

High Remission Rates in a Brazilian Cohort of Initial Rheumatoid Arthritis after 15 Years of Follow-Up

Heloisa Lima Heller^{1*} , Ana Paula Gomides Reis¹, Cleandro Albuquerque², Isadora Jochims², Luciana Muniz², Talita Yokoy², Licia Mota²

¹Centro Universitário de Brasília, UniCEUB, Brasília, Brasil

²Universidade de Brasília, UnB, Brasília, Brasil

Email: *heloheller98@gmail.com

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Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic systemic rheumatic disease which is usually treated with corticosteroids and immunobiologicals. The goal of this article is to carry out an assessment of disease activity indices in a cohort of patients with rheumatoid arthritis. **Patients and Methods:** This is a prospective cohort study. Individuals from the Initial Rheumatoid Arthritis Brasília Cohort, which is an incident cohort of early RA diagnosed patients, were monitored at the Rheumatology Service of the Hospital Universitário de Brasília (HUB), University of Brasília (UnB), Brazil. A cross-sectional analysis was carried out from 2017 to 2018 to evaluate patients with 15 or more years of follow-up, through a direct interview and review of medical records. The main focus of the study is on the assessment of disease activity, based on the indices: 28-joint Disease Activity Score based on C-reactive protein (DAS 28 CPR) and based on erythrocyte sedimentation rate (DAS 28 ESR), Clinical Disease Activity Index (CDAI), and Simple Disease Activity Index (SDAI). The reference remission criteria used were the Composite Disease Activity Indices. **Results:** 107 patients were evaluated, mostly women, mean age of 55.1 years. Concerning the disease characteristics, 75.5% of the patients were positive for rheumatoid factor and 12 (11.3%) had documented erosive disease. The mean Health Assessment Questionnaire (HAQ) at the time of assessment was 0.6 (median 0.35). The indices analyzed showed: DAS28-ESR 48.6% of patients were in remission and 12.1% had low activity levels, DAS28-CRP 55.1% and 11.2%, SDAI 42% and 26.1%, CDAI 41.1% and 27.1%. These remission and low disease activity levels are higher than those generally found in the literature. **Conclusion:** This study presents a cohort of patients with RA who started treatment at an early stage of the disease and

who achieved higher rates of remission and lower disease activity than those reported in the literature.

Keywords

Rheumatoid Arthritis, Remission Induction, Therapeutics

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic rheumatic disease that affects approximately 0.5% to 1% of the population. The main symptoms are present in the peripheral synovial joints due to chronic inflammatory processes. Joint manifestations are generally symmetrical and preferably in the hands and feet. The most common manifestations are pain, edema, erythema, morning stiffness, deformities, and systemic symptoms that can affect different organs. The disease has a variable clinical course, from mild and self-limited to rapidly progressive, and is often characterized by systemic involvement. The disease limitations compromise the patient's quality of life [1] [2] [3].

RA has genetic and environmental components. The disease is probably caused by gene modifications that promote loss of tolerance to B and T lymphocytes, dendritic cells, and auto-antibodies, mainly anti-citrullinated protein antibodies, leading to inflammation, cartilaginous degradation, bone erosion, and, consequently, pain and other manifestations [3] [4].

The inflammatory process is already underway when the first symptoms appear. Therefore, the consequences of prolonged exposure to the harmful environment are less likely when the diagnosis is made quickly [4] [5].

Early diagnostic and therapeutic conducts and regular monitoring are important for a better quality of life. Early disease detection is important due to the window of greater responsiveness to the treatment. Regular monitoring improves adherence to therapy, generates patient confidence in the treatment, and aids management of the disease [6] [7] [8].

Patients who start early medical therapy have higher chances of returning to work in the long term and having a lower cost of living, in addition to less radiographic progression and higher statistics of disease remission [8] [9].

Remission, which is the main goal of treatment, is difficult to achieve even when using all the therapeutic arsenal available. The effectiveness of immunobiologics, which are the most modern medications for treatment, vary between 10% and 22% according to the American College of Rheumatology 70% improvement criteria (ACR70) response assessment, which is an assessment criterion for improving the condition by 70% [10] [11].

The goal of this article is to carry out an assessment of disease activity indices in a cohort of patients with rheumatoid arthritis who have been regularly monitored since the onset of symptoms at a university hospital in Brazil.

2. Patients and Method

This is a prospective cohort study, including individuals from the Initial Rheumatoid Arthritis Brasília Cohort [12] [13], which is an incident cohort of early RA diagnosed patients, who were monitored at the Rheumatology Service of the Hospital Universitário de Brasília (HUB), University of Brasília (UnB), Brazil.

For inclusion of patients in this cohort, RA is defined as the occurrence of joint symptoms compatible with inflammatory joint pain and edema, with or without morning stiffness or other manifestations suggestive of inflammatory joint disease, assessed by a single observer [14] [15] lasting more than 6 weeks and less than 12 months, regardless of meeting the American College of Rheumatology (ACR) criteria [16]. All selected patients met the EULAR (European Alliance of Associations for Rheumatology)/ACR 2010 criteria [17]. The patients had a medical diagnosis within 1 year or less of manifestation.

Patients received the standard therapeutic regimen of the service, including synthetic or biological Disease-Modifying Antirheumatic Drugs (DMARDs) as needed. A cross-sectional analysis was carried out from 2017 to 2018 to evaluate patients with 15 or more years of follow-up, through a direct interview and review of the medical records. A structured questionnaire was applied to each patient, obtaining information on sex, age, ethnicity, civil status, years of formal education, socioeconomic status, physical activity practice, the disease activity index (Disease Activity Score 28—DAS28) [18], functional disability questionnaire (Health Assessment Questionnaire—HAQ) [19], lifestyle habits such as smoking or drinking, and the presence of comorbidities and drug treatment. The questionnaire can be viewed in the Supplementary Appendix.

The main focus of the study is on the assessment of disease activity, based on the indices: 28-joint Disease Activity Score based on C-reactive protein (DAS 28 CPR) and based on erythrocyte sedimentation rate (DAS 28 ESR), Clinical Disease Activity Index (CDAI), and Simple Disease Activity Index (SDAI). The reference remission criteria used were the Composite Disease Activity Indices.

The consecutively selected patients in the cohort participated voluntarily in the study, after receiving clarification of the content of the research and after signing the Free and Informed Consent Form. The study was approved by the Research Ethics Committee of the University of Brasília Faculty of Medicine (CEP-FM 074/2005).

To answer the objectives of the study, basic techniques of exploratory analysis were used, such as frequency and median analysis. $P < 0.05$ and 95% confidence intervals were considered significant. The analyses were conducted using the SAS 9.4 application.

3. Results

In total, 107 patients were evaluated, 95.3% female, with a mean age of 55.2 years (SD 13.13%). Regarding occupation, 39 patients worked with or without a formal contract (36.4%), 36 individuals declared themselves housewives (33.6%), 18

(16.8%) were retired, 9 (8.4%) received sickness assistance or were dismissed by the National Social Security Institute, and 5 (4.6%) were unemployed. A total of 13 (12.14%) individuals changed their occupation due to RA and only 3 patients (2.8%) had health insurance. Furthermore, 29% of the patients did not present any comorbidity, 31.7% one comorbidity, 20.5% two, 10.2% three, 6.5% four, and 1.8% five or more comorbidities. Other socio-demographic characteristics, comorbidity specifications, the prevalence of alcoholism and smoking, and the frequency of physical activity are described in **Table 1**.

Concerning the disease characteristics, 75.5% of the patients were positive for rheumatoid factor and 12 (11.3%) had documented erosive disease. The mean HAQ at the time of assessment was 0.6 (median 0.35). The data were analyzed and classified as low, moderate, or high activity by the Composite Disease Activity Indices. The disease was classified as high activity index by the DAS28 CRP in only 3.1% of the patients, and most of the patients were in remission or had low activity of the disease. The DAS 28 (CRP and ESR), SDAI, CDAI data can be seen in **Table 2**.

Regarding treatment, 61.6% of patients (66 individuals) were using corticosteroids, 150 patients were using synthetic disease-modifying drugs—DMARDs (monotherapy or combinations), and 20 were using biological DMARDs; some patients were using more than one or two medications. Three patients (2.8%) were not using any medication for RA treatment at the time of data collection. The frequency of use and dose of synthetic and biological DMARDs more commonly used in this cohort are summarized in **Table 3** with the data from the most used treatment schemes.

4. Discussion

The socio-demographic characteristics found in this study are similar to those demonstrated in other groups of RA patients. The female sex has a significantly higher prevalence [20]-[25]. The average age of the patients presented a variation between 45 - 57 years [20]-[25].

The ethnic variety is related to the territory which underwent a long process of miscegenation. In Latin America the phenotypes are very diverse [26]. The racial numbers found in this research corroborate with the Brazilian ethnic data, in which 47.7% of Brazilians consider themselves white and 43.4% brown [27].

With respect to education, as well as the NEW INDICES study [22] [23], in the current cohort most patients had low education, reflecting the average citizen treated in the Brazilian public system (SUS Sistema Único de Saúde) [28]. Regarding comorbidities, in a cohort conducted in Italy [22] [23], 27% of patients did not report any comorbidities, 25.5% only one comorbidity, 23.5% two, 10.7% three, 5.6% four, and 7.7% reported 5 or more comorbidities, which is similar to the data found in the current study.

Concerning the disease activity levels, a study based on the QUEST-RA database [25] analysed 19 European countries and seven non-European countries (United States of America, Canada, United Arab Emirates, Russia, Turkey,

Table 1. Socio-demographic and habit data.

Socio-demographic				Comorbidities			
Variables	Category	N	%		N	%	
Sex	Female	102	95.3	Cerebrovascular disease	1	0.9	
	Male	5	4.7	Arterial Hypertension	70	65.4	
Ethnicity	White	46	43	Myocardial infarction	5	4.7	
	Brown	51	47.6	Other heart diseases	4	3.7	
	Aboriginal	27	1.9	Asthma	2	1.9	
Civil Status	Single	37	34.6	Other chronic lung diseases	2	1.9	
	Married	45	42	Moderate or severe liver diseases	1	0.9	
	Divorced	10	9.35	Diabetes without damage to vital organs	1	0.9	
	Widow	10	9.35	Diabetes with damage to vital organs	1	0.9	
Education	Cohabitation	5	4.7	Dyslipidemia	32	30	
	Illiterate	7	6.5	Osteoporosis by bone densitometry	15	14	
	Incomplete Primary Education	40	37.4	Psychiatric illness	6	5.6	
	Complete Primary Education	12	11.2	Metastases without tumor	3	2.8	
	Incomplete High School	5	4.7	Connective tissue disease	2	1.9	
	Complete high school	24	22.5	Fibromyalgia	31	29	
	Incomplete higher education	6	5.6	Chronic low back pain	3	2.8	
	Complete higher education	7	6.5	Osteoarthritis	10	9.3	
Socioeconomic status	Postgraduate	6	5.6	Cataract	3	2.8	
	B1	3	2.8	Thyroid disease	11	10.3	
	B2	27	25.3				
	C1	30	28				
	C2	27	25.3				
	D-E	19	17.7				
Habit variables				Physical Activity			
Variables	Category	N	%		N	%	
Alcohol use	User	5	4.7	Does not exercise regularly	60	56.1	
	Ex-user	2	1.9	1 - 2 times/month	6	5.6	
	Non-user	10	93.5	1 - 2 times/week	18	16.8	
Tobacco use	User	7	6.5	3 or more times a week	23	21.5	
	Ex-user	19	17.8				
	Non-user	81	75.7				

Table 2. Composite disease activity indices.

Composite Disease Activity Indices (n/%)	Remission	Low Activity	Moderate Activity	High Activity	Average	Median	Total
DAS28 ESR	52 (48.6)	13 (12.1)	31 (29)	11 (10.3)	2.95	2.69	107
DAS28 CRP	59 (55.1)	12 (11.2)	31 (29)	4 (3.1)	2.8	2.34	107
SDAI	45 (42)	28 (26.1)	25 (23.4)	9 (8.4)	9.41	4.79	107
CDAI	44 (41.1)	29 (27.1)	19 (17.8)	15 (14)	8.64	4.39	107

DAS28 ESR (28-joint Disease Activity Score—Erythrocyte Sedimentation Rate); DAS 28—CPR (28-joint Disease Activity Score—C-Reactive Protein); SDAI (Simple Disease Activity Index); CDAI (Clinical Disease Activity Index).

Table 3. Pharmacological therapy.

Drug	Use Frequency (n/%)	Dosage Arithmetic (mean/median mg)	Usage Time (years) Mean/median/maximum
Synthetic DMARDs 150			
Methotrexate	75 (70)	18.13/20	10/8/37
Leflunomide	49 (45.8)	20/20	6.7/5/18
Hydroxychloroquine	9 (8.4)	400/400	6/4.5/15
Chloroquine	8 (7.47)	234.37/250	16.5/11.5/33
Sulfasalazine	8 (7.47)	1500/100	4.5/3/13
Cyclosporine	1 (0.9)	100/100	10/10/10
Biologic DMARDs 20			
Adalimumab	4 (3.73)	40/40	5.5/6/7
Infliximab	4 (3.73)	3.62/3.75	6.5/6/10
Tocilizumab	3 (2.8)	8/8	3.6/4/5
Abatacept	2 (1.86)	750/750	3/3/3
Golimumab	2 (1.86)	50/50	3/3/3
Certolizumab	2 (1.86)	400/400	4/4/4
Etanercept	1 (0.9)	50/50	4/4/4
Tofacitinib	2 (1.86)	5/5	3/3/3
Main Treatment Schemes			
Anti-Rheumatic drugs		Frequency of use n (%)	
Methotrexate monotherapy		29 (27.1)	
Leflunomide monotherapy		11 (10.28)	
Methotrexate + leflunomide		23 (21.49)	
Leflunomide + infliximab		3 (2.8)	
Methotrexate + hydroxychloroquine		3 (2.8)	
Methotrexate + cloroquine		3 (2.8)	
Methotrexate + leflunomide + chloroquine		3 (2.8)	
Hydroxychloroquine monotherapy		3 (2.8)	
Methotrexate + adalimumab		3 (2.8)	
Methotrexate + sulfasalazine		1 (0.9)	

DMARDs (Disease Modifying Anti-Rheumatic Drugs).

Brazil, and Argentina). In that study the DAS28 varied from 3.1 to 6.0 (the QUEST-RA Brazil index was 4.2), which is a higher mean than found in the current cohort (DAS28 CRP-2.8 and DAS28 ESR-2.95). With respect to the HAQ, all the countries had a median higher than 0.63, except Greece with 0.25. This cohort found a 0.35 median, lower than all the countries, except Greece.

The remission and low disease activity levels of this cohort are higher than those generally found in the literature: DAS28-ESR 48.6% of patients were in remission, DAS28-CRP 55.1%, SDAI 42%, CDAI 41.1%.

GLADAR [20] [21] showed that disease remission was achieved in 3.6% of the patients, low disease activity in 2.8%, moderate activity in 21.3%, and high activity in 72.3%. After 1 year of follow-up, 19.3% of patients had achieved remission (measured by DAS28-ESR) and 32.5% presented low disease activity or remission. In the second year of monitoring, the results were 24.3% and 38.9%, respectively.

The first recording of the ERAN [24] showed that, according to DAS28 score, 9% of patients were in remission, 9% had low disease activity, 36% medium, and 46% high. After a year of analysis, 25% were in remission, 14% low, 40% medium, and 21% high. In addition, a few patients had a two or a three-year follow-up. Those with a two-year follow-up, showed rates of 7% of disease remission, 10% low remission, 37% moderate, 46% high at the beginning of the study, and after two years 28% remission, 8% low, 45% moderate, and 19% high.

The first evaluation of the NEW INDICES cohort [22] [23] presented a DAS28-ESR arithmetic average of 6.02, evolving to 3.96 over 6 months. This evolution was also observed in the DAS28-CRP, from 4.38 to 2.79, SDAI from 38.19 to 16.81, and CDAI from 33.12 to 14.59.

The rates of remission found in the current cohort are significantly higher than the other studies analyzed. In contrast to GLADAR [20] [21] who showed 19.3% remission using the DAS28-ESR in the first year and 24.3% in the second, the current cohort has a 48.6% remission rate. In the ERAN study [24], the HAQ found was 1.0, compared to 0.6 in the current cohort, and even patients followed for a longer period (3 years) showed only 33% in remission.

Although in the NEW INDICES cohort [23], the DAS28-ESR average was 3.96 after 6 months follow up, the current cohort presented an average of 2.95. The DAS28-CRP presented a similar arithmetic mean between these studies, 2.79 and 2.80.

In the NEW INDICES cohort [22] [23] the SDAI and CDAI presented almost double the value of the data found in the current cohort. The average SDAI analyzed in Italy [22] [23] was 16.81 in contrast to the current study that presented 9.41, and the CDAI 14.59, compared to 8.64, respectively. The current cohort of patients had the highest disease remission rates and the lowest disease activity markers. GLADAR [20] [21] does not report the time of disease activity and the time period since the diagnosis of each individual. ERAN [24] analyzed newly diagnosed patients (in the previous 13 months) and the NEW INDICES [22]

[23] patients had a disease duration between 6.2 and 6.6 years.

The main limitation of this work refers to the type of study carried out. Since it is a cross-sectional analysis, it was not possible to carry out causality assessments between drugs and outcomes. In addition, the sample of patients analyzed was relatively small. Even so, the study brought an important conclusion that can serve as a basis for future research.

5. Conclusions

This study included a public service real-life scenario cohort setting in a developing country, whose population has low socioeconomic levels, and financial and structural limitations.

The cohort of patients with rheumatoid arthritis who started treatment at an early stage of the disease achieved higher rates of remission and lower disease activity than those reported in the literature.

Therefore, even in a real-life scenario with limitations, it is possible to obtain high rates of remission. Patient success can be justified by early diagnosis, targeted treatment, and continuous long-term monitoring of patients. A prompt approach to patients with symptoms suggestive of RA should be continually encouraged.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supplementary Appendix — Structured Questionnaire Variables

Variables	
Anamnesis and medical record review	Evaluation of inclusion and exclusion criteria
	Demographic data
	Socioeconomic data
	Personal data (age, sex, ethnicity, others)
	Habits
	Illness duration
	Time from symptoms onset to diagnosis
	Comorbidities
	Extra-articular manifestations
	Treatment
Physical examination	Blood Pressure
	Heart rate
	Body Mass Index
	Joint count
Laboratory	Erythrocyte sedimentation rate
	C-reactive protein (mg/dL)
	Rheumatoid Factor
X-Ray	Hands and feet bone erosions
Physician	Assessment of disease activity by the rheumatologist
Disease activity indices	DAS28 ESR
	DAS28 CPR
	CDAI
	SDAI
	HAQ