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Original article

Rheumatoid arthritis seems to have DMARD treatment decision influenced by fibromyalgia

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ABSTRACT

Objective: To compare DMARD use in patients with and without FM over time, including overtreatment and undertreatment rates in both groups.
Methods: A prospective cohort study with patients attending an RA outpatient clinic was conducted. Participants were consecutively recruited between March 2006 and June 2007 and were followed through December 2013. Data on DMARD use (prevalences, doses and escalation rates), DAS28, HAQ and radiographic progression were compared among RA patients with FM and without FM. Mistreatment clinical scenarios were allegedly identified and compared between groups.
Results: 256 RA patients (32 with FM) were followed for 6.2 ± 2.0 (mean ± SD) years comprising 2986 visits. At baseline, RA duration was 11.1 ± 7.4 years. DAS28 and HAQ were greater in RA with FM group, and were closer to RA without FM group towards the end. RA patients with FM used higher doses of tricyclic antidepressants, leflunomide and prednisone, and lower doses of methotrexate. When compared to RA patients without FM, participants with RA and FM used more often tricyclic antidepressants, leflunomide, prednisone, continuous analgesics and less often methotrexate. Groups presented similar 7-year biologic-free survival, and radiographic progression-free survival in Cox regression. RA patients with FM had greater proportions of visits in mistreatment scenarios when compared to RA patients without FM (28.4 *vs.* 19.8%, $p < 0.001$).

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Conclusions: RA patients with FM used more leflunomide and prednisone, and RA mistreatment was more frequent in FM patients. Certainly, RA patients with FM will benefit from a personalized T2T strategy, including ultrasound (when suitable) and proper FM treatment.

As decisões de tratamento com DMARD na artrite reumatoide parecem ser influenciadas pela fibromialgia

Palavras-chave:
Fibromialgia
Artrite reumatoide
Tratamento farmacológico

RESUMO

Objetivo: Comparar o uso de fármacos antirreumáticos modificadores da doença (DMARD) em pacientes com e sem fibromialgia (FM) ao longo do tempo, incluindo as taxas de tratamento excessivo e subtratamento em ambos os grupos.
Métodos: Estudo de coorte prospectiva com pacientes atendidos em um ambulatório de artrite reumatoide (AR). Os participantes foram recrutados consecutivamente entre março de 2006 e junho de 2007 e foram seguidos até dezembro de 2013. Compararam-se os dados de uso de DMARD (prevalências, doses e taxas de escalonamento), *28-Joint Disease Activity Score* (DAS28), *Health Assessment Questionnaire* (HAQ) e progressão radiográfica entre pacientes com e sem FM. Os cenários clínicos de tratamento supostamente incorreto foram identificados e comparados entre os grupos.
Resultados: Seguiram-se 256 pacientes com AR (32 com FM) por 6,2 ± 2,0 (média ± DP) anos, período que abrangeu 2.986 consultas. No início do estudo, a duração da AR era de 11,1 ± 7,4 anos. O DAS28 e o HAQ foram maiores no grupo AR com FM e estavam mais próximos do grupo AR sem FM no fim do estudo. Os pacientes com AR com FM usaram doses mais altas de antidepressivos tricíclicos, leflunomida e prednisona e doses mais baixas de metotrexato. Quando comparados com os pacientes com AR sem FM, os participantes com AR e FM usaram mais frequentemente antidepressivos tricíclicos, leflunomida, prednisona e analgésicos contínuos e menos frequentemente metotrexato. Os grupos apresentaram sobrevida em sete anos sem agentes biológicos e livres de progressão radiográfica semelhantes na regressão Cox. Os pacientes com AR com FM apresentaram uma maior proporção de consultas em cenários de tratamento supostamente incorreto quando comparados com os pacientes com AR sem FM (28,4 *vs.* 19,8%, $p < 0,001$).
Conclusões: Os pacientes com AR e FM usaram mais leflunomida e prednisona e o tratamento supostamente incorreto na AR foi mais frequente em pacientes com FM. Os pacientes com AR com FM certamente se beneficiarão de uma estratégia personalizada de tratamento por metas (T2T), incluindo ultrassonografia (quando apropriado) e controle da FM.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic destructive polyarthritis that may cause severe functional impairment and death.[1] To stop joint destruction and prevent worse outcomes clinicians should use disease-modifying antirheumatic drugs (DMARD) in a treat-to-target (T2T) strategy, where lower disease activity is pursued.[1–3] Disease activity level can be clinically estimated by 28-joint disease activity score (DAS28), a score that includes objective (number of swollen joints and erythrocyte sedimentation rate) and subjective parameters (number of tender joints and patient's global health evaluation using a visual analogue scale).[4,5]

Fibromyalgia (FM) is a chronic painful condition affecting up to 20% of RA patients. FM may falsely increase RA activity by augmenting the subjective components of DAS28 and, therefore, bias treatment decision. Both overtreatment (DMARD escalation when a higher DAS28 is due to FM) and undertreatment (no DMARD escalation when a higher DAS28 is due to RA) are possible.[6–10]

The primary goal of this study is to compare DMARD use in patients with and without FM over time. Also, we intend to compare overtreatment and undertreatment rates in both groups.

Patients and methods

A prospective cohort study was conducted with patients attending the RA outpatient clinic at Hospital de Clínicas de Porto Alegre since biologic DMARD became available in the institution. Participants were consecutively recruited between March 2006 and June 2007 and they were followed through December 2013. To be included patients had to fulfil 1987

American College of Rheumatology (ACR) classification criteria for RA.[11] Every participant was also assessed at baseline for the diagnosis of FM according to 1990 ACR classification criteria.[12] There were two unmatched groups under observation: RA patients with FM and RA patients without FM. Exclusion criteria were concomitant systemic lupus erythematosus, systemic sclerosis, idiopathic inflammatory myopathies, spondyloarthropathies, hepatitis B or C virus, or human immunodeficiency virus infection at baseline or during follow-up. Participants were also excluded if they did not have FM at baseline but developed diffuse chronic pain afterwards.

Data of each visit were collected in standardized research forms. DAS28 (ranges from 0.0 through 9.4; greater values represent higher disease activity) and health assessment questionnaire (HAQ; greater values represent worse functional status) calculation and FM diagnosis were made by different blinded examiners.[13,14] Charlson comorbidity index (CCI; ranges from 0 through 35; greater values represent higher comorbidity) was also calculated at baseline.[15]

Hospital de Clínicas de Porto Alegre is a public tertiary institution where patients have access to all DMARD as part of a national Government-funded programme. Also, analgesics, nonsteroidal anti-inflammatory drugs (NSAID), steroids, amitriptyline, fluoxetine and cyclobenzaprine are provided by the Government.

In the RA clinic, patients are treated according to a step-up T2T approach where DMARD are escalated up to remission or low disease activity.[16] For the purpose of this study, DMARD escalation was defined as any dose increment or drug switch to achieve treatment target, and treatment failure was defined as consistently moderate/high disease activity after three months of the highest tolerated dose of a synthetic DMARD or six months of a biologic DMARD. According to T2T, methotrexate was the first prescribed DMARD and started just after the diagnosis. If methotrexate monotherapy failed, a second line synthetic DMARD therapy was started. This second synthetic DMARD step consisted of leflunomide monotherapy, association of methotrexate and leflunomide or association of methotrexate, sulfasalazine and hydroxylchloroquine (or chloroquine). If the second DMARD scheme failed, a biologic DMARD, preferably an anti-tumour necrosis factor agent (anti-TNF), was started in association with a synthetic DMARD, preferably methotrexate. Treatment failure to the first biologic DMARD was an indication for biologic switching. Another anti-TNF, abatacept, rituximab and tocilizumab were the alternatives. The option for the next biologic took into account patients' clinical aspects and preferences in light of the existing evidence. Adalimumab, etanercept, infliximab and rituximab were available for use in the study centre since its onset in 2006. Abatacept and tocilizumab became available in 2010, and certolizumab and golimumab, in 2012. Steroids could be used anytime at the lowest dose to control synovitis. Nonsteroidal anti-inflammatory drugs (NSAID) were used for short periods of time to control worsening inflammatory symptoms. Analgesics NSAID (acetaminophen, dipyrone, tramadol, codeine) were used on demand for pain control. DMARD withdrawal was recommended in case of sustained remission without radiographic progression and consisted of gradual dose reduction or interval spacing over months. Biologic DMARD should be withdrawn before synthetic DMARD.[2]

During the study, patients were routinely assessed for the presence of widespread pain. FM treatment consisted of drug therapy, exercise and psychotherapy. Drug therapy included on-demand analgesics and continuous amitriptyline, fluoxetine, cyclobenzaprine, pregabalin or duloxetine. Pregabalin and duloxetine are available for FM treatment in Brazil since 2011.[17] FM patients were encouraged to attend the multidisciplinary Pain Treatment clinic.

Every three months, RA patients should perform blood and urine tests for drug safety monitoring. Tests for disease activity assessment were performed every three to six months. Radiographic monitoring of RA damage was performed once a year. Experienced musculoskeletal radiologists not aware of RA activity level or FM diagnosis read the X-rays and radiographic progression was defined in the presence of worsening or appearance of joint space narrowing or typical joint erosions in the hands or feet. Previous damage was visually considered worse, as no measuring was performed. Absence of radiographic progression was defined as no worsening or appearance of joint space narrowing or typical hands and feet erosions in two consecutive radiographs. After 2011, patients could be referred for ultrasound examination of RA activity. The disease activity assessment by ultrasound comprised seven joints (dominant wrist, second and third metacarpophalangeal, and second and fifth metatarsophalangeal joints) plus any symptomatic joints (tender and swollen). Referral for ultrasound examination and DMARD escalation decision afterwards were based on free clinician's judgement.

To verify the potential role of FM in inducing RA mistreatment, two clinical scenarios were analyzed. Scenario A comprised visits with continuous moderate/high disease activity despite DMARD escalation (treatment failure) without radiographic progression. In other words, whenever DMARD treatment was not escalated (DAS28 moderate/high) and radiographic progression was noticed, undertreatment was present. Scenario B comprised visits with persistent moderate/high disease activity without DMARD escalation but with radiographic progression identified. Therefore, in the absence of radiographic progression despite persistently moderate/high DAS28, DMARD escalation was considered overtreatment. Allegedly, scenarios A and B respectively represent overtreatment and undertreatment.

Statistical analyses were executed in SPSS software (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.). Previously, a difference of 0.29 in proportions of individuals with and without FM with moderate/high RA activity (0.97 and 0.68, respectively) was reported.[6] Our cohort of 32 RA patients with FM and 224 without FM had a power of 0.88 to detect such a difference with an alpha of 0.050. Outcome measures were mainly reported as rates (per patient-year) or frequencies (%) and measures of central tendency were mean ± standard deviation (SD) and median (interquartile range, IQR). Each variable distribution was tested for normality by Shapiro–Wilk's test. Comparisons between groups with and without FM were performed using Student's and Mann–Whitney's tests for continuous variables and Pearson's chi-square test for categorical variables. To compare DAS28 and HAQ over time between groups, generalized estimating

equations were used. Biologic DMARD-free survival, and radiographic progression-free survival were compared using Kaplan–Meier curves and tested using Cox proportional hazards models. Results of the Cox regressions were presented as hazard ratios (HR) and 95% confidence interval (CI). A p value of less than 0.050 was considered statistically significant.

This study was approved by the Research Ethics Committees of Hospital de Clínicas de Porto Alegre and Universidade Federal do Rio Grande do Sul. All patients signed written informed consent before entering the original cross-sectional study in 2006 and 2007,[6] and researchers signed a data utilization form to comply with the Declaration of Helsinki.

Results

Initially, 270 patients were recruited, but 14 participants were excluded due to diffuse pain or overlap syndrome development. Totally, 256 patients were followed for 6.2 ± 2.0 (mean ± SD) years (Table 1). They were mostly middle-aged (55.4 ± 12.6 years), caucasian (85.2%), married (50.4%), women (84.4%) with ≤8 years of school attendance (75.4%). Data from 2986 visits were analyzed. All patients regularly performed hands and feet radiographs throughout follow-up.

At baseline, FM was present in 12.5% of the participants (n = 32), Sjögren's syndrome in 4.7%, rheumatoid factor in 83.6% and joint erosions in 83.6%. Participants had RA for 11.1 ± 7.4 years and their CCI was 1.7 ± 1.0. Overall, DAS28 and HAQ scores significantly decreased from 4.1 ± 1.9 to 3.5 ± 1.4 (p < 0.001) and from 1.8 ± 0.8 to 0.7 ± 0.7 (p < 0.001), respectively.

Initially, RA patients with FM were slightly older, predominantly female and had greater DAS28 and HAQ compared to those without FM (Table 1). DAS28 and HAQ values were superior in RA with FM over time (Fig. 1). At the end of the study, DAS28 and HAQ were superior in RA patients with FM: 4.2 ± 1.3 vs. 3.3 ± 1.3, p = 0.001, and 1.3 ± 0.8 vs. 0.7 ± 0.7, p < 0.001, respectively. However, FM patients exhibited a greater decrease in DAS28 and HAQ values throughout the study (Fig. 1). According to generalized estimating equations analyses, between-group comparisons, intra-group (time-based) comparisons and group-time interactions were all statistically significant (p < 0.001). In other words, groups differed between each other, both of them changed over time and they did so in different ways.

Considering treatment response, 37.5% and 39.7% (p = 0.809) of RA patients with and without FM, respectively, had moderate/high disease activity at baseline and went down to remission/low disease activity in the last visit. In terms of remission rates, at baseline, 0.0% of patients with FM and 24.6% of patients without FM were in remission (p = 0.002), and, by the end of the study, remission rates were 18.8% and 32.1%, respectively (p = 0.124).

During follow up, amitriptyline was used by 24.2% of participants at 25.0 (25.0, 50.0) mg/day [median (IQR)], methotrexate by 89.5% at 20.0 (15.0, 20.0) mg/day, leflunomide by 50.8% at 20.0 (20.0, 20.0) mg/day, prednisone by 79.3% at 7.5 (5.0, 10.0) mg/day and biologic DMARD by 21.9% of individuals. RA patients with FM used higher doses of tricyclic antidepressants, leflunomide and prednisone, and lower doses of methotrexate (Table 2). Doses of prednisone prescribed by the physician in each visit were also higher among RA patients with FM: 5.0 (0.0, 10.0) vs. 2.5 (0.0, 7.5), p < 0.001. More RA patients with FM used tricyclic antidepressants than those without FM (Table 2). Cyclobenzaprine, fluoxetine, pregabalin, duloxetine, sulfasalazine, chloroquine and hydroxychloroquine were used by fewer than 50.0% of participants each. No patients used certolizumab or golimumab during the study. When compared to RA patients without FM, participants

Table 1 – Baseline patients characteristics.

	RA with FM (n = 32)	RA without FM (n = 224)	p value[a]
Age; mean (±SD)	59.9 (±12.8)	54.7 (±12.5)	**0.028**
Female (%)	96.9	82.6	**0.037**
Years since RA diagnosis; mean (±SD)	11.0 (±7.7)	11.1 (±7.3)	0.911
Years since FM diagnosis; mean (±SD)	5.8 (±3.9)	–	–
Charlson comorbidity index; mean (±SD)	1.8 (±1.0)	1.7 (±1.0)	0.388
DAS28; mean (±SD)	5.3 (±1.1)	3.9 (±1.5)	**<0.001**
Swollen joints count; median (IQR)	3.9 (1.0–5.5)	2.4 (0.0–5.0)	0.122
Tender joints count; median (IQR)	10.0 (5.0–17.0)	3.0 (0.0–8.0)	**<0.001**
Patient's global health visual analogue scale; median (IQR)	56.5 (41.5–90.0)	31.5 (14.0–52.2)	**<0.001**
ESR (mm/h); median (IQR)	28.5 (15.5–49.0)	26.0 (14.0–41.2)	0.335
HAQ; mean (±SD)	2.3 (±0.5)	1.7 (±0.8)	**0.001**
Caucasian (%)	93.8	83.9	0.233
Eight or less years of school (%)	78.2	75.1	0.947
Married (%)	37.5	52.2	0.135
Sjögren's syndrome (%)	3.1	4.9	0.655
Rheumatoid factor positive (%)	81.3	83.9	0.702
Joint erosions present on X-ray (%)	74.2	85.7	0.101

RA, rheumatoid arthritis; FM, fibromyalgia; DAS28, 28-joint disease activity score; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; SD, standard deviation; IQR, interquartile range.

[a] Student's, Mann–Whitney's or Pearson's chi-square test was used according to nature and distribution of data; alpha = 0.050. In bold, p values with statistical significance.

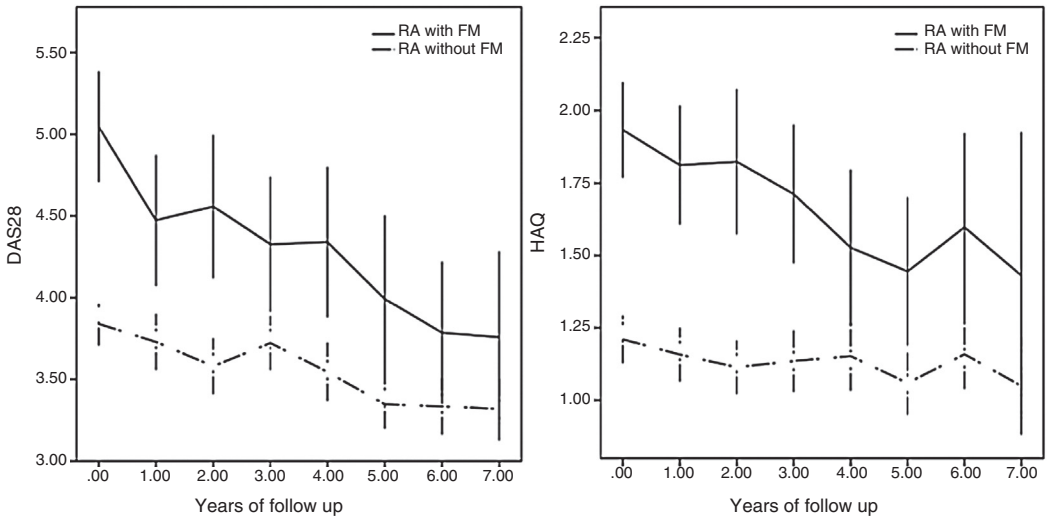

Fig. 1 – DAS28 and HAQ curves of RA patients with and without FM. DAS28, 28-joint disease activity score; HAQ, health assessment questionnaire; RA, rheumatoid arthritis; FM, fibromyalgia. RA patients with FM as a continuous line and RA patients without FM as an interrupted line. Generalized estimating equations; alpha = 0.050; error bars: 95% confidence interval; between-group comparisons, $p < 0.001$, intra-group (time-based) comparisons, $p < 0.001$; group-time interactions, $p < 0.001$.

with RA and FM used more often tricyclic antidepressants, leflunomide, prednisone, continuous analgesics and less often methotrexate throughout the study (Table 3). No difference was observed between groups regarding the prevalences of biologic DMARD use and DMARD escalations (Table 3).

Overall, DMARD escalation rate was 1.0 (0.7, 1.5) DMARD escalation/patient-year. In terms of biologics use, RA patients were on average under biologic DMARD in less than one visit per year (0.9 ± 0.5 visit under biologic DMARD/patient-year). DMARD escalation and biologics use did not differ between groups (Tables 2 and 3). Regarding ultrasound clinic attendance, FM was more frequently associated with ultrasound examination (6.1% vs. 2.9% of visits; $p = 0.047$). Among RA patients with FM, biologics use was less frequent when ultrasound examination was performed: 9.1% vs. 66.7% of visits; $p = 0.002$.

No statistically significant differences were found between groups concerning 7-year biologic-free survival, and radiographic progression-free survival in Cox regression adjusted by age, sex and CCI (Fig. 2). The only factor significantly influencing 7-year biologic-free survival was age, HR = 0.966 (0.944–0.988). Seven-year radiographic progression-free survival was not influenced by any of the variables.

Scenario A (overtreatment) was present in 15.3% of all visits and scenario B (undertreatment) was identified in 5.5% of all visits. Overall, RA patients with FM were more frequently over- and undertreated (scenarios A + B) when compared with those without FM (28.4 vs. 19.8%, $p < 0.001$; Table 3).

Discussion

To our best knowledge, this is the first longitudinal study dedicated to quantify the impact of FM on DMARD escalation decision in an RA cohort. Recently, Lage-Hansen et al. described an increase in biologic DMARD use among RA patients with FM in a cross-sectional study.[18] However, due to its transverse design no causality could be established. In our study, DMARD escalation was not affected by FM possibly due to physicians awareness of its presence. In 2009, our group demonstrated the impact of FM on DAS28 in patients attending the same clinic.[6] Therefore, rheumatologists were aware of this interference early on in the study. Also, compared to other disease activity scores, DAS28 is particularly prone to FM interference, due to the heavier weight of subjective components (tender joints count and visual analogue scales) in its formula.[14,19] By knowing DAS28 characteristics beforehand, rheumatologists were more careful in escalating DMARD in RA patients with FM, emphasizing objective measures, such as swollen joints count, erythrocyte sedimentation rate and C-reactive protein, for treatment decision.[10,20] In addition, since 2010, ultrasound has been performed for synovitis quantification in our centre. As previously demonstrated, synovitis on Doppler may better represent RA activity level than clinical indexes in patients with concomitant FM.[21,22] Moreover, FM-induced DAS28 and HAQ overestimations diminished during the study, possibly minimizing overtreatment. However, no definite conclusion can be drawn from this observation.

RA patients with FM showed a deeper decline in DAS28 and HAQ values during follow up than those without FM, probably because of several factors, such as the growing body of evidence on FM treatment, the availability of new Government-funded drugs for FM in 2011, the greater use of tricyclic antidepressants among FM patients and the growing access to the multidisciplinary Pain Treatment clinic in our institution. Unfortunately, we do not have the frequency of Pain Treatment clinic attendance or non-pharmacological treatment (exercise and psychotherapy) adherence among FM patients to verify this hypothesis. In 2008, Sokka et al. reported a remission rate of 19.6% in a real-life setting.[23] In another

Table 2 – Treatment-related characteristics of patients per group throughout the study.

	RA with FM ($n=32$)	RA without FM ($n=224$)	p value[a]
Years of follow up; mean (±SD)	5.7	6.2	0.301
Amitriptyline dose (mg/day); median (IQR) and mean (±SD)	0.0 (0.0, 25.0) 13.4 (±23.5)	0.0 (0.0, 0.0) 4.6 (±14.2)	**<0.001**
Methotrexate dose (mg/day); median (IQR) and mean (±SD)	15.0 (0.0, 20.0) 12.7 (±9.2)	15.0 (7.5, 20.0) 14.2 (±8.6)	**<0.001**
Leflunomide dose (mg/day); median (IQR) and mean (±SD)	0.0 (0.0, 20.0) 8.2 (±9.9)	0.0 (0.0, 20.0) 5.2 (±8.7)	**<0.001**
Prednisone dose (mg/day); median (IQR)	5.0 (0.0, 10.0)	2.5 (0.0, 8.8)	**<0.001**
Number of visits in use of biologics per patient-year; median (IQR)	0.9 (0.3, 1.2)	1.0 (0.6, 1.4)	0.638
DMARD escalations per patient-year; median (IQR)	1.0 (0.7, 1.5)	1.0 (0.7, 1.5)	0.530
Radiographic progression (%)	46.9	39.7	0.442

RA, rheumatoid arthritis; FM, fibromyalgia; SD, standard deviation; IQR, interquartile range; analgesics, acetaminophen, dipyrone, tramadol, codeine; DMARD, disease-modifying antirheumatic drug.

[a] Student's, Mann–Whitney's or Pearson's chi-square test was used according to nature and distribution of data; alpha = 0.050. In bold, p values with statistical significance.

Table 3 – Treatment characteristics of each group measured in visits throughout the study.

	RA with FM ($n=373$ visits)	RA without FM ($n=2613$ visits)	p value[a]
Tricyclic antidepressants (%)	31.4	13.2	**<0.001**
Methotrexate (%)	69.4	79.8	**<0.001**
Leflunomide (%)	41.3	26.2	**<0.001**
Prednisone (%)	65.4	52.9	**<0.001**
Continuous analgesics (%)	21.7	12.7	**<0.001**
Continuous NSAIDs (%)	26.5	22.0	0.076
Biologic DMARD (%)	10.5	12.4	0.292
Abatacept (%)	1.1	0.9	0.773
Adalimumab (%)	1.3	2.1	0.346
Certolizumab (%)	0.0	0.0	NS
Etanercept (%)	0.0	3.2	**<0.001**
Golimumab (%)	0.0	0.0	NS
Infliximab (%)	5.1	3.4	0.112
Rituximab (%)	2.9	1.9	0.186
Tocilizumab (%)	0.0	0.8	0.075
DMARD escalations (%)	46.9	47.2	0.960
DMARD escalations in the first year of follow up (%)	51.6	49.5	0.400
Scenario A (%)	20.4	14.6	**0.004**
Scenario B (%)	8.0	5.2	**0.023**

DMARD, disease-modifying antirheumatic drug; RA, rheumatoid arthritis; FM, fibromyalgia; analgesics, acetaminophen, dipyrone, tramadol, codeine; NSAID, nonsteroidal anti-inflammatory drug; NS, not stated; scenario A, DAS28 moderate/high, DMARD, escalated and radiographic progression absent; scenario B, DAS28 moderate/high, DMARD, not escalated and radiographic progression present.

[a] Student's, Mann–Whitney's or Pearson's chi-square test was used according to nature and distribution of data; alpha = 0.050. In bold, p values with statistical significance.

T2T study in long-standing RA, DAS28 and HAQ diminished after 3 years ($p=0.004$ and $p<0.001$, respectively) and the final scores were comparable to ours: DAS28 = 3.3 ± 1.4 and HAQ = 1.1 ± 0.4. In this same study, remission was achieved by 35.3% of patients initially refractory to synthetic DMARD.[24] Santos-Moreno et al. studied moderately to highly active RA patients treated to target for 6 months and found a significant decrease both in DAS28 and HAQ ($p<0.001$). Their final values were: DAS28 = 2.5 (2.3, 3.2), HAQ = 0.1 (0.1, 0.3) and remission rate = 51%.[25] In our study, the longer observational period, joint deformities and chronic proliferative synovitis seen in long-standing disease, as well as lower educational level may have contributed to the final DAS28 slightly above the target.[8,26] Despite the greater decrease of DAS28 over time among FM patients, the final score was higher in this group but not the radiographic progression rate, suggesting that the interference of the painful condition in RA activity scoring was attenuated but still present throughout the study.

RA patients with FM used more often tricyclic antidepressants, leflunomide, prednisone and continuous analgesics, but less often methotrexate than those without FM. Tricyclic antidepressant indication was not collected and other conditions, such as diabetic neuropathy, could have influenced this difference. The greater use of the preferably second-line agent leflunomide (Table 3) may indicate an interference of the painful condition in DMARD escalation (methotrexate discontinuation). Also, prednisone dose was greater among FM patients (Table 3), suggesting FM could have pushed steroid therapy forward. In the study by Anderson et al., chronic widespread pain patients were treated with prednisone to a greater extent than those with chronic regional pain syndrome but a similar rate of DMARD treatment.[9]

Radiographic progression was the same between groups and comparable to other T2T studies.[27,28] Possibly, no joint damage difference was observed in the presence of FM because DMARD escalation was similar to those without FM. In addition, FM interference on treatment decision could have been attenuated by ultrasound examination. Speculatively, DMARD escalation decision could have become less biased by FM afterwards.[21,29,30]

Kaplan–Meier curves contemplate the time elapsed to a certain event and no differences between groups were observed regarding biologic-free, and radiographic progression-free. In other words, FM does not seem to anticipate biologic use or radiographic progression among RA

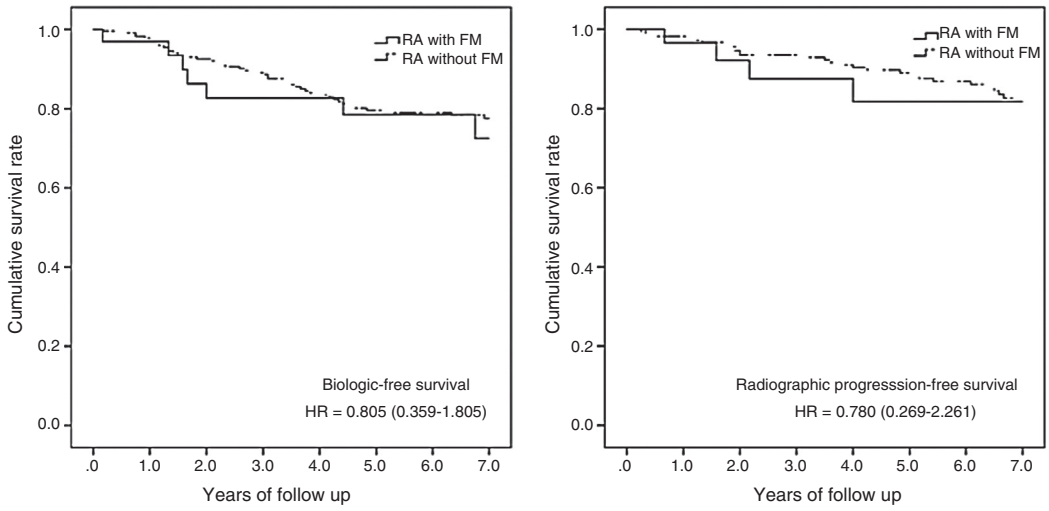

Fig. 2 – Kaplan–Meier curves of RA patients with and without FM. (A) 7-year biologic-free survival; (B) 7-year radiographic progression-free survival. RA, rheumatoid arthritis; FM, fibromyalgia. RA patients with FM as a continuous line and RA patients without FM as an interrupted line. Cox proportional hazards models adjusted by age, sex, Charlson comorbidity index and prednisone dose; HR: hazard ratio (95% confidence interval); alpha = 0.050.

patients. These results have not been described in equivalent studies yet.

Our findings suggest that RA patients with FM could have been more frequently mistreated than RA patients without FM in two arbitrary scenarios. In theory, these scenarios intend to represent both over- and undertreatment frequencies. Nonetheless, no definite conclusion can be drawn, since radiographic progression was not quantified in a score and these scenarios require further validation as true outcome measures. Moreover, ultrasound scoring could be used in future studies as a comparator in each scenario, since it has been validated as an objective measure of synovitis and as a radiographic progression predictor.[21,29]

Ultrasound-based synovitis assessment could have influenced DMARD escalation decision, contributing to reduce the supposed influence of FM on RA treatment.[21] A longitudinal study with RA patients with FM divided in two groups according to ultrasound assessment could address this issue more properly. Another imperfection was the existence of various DAS28 examiners throughout the study, as it has been demonstrated that clinical reliability of the score is highly dependent on the examiner.[31] Since DAS28 was usually performed by the trainee and confirmed by the senior rheumatologist and our results are similar to those of other real-life studies, we believe the examiners variation was not a major bias for the results.

Conclusions

In the present RA cohort, FM did not significantly impact overall DMARD escalation, and FM-induced DAS28 and HAQ overestimations diminished towards the end of the study. However, RA patients with FM used more leflunomide and prednisone, and RA mistreatment seems to be more frequent in FM patients. Certainly, RA patients with FM will benefit from a personalized T2T strategy, including objective synovitis biomarkers, such as ultrasound, parallel to a permanent FM treatment optimization. Personalized medicine in RA is a proficuous research field and more studies on the impact of FM on RA treatment would probably help improve decision-making process in benefit of patients and the society.

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Conflicts of interest

The authors declare no conflicts of interest.

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