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The effect on treatment response of fibromyalgia symptoms in early rheumatoid arthritis patients: results from the ESPOIR cohort

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Boston University
THE EFFECT ON TREATMENT RESPONSE OF FIBROMYALGIA
SYMPTOMS IN EARLY RHEUMATOID ARTHRITIS PATIENTS:
RESULTS FROM THE ESPOIR COHORT

by

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JOSEFINA DURAN SANTA CRUZ

ABSTRACT

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease that can lead to important functional impairment. Although improvements in treatment have been made, still there are a high proportion of patients in whom response to treatment is not complete. Fibromyalgia (FM) is a condition characterized by bodily pain that often coexists with RA. Cross-sectional studies have shown that patients with RA and FM symptoms, or fibromyalgic RA (FRA), have higher disease activity scores than patients with RA and no FRA. Concern has been raised regarding the validity of RA disease activity scores in patients with coexistent RA and FM. In this prospective study, we hypothesized that patients with FRA have an impaired response to treatment measured by traditionally used scores.

The present analysis used a study sample obtained from the ESPOIR French cohort. This is a longitudinal prospective cohort of adults with early RA. Patients with RA were classified in two groups according to the presence of FRA. RA disease activity scores (DAS28, SDAI, CDAI and HAQ) were compared as a measure of response to treatment at 6, 12 and 18 months. Results showed that
after adjusting for confounders, patients with FRA (120) had higher activity scores than patients with RA and no fibromyalgic characteristics (548). DAS28 and other disease activity scores started out higher in subjects with FRA and while they improved to a similar extent as in the isolated RA group, they remained consistently higher among FRA patients. Achievement of low disease activity and of remission according to established activity score cut-points was significantly less likely in subjects with FRA. In conclusion, patients with FRA and RA had a similar response to treatment according the decrease in indexes of disease activity but more frequently missed the target of remission or low disease activity. These findings may have implications in RA treatment in patients with FRA, as therapy is escalated not in relation to change in scores but to achieving remission.
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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease that affects 0.5%-1% of the population [1]. The pain and physical limitation it produces severely compromise functioning, generating work disability in 30-50% of patients at 10 years. [2, 3, 4]

A “treat-to-target” strategy has been shown to improve outcomes and is advocated in early RA to tailor treatment [5]. This strategy is based on the use of activity scores to define remission or low disease activity (LDA) and adjust treatment according to these aims. DAS28 has been the most studied and used score. [6] This score gives a particularly high weight to tender joint counts (TJC) versus swollen joint counts (SJC). This may lead to classifying patients as having active disease based mainly on tenderness.[7] While they do include TJC and SJC, the Simple Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) do not give differential weights to these joint count measures. [8] With advances in RA treatment, remission is an achievable target. However, regardless of how remission is defined, a majority of patients still have some residual disease activity [9]. Although several factors that predict a poor response to therapy have been identified, there is limited capacity to anticipate who will require aggressive management. [10, 11] Drugs used in RA are associated with important adverse events and potentially substantial costs; therefore it is crucial to determine who will truly benefit from intense therapy. [12, 13, 14]
Fibromyalgia (FM) often coexists with RA. [15] The prevalence of FM in the general population is 2.7-5.1% and in RA it reaches a prevalence of up to 20%. [16, 17, 18, 19]. Concern has been raised regarding the validity of RA disease activity scores in patients with coexistent RA and FM, making a “treat-to-target” strategy questionable in these patients. [20] Cross-sectional studies have shown that FM patients have higher DAS28, higher TJC, worse self-reported global health (GH), and worse functional impairment. [21, 21, 23, 24] Regarding “fibromyalginess” without meeting FM criteria, a study by Wolfe et al. using the National Data Bank for rheumatic diseases evaluated the effect of the spectrum of FM symptoms measured using the PSD (polysymptomatic distress scale) on response to therapy in RA patients (REF). This study showed that with increasing PDS, clinical variables became more abnormal, including CDAI. In addition, the greater the PSD score the more patient-reported response variables predominated over physician and laboratory measurements, particularly when using composite measures. Authors of this study concluded, “It is not necessary for fibromyalgia criteria to be satisfied for these effects to take place”. [25]

Tender points are part of the 1990 ACR classification criteria traditionally used to diagnose FM, with a cutpoint of ≥11 tender points. [26] However measuring them is time consuming and not always performed in RA clinics. An index was developed by Pollard et al to identify “fibromyalgic RA” (FRA) using RA patients’ physical examination measures instead of tender points to diagnose it. This score was developed in a RA cohort in which the relationship of TJC
minus SJC had a ROC area under the curve of 0.86 to predict FM, and TJC-SJC ≥7 predicted the presence of ≥11 tender points with 83% sensitivity and 80% specificity. The score was validated in a replicate cohort with high sensitivity and specificity (72% and 98%) for FM. [27]

Worse disease activity in FRA could be a consequence of a blunted response to RA treatment or it could be due to the effect of persistent tenderness and fibromyalgia symptoms on disease activity measures. If response to treatment is poor, then the treat to target approach might need to be reconsidered in this large subset of patients. To our knowledge, no prospective longitudinal studies that have followed patients from beginning of treatment have been carried out to address this question.

In this prospective study, using the TJC-SJC index to characterize the presence of fibromyalgic RA, we hypothesized that patients with this condition have an impaired response to treatment measured by traditionally used scores. In spite of this, we postulate they do not have increased structural damage.

MATERIALS AND METHODS.

Study Subjects We addressed our questions using the ESPOIR cohort, a prospective multi-center early arthritis cohort. This cohort included patients aged 18–70 years, with 2 or more swollen joints with a duration of joint swelling of > 6 weeks and < 6 months, no previous disease-modifying drugs (DMARDS), no previous steroids, and no definite diagnosis of a disease other than RA or
undifferentiated arthritis. In our study, we included only patients with RA defined by the 1987 ACR and/or the 2010 ACR/EULAR classification criteria. Our inclusion criteria required a subject to meet either of the aforementioned criteria and have a TJC and SJC performed at the baseline visit. We excluded participants classified as having undifferentiated arthritis, and those with missing values of DAS28, SDAI or CDAI at baseline and at all follow up visits.

**Exposure:** Presence of FRA was defined at baseline as having a TJC–SJC ≥7. This represented our exposure. Participants were classified into two groups according to the presence or absence FRA. We shall label this latter group “isolated RA”.

**Study outcomes** The main outcome of this study was response to treatment in subjects with and without FRA. Response to treatment was defined using activity score measures in RA, including DAS28, CDAI, SDAI and HAQ. In addition the core components of DAS28 were evaluated.

Our secondary outcomes were the attainment of low disease activity (LDA) according to DAS28 (DAS28≤3.2) and of remission according to DAS28 (≤2.6), CDAI (CDAI≤2.8) and SDAI (SDAI≤3.3). In addition, SHARP score was compared at baseline and 12 months. Finally, treatment during follow-up was compared among the two groups.
Analytic approach:

Baseline characteristics: At baseline, differences in demographics between study groups were explored including age, gender, race, body mass index (BMI), and smoking status (defined as current or past smokers vs never smokers). BMI was categorized as obese (BMI≥30 kg/m²) vs non-obese (BMI<30 kg/m²). In addition, a comparison of RA characteristics was performed: serologic markers (rheumatoid factor (RF) and anti-cyclic Citrullinated Peptide (anti-CCP), TJC, SJC and presence of erosions (none vs. one or more) evaluated in bilateral hands and feet radiographs. RA activity scores including DAS28, CDAI and SDAI were calculated as well as HAQ (Health Assessment Questionnaire) to evaluate functional impairment and the van der Heijde-modified total Sharp radiologic score (mTSS). Drugs were classified as analgesics, non-steroidal anti-inflammatory drugs (NSAIDS), oral corticosteroids, monotherapy with non-biologic DMARDs, combination of non-biologic DMARDs, monotherapy with biologic DMARDs, and combination of non-biologic with biologic DMARDs. Baseline characteristics are reported as number (%) or mean±SD. A two sample T-Test was used to compare quantitative variables and a χ² test (or Fisher’s exact test) for categorical variables.

Outcomes: All outcomes were compared at six, twelve and eighteen months of follow-up between patients who were classified as having FRA versus patients with isolated RA. DAS28 and its core measurements was the main outcome.
Also, CDAI, SDAI and HAQ were compared. These outcomes were compared at each time-point between the two groups (FRA vs. no FRA) using a mixed linear regression model for repeated measures. We adjusted for the baseline value of the outcome being measured as well as other potential confounders: gender, age and smoking status. This model was used for activity scores as well as score components. Each of the score’s components was analyzed including SJC, TJC, physician global health (phGH) visual analogue scales (VAS), patient global health (ptGH) VAS, C-reactive protein and ESR.

As secondary outcomes an analysis was performed of the attainment DAS28 LDA (DAS28<3.2) and of remission according to DAS28 (≤2.6), CDAI (CDAI≤2.8) and SDAI (SDAI≤3.3). Additionally, treatment during follow-up was compared using the same categorical classification as in the baseline characteristics’ analysis.

We examined the risk of attaining all secondary outcomes in each of our study groups at each of the time-points (6, 12, 18 months) using a log binomial regression with an estimation of risk ratios (RRs) with repeated measurements. RRs were obtained using a generalized estimating equation (GEE) model to adjust for multiple observations per subject. Lastly, to evaluate structural damage, mTSS was evaluated at 12 months using a two sample T-test.

For all analysis, a p<0.05 was considered statistically significant. SAS 9.3 was used to perform all statistical calculations.
Power calculation:
We had 99% power to detect a DAS28 difference between groups of 0.5, considering a standard deviation of 1.3 using 120 subjects with FRA and 548 without, 3 visits per subject and an intraclass correlation coefficient for repeated measures of DAS28=0.6.

RESULTS
Baseline Patient Characteristics
There were 697 subjects with RA at baseline among the 813 ESPOIR cohort participants. Of these, 24 did not come to any of the follow-up visits and were excluded. We further excluded 5 subjects with all activity scores missing at follow-up. As a consequence, 668 subjects were included in the analysis. (Figure 1)

Subjects had a mean age of 48.3 years at baseline, 76.1% were females and 92.1% Caucasian. There were 47.3% ever smokers (see table 1). At baseline, patients had active disease with a mean DAS28 of 5.32. Erosions were present in 63.6% of patients.

FRA was present in 120 (17.96%) patients. There was no significant difference in baseline demographic characteristics according to the presence of FRA (see Table1). However, patients with FRA met ACR/EULAR 2010 RA criteria more frequently than patients without FRA (p=0.04), with no difference in ACR 1987 criteria (p=0.54). They also had a lower frequency of seropositivity
(RF and antiCCP) (p=0.0003).

RA activity scores and HAQ were higher in the FRA group. Also, TJC and GH evaluation by the physician and the patient were higher in these patients. On the other hand, ESR and the mTSS score were significantly lower in spite of the presence of higher activity scores. There were no differences in use of medications of any kind (Table 1).

Patients with missing values in any visit did not have significant differences in baseline characteristics from those without missing values.

**Activity scores in FRA patients over time.**

In a multivariate analysis incorporating the three study visits, adjusting for the baseline score, we found that patients with FRA had a higher DAS28 than patients with isolated RA (p<0.0001). DAS28 scores started out higher in subjects with FRA and while they improved to a similar extent as in the isolated RA group, they remained consistently higher among FRA subjects. In none of the visits in FRA subjects did the average DAS28 score reach LDA (Figure 2). It is noteworthy that although TJC showed an important decrease in both groups after treatment, they remained significantly higher in subjects with FRA. Patient and physician global health scores also remained worse in the FRA group at follow-up. On the other hand, SJC decreased to such an extent in both groups that there was no difference between them during follow-up. Regarding inflammatory parameters (ESR and CRP), there was no difference between groups after
treatment. (Figure 3) (Figure 4)

As shown in Table 2, other activity scores including SDAI, CDAI and HAQ were also higher in the group with FRA. These scores had a similar behavior as DAS28, starting higher and presenting a similar decrease in both groups (data not shown). In contrast, mTSS score was similar between groups during follow up (Table 2).

The overall achievement of LDA at 6, 12 and 18 months was significantly less likely in subjects with FRA, with a RR of 0.77 (95% confidence interval CI 0.63-0.94). Also there was less attainment of remission according to DAS28 and SDAI in this study group: RR=0.61 (95%CI 0.46-0.81) and 0.65 (95%CI 0.43-0.97) respectively. FRA patients had a modestly lower risk of achieving CDAI remission too: RR=0.70, with a borderline p value=0.06. (Table 3)

**Association between FRA and therapy.**

We did not find an association between FRA and analgesic use with an estimated RR=1.12 and a p value=0.0705. Also no association was identified with NSAIDS nor corticosteroids with an RR=1.0 (p value=0.9759) and an RR=1.07 (p value=0.4785), respectively. Non-biologic DMARDS both as monotherapy and combination therapy were also not associated with the presence of FRA (RR=0.82, p=0.98 and RR=0.53, p=0.9205. Finally, no difference existed in the use of biologic DMARDS as monotherapy (RR=0.26, p=0.2928) and combined with non-biologic DMARDS (RR=0.52, p=1.222).
DISCUSSION

In this cohort, subjects with FRA had higher baseline DAS28, CDAI, SDAI and HAQ than those with isolated RA. In addition, although FRA subjects improved with treatment to a similar extent as subjects without FRA, they maintained higher scores after treatment at all time-points. TJC also continued to be higher in participants classified as having FRA. In contrast, SJC, acute phase reactant levels, and mTSS scores were higher in subjects with isolated RA at baseline, but there was no difference between groups in both measures at follow-up. Therefore, both activity scores and core measurements decreased after treatment in both groups, reflecting that a response to therapy existed in all patients, but TJC and activity scores values remained higher in subjects with FRA.

In the only other study examining a similar issue in a longitudinal study, Andersson et al. addressed the question of response to treatment in RA patients with chronic widespread pain (CWP), a condition in the same spectrum of conditions as FM. They classified patients as having CWP based on self-report of pain in all four body quadrants at nine years of follow-up and retrospectively looked at response to treatment in an earlier five year period. They found that patients with CWP had worse disease activity scores after having been treated.[29] Patients with active RA without FRA could have met their definition of CWP, and the number of RA patients in this subset in their study (34%) was larger than any other subset and much higher than the usual estimate of 10-20%
for FM raising questions as to whether all of these patients had FRA.

Our baseline findings are concordant with previous cross-sectional studies. [21, 22, 23, 24, 25] One important question is if the traditionally used scores reflect more active RA or if scores in patients in the fibromyalgic spectrum do not necessarily measure RA activity, but a mixture of RA and fibromyalgia-like symptoms. The reliability of DAS28 has been shown to be inferior in patients with FM. [30]

It could be argued that our finding of a higher baseline DAS28 is secondary to our definition of FRA. However, while DAS28 gives more weight to TJC than SJC, CDAI and SDAI do not and these two scores were also higher in patients with FRA. Still, all of these scores include TJC and a Global health measure and it has been shown they are influenced by the patient's pain perception. [31]

The HAQ score, which does not include TJC, measures functional limitation and is also higher in patients with FRA. This score is probably affected by the symptoms generated by FRA per se and not necessarily due to more aggressive RA.

When analyzing response to treatment, at first impression the fact that activity scores continued to be higher in the FRA groups can be interpreted as a poor response to therapy. However, the decrease in score was similar in both groups (Figure 2), and patients with FRA had higher baseline values. Therefore, patients with FRA do respond to treatment, but have persistently higher activity
scores. The maintenance of scores could have two explanations. First, because DAS28 weights TJC more than SJC, it is more likely that patients with FRA would be assessed as continuing to have activity due to pain which may be secondary to FRA and not RA disease activity. It has been shown that patients with FRA can have no clinical evidence of inflammation and still be categorized as active by DAS28. [7] On the other hand, patients with FRA may have central sensitization that may in turn affect their response to therapy regarding pain control. [32, 33, 34] As a consequence, high disease activity scores may be produced by a diminished response of pain in patients with FRA and not necessarily because of a lack of accuracy of scores. In either situation, this instrument could misclassify patients as having inflammation. It is noteworthy that although at study initiation the existence of higher TJC could be related to our definition of FRA, during follow up TJC as well as SJC decreased in both groups, showing that they do respond to therapy, but there is residual pain in patients who have a fibromyalgic spectrum that prevents them from reaching LDA or remission. The TJC scores continued to be higher in FRA patients at follow-up after controlling for baseline values. The same occurred with the Global Health measure. Nevertheless, there was no difference in SJC and ESR between the two groups after treatment, two elements that do not rely on patient reports to characterize active RA.

Finally, the fact that modified Sharp scores were not higher in patients with FRA supports the hypothesis that patients’ activity scores in this group do not
reflect only RA activity, although the follow-up period may be too short to evaluate radiologic differences between groups.

Remission and LDA were less frequently achieved in patients with FRA (Figure 2). The classification of patients as having active disease could lead to escalating the intensity of treatment of RA. Treatment for arthritis is aimed at controlling inflammation and in patients with FRA these scores may reflect pain and not necessarily inflammation. As a consequence, patients with FRA may be overtreated using a “treat-to-target” strategy. This would increase the risk of adverse events and cost. Since current target score values are unlikely to be met in FRA patients, a less stringent target may need to be established for this group. On the other hand, the drug algorithm that treatment guidelines using “treat-to-target” propose, could be modified in cases that high activity scores are caused by high pain, focusing more on analgesic treatment. [5, 35] McWilliams et al. have created a score called DAS28-P that focuses in TJC and ptGH and that was shown to predict bodily pain at 12 months. [36] Although it needs further validation, this could be used in patients with FRA. Similarly, Kristensen et al. showed in a prospective study that a SJC/TJC ratio predicted response to antiTNF in patients refractory to traditional DMARDS. [37] This ratio could represent a way to categorize patients regarding response to treatment in presence of CWP, a condition that shares many properties with FRA.

The definition we used of FRA could generate misclassification of patients with RA who have high disease activity as having FRA, when this is not the case.
However, given the diagnostic performance of the TJC-SJC measure [27], it is unlikely especially since there are not many false positives (i.e. the specificity of this approach is high) and the use of TJC-SJC should be a valid representation of persons with FRA. Further, the maintenance of the TJC and SJC discordance in these patients argues against this misclassification phenomenon (Figure 4). On the other hand, given the sensitivity if the difference in joint counts to detect FRA some patients could have been missed. If this were the case our estimate would have been biased towards the null so this does not invalidate our findings.

One limitation of our work is that the disease activity scores we used may generate misclassification of our outcome of response to treatment. DAS28, in particular, has been shown to allow for inflammation to exist in a state of remission.[38, 39, 40] The new ACR/EULAR remission criteria avoid this misclassification but SDAI, which is an index recommended by these criteria, showed the same results as DAS28 in our study. [41] The ACR/EULAR Boolean definition of remission could also generate misclassification in FRA patients because patient global assessment has been shown to be the factor that more frequently prevents remission from being attained. [42]. Another limitation of our work is that we did not formally evaluate patients for fibromyalgia. It is likely that those with FRA include many with fibromyalgia, but others may not have had comorbid fibromyalgia, and it is also possible that a number of persons with coexistent fibromyalgia and RA were not captured by our approach.

Loss to follow up, considered as missing all visits was extremely low
(3.6%) and there was no difference between these patients and patients analyzed. Therefore, it is unlikely to represent a source of selection bias.

In relation to confounding, we adjusted for the main known confounder age, smoking and gender. However other confounders may exist such as socioeconomic status, depression and/or anxiety disorders, comorbidities, alcohol use and unknown confounders.

Although adjusting for baseline score values could have generated bias if fibromyalgic symptoms preceded the baseline measurements in this case we considered it necessary to adjust for these values given that RA high scores is associated with a higher frequency of fibromyalgia symptoms. The fact that the prevalence of FRA in our population corresponds to the prevalence in an RA population leads to the conclusion that RA activity was present before the classification of patients as having FRA. The analysis was also performed excluding the baseline score term and findings did not change (data not shown).

Finally, in relation to generalizability, this study was performed in a mainly Caucasian population and in a country where there is a good access to second line treatment in RA. However, the study the effect of fibromyalgic symptoms on disease scores and this is unlikely to be affected by these conditions. Therefore our results should be applicable to RA patients in general.

The fact that RA may cause central sensitization and therefore FRA makes it difficult to determine if it is the coexistence of FRA that determines less response to treatment or if it is explained by patients that have an aggressive
form of RA developing FRA more frequently [43]. The ESPOIR cohort’s short
duration of disease at baseline makes it less likely, although not impossible, that
at baseline a chronic sensitization phenomenon due to RA existed.[44, 45] In
addition, this would not invalidate our findings that in patients that FRA exists,
regardless of its origin, scores will have a worse response to therapy.

Conclusion
In conclusion, patients with FRA have a worse response to treatment according
to traditional disease activity scores with respect to the absolute final value
achieved rather than the relative decrease in score. However, RA inflammation
may be responding as the scores drop and the residual activity measured could
correspond mainly to residual pain related to FRA. We must reconsider the use
of a treat-to-target strategy, as it is currently defined, in patients with FRA.
<table>
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<td>DAS 28, mean (SD)</td>
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<td>CDAI, mean (SD)</td>
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<td>37.94 (10.38)</td>
<td>26.76 (13.06)</td>
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<td>SDAI, mean(SD)</td>
<td>31.0 (14.45)</td>
<td>39.78 (11.37)</td>
<td>29.09 (14.35)</td>
<td>&lt;0.0001</td>
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<td>HAQ, mean (SD)</td>
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<td>0.98 (0.68)</td>
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<td>SJC, mean (SD)</td>
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<td>7.15 (0.37)</td>
<td>8.17 (5.66)</td>
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<td>TJC, mean (SD)</td>
<td>9.36 (7.12)</td>
<td>18.29 (5.01)</td>
<td>7.41 (5.93)</td>
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<td>PtGH VAS (cm), mean (SD)</td>
<td>6.13(2.48)</td>
<td>6.73 (2.15)</td>
<td>5.99 (2.53)</td>
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<td>PhGH VAS (cm), mean (SD)</td>
<td>5.34 (6.13)</td>
<td>5.85 (2.11)</td>
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<td>ESR (mm/h), mean (SD)</td>
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<td>24.9 (20.5)</td>
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<td>CRP (mg/l), mean (SD)</td>
<td>21.4 (33.6)</td>
<td>17.4 (24.9)</td>
<td>22.3 (35.2)</td>
<td>0.071</td>
</tr>
<tr>
<td>RF (%)</td>
<td>54.6</td>
<td>40</td>
<td>57.9</td>
<td>0.0004</td>
</tr>
<tr>
<td>CCP (%)</td>
<td>45.7</td>
<td>29.2</td>
<td>49.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RF + CCP (%)</td>
<td>41.3</td>
<td>26.7</td>
<td>44.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Erosions (%)</td>
<td>63.6</td>
<td>63.7</td>
<td>61.2</td>
<td>0.61</td>
</tr>
<tr>
<td>Sharp score (SD)</td>
<td>6.29 (8.07)</td>
<td>5.12 (6.02)</td>
<td>6.54(8.44)</td>
<td>0.038</td>
</tr>
<tr>
<td>Analgesics (%)</td>
<td>70.8</td>
<td>75.8</td>
<td>69.7</td>
<td>0.18</td>
</tr>
<tr>
<td>NSAIDS (%)</td>
<td>90.7</td>
<td>89.2</td>
<td>91.1</td>
<td>0.52</td>
</tr>
<tr>
<td>Corticosteroids (%)</td>
<td>13.0</td>
<td>14.2</td>
<td>12.8</td>
<td>0.68</td>
</tr>
<tr>
<td>DMARDs Monotherapy (%)</td>
<td>7.7</td>
<td>7.5</td>
<td>7.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Combined DMARDs (%)</td>
<td>0.5</td>
<td>0.6</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Biologic DMARDs (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Table 1.** Demographic and disease characteristics at inclusion of the 668 patients with rheumatoid arthritis (RA), grouped by fibromyalgic RA (FRA) presence. P-values denote the overall significance of differences between groups.
calculated by a two-sample T-Test or by the chi-squared test. Obesity: (BMI≥30kg/m²); DAS28: 28-joint Disease Activity Score; the Simplified Disease Activity Index (SDAI) or the Clinical Disease Activity Index (CDAI); HAQ: Health Assessment Questionnaire; SJC: swollen joint counts, TJC: tender joint counts PtGH: patient global health; PhGH: physician global health; VAS: visual analog scale; RF: rheumatoid factor; CCP: Anti-citrullinated protein antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.
<table>
<thead>
<tr>
<th></th>
<th>FRA</th>
<th>No FRA</th>
<th>Difference in Adjusted scores</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS 28</td>
<td>3.5045</td>
<td>3.0541</td>
<td>0.4505</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SDAI</td>
<td>16.0891</td>
<td>11.5378</td>
<td>4.5514</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CDAI</td>
<td>14.9819</td>
<td>10.7510</td>
<td>4.2309</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.6293</td>
<td>0.4454</td>
<td>0.1739</td>
<td>0.0002</td>
</tr>
<tr>
<td>SJC</td>
<td>2.32</td>
<td>2.18</td>
<td>0.14</td>
<td>0.5476</td>
</tr>
<tr>
<td>TJC</td>
<td>7.97</td>
<td>3.27</td>
<td>4.70</td>
<td>0.0001</td>
</tr>
<tr>
<td>PtGH VAS</td>
<td>3.82</td>
<td>3.01</td>
<td>0.81</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PhGH VAS</td>
<td>2.88</td>
<td>2.38</td>
<td>0.51</td>
<td>0.0044</td>
</tr>
<tr>
<td>CRP</td>
<td>0.75</td>
<td>0.84</td>
<td>0.09</td>
<td>0.4147</td>
</tr>
<tr>
<td>ESR</td>
<td>13.99</td>
<td>15.05</td>
<td>1.06</td>
<td>0.3602</td>
</tr>
<tr>
<td>SHARP</td>
<td>7.3315</td>
<td>7.6756</td>
<td>0.341</td>
<td>0.3125</td>
</tr>
</tbody>
</table>

**Table 2.** Comparison of rheumatoid arthritis activity scores and radiologic scores over follow up according to the presence of fibromyalgic RA (FRA). P-values denote the overall significance of a linear regression adjusting for baseline score, gender, age and smoking status. DAS28: 28-joint Disease Activity Score; Simplified Disease Activity Index (SDAI) or the Clinical Disease Activity Index (CDAI); HAQ: Health Assessment Questionnaire; SJC: swollen joint counts, TJC: tender joint counts PtGH: patient global health; PhGH: physician global health; VAS: visual analog scale; RF: rheumatoid factor; CCP: Anti-citrullinated protein antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.
<table>
<thead>
<tr>
<th></th>
<th>Risk Ratio (95% Confidence Interval)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS low activity</td>
<td>0.77 (0.63, 0.94)</td>
<td>0.0101</td>
</tr>
<tr>
<td>DAS remission</td>
<td>0.61 (0.46, 0.81)</td>
<td>&lt;0.0007</td>
</tr>
<tr>
<td>SDAI remission</td>
<td>0.65 (0.43, 0.97)</td>
<td>0.0366</td>
</tr>
<tr>
<td>CDAI remission</td>
<td>0.70 (0.49, 1.01)</td>
<td>0.0581</td>
</tr>
</tbody>
</table>

**Table 3.** Low activity and remission attainment according to Fibromyalgic RA groups. P-values denote the overall significance of a log binomial regression adjusting for baseline score, gender, age and smoking status. DAS28 low activity; DAS28 ≤3.2; DAS28 remission: DAS28 ≤2.6; CDAI remission: CDAI≤2.8 and of SDAI (SDAI≤3.3).
Figure 1. Flow diagram documenting number of patients in this study. RA includes patients that meet either ACR 1987 classification criteria or ACR/EULAR 2010 classification criteria. FRA = Fibromyalgic rheumatoid arthritis.
Figure 2. DAS28 score at different time points grouped by fibromyalgic rheumatoid arthritis presence.
Figure 3. DAS28 core measures of disease activity at different time points grouped by fibromyalgic rheumatoid arthritis presence. A: Erythrocyte Sedimentation Rate (ESR), B: C Reactive Protein (CRP), C: Tender Joint Count (TJC), D: Swollen Joint Count (SJC)
Figure 4. TJC – SJC difference during follow up in subjects grouped by FRA presence.
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