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Decreasing delays in the diagnosis and treatment of rheumatoid arthritis in Brazil: a nationwide multicenter observational study

Cleandro Pires de Albuquerque[1*], Ana Paula Monteiro Gomides Reis[2], Ana Beatriz Vargas Santos[3], Manoel Barros Bértolo[4], Paulo Louzada Júnior[5], Rina Dalva Neubarth Giorgi[6], Sebastião Cezar Radominski[7], Maria Fernanda B. Resende Guimarães[8], Karina Rossi Bonfiglioli[9], Maria de Fátima L. da Cunha Sauma[10], Ivânio Alves Pereira[11], Claiton Viegas Brenol[12], Licia Maria Henrique da Mota[1], Leopoldo Santos-Neto[1] and Geraldo R. Castelar Pinheiro[3]

Abstract

Background Management delays imply worse outcomes in rheumatoid arthritis (RA) and, therefore, should be minimized. We evaluated changes in diagnostic and treatment delays regarding RA in the last decades in Brazil.

Methods Adults fulfilling the ACR/EULAR (2010) criteria for RA were assessed. Delays in diagnosis and treatment, and the frequencies of early management initiation within thresholds (windows of opportunity) of 3, 6, and 12 months from symptoms onset were evaluated. The Mann–Kendall trend test, chi-squared tests with Cramer's V effect sizes and analysis of variance were conducted.

Results We included 1116 patients: 89.4% female, 56.8% white, mean (SD) age 57.1 (11.5) years. A downward trend was found in diagnostic (tau = − 0.677, $p < 0.001$) and treatment (tau = − 0.695, $p < 0.001$) delays from 1990 to 2015. The frequency of early management increased throughout the period, with ascending effect sizes across the 3-, 6-, and 12-month windows (V = 0.120, 0.200 and 0.261, respectively). Despite all improvements, even in recent years (2011–2015) the diagnostic and treatment delays still remained unacceptably high [median (IQR): 8 (4–12) and 11 (5–17) months, respectively], with only 17.2% of the patients treated within the shortest, 3-month window.

Conclusion The delays in diagnosis and treatment of RA decreased during the last decades in Brazil. Improvements (effect sizes) were greater at eliminating extreme delays (≥ 12 months) than in attaining really short management windows (≤ 3 months). Very early treatment was still an unrealistic goal for most patients with RA.

Keywords Rheumatoid arthritis, Therapeutics, Epidemiology, Outcome and process assessment, Health care

*Correspondence:
Cleandro Pires de Albuquerque
cleandro.albuquerque@gmail.com
Full list of author information is available at the end of the article

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Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with significant disability and an impaired quality of life, with a global prevalence of approximately 0.5% [1]. RA represents a major public health challenge [2], and the need for early treatment aiming at better long-term outcomes is currently a well-accepted concept [3–8]. International efforts have aimed to increase the proportion of patients with RA attaining early treatment [9–12]. These initiatives were well developed in Europe and in some other wealthy nations (from other regions), leading to the establishment of "early arthritis clinics" designed to reduce delays regarding RA management [13–16].

However, this scenario is less clear in the developing countries, where data tend to be scarce, and the health care resources are more limited. Regional data gaps limit the understanding of early RA management status from a global perspective, thus hindering comparisons between regions and countries. Moreover, all efforts and initiatives to reduce RA management delays should be assessed regularly to allow for adjustments whenever required. Brazil is one of the largest countries in Latin America, a region where robust data on the status of early RA management is lacking [17].

Accruing evidence supports the concept of a window of opportunity regarding RA management: an early and limited period in the beginning of the disease when the treatment benefits are the best possible, as opposed to the concept of a smooth continuum where the sooner the treatment is started, the better the outcomes regardless of the disease duration [18–21]. The width of that window is not precisely defined, but most studies now identify an upper limit of approximately 3–6 months after symptoms onset [4, 18, 19, 22].

The existence of such a window of opportunity implies that monitoring only the changes in mean delays could be misleading when assessing the effectiveness of initiatives to achieve early RA management. The mean delay could decrease simply by gradually eliminating extreme delays, without necessarily guaranteeing that most patients will fall within some targeted window. Thus, the attainment of early RA management should rather be measured directly, through the proportion of patients initiating treatment within predefined time limits.

In this study, we evaluated changes in the mean diagnostic and treatment delay concerning RA, in the last 3 decades in Brazil. However, more importantly, we also investigated changes in the proportions of patients that initiated treatment within predefined windows of opportunity for early RA management in the same period.

Methods

This study was conducted as part of the REAL Study, a multicenter observational cohort designed to assess the current patterns of RA management under real-life conditions [23]. From August 2015 to April 2016, patients attending outpatient clinics of eleven public hospitals in different regions of Brazil were included. All participants were 18+ years old and met the ACR/EULAR (2010) or ARA (1987) classification criteria for RA. Patients underwent a structured clinical interview with physical examination, and their medical records were reviewed. Patients unable to complete the interview due to comorbidities or cognitive impairment were excluded. The data reported herein were obtained from the baseline assessment of participants in the REAL Study, thus being cross-sectional in nature. The sample size was defined a priori, aiming to achieve national representativeness, with each participating center committed to include at least 100 participants.

The participants were stratified according to the year their articular symptoms began. Comparisons were then made between these ordered strata. Trend analyses were primarily conducted on a year-to-year basis. Other assessments and comparisons were conducted considering the following time intervals (for the year of articular symptoms onset): before 1990, 1991–1995, 1996–2000, 2001–2005, 2006–2010, and 2011–2015.

Participants were inquired regarding the delays between the articular symptoms onset, RA diagnosis, and treatment initiation, i.e., the use of the first disease-modifying anti-rheumatic drug (DMARD). The delays were ascertained using medical records whenever possible. The proportions of patients receiving early RA diagnosis and treatment were assessed across the successive time intervals using 3 different cutoff points to define an early diagnosis or treatment: ≤ 3 months, ≤ 6 months, and ≤ 12 months from symptoms onset. This approach accounted for the current uncertainty as to when the window of opportunity precisely closes [19, 24]. More importantly, this triple cutoff provided insight on the consistency of the results (sensitivity analysis), while also allowing for the identification of non-uniform changes in magnitude across the different windows.

Trends in the median diagnostic and treatment delays from 1990 to 2015 (on a year-to-year basis) were assessed with the Mann–Kendall trend test. Associations between unordered categorical variables were verified using the Pearson's chi-squared test; for ordered categorical variables, the Mantel–Haenszel "linear-by-linear" chi-squared test was used instead. Effect sizes for associations based on chi-squared tests were calculated using Cramer's V. Odds ratios (OR) were also computed when 2×2 tables were applicable. Comparisons between multiple groups

regarding continuous variables were made by one-way analysis of variance (ANOVA) with Welch's correction (homogeneous variance not assumed) and Games-Howell post-hoc tests. No data imputation was conducted. The significance level was set at 0.05. Statistical analyses were performed using SPSS 25 and R 3.6.2.

The study was approved by a central ethics review board and by institutional boards in each participating center (https://plataformabrasil.saude.gov.br/, protocol number CAAE 45781015.8.1001.5259) and was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. All patients provided written informed consent prior to inclusion in the study.

Results

The current study included 1116 participants from the REAL cohort, whose detailed characteristics have already been published [23]. Patients were predominantly female (89.4%), white (56.8%), seropositive for the rheumatoid factor (78.6%), and had a high prevalence of erosive joint disease (54.9%); their mean (standard deviation [SD]) age was 57.1 (11.5) years and the mean (SD) disease duration was 174.9 (115) months.

The mean delays with 95% confidence intervals (CI) for RA diagnosis and treatment according to the year of symptoms onset from 1990 to 2015 are shown in Figs. 1 and 2, respectively. Downward trends were found in the delays for RA diagnosis ($S=-183$, $tau=-0.677$, $p<0.001$; Mann–Kendall test) and treatment ($S=-197$, $tau=-0.695$, $p<0.001$; Mann–Kendall test) between 1990 and 2015.

The year of symptoms onset (as arranged in time intervals: ≤1990, 1991–1995, 1996–2000, 2001–2005, 2006–2010, and 2011–2015) was associated to the percentages (relative frequencies) of individuals attaining early RA diagnosis, considering all defined cutoff points: ≤3 months ($\chi^2(1)=9.76$, $V=0.113$, $p=0.002$), ≤6 months ($\chi^2(1)=24.2$, $V=0.162$, $p<0.001$), and ≤12 months ($\chi^2(1)=57.61$, $V=0.237$, $p<0.001$); p-values computed from the Mantel-Haenzel linear-by-linear chi-squared test. The more recent the period of disease onset, the higher the percentage of individuals being diagnosed within each of these thresholds (Table 1).

Likewise, the year of symptoms onset (in time intervals: ≤1990, 1991–1995, 1996–2000, 2001–2005, 2006–2010, and 2011–2015) was associated with the percentages (relative frequencies) of participants receiving their first DMARD within 3 months ($\chi^2(1)=11.25$, $V=0.120$, $p=0.001$), 6 months ($\chi^2(1)=34.84$, $V=0.200$,

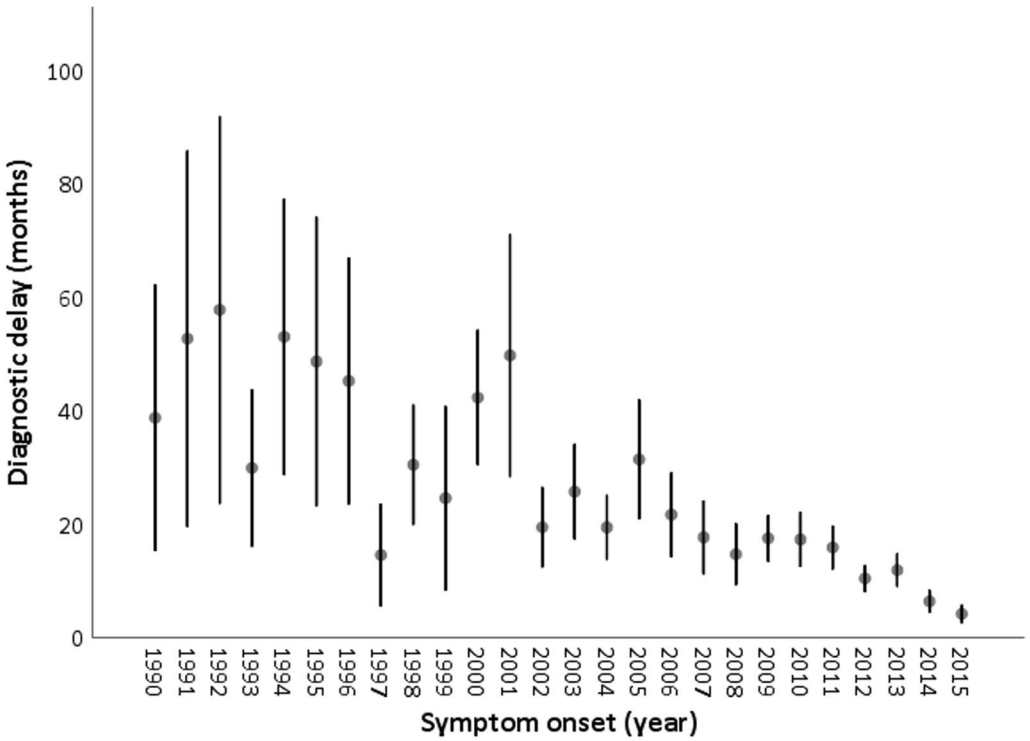

Fig. 1 Rheumatoid arthritis diagnostic delay (months) according to the year of symptoms onset in Brazil. *Note*: The dots and bars represent the point estimates and 95% confidence intervals for the means, respectively

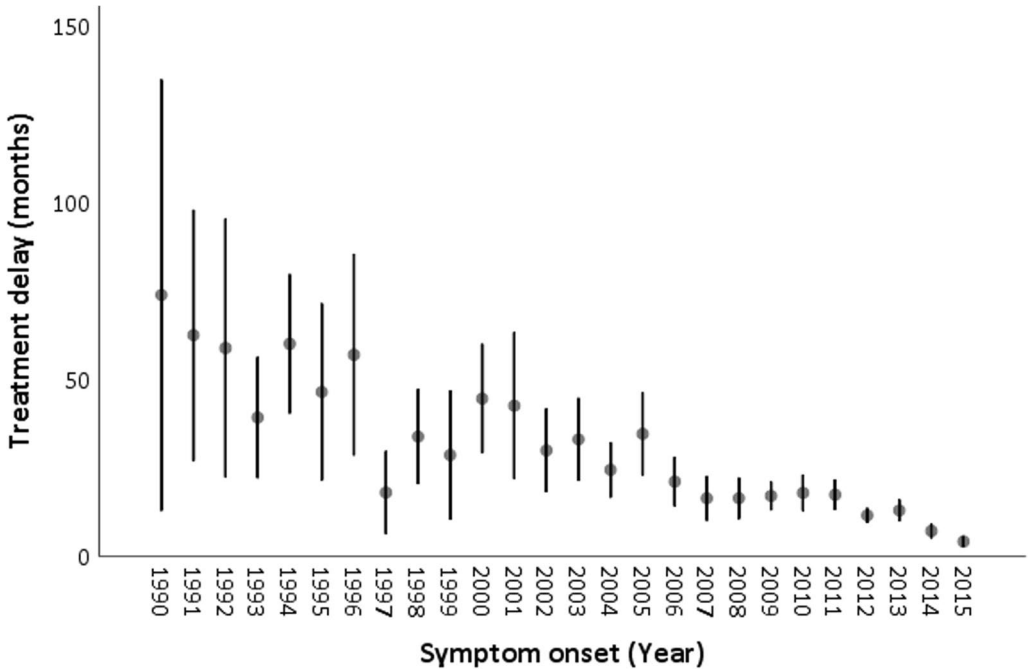

Fig. 2 Rheumatoid arthritis treatment delay (months) according to the year of symptoms onset in Brazil. *Note*: The dots and bars represent the point estimates and 95% confidence intervals for the means, respectively

Table 1 Frequencies of early RA diagnosis in Brazil according to the year of disease onset

Disease onset (year)	Delay from symptoms onset to RA diagnosis[a], [b]			N*
	≤ 3 months	≤ 6 months	≤ 12 months	
≤ 1990	12.4%	23.6%	41.6%	161
1991–1995	10.7%	24.3%	44.7%	103
1996–2000	10.5%	25.3%	48.1%	162
2001–2005	13.9%	29.1%	57.4%	237
2006–2010	19.9%	39.1%	65.6%	256
2011–2015	20.6%	43.8%	76.9%	160

RA: rheumatoid arthritis

*Numbers of participants with data available for the analyses

[a] The table shows the frequencies (%) of early diagnoses considering different delay thresholds (windows of opportunity)

[b] A significant association between the year (period) of disease onset and the frequency of early RA diagnoses was observed within all considered windows, i.e., for the 3-month ($p = 0.002$), 6-month ($p < 0.001$) and 12-month ($p < 0.001$) delay thresholds; the Mantel–Haenszel linear-by-linear chi-squared test

Table 2 Frequency of early RA treatment in Brazil according to the year of disease onset

Disease onset (year)	Delay from symptoms onset to the first DMARD[a],[b]			N*
	≤ 3 months	≤ 6 months	≤ 12 months	
≤ 1990	8.5%	14.9%	33.3%	141
1991–1995	5.3%	15.8%	34.7%	95
1996–2000	12.3%	24.7%	44.5%	146
2001–2005	11.5%	26.3%	49.8%	217
2006–2010	17.2%	38.9%	61.1%	239
2011–2015	17.2%	36.3%	72.0%	157

RA, rheumatoid arthritis; DMARD, disease-modifying anti-rheumatic drug

*Numbers of participants with data available for the analyses

[a] The table shows the frequencies (%) of early RA treatment (early initiation of the first DMARD) considering different delay thresholds (windows of opportunity)

[b] A significant association ($p < 0{,}001$) was found between the year of disease onset and the frequency of early RA treatment within all considered windows (delay thresholds); the Mantel–Haenszel linear-by-linear chi-squared test

$p < 0.001$), and 12 months ($\chi^2(1) = 64.79$, $V = 0.261$, $p < 0.001$) of symptoms onset; p-values based on the Mantel-Haenzel linear-by-linear chi-squared test. The more recent the period of disease onset, the higher the percentages of patients being treated within each of these predefined windows (Table 2).

Compared to participants whose symptoms began before 1990, patients whose symptoms started between 2011 and 2015 showed higher odds of receiving a diagnosis within 3 months (OR 1.83; 95% confidence

Table 3 Delays in RA management in Brazil according to the year of disease onset

Disease onset (year)	Diagnostic delay (months)		N*	Treatment delay (months)		N*
	Mean (SD)	Median [IQR]		Mean (SD)	Median [IQR]	
≤ 1990	71.2 (92.6)	24 [8–120]	161	101.7 (118.5)	60 [12–163]	141
1991–1995	47.8 (56.2)	24 [8–72]	103	52.5 (1.3)	36 [12–82]	95
1996–2000	35.3 (44.3)	21 [6–48]	162	40.0 (53.3)	24 [6.75–49]	146
2001–2005	28.2 (38.3)	12 [6–36]	237	32.5 (41.5)	13 [6–37.5]	217
2006–2010	17.8 (19.8)	12 [5–24]	256	17.8 (19.0)	12 [5–24]	239
2011–2015	11.1 (9.4)	8 [4–12]	160	12.2 (9.8)	11 [5–17]	157

RA, rheumatoid arthritis; SD, standard deviation; IQR, interquartile range

*Numbers of participants with data available for the assessments

interval [CI] 1.00–3.35), 6 months (OR 2.52; 95% CI 1.56–4.07), and 12 months (OR 4.66; 95% CI 2.88–7.56) of symptoms onset. Similarly, patients whose symptoms initiated between 2011 and 2015 had higher odds of receiving their first DMARD within 3 months (OR 2.23, 95%CI [1.08–4.50]), 6 months (OR 3.26, 95%CI [1.85–5.74]), and 12 months (OR 5.14, 95%CI [3.14–8.42]) of symptoms onset when compared to those whose symptoms began before 1990.

Diagnostic and treatment delays decreased along the successive time intervals for the year of symptoms onset (Table 3). Groups stratified according to these intervals differed as to the mean delay (in months) to RA diagnosis [$F(5, 411.3) = 37.6$; $p < 0.001$] and treatment [$F(5, 372.8) = 41.9$; $p < 0.001$]. Post-hoc analyses revealed that participants whose symptoms began between 2011 and 2015 had significantly lower diagnostic and treatment delays when compared to all other groups (Table 4).

Discussion

Rheumatoid arthritis is a major global health problem, associated with a high burden of disease from both individual and societal perspectives [2]. Early RA treatment provides the best opportunities to achieve disease remission and long-term damage prevention [6, 7, 25]. The existence of a window of opportunity for better treatment outcomes with an upper limit situated between 3 to 6 months after disease onset is now widely accepted [4, 18, 21]. Widespread efforts to reduce delays in RA diagnosis and treatment are needed, but the accomplishments of such initiatives in developing countries remain unclear due to scarcity of data.

We observed a significant decrease in diagnostic and treatment delays in the last decades in Brazil (Figs. 1, 2), such as reported in other nations [26–28]. Before 1990, the median delay to RA diagnosis in Brazil was 24 months and to receive the first DMARD was 60 months. These delays have decreased ever since and converged to a median of 8 months for diagnosis and 11 months for treatment in the period 2011–2015 (Table 3). Despite all the improvements, these numbers were still higher than those reported in developed countries, where treatment delay has mostly been situated around 4–8 months from disease onset [28–30]. This finding reinforces the need for regional data in order to understand the status of early RA management from a global perspective; generalizations are not warranted.

The proportion of patients receiving early RA diagnosis and treatment increased along the studied period considering all defined windows (Tables 1, 2). In 2011–2015,

Table 4 Changes in delays for RA management in Brazil across periods

Reference period	Comparison period	Mean difference [95% CI] (months)	
		For diagnostic delay	For treatment delay
2011–2015	≤ 1990	− 60,2 [− 81.3, − 39.0]	− 89,6 [− 118.5, − 60.6]
	1991–1995	− 36,7 [− 52.9, − 20.5]	− 40,4 [− 55.9, − 24.8]
	1996–2000	− 24,2 [− 34.5, − 13.9]	− 27,8 [− 40.7, − 14.9]
	2001–2005	− 17,1 [− 24.6, − 9.7]	− 20,3 [− 28.7, − 11.9]
	2006–2010	− 6,7 [− 10.8, − 2.6]*	− 5,7 [− 9.8, − 1.5]

RA, rheumatoid arthritis; CI, confidence interval

*$p = 0.002$; all other differences shown in the table were significant at $p < 0.001$ on Games-Howell post-hoc tests following one-way ANOVA

more than 70% of the patients with RA were diagnosed and treated within 12 months of symptoms onset. Nevertheless, in the same period, only 36.3% received treatment within 6 months and 17.2% within 3 months of symptoms onset (Table 2). This shorter (3-month) window has been associated with the best outcomes [4, 31, 32]. Therefore, despite all the improvements, even recently a very early beginning of RA treatment (where the most promising results are expected) was still difficult to achieve in Brazil.

We noted increasing effect sizes (V values) for the association between the year of symptoms onset (arranged in time intervals) and the proportions of patients receiving early RA management across the 3, 6, and 12-month thresholds. This indicated that the magnitude of changes in diagnostic and treatment delays was not the same in these 3 windows. Instead, changes were greater around the 12-month threshold. This phenomenon can also be perceived with the increasing odds ratios for early treatment across the 3, 6, and 12-month windows when comparing patients whose symptoms initiated in the 2011–2015 period and those with symptoms onset before 1990. In other words, large delays (of more than 12 months) were more easily reduced, whereas achieving delays of less than 3–6 months (which are the ideal goals of early management) proved to be more difficult.

The mean diagnostic and treatment delay decreased progressively across the studied periods. Patients whose symptoms initiated in 2011–2015 (reference group) had significantly shorter delays in both diagnosis and treatment when compared to all other groups; the further removed into the past the period of symptoms onset, the greater the differences in comparison to the reference group (Table 4). These findings suggest a sustained decrease in mean delays throughout the assessed period, rather than a transient phenomenon at some particular occasion.

However, as noticed before, the sustained decrease in mean diagnostic and treatment delays in the last decades did not imply a uniform change across the different window thresholds. Rather, the decreases were influenced more by the progressive elimination of very large delays (greater effect sizes around the 12-month windows) than by the increments in frequency of short delays (smaller effect sizes around the 3-month widows). This finding indicates that measuring the proportions of patients being treated within the targeted windows could be more useful for policy adjustments than simply measuring changes in mean delays.

The main limitation of this study was that it relied to a great extent on the information provided directly by participants regarding the delays between symptoms onset and the diagnosis and treatment of RA. When feasible, diagnostic and treatment delays were ascertained using medical records, but for most participants these data were not retrievable from previous records. Confidence intervals (CI) for the mean delays were computed on a year-to-year basis (Figs. 1, 2), revealing greater imprecision (larger CI), as expected, around the older point estimates in comparison to the more recent ones. Despite this limitation, our findings of decreasing delays in RA management are consistent with those reported in other countries [26–28].

Conclusions

Delays in the diagnosis and treatment of RA decreased progressively, and more patients could receive early treatment in the last decades in Brazil. Nevertheless, even in recent years (2011–2015), the median delay to treatment remained unacceptably high (11 months). Improvements were greater in the elimination of very large delays ($\geq$ 12 months) than in the attainment of really short (and desirable) management windows ($\leq$ 3 months). Very early treatment of RA remained difficult to achieve. Additional efforts are clearly needed in pursuit of that goal in Brazil, which might also be the case in other developing nations where robust data tend to be scarce. Country-level data as we provided herein are essential for a proper understanding of the status of early RA treatment from a global perspective.

Abbreviations

ACR	American College of Rheumatology
ANOVA	Analysis of variance
ARA	American Rheumatism Association
CI	Confidence interval
DMARD	Disease-modifying anti-rheumatic drugs
EULAR	European League Against Rheumatism
IQR	Interquartile range
OR	Odds ratio
RA	Rheumatoid arthritis
SD	Standard deviation

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Author 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 made substantial contributions to study conception and design, and CPA made substantial contributions to data analysis and interpretation. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Not applicable for materials.

Declarations

Ethics approval and consent to participate
The study was approved by a central ethics review board (https://plataformabrasil.saude.gov.br/, protocol number CAAE 45781015.8.1001.5259) and by institutional boards in each participating center. All participants granted informed consent to participate in the study. All procedures were in accordance with ethical standards of the National Commission of Ethics in Research (CONEP) and with the 1964 Helsinki declaration and its later amendments.

Consent for publication
All participants granted informed consent for publication.

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

Author details
[1]Rheumatology Service, Universidade de Brasília (UnB), Campus Universitário Darcy Ribeiro, Brasília, DF 70910-900, Brazil. [2]School of Medicine, Centro Universitário de Brasília (CEUB), Brasília, DF, Brazil. [3]Department of Rheumatology, Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ, Brazil. [4]Medical Sciences, Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil. [5]School of Medicine, Universidade de Ribeirão Preto, Universidade de São Paulo (USP), Ribeirão Preto, SP, Brazil. [6]Instituto de Assistência Médica ao Servidor Público Estadual, Hospital do Servidor Público Estadual de São Paulo (IAMSPE), São Paulo, SP, Brazil. [7]Department of Internal Medicine, Universidade Federal do Paraná (UFPR), Curitiba, PR, Brazil. [8]Department of Rheumatology, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil. [9]Department of Rheumatology, Hospital das Clínicas, USP, São Paulo, SP, Brazil. [10]Department of Rheumatology, School of Medicine, Universidade Federal do Pará, Belém, PA, Brazil. [11]Department of Rheumatology, Universidade Federal de Santa Catarina (UFSC), Florianópolis, SC, Brazil. [12]Department of Internal Medicine, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil.

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