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The REAL study: a nationwide prospective study of rheumatoid arthritis in Brazil

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Abstract

Background: There are few data on the epidemiology, clinical manifestations and management of RA in Brazil, even with the recognition of the high direct, indirect and societal costs of this disease. Herein, we report the formation of the REAL - Rheumatoid Arthritis in Real Life, the first nationally representative multicenter prospective observational study in Brazil.

Methods: The REAL study was designed to include a total of 1300 evaluable patients from 13 tertiary care public health centers specialized in RA management and representative of 5 regions of Brazil. Each center was expected to enroll ~ 100 consecutively seen patients and follow them prospectively in a systematic protocol-driven fashion with scheduled visits at baseline, 6 and 12 months. Core clinical, laboratory and patient-reported outcomes measures were required to be collected at each visit.

Results: A total of 1115 patients (89.4% female, mean age of 56.7 years and median disease duration of 12.7 years) were enrolled from 11 participating centers. Almost 80% of patients were of middle-low or low socioeconomic classes. The median educational time was 8 years, with 3.23% being below literacy level. The interval between symptoms and diagnosis varied from 1 to 457 months (median 12 months). Almost half of the patients were on glucocorticoids, 96.5% on DMARDs, with 35.7% on biologics. Median HAQ-DI was 0.875, ranging from 0 to 3. Median DAS28-ESR was 3.5, with 58.7% of patients presenting moderate or high disease activity.

Conclusions: The first large cohort of Brazilian patients with RA in a real-life setting shows several striking differences from previously published cohorts from other countries. The long delay for diagnosis and start of DMARDs may partly explain the high frequency of erosive disease. An elevated percentage of patients on moderate or high disease activity was seen, despite of the high frequency of corticosteroid and biologics utilization. Data from this cohort may enable public health managers of developing countries better allocate the limited resources available for the care of RA patients.

Keywords: Rheumatoid arthritis, Brazilian cohort, Observational study

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Background

Rheumatoid arthritis (RA) is a systemic, chronic and progressive disease, characterized by synovial inflammation of peripheral joints. Inadequate treatment often results in reduced health-related quality of life and excess mortality [1]. The current concept of RA management relies on early diagnosis, immediate initiation of a disease-modifying antirheumatic drug (DMARD) and effective suppression of inflammation [2]. Advances in diagnostic tools, the availability of new therapeutic options, mainly the biologic agents, and the adoption of a treat-to-target strategy have been of utmost importance for improving patient outcomes [3]. Despite all this progress, in many areas of the world, the diagnosis of RA is delayed and patients remain undertreated, resulting in great negative humanistic and socioeconomic impact [4, 5].

Brazil is the largest country in Latin America, with a multiethnic population of around 200 million inhabitants [6]. There are few data on the epidemiology and management of RA in Brazil, even with the recognition of the high direct, indirect and societal costs of this disease [7]. A better understanding of the profile of RA patients seen in public health care centers in Brazil can underpin public health policy, enabling a rational allocation of resources and the setting of priorities in this sector.

The REAL – Rheumatoid Arthritis in Real Life – is a multicenter prospective observational cohort study, with twelve-month follow-up period. The aims of this study were to describe the demographic, clinical and therapeutic features of Brazilian patients with RA, and to evaluate adherence to treatment, safety of pharmacologic treatment, and impact on quality of life, physical function and work capacity of these patients. In this first report of REAL study, we describe the methodology and the baseline characteristics of this cohort.

Methods

Setting

Thirteen tertiary care public healthcare centers (Appendix 1) specialized in RA management were selected to represent the five geographic regions in Brazil. Eventually, 11 centers from 4 regions enrolled in the program. The recruitment period started on August 12th, 2015 and ended on April 15th, 2016. Patients were followed for ~ 12 months, with systematic data collection at the initial visit (baseline), at the intermediate visit (6 months ±1 month) and at the final visit (12 months ±1 month), with additional descriptive report of any other unscheduled visit.

Participants

The inclusion criteria were 1) fulfillment of the 1987 American Rheumatism Association (ARA) or the 2010 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis [8, 9]; 2) age 18 years or older; and 3) documented medical record data of at least 6 months of follow up in their healthcare center prior to study enrollment.

Each center was expected to enroll ~ 100 patients consecutively. Since all centers were tertiary-care academic rheumatology practices, they were requested to limit the enrollment of biologic-treated patients to roughly the proportion of these patients being treated in their center.

Variables, data sources and data collection

Table 1 shows the study visit protocol, with all the items systematically evaluated and respective time of assessment. Most data were collected during the medical appointments, with previous medical records used as secondary sources. All data were collected on an electronic medical chart and gathered in a centralized dataset.

Initial visit

At the initial visit the study physician formally assessed the RA classification criteria fulfillment and collected demographic and contact data, socioeconomic profile, family history of RA, other autoimmune diseases or associated conditions, personal history of comorbidities and lifestyle habits (smoking, alcohol consumption and physical activity). For the socioeconomic classification we used the Brazilian Economic Classification Criterion (BECC), a score system updated in 2015 that includes variables such as the number of household electrical appliances, level of education of the householder and access to public services [10]. The score range is stratified from A to D-E, with each stratum corresponding to an estimated household income (Table 2).

The study physician also assessed the following RA aspects: disease duration, time between symptoms onset and diagnosis, time to first DMARD prescription, health facility and physician specialty at first contact with healthcare due to RA symptoms, presence of extra-articular manifestations, positive rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), and presence of bone erosions on radiographic study on both hands and feet. Erosive disease was defined when an erosion (defined as a cortical break) was seen in at least three separate joints at any of the following sites: the proximal interphalangeal, the metacarpophalangeal, the wrist (counted as one joint) and the metatarsophalangeal joints. In addition, prior pharmacologic treatments for RA were described (with respective reasons for discontinuation), history of orthopedic surgery and history of intra-articular or periarticular steroid injections.

Table 1 Variables assessed in study visits

Variables		Initial visit	Intermediate visit (6 ± 1 months)	Final visit (12 ± 1 months)
Study entry	Invitation	x		
	Informed consent	x		
Medical history with chart review	Evaluation of inclusion and exclusion criteria	x		
	Demographic data	x		
	Socioeconomic data	x		
	Disease duration	x		
	Time from symptoms onset to diagnosis	x		
	Time from symptoms onset to the 1st DMARD	x		
	Local and medical specialty of the physician on the 1st appointment related with the onset of symptoms	x		
	Previous medications/ injections	x		
	History of joint surgeries	x		x
	Comorbidities	x		x
	Extra-articular manifestations	x		x
	Alcohol consumption	x		x
	Smoking	x		x
	Physical exercise frequency	x		x
	Employment situation	x	x	x
	Medications in use/injections	x	x	x
Physical Exam	Blood pressure	x	x	x
	Heart rate	x	x	x
	Body mass index	x	x	x
	Joint count	x	x	x
Patient reported outcomes	Functional capacity (HAQ-DI)	x	x	x
	Pain (VAS)	x	x	x
	General health (VAS)	x	x	x
	Disease activity within in the previous 6 months VAS	x	x	x
	Current disease activity VAS	x	x	x
	Fatigue (VAS)	x	x	x
	Morning stiffness (VAS)	x	x	x
	Quality of life (SF-12 / SF-6D)	x	x	x
	DMARD use and adherence	x	x	x
	Articular index assessment	x	x	x
Laboratory	Erythrocyte sedimentation rate (mm)	x	x	x
	C-reactive protein (mg/dL)	x	x	x
	Rheumatoid factor	x		
	Anti-citrullinated protein antibody	x		
X-ray	Bone erosions of hands and feet	x		
Physician assessment	Assessment of disease activity by a rheumatologist	x	x	x
Disease activity index	DAS28-ESR	x	x	x
	DAS28-CRP	x	x	x
	CDAI	x	x	x
	SDAI	x	x	x

Table 1 Variables assessed in study visits *(Continued)*

Variables	Initial visit	Intermediate visit (6 ± 1 months)	Final visit (12 ± 1 months)
RADAI	x	x	x

DMARD disease-modifying antirheumatic drug, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *VAS* visual analogue scale, *SF-12* 12-Item Short-Form Health Survey, *SF-6D* Short-Form 6 dimensions, *DAS28* Disease Activity Score 28-joint count, *CDAI* Clinical Disease Activity Index, *SDAI* Simplified Disease Activity Index, *RADAI* Rheumatoid Arthritis Disease Activity Index

Clinical evaluation included vital signs, anthropometric measures, tender and swollen joint counts, and physician score on the visual analogue scale (VAS) of disease activity. Patient reported outcomes included pain (VAS), global health (VAS), current and previous 6 months disease activity (VAS), fatigue (VAS), morning stiffness (VAS) and articular index, in which the patient evaluates the presence of pain and respective intensity in 16 joints. All laboratory tests, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were recorded. Compliance to prescribed medications as well as scheduled medical appointments and laboratory tests were also recorded.

The disease activity score-28 joints (DAS28), clinical disease activity index (CDAI), simplified disease activity index (SDAI) and the rheumatoid arthritis disease activity index (RADAI) were also calculated for each appointment [11–13].

The translated and validated versions of the Health Assessment Questionnaire-Disability Index (HAQ-DI), Short Form-12 (SF-12) and SF-6D evaluated, respectively, physical function, functional capacity and wellbeing, and health status from the patient's perspective [14–16].

In this report, we summarize important demographic and clinical data at the baseline visit of all enrolled patients.

Intermediate and final visits

At the intermediate and the final visits, some variables from the medical history, such as change in the marital and employment status, onset of new extra-articular manifestations or comorbidities and medical intercurrences were reassessed. All the items within the physical exam domain, the patient reported outcomes, the lab tests ESR and CRP along with the disease activity indexes, were evaluated at the three scheduled visits (Table 1). Additionally, at the final visit, physicians were requested to describe their therapeutic plan.

Table 2 Brazilian Economic Classification Criterion (BECC): relation between socioeconomic strata and estimated household income

Socioeconomic Strata	Household income (US dollar[a])
A	5921.00
B1	2623.00
B2	1357.00
C1	766.81
C2	460.65
D-E	217.71

[a]Conversion of Brazilian reais into US dollars made in accordance with the exchange rate of April 16, 2016- US$1,00: R$ 3,5276

Ethical aspects

This study was approved by the National Commission of Ethics in Research (CONEP - Comissão Nacional de Ética em Pesquisa) – Ministry of Health. The coordinating center was the Rio de Janeiro State University, and the approval number was 45781015.8.1001.5259. Each of the centers also obtained approval from the respective Institutional Review Boards. All patients signed the informed consent form.

Results

A total of 1115 patients were enrolled in the study. The general demographic and clinical data of the population at the time of the initial evaluation are presented in Tables 3 and 4. Approximately 90% were female, with a mean age of 56.7 years and median disease duration of 12.7 years. The majority of subjects were white, with minorities from Asian and Brazilian-Indian origins making up 1% of the sample. Almost 80% of patients were classified as pertaining to middle-low or low socioeconomic classes. Median BMI was 27 kg/m^2, with 64% of the patients classified as overweight or obese. The median educational time was 8 years, with 3.23% being below literacy level. About 40% were either current or former smokers.

The interval between symptoms and diagnosis varied from 1 to 457 months (median 12 months). The gap between symptoms onset and first DMARD initiation was wider, ranging from 1 to 624 months, but the same median value of 12 months.

The seropositivity rate was similar between RF (78%) and ACPA (77%), but it is important to highlight that the latter was assessed in less than half of the patients.

Interestingly, similar numbers of patients fulfilled the ARA 1987 and the 2010 ACR-EULAR classification criteria for RA, with 80.8% of subjects meeting both criteria. All patients met at least one criteria.

Table 3 Baseline demographic data of patients enrolled in the REAL study

Demographic data	Absolute value or %	N
Age, years, median (range)	56.7 (22.1–88.8)	1115
Female gender, %	89.4	1115
Ethnicity/race/color, %		1115
White	56.8	
Pardo[a]	31.3	
Black	10.9	
Others	1.0	
Smoking, %		1115
Smoker	10.9	
Former smoker	28.6	
Never smoked	60.5	
BMI categories, %		1046
Low weight	5.0	
Normal	31.5	
Overweight	35.3	
Obesity	28.2	
Total formal education time, years, median (range)	8 (0–20)	1075
Brazilian Economic Classification Criterion: Socioeconomic Strata: Gross family income in the month in US dollar[b], %		1101
A (5,921.00)	1.4	
B1 (2623.00)	3.5	
B2 (1357.00)	18.4	
C1 (766.81)	27.4	
C2 (460.65)	31.3	
D-E (217.71)	18.0	

[a]Mixed white and black ethnicities. *BMI* Body mass index. [b]Conversion of Brazilian reais into US dollars made in accordance with the exchange rate of April 16, 2016 - US$1,00: R$ 3,5276

Almost half of the patients were on glucocorticoids, 96.5% on DMARDs, with 35.7% on biologics. Of those on biologics (n = 398), 15.6% were on monotherapy.

Median HAQ-DI was 0.875, ranging from 0 to 3. Median DAS28-ESR was 3.5, with 58.7% of patients presenting moderate or high disease activity. When assessed by CDAI, the median score represented low disease activity (CDAI = 9), with 46.7% of subjects classified as presenting moderate to high disease activity.

Discussion

We describe the formation of the first large cohort of Brazilian patients with RA in a real-life setting, with consecutive enrollment of subjects and systematic data collection. The demographic, clinical, serological and radiographic characteristics of the patients being followed have several similar but some divergent characteristics from previously published North American, European and Latin American cohorts [17–21]. Particularly notable are the long delay for diagnosis, the high frequency of corticosteroid use and of erosive disease, as well as, the elevated percentage of patients on moderate or high disease activity. The high frequency of biologic DMARD use, considering the economic limitations in Brazil, is also remarkable. The fact that most patients were either RF or ACPA positive and had a delay in the initiation of DMARD may explain the observed high frequency (almost 60%) of moderate or high disease activity and erosive disease. The ethnic and socioeconomic class distribution reflects the Brazilian population in general, and is considerably different from other international cohorts [17–22]. It is important to note that the socioeconomic class distribution likely reflects the patients seen at the participating centers, which provide free health care within the Brazilian Public Health System -Sistema Único de Saúde (SUS). In Brazil, three quarters of the population is served by this public and free system, with the others using various private and paid health plans [23] and the latter were likely not represented to a significant degree in this study. About 11% of REAL patients were currently smokers, a number lower than

Table 4 Baseline clinical data of patients enrolled in the REAL study

Clinical Data	Absolute value or %	n
Disease duration, years, median (range)	12.7 (0.7–56.9)	1114
Time from symptoms to diagnosis, months, median (range)	12 (1–457)	1078
Time from symptoms to 1st DMARD, months, median (range)	12 (1–624)	994
Patients with ≥1 extra-articular manifestation, %	23.3	1115
Positive rheumatoid factor, %	78.2	1105
Positive anti-citrullinated peptide antibody, %	77.2	477
Erosive disease, %	54.9	1095
Patients fulfilling classification criteria, %:		
ARA 1987	90.0	1115
ACR/EULAR 2010	90.9	1115
Both	80.8	1115
Drugs in use, %:		
Glucocorticoids	47.4	1115
Nonsteroidal anti-inflammatory drugs	9.1	1115
Synthetic DMARD	90.9	1115
Methotrexate	66.5	1115
Biologic DMARD	35.7	1115
Biologic DMARD in monotherapy	5,6	1115
ESR, median (range)	21 (1–140)	923
CRP median (range)	0.7 (0–76.1)	944
Pain (VAS 0–100), median (range)	40 (0–100)	1115
Fatigue (VAS 0–100), median (range)	40 (0–100)	1115
Global health assessment (VAS 0–100), median (range)	38 (0–100)	1115
DAS28-ESR, median (range)	3.5 (0.3–8.2)	923
Remission	26.2	
Low disease activity	15.1	
Moderate disease activity	41.8	
High disease activity	16.9	
CDAI, median (range)	9 (0–70)	1113
Remission	20.1	
Low disease activity	33.2	
Moderate disease activity	27.5	
High disease activity	19.2	
HAQ-DI, median (range)	0.875 (0–3)	1111
SF-12 physical, median (range)	36.1 (17.5–55.9)	1079
SF-12 mental, median (range)	47.1 (14.3–72.0)	1079

ARA American Rheumatism Association, *ACR* American College of Rheumatology, *EULAR* European League Against Rheumatism, *DMARD* disease-modifying antirheumatic drug, *VAS* visual analogue scale, *ESR* erythrocyte sedimentation rate (mm/first hour), *CRP* C-reactive protein (mg/dL), *DAS28* Disease Activity Score 28-joint count, *CDAI*: Clinical Disease Activity Index, *HAQ* Health Assessment Questionnaire-Disability Index, *SF-12* 12-Item Short-Form Health Survey

that published in previous RA studies from other parts of the world (25–33%), but consistent with the relatively low rates of smoking in the Brazilian population (females: 8.2% and males: 12.6%) [24–27]. Subsequent publications will explore the relationship of these differences with clinical and outcome variables.

We recognize several limitations of the REAL study. All the sites enrolled in the study are "reference centers", and thus are unlikely to represent the broader management of RA across the country. It is probable that these patients present more severe disease, with a less favorable prognosis. REAL study was designed to be

representative of the entire Brazilian population, but one center in the Northeast (representing 27.9% of population) could not participate because of delays in the Ethics Committee approval. Also, our cohort does not include patients from among the 25% of Brazilian population receiving their healthcare outside of the public health system. On the other hand, the REAL study data reflects perhaps a more optimal standard of care possibly resulting in better outcomes in comparison with those treated in less prepared facilities. Further publications will study multiple management strategies and their effects on patient outcomes.

Conclusions

The first large cohort of Brazilian patients with RA in a real-life setting shows several striking differences from previously published cohorts from other countries. The long delay for diagnosis and start of DMARDs may partly explain the high frequency erosive disease. An elevated percentage of patients on moderate or high disease activity was seen, despite of the high frequency of corticosteroid and biologics utilization. Data from this cohort may enable public health managers of developing countries better allocate the limited resources available for the care of RA patients.

Appendix 1

Table 5 Thirteen tertiary care public healthcare centers specialized in RA management representing the five geographic regions in Brazil

Centers	Number of patients included	Geographic region
Universidade Estadual de Campinas	111	Southeast
Universidade de Brasília	107	Midwest
Universidade Federal do Pará	102	North
Universidade do Estado do Rio de Janeiro	100	Southeast
Universidade Federal do Paraná	100	South
Universidade Federal do Rio Grande do Sul	102	South
Universidade Federal de Santa Catarina	100	South
Universidade de São Paulo - Ribeirão Preto	99	Southeast
Universidade Federal de Minas Gerais	99	Southeast
Hospital do Servidor Público Estadual de São Paulo	99	Southeast
Universidade de São Paulo – São Paulo	98	Southeast
Universidade Federal do Ceará	0	Northeast
Universidade Federal de São Paulo	0	Southeast
TOTAL	1115	

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Authors' contributions
All authors made substantial contributions to the acquisition of data, have been involved in drafting the manuscript or revising it critically for important intellectual content, gave final approval of the version to be published and have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. In addition, GRCP, ABVS and LMHM also made substantial contributions to conception and design of the study.

Ethics approval and consent to participate
This study was approved by the National Commission of Ethics in Research (CONEP - Comissão Nacional de Ética em Pesquisa) – Ministry of Health. The coordinating center was the University of the State of Rio de Janeiro, and the approval number was 45781015.8.1001.5259. Each of the centers also obtained approval from the respective Institutional Review Boards. All patients signed the informed consent form.

Competing interests
GRCP: Has received consulting fees from AbbVie, Bristol-Myers Squibb, Eli Lilly, Glaxosmithkline, Janssen, Pfizer, Sanofi Genzyme and Roche; ABVS: Has received supporting for international medical events from AbbVie and Janssen; CPA: Has received personal fees and/or non-financial support from Pfizer, AbbVie, AstraZeneca, Janssen, Bristol-Myers Squibb, Roche, Novartis and UCB, outside the submitted work; MBB: Has participated in clinical and/or experimental studies related to this work and sponsored by Roche; has delivered speeches at events related to this work and sponsored by AbbVie and Pfizer; PLJ: Has received supporting for internationals congresses from Bristol-Myers Squibb, UCB and consulting fees from Pfizer; RDNG: Has received consulting fees, speaking fees and supporting for internationals congresses from Roche, Pfizer, Bristol-Myers Squibb, UCB, Eli-Lilly, AbbVie, Abbott and EMS; SCR: Has received consulting and speaking fees from Abbvie, Janssen, Pfizer, Roche and UCB; MFBRG: Has received speaking fees and supporting for congresses from AbbVie, Bristol-Myers Squibb, Janssen, Novartis, Pfizer, Roche and UCB; KRB: Has received speaking fees and supporting for international congresses from Roche, Pfizer, Bristol-Myers Squibb, Abbvie and Janssen; MFLCS: No financial disclosures; CVB: Has participated in clinical and/or experimental studies related to this work and sponsored by AbbVie, BMS, Janssen, Pfizer and Roche; has received personal or institutional support from AbbVie, BMS, Janssen, Pfizer and Roche; has delivered speeches at events related to this work and sponsored by AbbVie, Janssen, Pfizer and Roche; IAP: Has received consulting fees, speaking fees and supporting for internationals congresses from Roche, Pfizer, UCB Pharma, Eli-Lilly, Abbvie and Janssen; ESFC: No financial disclosures; LMHM: Has received personal or institutional support from AbbVie, Janssen, Pfizer and Roche; has delivered speeches at events related to this work and sponsored by AbbVie, Janssen, Pfizer, Roche and UCB.

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