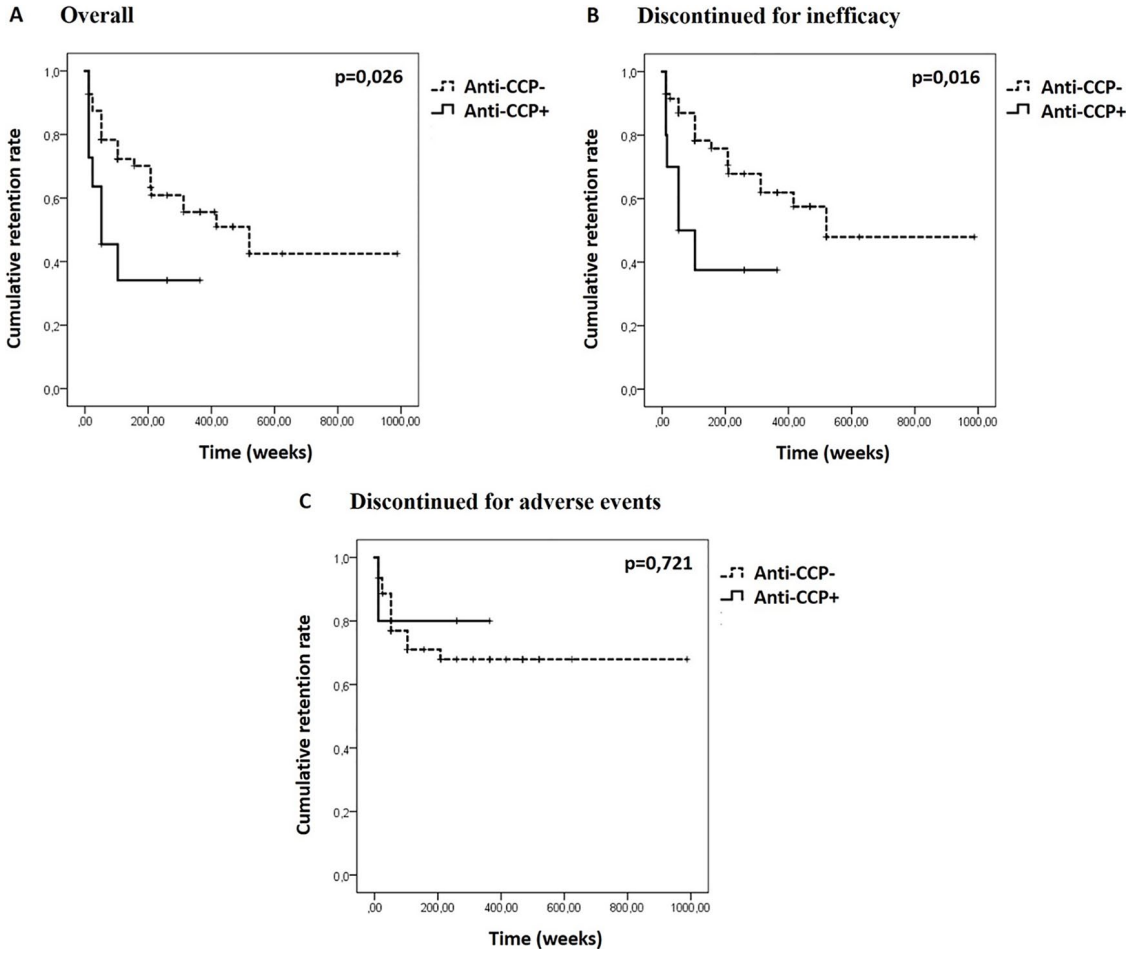

Figure 1. Kaplan–Meier method. Methotrexate monotherapy survival in the groups of psoriatic arthritis patients with anti-cyclic-citrullinated-protein-antibodies (anti-CCP+) and those without (anti-CCP–). (A) Overall; (B) discontinuation of methotrexate because of inefficacy; (C) discontinuation of methotrexate because of adverse events.
Statistical significance was set at $p \leqslant 0.05$.

possibility to strengthen this hypothesis in other studies could corroborate the validity of this model in RA and could extend its applicability in PsA.

PsA patients with anti-CCP positivity seem to present a more severe articular disease, with bone erosion at X-ray, polyarticular involvement, dactylitis, DMARDs use, and female sex prevalence.[13–17,22]

In our study we found in PsA patients with anti-CCP+ higher values of ESR at the time of diagnosis, higher scores of DAS 28 and DAPSA at baseline, greater number of tender joints, and use of higher dose of steroid. Moreover, a trend to longer period of steroid use, higher values of CRP, and greater number of swollen joints was observed in anti-CCP+ patients. All these results support previous findings that anti-CCP in PsA patients could be a marker for a more severe course of disease.[13–17,22,27]

To our best knowledge this is the first study on biotechnological drug survival in PsA patients with anti-CCP+ and RF–. We found a significative shorter first line biotechnological drug survival in PsA patients with anti-CCP with higher risk of discontinued first line b-DMARDs for failure compared with those without anti-CCP. A recently published study evidenced a resistance to anti-TNF α after 6 months of treatment in a group of PsA patients with anti-CCP+.[28] It is important to note that the authors included PsA patients with RF+ in the study. In addition, in our study

Table 2. Comparison of treatments at follow-up visits of psoriatic arthritis between patients with anti-cyclic-citrullinated-protein-antibodies (anti-CCP+) and those without anti-cyclic-citrullinated-protein-antibodies (anti-CCP–).

		Anti CCP–	Anti CCP+	*p*-value
MTX failure		22 (26%)	6 (56%)	0.071
MTX adverse event		18 (22%)	1 (9%)	0.560
Start b-DMARDs		42 (42%)	8 (67%)	0.053
Line of b-DMARDs at the end of study	I line	26 (62%)	2 (25%)	0.080
	II line	10 (24%)	2 (25%)	0.106
	⩾III line	6 (14%)	4 (50%)	**0.035***
I line b-DMARDs failure	Adalimumab	5 (31%)	5 (83%)	**0.050***
	Etanercept	5 (31%)	1 (17%)	0.074
	Golimumab	1 (6%)	0 (0%)	0.132
	Infliximab	5 (31%)	0 (0%)	0.096
	Certolizumab	0 (0%)	–	–
	Secukinumab	0 (0%)	–	–

Data are shown as mean ± SD or *n* (%).
*Statistical significance was set at $p \leqslant 0.05$.
b-DMARDs, biotechnological drug; MTX, methotrexate.

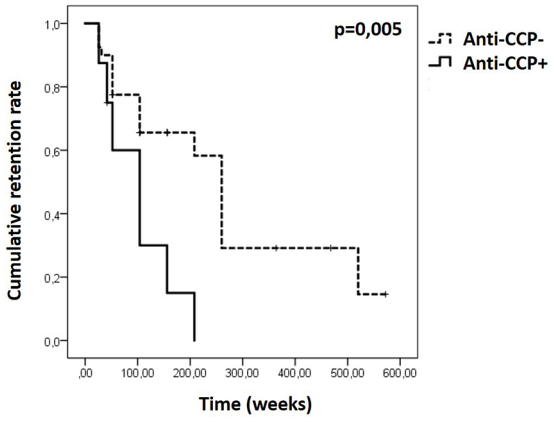

Figure 2. Kaplan–Meier method. First line of biotechnological drug survival in the groups of psoriatic arthritis patients with anti-cyclic-citrullinated-protein-antibodies (anti-CCP+) and those without (anti-CCP–).
Statistical significance was set at $p \leqslant 0.05$.

we noted in the group of patients with anti-CCP+ a higher rate of multi-failure to b-DMARDs. All these outcomes of ours could be consistent with more resistant and severe disease hypothesis in anti-CCP+ PsA patients. The highest rate of adalimumab failure in PsA group with anti-CCP could be an occasional finding due to the small size of the PsA group with anti CCP+, most of which (5/8) were treated with adalimumab as I line b-DMARDs; bias principally due to recruitment period (started in 2009).

As regards MTX monotherapy in PsA, we observed a shorter survival in subgroup of PsA patients with anti-CCP, with higher risk of overall discontinuation and discontinuation for failure. MTX efficacy is widely demonstrated in RA but only minimally in PsA.[29–31] Overall, our results partially echoed previous studies, but we noted a lower MTX retention rate in PsA patients with anti-CCP+. These last findings had no feedback in published studies; so, we should suggest a careful follow-up and more aggressive treatment in this particular subset (anti-CCP+) of PsA patients.

How the presence of anti-CCP could interfere with treatment response is not well understood. Few studies have assessed the predictive role of anti-CCP for treatment response, with contrasting

data. In RA patients the presence of anti-CCP is associated with a better response to abatacept.[32] Conversely, in a published study, a poorer response to anti-TNF α was observed in RA patients with anti-CCP.[33] The worse drug (MTX and/or b-DMARDs) response observed in anti-CCP+ PsA patients in our study could be explained by the more active disease[12] or by genetic factors, not yet defined, that could play a role in drug response, as supposed in RA patients.[33–35]

In published studies on anti-CCP in PsA it is in doubt whether the inflammatory arthritis is truly PsA or whether it is RA with psoriasis or family history of psoriasis. Several favorable features confirm the clinical relevance of anti-CCP in RA as predictor for RA development, a factor associated with more severe disease course[36] and predictor for radiographic progression.[37] It is observed that nearly 90% of patients with undifferentiated arthritis with anti-CCP positivity develop RA characteristics within 3 years.[37] In our study the data of patients have been recorded for more than 3 years and none of the patients developed clinical characteristics of RA or satisfied RA classification criteria during the time span of the study. Moreover, to avoid including RA patients in this study, in addition to a CASPAR score of 3, the patients must have had at least one additional clinical characteristic among asymmetrical arthritis or dactylitis, in addition to presenting at hands or feet X-rays juxta-articular osteo-proliferative signs, or pencil-in-cup phenomenon or distal interphalangeal involvement. These strict inclusion criteria, long observational period of the study, and the exclusion of RF positive patients make the diagnosis of PsA in our patients as reliable as possible.

Because of the retrospective design of the study, some limitations of this study have to be taken into account: patient selection bias, assignment of treatment, and incomplete efficacy data. Anyway, drug survival, risk of discontinuation of drug, and the rate of multi-failure could be considered a reliable tool for assessing disease severity in clinical practice. Another matter that could influence the results of this study is related to the small sample size of our PsA cohort, in particular those anti-CCP+, that might limit the statistical power for several analyses. Finally, the high rate of anti-TNF α as first line b-DMARD is principally due to the study period's starting in 2009.

Nonetheless, our study clearly confirms a more severe PsA course in patients with anti CCP+, but newly finds that the presence of anti-CCP defines a cluster of PsA patients characterized by high probability of non-response to MTX and to first line b-DMARDs, and higher chance to be b-DMARDs multi-failure. An earlier and more aggressive therapeutic strategy in PsA patients with anti-CCP+ should be suggested. The possibility to strengthen these results in other cohorts of PsA patients with anti CCP+ could corroborate the clinical validity of these findings.

Author contributions

CR, AC equally contributed to the work. CR, AC, DC, FPC designed the study, wrote, and critically revised the final draft of the manuscript and approved the submitted version. CR, AC performed the statistical analysis and interpreted the data. DC and SB collected the data.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethics statement

The study has been approved by the Ethics Committee of Policlinico Riuniti, Foggia, Italy. The study protocol conformed to the tenets of the Declaration of Helsinki and informed consent was obtained from all patients enrolled.

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