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Sarar cohort: disease activity, functional capacity, and radiological damage in rheumatoid arthritis patients undergoing total hip and knee arthroplasty

Bernardo Matos da Cunha[a,*], *Sandro Barbosa de Oliveira*[a], *Leopoldo Luiz dos Santos-Neto*[b]

[a] *Hospital SARAH, Brasília, DF, Brazil*
[b] *Clínica Médica, Universidade de Brasília, Brasília, DF, Brazil*

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ABSTRACT

Objectives: The *Sarar* cohort consists of patients with rheumatoid arthritis and juvenile idiopathic arthritis who underwent hip or knee arthroplasties at hospital SARAH-Brasília. The objective of this study was to evaluate clinical and laboratory factors associated with disease activity, functional capacity and radiological damage in rheumatoid arthritis patients, participants in this cohort.
Methods: Cross-sectional study, with data collection achieved from medical records review.
Results: Thirty-two patients were included, with a mean time of disease onset of 240 months. Nineteen patients underwent total knee and 17 total hip arthroplasty. There was a positive correlation between maximum dose of methotrexate and Clinical Disease Activity Index ($R = -0.46$, $p = 0.011$), and a negative one with Simplified Erosion and Narrowing Score ($R = -0.58$, $p = 0.004$). Simplified Erosion and Narrowing Score values were higher in patients with rheumatoid factor ($p = 0.005$) and anti-cyclic citrullinated peptide antibody 3 positivity ($p = 0.044$), in those with higher rheumatoid factor ($p = 0.037$) and anti-cyclic citrullinated peptide antibody 3 ($p = 0.025$) titers, and lower in patients with family history of rheumatoid factor ($p = 0.009$). Health Assessment Questionnaire values were higher in older patients ($p = 0.031$). In multiple linear regression, only "maximum dose of methotrexate" and "family history" remained with significant association with Simplified Erosion and Narrowing Score ($r^2 = 0.73$, $p < 0.001$ for both variables). In the model evaluating "Clinical Disease Activity Index" only "maximum dose of methotrexate" remained significantly associated ($r^2 = 0.35$, $p = 0.016$).
Conclusion: In the *Sarar* cohort, clinical and laboratory factors were related to disease activity, functional capacity and radiological damage, similar to studies evaluating patients with lower disease duration.

* *Corresponding author.*
E-mail: bmcunha@sarah.br (B.M. da Cunha).
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Coorte Sarar: atividade de doença, capacidade funcional e dano radiológico em pacientes com artrite reumatoide submetidos à artroplastia total de quadril e joelho

Palavras-chave:
Artrite reumatoide
Artroplastia
Dano radiológico
Capacidade funcional

RESUMO

Objetivos: A coorte Sarar é composta por pacientes portadores de artrite reumatoide (AR) e artrite idiopática juvenil (AIJ) submetidos a artroplastias de quadril e joelho no hospital SARAH-Brasília. O objetivo deste estudo foi avaliar fatores clínicos e laboratoriais associados à atividade de doença, capacidade funcional e dano radiológico em pacientes com AR, participantes dessa coorte.

Métodos: Estudo transversal, com coleta de dados em revisão de prontuário.

Resultados: 32 pacientes foram incluídos, com tempo médio de início da doença de 240 meses. Dezenove pacientes foram submetidos a ATJ e 17, a ATQ. Foi encontrada correlação positiva entre dose máxima de metotrexato (MTX) durante a evolução e *Clinical Disease Activity Index* (CDAI) (R = -0,46, p = 0,011) e negativa com *Simplified Erosion and Narrowing Score* (SENS) (R = -0,58, p = 0,004). Valores de SENS foram maiores nos pacientes com fator reumatoide (FR) (p = 0,005) e anticorpo anti-peptídeo cíclico citrulinado 3 (anti-CCP3) positivo (p = 0,044), nos com maiores títulos de FR (p = 0,037) e Anti-CCP3 (p = 0,025) e menores nos pacientes com história de familiar de AR (p = 0,009). Valores de HAQ foram maiores em pacientes mais idosos (p = 0,031). Na regressão linear múltipla, somente "dose máxima de MTX" e "história familiar" permaneceram com associação significativa com SENS ($r^2 = 0,73$, p < 0,001 para ambas as variáveis). No modelo que avaliou "CDAI", apenas "dose máxima de MTX" permaneceu com associação significativa ($r^2 = 0,35$, p = 0,016).

Conclusão: Na coorte Sarar, fatores clínicos e laboratoriais estiveram relacionados à atividade de doença, capacidade funcional e dano radiológico, semelhantemente a estudos que avaliaram pacientes com menor tempo de doença.

Introduction

Rheumatoid arthritis (RA) is a common disease in Brazil, affecting 0.2–1% of the Brazilian population.[1] Brazilian guidelines for treating RA recommend early use of at least one disease-modifying anti-rheumatic drugs (DMARDs), with or without the use of corticosteroids, since the onset of the disease.[2] The main objective is to prevent or at least slow the progression of radiographic joint damage, which can lead to deformities and functional disability, with reduced quality of life and work capacity. However, the treatment of RA is often suboptimal in our environment[3] and, therefore, many patients develop secondary osteoarthritis, requiring surgical treatment with total arthroplasties, significantly increasing health care costs.[4]

The SARAH Network is a reference center for rehabilitation in Brazil, with units in several Brazilian states, including the Federal District. In this context, the institution focuses on the treatment of patients with RA or juvenile idiopathic arthritis (JIA) at an advanced stage, with permanent sequelae of the disease by means of orthopedic surgeries and rehabilitation.

The *Sarar* cohort consists of adult patients of all age groups, patients with long-standing RA or JIA, with great functional disability and extensive radiological damage, participating in a rehabilitation program and having orthopedic treatment for sequelae of the disease in the hospital SARAH-Brasília. Its goal is to evaluate these patients' long-term progress after undergoing primary or review total hip and/or knee replacement. Patients are usually referred from public or private rheumatology clinics, for rehabilitation. The inclusion of patients in the cohort began in October 2008 and ended in January 2013. After the initial inclusion, patients were evaluated in some of their follow-up visits with the Orthopedics team.

The clinical characteristics of patients with RA who are candidates for orthopedic surgery can influence the degree of disability and instability at work,[5] inflammatory activity and radiological damage.[6] Therefore, the objective of this study is to evaluate the clinical, radiological and laboratory profile of RA patients followed by the *Sarar* cohort, and evaluate which factors are associated with disease activity, functional capacity and radiological damage.

Methods

Study design

Cross-sectional analysis of data from the *Sarar* cohort with data collection achieved from medical chart review.

Inclusion and exclusion criteria

We included all patients aged ≥18 years admitted at the Adult Orthopedics and Neurosurgery Department to undergo total hip (THA) or knee (TKA) arthroplasty at the hospital Sarah-Brasilia, who had RA with diagnosis established according to the criteria of the American College of Rheumatology.[7] As

explained above, patient inclusion occurred between October 2008 and January 2013.

RA patients have been excluded if: the indication of arthroplasty was due to avascular necrosis, other inflammatory diseases justified the articular condition better than RA, and patients who underwent previous arthroplasty during the inclusion period. Specifically in this study, we excluded patients with JIA.

Data collection

The standardized assessment was performed by means of the electronic medical record data review, supplemented by patient interview when needed, one day before the date of the proposed surgery. The following data were recorded: duration of disease; time interval between the onset of symptoms and the correct diagnosis; date of initiation of treatment with DMARDs with description of medications on prior and current use, including the dose; time of follow-up with a rheumatologist; preoperative orthopedic diagnosis; associated autoimmune conditions; history of smoking; family history of RA; presence of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody 3 (anti-CCP3), both by ELISA, when available, with the most recent date of examination in the medical record being considered.

Inflammatory activity was assessed with the Clinical Disease Activity Index (CDAI),[8] which takes the count of tender and swollen joints, together with the overall health assessment score by the patient and the physician, by visual analog scale, into account for its calculation.

Preoperative functional capacity was assessed with the Health Assessment Questionnaire-Disability Index (HAQ) translated and validated for the Portuguese language, and self-administered.[9,10]

The established joint damage was assessed with simple digital radiographs of hands and feet using the Simplified Erosion Narrowing Score (SENS),[11] which counts the number of joints in which there is the presence of joint space narrowing and/or erosions. For this assessment, we used the Efilm Workstation software version 2.1.2, which allowed the use of image magnification features. A rheumatologist examined all radiographs (BMC).

The study was approved by the Research Ethics Committee of the SARAH Network, registered at Plataforma Brasil with the number 07477412.2.0000.0022.

Statistical analysis

Descriptive analysis was performed. RF values and anti-CCP3 were divided into four categories, with the former according to the quartiles, and the latter to negative, weakly positive, moderately positive and strongly positive, according to the manufacturer's references. Spearman correlation tests were performed between continuous independent variables and the dependent variables (CDAI, HAQ and SENS). Mann–Whitney *U* test was performed for comparison of means including independent variables with two categories, and the Kruskal–Wallis *H* test for comparison of means including independent variables with more than two categories being conducted.

Subgroup analysis was performed among patients undergoing THA and TKA.

Multiple linear regression model was developed, including the independent variables with significant association, assuming a normal distribution of data.

To verify the intra-examiner variability of evaluation of radiographs, we calculated the intraclass correlation coefficient, model 3.1[12] and performed paired *t*-test including 10 patients who were randomly selected by a computer program among the study sample.

The software used was the SOFA version 1.4.0 and SPSS version 21.

Results

Thirty-two patients were included, with 28 female patients. The mean age was 59 years old (40–84). Most patients lived in the Federal District (24 individuals), but 5 patients from the state of Minas Gerais, one from the state of Paraíba, one from Tocantins and 1 from Sao Paulo were included. Patients referred by the Brazilian National Health Service (SUS) totaled 44% of cases; within patients from places other than the Federal District, only one was followed in a public health center. Seventeen patients were retired. Nineteen patients underwent TKA and 17, THA.

Five patients were not regularly followed by a rheumatologist. Forty-eight percent of patients had missed rheumatologist follow-up for a period, since the first contact with the specialist. Among the patients who had intervals without rheumatology monitoring, unaccompanied average time was 45 months (0–432).

The average time between the onset of the disease and the surgery was 240 months (47–506) and the mean time between onset of symptoms and the diagnosis of RA was 27 months (1–369). Thirteen patients were current or previous smokers and 16 patients had family history of RA in first-degree relatives.

Eighty-seven percent of the patients had active disease (39% mild activity, 23% moderate and 26% severe), with a mean CDAI of 14.7 (0.5–56.4). The average duration of morning stiffness was 25 min (0–240). The average HAQ was 1.8 (0.25–2.875).

Twenty-seven patients were taking DMARDs (Table 1), although 3 of these patients had reported having used <80% of doses. Considering the previous and current use, methotrexate (MTX) was taken by 84% of the patients during follow-up, but only 41% were on current treatment. The maximum dose prescribed by rheumatologists in the course of the disease was on average 15.1 mg (2.5–20). Five patients have never been treated with MTX, including one with 115 months of disease duration. Only two patients did not receive antimalarial drugs during follow-up. Leflunomide was taken by 66% of the patients, sulfasalazine by 31% and gold salts by 22%. Among the biological drugs (received by 31% of the patients), the most frequent were etanercept and adalimumab, with four cases each.

Table 1 – Current use of disease-modifying drugs (DMARDs).

DMARD	*n*	Dose		
		Mean	SD	min–max
Methotrexate (mg/week)	13	14.4	2.9	2.5–20
Leflunomide (mg/day)	15	20	0	20
Sulfasalazine (mg/day)	2	750	350	500–1000
Chloroquine (mg/day)	5	250	0	250
Hydroxychloroquine (mg/day)	3	333.3	115.5	200–400
Infliximab (mg/dose)	1	200	0	200
Etanercept (mg/week)	2	50	0	50
Adalimumab (mg/dose)	3	40	0	40
Rituximab (mg/dose)	2	2000	0	2000
Abatacept (mg/dose)	1	500	0	500

Complications directly related to surgery occurred in seven cases, with three being dislocations of prosthesis, a periprosthetic fracture, a surgical site infection, a graft infection and a heterotopic ossification.

Among the associated autoimmune conditions, the only one present was thyroid autoimmune disease (hypo- or hyperthyroidism) in 34% of the patients.

RF was positive in 51% of the patients, with a mean value of 371 U/ml (29–3140). The anti-CCP3 was positive in 62% of cases, being weakly positive in 3%, moderate in 9%, and strongly positive in 50%. The average SENS was 34.8 (1–75).

When the dependent variable "CDAI" was analyzed, a negative correlation was found with time of disease onset, and a positive one with the maximum dose of MTX. Moreover, a positive correlation was found between HAQ and age, and between SENS and the maximum dose of MTX (Table 2).

On comparison of means, when the dependent variables "CDAI" and "HAQ" were assessed, no significant associations were found. In the analysis of the dependent variable "SENS", a positive association was found with the presence of RF and Anti-CCP3, and a negative one with smoking and family history of RA. Patients were stratified into categories, according to the titers of RF and Anti-CCP3, with the highest titers being associated with higher SENS values (Table 3).

The multiple linear regression model included the clinical and laboratory variables with significant association with SENS and CDAI. Regarding the dependent variable "SENS", two models were constructed, one including the RF and anti-CCP3 as categorical variables (present or absent) and another one as ordinal variables. In both of them, only the variables "maximum dose of MTX" and "family history" remained with significant association ($p < 0.001$ in both variables). The final model explained approximately 73% of the variability of SENS. In the model that evaluated the independent variable "CDAI",

Table 2 – Spearman Correlation Tests among continuous independent variables, Health Assessment Questionnaire (HAQ), Clinical Disease Activity Index (CDAI) and Simplified Erosion Narrowing Score (SENS).

	R	CI	*p*
CDAI			
Age	−0.04	−0.39; 0.32	0.816
Time onset	−0.46	−0.70; −0.12	0.011
Δ time-diag	0.17	−0.20; 0.50	0.365
MTX Max Dose	0.55	0.22; 0.77	0.003
HAQ			
Age	0.39	0.04; 0.65	0.031
Time onset	0.07	−0.3; 0.42	0.704
Δ time-diag	0.08	−0.29; 0.43	0.676
MTX Max Dose	0.01	−0.37; −0.39	0.957
SENS			
Age	−0.09	−0.45; 0.29	0.653
Time onset	0.32	−0.07; 0.62	0.101
Δ time-diag	0.16	−0.23; 0.51	0.431
MTX Max Dose	−0.58	−0.80; −0.22	0.004

Δt onset-diag, time span between symptoms appearance and diagnosis; MTX, methotrexate.

Table 3 – Mann–Whitney and Kruskal–Wallis tests for comparison among groups with presence or absence of clinical and laboratory variables.

Variable	CDAI	HAQ	SENS
		p	
Positive RF	0.563	0.611	0.005
RF titer (1–4)	0.532	0.181	0.037
Anti-CCP3 +	0.351	0.301	0.044
Anti-CCP3 titer (1 × 4)	0.575	0.458	0.025
Gender	0.86	0.616	0.87
Smoking	0.936	0.054	0.08
Family history of RA	0.58	0.406	0.009
MTX	0.724	0.204	0.674
LFN	0.833	0.611	0.51
SSZ	0.151	0.719	0.811
Antimalarial	0.127	0.778	0.964
Gold Salts	0.108	0.124	0.466
Biological drug	0.057	0.33	0.98
TKA	0.776	0.109	0.502

HAQ, *Health Assessment Questionnaire*; CDAI, *Clinical Disease Activity Index*; SENS, *Simplified Erosion Narrowing Score*; RF, rheumatoid factor. RF titers were divided according to the quartiles. Anti-CCP3, anti-cyclic citrullinated peptide antibody 3. Anti-CCP3 titers were divided in negative, weakly positive, moderately positive and strongly positive. MTX, methotrexate; LFN, leflunomide; SSZ, sulfasalazine; TKA, total knee arthroplasty; RA, rheumatoid arthritis.

only "maximum MTX dose" remained significantly associated ($r^2 = 0.35$, $p = 0.016$).

There were no significant differences between patients undergoing THA and TKA, for CDAI, HAQ and SENS.

The intraclass correlation coefficient for the evaluation of 10 radiographs was 0.92 (95% CI 0.73–0.98) and the average difference among peer evaluations was 3.4 (SD 7.183). There was no significant difference ($p = 0.169$).

Discussion

Our results identified possible improvements that could be implemented in the management of patients with RA who are referred for rehabilitation and surgery. The small number of patients who were in current use of MTX, the main drug for RA treatment, is notable. This can be explained in part because they are long-standing patients, who in many cases were exposed to medication for a long time, which can increase the chance of medication discontinuation due to adverse events[13,14] mainly in the liver.[15] Furthermore, some patients might not have had a good response to the medication. On the other hand, 49% of the patients had moderate to severe inflammatory disease activity, what we consider an inappropriate situation in the perioperative setting. This cannot be justified only by the severity of the cases, since many patients had suboptimal dose of DMARDs. Joints with damage may have persistent inflammation. If drug therapy was optimized, patients with active disease could express less pain symptoms in the joint where the surgery was indicated, and surgery could be postponed. Additionally, disease activity makes patients more disabled, which can reduce compliance to rehabilitation activities.

The frequency of RF positivity and anti-CCP3 was lower than that reported in the international literature, but similar to that found in Brasilia cohort,[16] composed of early RA patients whose initial blood samples were collected before treatment. In that study, RF titers increased after one year, which may explain the mean titer of RF being much higher than in our study. These data contrast with the description by Bos et al., on which a reduction of RF levels or even negativation of test results was observed in some of the cases after initiation of adalimumab treatment,[17] and with the study by Vaz et al., in which there was significant reduction in anti-CCP titers during treatment with infliximab.[18] These findings may be related to specific characteristics of anti-TNF inhibitors.

Similarly to this study, other groups have found no correlation between the positivity or titers of RF with functional capacity and disease activity.[19,20] The association between RF positivity and radiographic progression is known, especially in patients with early disease[21,22] but how the joint damage accumulates over decades is not known. In this study, there was no independent correlation between RF and SENS, but patients of an average of 20 years of disease onset with many accumulated joint damage were evaluated. Note that no correlation was found between age and radiological damage, suggesting that damage appearance can get stable over time.

There was a positive correlation between age and functional ability, irrespective of the degree of radiological damage, suggesting that other factors are influencing HAQ, for example, the natural aging process.[23]

In our study, smoking was not independently associated to greater radiographic progression. The results contrast with those of a prospective study by Vesperini et al., who recently showed a lower risk of progression in patients with early RA,[24] but are in agreement with the results of two other studies.[25,26] Conversely, the study by Ruiz-Esquide et al. demonstrated greater radiographic progression in smokers.[27] Therefore, the association between smoking and radiographic progression is still controversial.

Regarding family history of RA, the results of this study contradict those by Rojas-Villajaga et al., which demonstrated that early RA patients with a family history developed radiographic damage more quickly, although the cumulative damage was not evaluated,[28] as was the case in our study, which evaluated patients with long-standing disease. Factors such as ethnic differences, disease duration, differences in treatment with DMARDs, and radiographic evaluation methods can be the origin of this disparity.

Patients with long-standing disease activity have a higher cumulative radiological damage,[29] which may explain the use of larger previous doses of MTX in patients with higher SENS and CDAI values, because they probably had, throughout evolution, activity of the disease that is more difficult to control.

The *Sarar* cohort, in a way, makes an interesting counterpoint to the Brasília cohort, once it comes to patients with advanced disease, from the same region of Brazil. To our knowledge, this is the first study in Brazil that assessed disease activity, functional capacity and radiological damage in patients with RA of such long-standing disease, which is interesting in a time when all eyes are focused on patients with early RA. Currently, a change in the evaluation and management of patients with RA undergoing rehabilitation treatment at SARAH-Brasilia hospital is being planned, motivated by the results of this study, so that such patients are grouped for rehabilitation at a specialized clinic.

This study has limitations. It is a cross-sectional study, the findings of which require confirmation in prospective studies; temporal data and maximum doses of DMARDs were reported by the patients who recovered it from memory, which can lead to inaccuracies (e.g., the assessment of family history), considering the long term of the disease; RF detection had great temporal variation preceding hospitalization, so in some cases they may not have represented the current immune status of patients; due to technical reasons related to the bidimensionality of the radiographs, it was not possible to assess the SENS of a patient with severe deformities, which excluded from the analysis a case with very severe radiological changes.

In summary, patients of the *Sarar* cohort treated at the hospital SARAH-Brasilia, received a late diagnosis of RA in their health centers of origin. About half of the patients had moderate to severe inflammatory activity, with non-optimized treatment according to the consensus of the Brazilian Society of Rheumatology[2] and the recommendations of the RA Treat To Target.[30] Patients with family history of RA had less radiological damage, while patients using higher maximum dose of MTX had major damage. Older patients had greater

functional disability. The maximum dose of MTX during evolution was associated with higher disease activity.

Conflicts of interest

The authors declare no conflicts of interest.

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