Relationship Between the Prevalence of Subclinical Tenosynovitis and treatment in Patients with RA in Clinical Remission: STARTER study

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Keywords: rheumatoid arhritis, ultrasonography, biological therapy, DMARDs, immunotherapy, remission, synovitis, tenosynovitis, power doppler, management.

Key Messages

1 Patients on combination therapy (csDMARD + bDMARD) appear to maintain a more sustained remission
2 Patients on monotherapy (csDMARD or bDMARD alone) present significant levels of subclinical inflammation at ultrasound
3. This study demonstrates how ultrasound is useful to identifying populations most at risk of relapse

Abstract

Objective: This study is a sub-analysis from the patient cohort of the STARTER (Sonographic Tenosynovitis Assessment in RheumaToid arthritis patiEnts in Remission) study. The aim was to evaluate differences in ultrasound-detected joint and/or tendon involvement between patients receiving therapies based on a combination of csDMARDs and bDMARDs and those who were treated with either csDMARDs or bDMARDs in monotherapy.

Methods: 427 consecutive patients with a diagnosis of rheumatoid arthritis were recruited between October 2013 and June 2014.They were divided into 3 subgroups based on their therapy at baseline: patients with bDMARDs in monotherapy, patients with csDMARDs in monotherapy, patients in combination therapy (csDMARD+bDMARD). At baseline, 6 months and 12 months, a clinical examination (28 joint count), an ultrasound evaluation were performed in each patient. A score of Grey Scale (GS) and Power Doppler (PD)-synovitis and -tenosynovitis, was calculated based on the OMERACT scoring systems.

Results: 256 patients completed the observation period: 48 patients from the bDMARDs group (19.7%), 152 patients from the csDMARDs group (59.1%) and 56 pts from csDMARD+bDMARD group (21.8%).The analysis has shown that GS-tenosynovitis and PD-tenosynovitis are better controlled in combination therapy than they are with csDMARDs alone (p:0.025 and p:0.047, respectively);for PD synovitis, there was a better response in those who were treated with the combination therapy when compared to the patients in csDMARD (p:0.01) and those in bDMARD (p:0.02).

Conclusion: The analysis showed a lower prevalence of subclinical inflammatory manifestations detected with ultrasound imaging in those patients treated with the combination therapy than in those in monotherapy.

Introduction

Ideally, Rheumatoid Arthritis (RA) remission should include both the absence of disease symptoms and the lack of structural progressions over time [1,2]. However, there is evidence that some patients with RA may experience radiographic progression despite being in clinical remission [3] due to the persistence of subclinical joint inflammation. This element can be detected thanks to sensitive imaging techniques such as magnetic resonance and musculoskeletal ultrasound, the latter being often performed by rheumatologists themselves [4-6]. In the clinical setting, remission is measured with the use of several definitions but discordances in the results of different indexes may occur [1, 7].

Biomarkers are key element to achieve patient-centered medicine; they constitute a collection of objective indicators of the state of a biological process or disease. They help to define various aspects of pathogenesis, disease activity, therapeutic response, and disease outcome [8]. Undeniably, the great availability of non-biological and biological agents has recently led to more personalized medicine, which can help predict patients who will benefit from a given treatment.

The association of power Doppler ultrasound (PDUS) and disease activity score for 28 joints (DAS28), along with histological analysis, supports the current opinion that PDUS can be intended as a biomarker of response to treatment since it reflects both clinical and histological markers of disease activity in RA patients [9, 10].

The concept of ultrasound remission, however, is not so simple. Some authors define it as an absence of power Doppler (PD) signal in the analyzed joints [11-14], while others propose a stricter definition that requires the absence of synovitis on greyscale (GS) and PDUS [15] at the same time. Still others [16] accept a minimal amount of synovitis on GS in the concept of remission, since they define an ultrasound remission as a GS grade of synovitis ≤1 and PD grade of synovitis = 0 for each scanned joint; lastly, Horton et al. accept a minimal residual PD signal (total PD activity score ≤1) [17]. However, it is important to highlight that some studies have shown that clinical remission established with different indexes (DAS28, SDAI, CDAI, and ACR/EULAR Boolean) does not entirely correspond to imaging remission and some patients might experience radiographic progression despite being in clinical remission [3, 18].

With the introduction of biologic therapy for the treatment of rheumatic diseases, the management of RA has deeply changed over the last 20 years. In order to assess disease activity, the European Alliance of Associations for Rheumatology (EULAR) recommends ultrasound imaging, in some cases, to establish a diagnosis of RA (when there is diagnostic doubt with clinical criteria alone) and as a predictor of progression; it also recommends to perform ultrasound for the detection of structural damage, as a predictor for disease outcome, for monitoring the effectiveness of treatments and for the assessment of remission [19]. However, two randomized studies (TaSER and ARCTIC) examining the benefit of ultrasound in a tight clinical T2T control regimen in patients with early RA concluded that the use of ultrasound does not provide an added value to the clinical management of disease when establishing a therapy as it may be both time-consuming and economically unfavorable [20, 21].

The STARTER study (22, 23), in which a population of patients in clinical remission was analyzed, demonstrated that inflammation of tendons could also be predictive of flares in patients in remission according to clinical indexes, thus highlighting a gap in the management of those patients. In fact, tendon inflammation is not included in the disease activity indexes and it is challenging to assess it clinically.

The aim of this supportive study was to evaluate ultrasound detected joint and/or tendon involvement between patients receiving therapies based on a combination of csDMARDs and bDMARDs and those who were treated with either csDMARDs or bDMARDs in monotherapy thus defining who could benefit from a

different approach in order to prevent clinical flares. To achieve this sub-analysis, data from the patient cohort of the STARTER study were elaborated [22, 23].

Methods

Patient and study design

This is a longitudinal analysis of the STARTER study that included 25 rheumatology centers. Inclusion criteria are fully described in the main study [23]. Consecutive patients with a diagnosis of RA as per American College of Rheumatology 1987 (ACR) criteria or ACR/EULAR (European Alliance of Associations for Rheumatology) 2010 criteria and in clinical remission (remission was defined as: DAS28 <2.6, SDAI ≤3.3, CDAI ≤2.8, ACR/EULAR Boolean definition, the absence of swollen/tender joints on 28 joints17 or remission based on clinical evaluation of an expert rheumatologist [22]) were recruited between October 2013 and June 2014. At baseline (T0), 6 months (T1) and 12 months (T2), a clinical examination (performed by rheumatologists blinded to the ultrasound data) and an ultrasound -examination performed by using a semi-quantitative score 0-3 GS and a PD with an evaluation of the metacarpal-phalangeal joints (MCPs), hand proximal interphalangeal joints (PIPs), wrist joints, flexor and extensor tendons of the fingers and wrists were performed for each patient. At the end of each ultrasound exam, total scores for GS tenosynovitis, PD tenosynovitis, GS synovitis and PD synovitis were calculated by summing the scores detected at different sites. The ultrasound remission was arbitrarily defined in presence of a score = 0. The patients were divided into 3 subgroups based on the background therapy at baseline: patients with bDMARDs in monotherapy, patients with csDMARDs in monotherapy, patients in combination therapy (csDMARD + bDMARD). All participants gave written informed consent.

Clinical assessment

Demographic (age, sex) and clinical variables (disease and remission duration, treatment), rheumatoid factor (RF), and anti-citrullinated protein antibodies (ACPA) were recorded at baseline. Clinimetric measures (the Italian version of the health assessment questionnaire - HAQ [26], visual analogue scale for pain, physician global assessment, patient global assessment, global health), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and 28-joint count were collected before performing a clinical examination at baseline, 6 and 12 months by a rheumatologist blinded to ultrasound findings.. The referring physician could modify treatments (including csDMARDs, bDMARDs, corticosteroids and NSAIDs).

Outcome measures

Ultrasound variables were measured at baseline while outcomes were evaluated at 12 months. A secondary analysis evaluated the impact of the baseline ultrasound on the flare at 6 months as well as the impact of a 6 months ultrasound at 12 months; dichotomous variables were included in the model for the evaluation of the dose reduction (defined as a decrease or withdrawals of csDMARDs, bDMARDs or glucocorticoids, including a modification of the dose-related to adverse events) as well as for an increase (defined as an increment of the dosage or the introduction of a new drug). Furthermore, in order to test the validity of our results, the main analysis was repeated by introducing the center as a random effect.

Ultrasonographic assessment

In this study, ultrasound imaging tests were performed by rheumatologists, experts in musculoskeletal ultrasound, selected by an inter- and intra-observer reliability exercise VS a standardized level (AI) concerning static images. A good-to-excellent reliability (weighted kappa ≥0.7) [23] was required. Centers providing high-level ultrasound machines (MyLab 70XVG, MyLab Twice, Logiq9, LogiqE9) with high-frequency probes (14-18 MHz) were included in the study [23 supplementary file S1]. At each site, PDUS following the EULAR guidelines [19] was performed by a single ultrasonographer blinded to clinical data at baseline, 6 months, and 12 months.

A detailed description of the scanning protocol has been previously reported [23]. The flexors of the fingers, the flexor carpi radialis, the extensor tendons of the wrist were scanned bilaterally. The dorsal aspects of wrists (radiocarpal and midcarpal joints), MCPs, and the palmar aspects of the hand PIPs were scanned bilaterally.

Tenosynovitis, joint effusion, and synovial hypertrophy were identified as per Outcome Measures in Rheumatology Clinical Trials (OMERACT) definitions [27]. PD assessment was performed under standardized settings [23]. Representative images were recorded.

GS and PD tenosynovitis and synovitis were semi-quantitatively scored from 0 to 3. Total scores for GS and PD tenosynovitis and synovitis were obtained as the sum of single sites. An image atlas with examples of the scoring was distributed to the sonographers.

Tenosynovitis and synovitis were treated as categorical variables, defining their presence in the case of GS or PD≥1. To test the validity of our results, alternative definitions were tested (GS>1, PD>1 for tenosynovitis and synovitis).

The patients were divided into 3 subgroups: patients receiving therapies based on a combination of csDMARDs and bDMARDs, patients treated with csDMARDs alone and patients treated with bDMARDs alone. This was not specified in the initial Starter protocol, but is a retrospective evaluation, specific assessment of this sub-analysis.

Statistical analysis

Continuous variables are presented as mean and standard deviation (SD) or median and inter-quartile range (IQR). For categorical variables, absolute and relative frequencies are reported. To test differences between bDMARD, csDMARD, and combined therapy, Kruskal – Wallis test and Pearson's X-squared test were performed for quantitative variables and categorical variables, respectively.

The association between ultrasound variables and treatment with cs- and bDMARDs was evaluated by using logistic regression; results were presented as OR with a 95% confidence interval (CI), both crude and adjusted for pre-specified confounders such as age, sex, disease duration, remission duration, musculoskeletal comorbidities, erosive RA, HAQ, RF or ACPA positive, non-steroidal anti-inflammatory drugs (NSAIDs), systemic and local injected glucocorticoids.

Data were collected and managed using Research Electronic Data Capture (REDCap) [28] and all the analyses were performed using R statistical software (Foundation for Statistical Computing, Vienna, Austria).

Results

The initial sample consisted of 361 patients; among these, 105 patients were discarded from the analysis due to incomplete data. Two-hundred-fifty six patients completed the observation period: divided into 48 patients in the bDMARD group (19.7%, F34 / M14), 152 patients in the csDMARD group (59.14% - F105 / M47) and 56 patients in csDMARD + bDMARD group (21.79% - F47 / M9).

The demographic and clinical characteristics at baseline are presented in Table 1. A significantly longer duration of illness emerged in the group of patients on the bDMARD group ($p < 0.001$), while the combo group (csDMARD+bDMARD) had a higher percentage of ACPA positivity ($p = 0.001$).

The characteristics of baseline ultrasound variables are shown in table 2 and no significant differences are highlighted ($p > 0.05$).

The three groups and the ultrasound variables were compared with the analysis of crude and adjusted models; the results are shown in Forest Plot (Fig. 1). In both models, it is shown that patients in combined therapy have better ultrasound outcomes. In particular, GS-tenosynovitis and tenosynovitis are better controlled in patients with combination therapy than they are among those in therapy with csDMARDs only

(p: 0.025, p: 0.047, respectively – Table 3); no significant differences emerged regarding PD tenosynovitis. Synovitis GS is statistically associated with age (p:0.002 – Table 3), disease duration (p: 0.006 – Table 3) and disability (p: 0.004 – Table 3). As for PD synovitis, there was a better response in the group of patients treated with the combo therapy when compared to the patients in the bDMARDs and csDMARDs alone group (p: 0.01 and p:0,02, respectively – Table 3). When the PD signal is present in both synovitis and tenosynovitis (Power Doppler T+S), the best response is confirmed in patients in combo-therapy VS the other two groups (vs csDMARD p: 0.014, vs bDMARD p: 0.023 – Table 3) and there is an association with the duration of disease (p: 0.027). The other variables, such as joint erosion, other musculoskeletal comorbidities, the duration of remission, the positivity of RF and ACPA, and the intake of NSAIDs and steroids, are not significantly associated with ultrasound alterations (Table 3).

Patients who experienced flare (according to protocol criteria: Δ DAS28 > 1.2 or > 0.6 if final $\Delta \geq 3.2$ or the intention of the treating physician to increase therapy [22[) were 67/256, bDMARD monotherapy 35.42%, csDMARD monotherapy 26.90%, csDMARD + bDMARD 21.43% respectively, and the differences were not were significant (p: 0.276). Figure 2 shows the trend of the ultrasound variables examined from the baseline until the end of the follow-up. The combo therapy group has a more favorable trend compared to the other two groups.

The accuracy of the initial hypothesis was also verified with further analysis. The raw and adjusted models were also analyzed by comparing patients who presented clinical remission (according to inclusion criteria), baseline ultrasound remission, and patients who presented only clinical remission but no ultrasound remission (see Table 4 and 5 supplementary material).

Discussion

According to the latest EULAR recommendations, the treatment of RA should aim at achieving a clinical remission [29] (defined by clinical indices) to prevent joint damage and the worsening of its function. However, clinical indices consider neither the tendon sheath involvement, which is frequent [30-32] nor the sub-clinical inflammation detected with ultrasound in clinical remission nor its association with flares and radiographic progression [3,4,33-40]. Recently, Acebes et al [36] recognized that the current medical instrumentation possesses some important limitations. Imaging techniques have helped to define disease status more accurately as it has become more and more helpful to understand its characteristics. However, Acebes et al [36] do not recognize such techniques as an instrument capable of being the gold standard to investigate the remission on their own, but rather as a tool to reinforce existing instruments and measures. Their suggestion is to not generate a universal definition of remission (that could cover all aspects), but rather to develop definitions of remission for the different settings that could be weighted by the patient perspective. This level of clinical and biological remission is close to ultrasound remission as observed in a previous study [13], as well as in ours, in which three out of four patients had a global (GS plus PD) ultrasound-DAS 28 score of 0. Moreover, the duration of remission appears to be an important requirement to consider the withdrawal of the therapy with bDMARDs. Since subclinical disease activity may persist several years in clinically inactive joints and since ultrasound PD-positive synovitis is related to subsequent flares [18, 39], a deep remission based on ultrasound-DAS28 findings is also desirable. The results of the study by Stein et al. [41] may be explained by the fact that clinical criteria of remission are not sufficiently sensitive to detect clinically relevant levels of inflammation in a proper way thus indicating, as suggested by Brown et al. [42], that imaging is a necessary tool for the accurate evaluation of disease status and for a proper definition of ‘true’ remission; this element would imply, for the patients in clinical remission, the absence of synovitis. Karim et al. [43] also suggested that the information obtained on the presence of synovitis by ultrasound evaluations might be superior to a mere clinical examination; Nakagomi et al. [44] also demonstrated the potential of imaging in improving RA assessment accuracy. Musculoskeletal ultrasound is a valuable point-of-care non-invasive imaging tool that can accurately evaluate intra-articular

and periarticular structures involved in rheumatic diseases [45]. GS and PD have been found to be more sensitive in detecting synovitis than clinical examination and to be predictive of joint deterioration [46].

As shown in the STARTER study [22, 23], the prevalence of sub-clinical tenosynovitis is relevant in the subpopulation of patients with RA in clinical remission. It also demonstrated that tendon and joint ultrasound can be useful in assessing inflammatory changes in RA when in clinical remission since it is also capable of predicting disease flares. [22]. The analysis into therapy-based subgroups, performed in this supportive study, was intended to further define the impact of ultrasound based on the treatment; data seem to confirm a lower prevalence of inflammatory manifestations of the tendons of the hands and wrists in favor of those patients with combination therapy (csDMARD + bDMARD) rather than in patients with either csDMARD or bDMARDs in monotherapy. The onset of flares did not show significant differences between the 3 groups and therefore was unable to identify which patients might be more at risk than others, which instead managed to do the ultrasound. These results indicate a higher probability of a flare in patients treated by mono-therapy, because there is more subclinical inflammation; therefore, a more tight follow up even during clinical remission in these patients might be beneficial. Similar to our findings, Sapundzhieva T et al [2] found out that the rate of ultrasound-based remissions at 12 months was higher for the bDMARDs group when compared to the csDMARDs group, even though the difference was not statistically significant. Conversely, Spinella et al found that the rate of imaging-related remission does not depend on the type of treatment (either conventional or biologic); however, they only examined the II and III flexor tendon of the hands, rather than MCPs, PIPs and wrist joints [47]. It is to be pointed out that all studies agree with the current one when concluding that there is a certain discordance between clinical remission obtained by DAS28 and ultrasound-related remission.

Furthermore, in the previous analysis of the STARTER study [22], it was highlighted that disease flares are not always associated with clinical and/or laboratory worsening but mainly with a change in the Patient Reported Outcomes (PROs), which might be influenced by comorbidities. PDUS could confirm the active disease in case of PRO-driven flare hence driving the therapeutic decision above the aforementioned composite indexes, in accordance with a recent proposal by a group of ultrasound experts [48].

Lastly, the STARTER study demonstrated that taking tenosynovitis into consideration could properly guide therapeutic choices for the better as the usage appears to be more relevant in patients where the treatment is tapered. In this sub-analysis, it emerged that the tenosynovitis is less likely to be observed in patients with combination therapy since they seem to have a better subclinical response. Indeed, patients on combination therapy have more lower PDUS scores than patients on monotherapy as they are likely to have achieved stable clinical and imaging-based remission. This study confirmed that appropriate treatment can lead to clinical remission, with an equal or even a better integration from the ultrasound imaging point of view. In order to improve disease outcomes, ultrasound examination in patients in clinical remission may be used to guide therapeutic decisions, as already demonstrated by other studies on drug tapering [49]. Moreover, the use of different ultrasound machines along with their use from different operators probably allows assuming a greater generalization of the result, which is more likely to be reproduced in a real world context.
This study has some limitations. 105 patients (29.01%) could not be included in the assessment due to incomplete follow-up data. However, analyzing their characteristics as far as possible, no significant differences emerged (Tab. 6 supplementary material), so it is reasonable to think that the impact of this data is not significant. There were some discrepancies in terms of homogeneity between groups; as expected, patients in combination therapy had the highest percentage of positive ACPA. The ratio is more unfavorable for combo-therapy and therefore in favor of our results (it was the group with the worst prognostic factor).

The disease duration was higher in patients treated with bDMARD alone, partly due to the progressive intolerance that patients could develop towards csDMARDs (in particular Methotrexate).

It is important to underline that statistical interpretations with p-value> 0.01 are affected by the problem of multiple tests and should be further verified with ad hoc studies, however, the models used in tables 4 and 5 seem to support our claims.

Conclusion

Ultrasound evaluation is essential for patients in clinical remission, especially if a tapering strategy is opted. Patients in combination therapy seem to be in deeper remission, while patients in monotherapy, either with csDMARD or bDMARD alone, present significant levels of subclinical inflammation at ultrasound thus emerging to be more likely to relapse. Ultrasound could therefore be useful to plan patient follow-up times, saving a shorter interval for those patients who are monotherapy and producing an optimization of the patient's follow-up strategy.

Competing interests: None.

Contributorship: Simone Parisi contributed to interpretation of data, draft and review the manuscript. Anna Zanetti, Greta Carrara e Carlo Alberto Scirè equally contributed to study design and analysis of data. Annamaria Iagnocco e Georgios Filippou contributed to the data analysis and revision of the manuscript All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Acknowledgements: the authors would like to thank ESAOTE for providing high-level equipment in centres where this was unavailable.

Funding info: N/A

Ethical approval information: study protocol has been approved by all local CE of participating centres.

Data sharing statement: no additional data available.

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TABLES AND FIGURES

Table 1. Baseline characteristics for each treatment group

Demographic and clinical characteristics	bDMARD (monotherapy)	csDMARDs (monotherapy)	csDMARD + bDMARD (combined therapy)	P-value
Number of patients	N = 48	N = 152	N = 56	
Female sex - n (%)	34 (70.83)	105 (69.08)	47 (83.93)	0.098
Age (years) - median (IQR)	54.4 (± 13.41)	57.59 (± 13.6)	55.36 (± 11.79)	0.206
Disease duration (year) - median (IQR)	12.6 (8.9 - 18.5)	4.92 (2.3 - 9.2)	8.06 (5.7 - 14.6)	<0.001
Remission duration (months) - median (IQR)	17 (10 - 30)	12 (6 - 24)	14 (9.8 - 24)	0.106
Corticosteroids – n (%)	21 (43.75)	74 (48.68)	21 (37.5)	0.346
NSAID – n (%)				
On demand	26 (54.17)	76 (50)	28 (50)	0.606
Full dosage	1 (2.08)	1 (0.66)	2 (3.57)	
RF - n (%)				
Negative	13 (27.08)	63 (41.45)	18 (32.14)	0.401
Negative, but previously positive	5 (10.42)	14 (9.21%)	5 (8.93)	
Positive	30 (62.5)	75 (49.34%)	33 (58.93)	
ACPA - n (%)				
Negative	13 (27.08)	67 (44.37)	17 (30.36)	0.001
Negative, but previously positive	10 (20.83)	4 (2.65)	3 (5.36)	
Positive	25 (52.08)	80 (52.98)	36 (64.29)	
HAQ - median (IQR)	4 (0 - 17.8)	2 (0 - 10)	1 (0 - 7.2)	0.328
DAS28 - mean (sd)	1.97 (± 0.71)	2.07 (± 0.66)	1.86 (± 0.7)	0.093

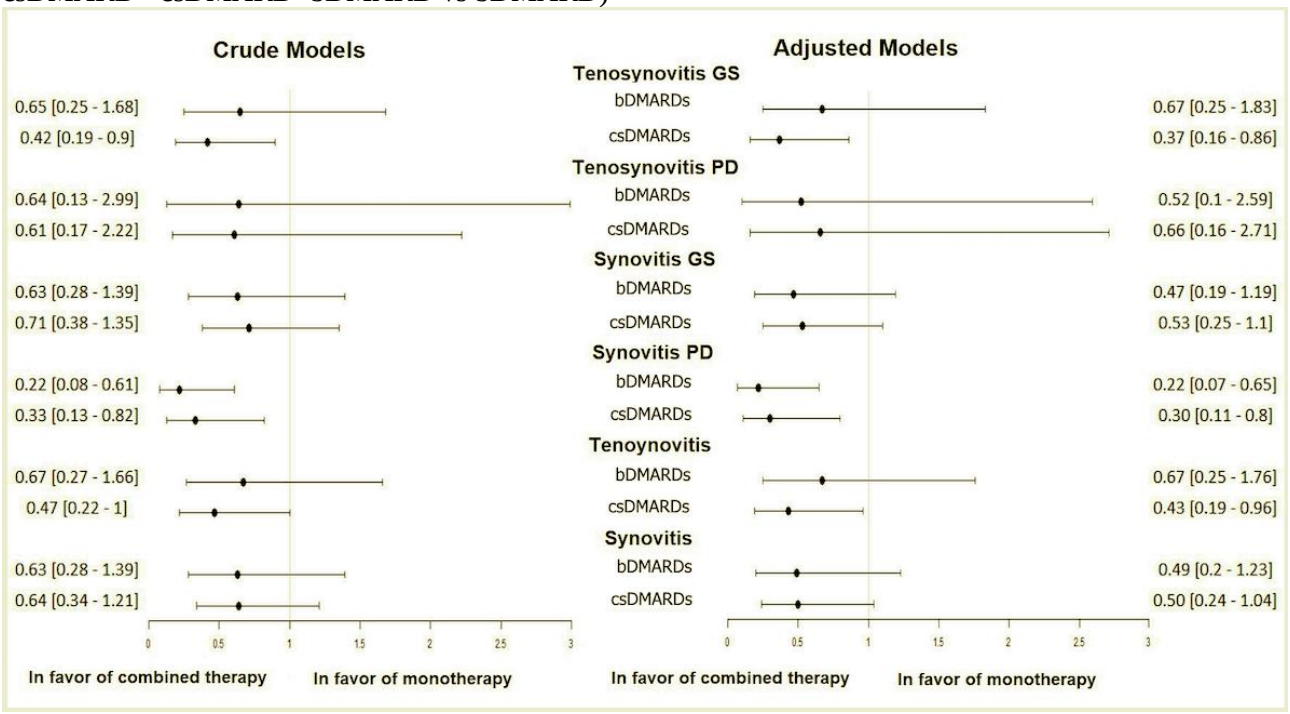
bDMARD, biologic Disease Modifying Anti-Rheumatic Drugs; csDMARD, conventional-synthetic Disease Modifying Anti-Rheumatic Drugs; RF, Rheumatoid Factor; ACPA, anti-citrullinated protein antibodies; HAQ, Health Assessment Questionnaire; DAS28, Disease Activity Score on 28 joints

Table 2. Characteristics of baseline ultrasound variables

US characteristics	bDMARD (monotherapy)	csDMARD (monotherapy)	csDMARD + bDMARD (combined therapy)	P-value
Number of patients	N = 48	N = 152	N = 56	
Tenosynovitis GS - n (%)	23 (47.92%)	86 (56.58%)	30 (53.57%)	0.572
Tenosynovitis PD - n (%)	7 (14.58%)	34 (22.37%)	10 (17.86%)	0.454
Synovitis GS - n (%)	33 (68.75%)	115 (75.66%)	41 (73.21%)	0.633
Synovitis PD - n (%)	19 (39.58%)	75 (49.34%)	18 (32.14%)	0.069
Tenosynovitis GS + PD - n (%)	23 (47.92%)	88 (57.89%)	32 (57.14%)	0.467
Synovitis GS + PD - n (%)	33 (68.57%)	119 (78.29%)	42 (75%)	0.400

US, ultrasound; GS, Grey Scale; PD, Power Doppler, bDMARD, biologic Disease Modifying Anti-Rheumatic Drugs; csDMARD, conventional-synthetic Disease Modifying Anti-Rheumatic Drugs

Figure 1. Forest Plot: comparison between combined therapy and monotherapy (csDMARD+bDMARD vs csDMARD - csDMARD+bDMARD vs bDMARD)



US, ultrasound; GS, Grey Scale; PD, Power Doppler; bDMARD, biologic Disease Modifying Anti-Rheumatic Drugs; csDMARD, conventional-synthetic Disease Modifying Anti-Rheumatic Drugs

Table 3 Association between the analyzed variables

Variables	OR (CI 95%)	p-val
Tenosynovitis GS		
bDMARD vs combo therapy	0.68 [0.25;1.85]	0.454
csDMARD vs combo therapy	0.38 [0.17;0.89]	0.025
Female	0.95 [0.5;1.81]	0.884
Age at baseline	0.98 [0.96;1]	0.113
F0 disease duration	0.96 [0.92;1]	0.072
F0 RA erosive vs RA no erosive	0.94 [0.51;1.75]	0.85
F0 HAQ ≥0.5 vs <0.5	1.88 [0.82;4.32]	0.138
MSK comorbidity	1.09 [0.56;2.12]	0.811
Duration of remission ≥12 vs <12 mesi	1.37 [0.76;2.48]	0.3
F0 NSAIDs	1.02 [0.57;1.83]	0.948
F0 steroids ongoing vs no steroids	0.77 [0.43;1.38]	0.383
F0 RF/ACPA	1.01 [0.53;1.92]	0.982
Tenosynovitis PD		
bDMARD vs combo therapy	0.55 [0.11;2.78]	0.473
csDMARD vs combo therapy	0.71 [0.17;2.87]	0.626
Female	0.98 [0.34;2.87]	0.974
Age at baseline	0.98 [0.94;1.02]	0.318
F0 disease duration	1.02 [0.94;1.1]	0.691
F0 RA erosive vs RA no erosive	1.02 [0.36;2.92]	0.969
F0 HAQ ≥0.5 vs <0.5	2.24 [0.46;10.82]	0.315
MSK comorbidity	1.87 [0.54;6.47]	0.321
Duration of remission ≥12 vs <12 mesi	1.45 [0.52;4]	0.474
F0 NSAIDs	2.21 [0.78;6.29]	0.137
F0 steroids ongoing vs no steroids	1 [0.38;2.64]	0.993
F0 RF/ACPA	2.18 [0.6;7.99]	0.238
Synovitis GS		
bDMARD vs combo therapy	0.59 [0.24;1.44]	0.245
csDMARD vs combo therapy	0.6 [0.29;1.26]	0.178
Female	0.78 [0.41;1.48]	0.454
Age at baseline	0.96 [0.94;0.99]	0.002
F0 disease duration	0.94 [0.9;0.98]	0.006
F0 RA erosive vs RA no erosive	0.77 [0.42;1.41]	0.404
F0 HAQ ≥0.5 vs <0.5	3.16 [1.43;7]	0.004
MSK comorbidity	1.5 [0.77;2.92]	0.232
Duration of remission ≥12 vs <12 mesi	1.63 [0.91;2.9]	0.1
F0 NSAIDs	0.67 [0.38;1.18]	0.165
F0 steroids ongoing vs no steroids	0.58 [0.33;1.03]	0.065
F0 RF/ACPA	1.21 [0.65;2.26]	0.546
Synovitis PD		
bDMARD vs combo therapy	0.24 [0.08;0.71]	0.01
csDMARD vs combo therapy	0.31 [0.12;0.83]	0.02
Female	0.88 [0.44;1.76]	0.718
Age at baseline	0.99 [0.97;1.02]	0.504
F0 disease duration	0.96 [0.92;1]	0.056
F0 RA erosive vs RA no erosive	1.07 [0.55;2.09]	0.836
F0 HAQ ≥0.5 vs <0.5	1.65 [0.7;3.88]	0.252
MSK comorbidity	0.84 [0.41;1.71]	0.623
Duration of remission ≥12 vs <12 mesi	1.25 [0.66;2.36]	0.487
F0 NSAIDs	1.03 [0.56;1.92]	0.914
F0 steroids ongoing vs no steroids	0.64 [0.34;1.19]	0.158
F0 RF/ACPA	1.11 [0.56;2.21]	0.771

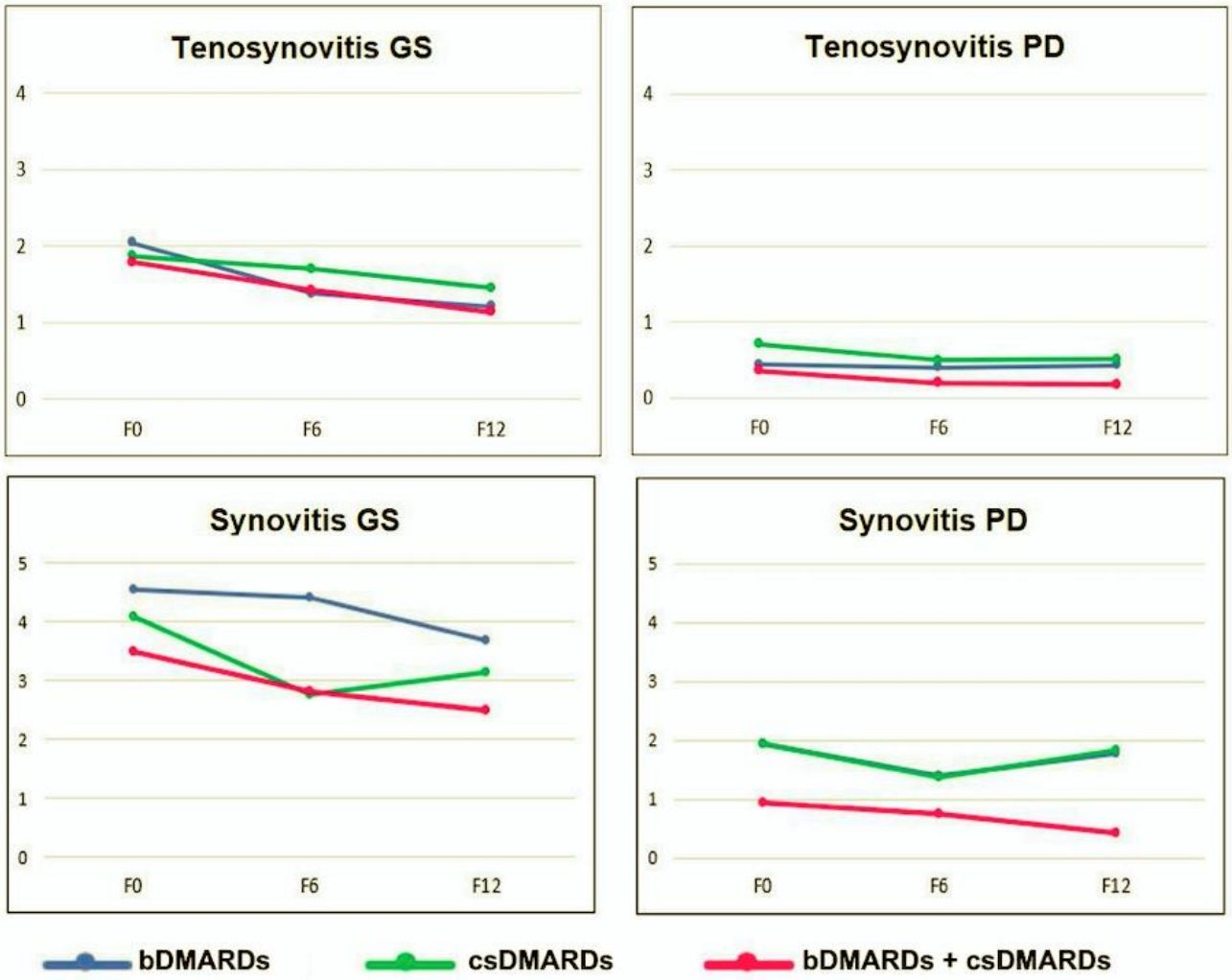
bDMARD, biologic Disease Modifying Anti-Rheumatic Drugs; csDMARD, conventional-synthetic Disease Modifying Anti-Rheumatic Drugs; RF, Rheumatoid Factor; ACPA, anti-citrullinated protein antibodies; HAQ, Health Assessment Questionnaire; DAS28, Disease Activity Score on 28 joints; MSK, Musculoskeletal; NSAIDs, Non Steroidal Anti-Inflammatory Drugs.

Table 3 (continued) Association between the analyzed variables

Variables	OR (CI 95%)	p-val
Tenosynovitis		
bDMARD vs combo therapy	0.68 [0.26;1.79]	0.438
csDMARD vs combo therapy	0.44 [0.2;0.99]	0.047
Female	1.01 [0.54;1.9]	0.97
Age at baseline	0.98 [0.96;1.01]	0.151
F0 disease duration	0.97 [0.93;1.01]	0.168
F0 RA erosive vs RA no erosive	0.87 [0.47;1.6]	0.65
F0 HAQ ≥0.5 vs <0.5	1.61 [0.72;3.6]	0.248
MSK comorbidity	1.12 [0.58;2.18]	0.734
Duration of remission ≥12 vs <12 mesi	1.39 [0.78;2.49]	0.269
F0 NSAIDs	0.96 [0.54;1.7]	0.876
F0 steroids ongoing vs no steroids	0.84 [0.47;1.49]	0.548
F0 RF/ACPA	1.05 [0.55;1.99]	0.88
Synovitis		
bDMARD vs combo therapy	0.6 [0.25;1.45]	0.253
csDMARD vs combo therapy	0.56 [0.27;1.16]	0.119
Female	0.85 [0.45;1.61]	0.617
Age at baseline	0.96 [0.94;0.99]	0.002
F0 disease duration	0.94 [0.9;0.99]	0.009
F0 RA erosive vs RA no erosive	0.86 [0.47;1.58]	0.632
F0 HAQ ≥0.5 vs <0.5	3.2 [1.46;7.04]	0.004
MSK comorbidity	1.49 [0.77;2.89]	0.242
Duration of remission ≥12 vs <12 mesi	1.43 [0.81;2.55]	0.22
F0 NSAIDs	0.74 [0.42;1.31]	0.297
F0 steroids ongoing vs no steroids	0.57 [0.32;1.01]	0.053
F0 RF/ACPA	1.24 [0.67;2.32]	0.491
Power Doppler (T + S).		
bDMARD vs combo therapy	0.29 [0.11;0.78]	0.014
csDMARD vs combo therapy	0.36 [0.15;0.87]	0.023
Female	0.95 [0.49;1.84]	0.888
Age at baseline	0.99 [0.97;1.01]	0.412
F0 disease duration	0.95 [0.92;0.99]	0.027
F0 RA erosive vs RA no erosive	1.14 [0.6;2.15]	0.689
F0 HAQ ≥0.5 vs <0.5	1.91 [0.83;4.38]	0.128
MSK comorbidity	0.85 [0.43;1.68]	0.634
Duration of remission ≥12 vs <12 mesi	1.3 [0.71;2.37]	0.403
F0 NSAIDs	1.1 [0.61;1.99]	0.743
F0 steroids ongoing vs no steroids	0.68 [0.38;1.24]	0.212
F0 RF/ACPA	1.07 [0.55;2.06]	0.842

bDMARD, biologic Disease Modifying Anti-Rheumatic Drugs; csDMARD, conventional-synthetic Disease Modifying Anti-Rheumatic Drugs; RF, Rheumatoid Factor; ACPA, anti-citrullinated protein antibodies; HAQ, Health Assessment Questionnaire; DAS28, Disease Activity Score on 28 joints; MSK, Musculoskeletal; NSAIDs, Non Steroidal Anti-Inflammatory Drugs.

Fig.2 Trend of ultrasound variables during follow up



US, ultrasound; GS, Grey Scale; PD, Power Doppler; bDMARD, biologic Disease Modifying Anti-Rheumatic Drugs; csDMARD, conventional-synthetic Disease Modifying Anti-Rheumatic Drugs.