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Drugs for rheumatoid arthritis provided by the Unified Health System in 2019 in Brazil: a cohort study

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Abstract *This study analyzes supply characteristics and factors associated with the treatment of rheumatoid arthritis in Brazil, with a focus on disease course-modifying biological drugs (bioDMARDs). A retrospective study was conducted with secondary data from the Outpatient Information System of the Unified Health System. Patients aged 16 years or older who were treated in 2019 were eligible. The analyses were performed with exposure factors in relation to the outcomes: bioDMARD use and population size. The study included 155,679 patients, 84.6% of whom were women. There was a greater exchange of bioDMARDs and a greater supply of rheumatologists in the larger municipalities (more than 500,000 inhabitants). Almost 40% of the patients used bioDMARDs, and they showed greater adherence to treatment (57.0% versus 64%, p=0.001). The dispensing of bioDMARDs occurred in more than one-third of the patients treated for rheumatoid arthritis (RA) in Brazil and was associated with a higher percentage of availability of rheumatologists and larger population size.*

Key words *Rheumatoid Arthritis, Biological drugs, Pharmaceutical Services*

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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, immune-mediated disease of poorly defined etiology[1] that most often affects females (three women for every man) with a mean age of 50 years[2]. It is characterized by inflammation of the peripheral synovial joints, in addition to other extra-articular manifestations, such as pleural effusion, pericarditis, vasculitis, and Sjögren's syndrome, among others[3].

The prevalence of RA varies between 0.2% and 1% in the Brazilian population[4]. Delayed diagnosis and inadequate control of disease activity can lead to irreversible loss of function, reducing the quality of life and productivity of affected individuals[5].

The use of biologic disease-modifying drugs (bioDMARDs) represents a promising therapeutic possibility, especially when treatment with synthetic disease-modifying antirheumatic drugs (csDMARDs) fails. Studies indicate improvement in the quality of life of patients with RA after the use of bioDMARDs associated or not with csDMARDs[6,7].

Among the 20 drugs recommended for RA in the Clinical Protocols and Therapeutic Guidelines (PCDT) of 2019, 16 were available in the Specialized Component of Pharmaceutical Assistance (CEAF), and 11 belonged to funding Group 1A[8]. These 11 drugs, acquired directly by the Ministry of Health (MoH), have a significant financial impact[9]. The average federal expenditure on purchases of bioDMARDs for RA from 2012 to 2017 was R$273 million per year[10].

Established in 2009, the CEAF provides drugs included in the National List of Essential Medicines (RENAME) of the Unified Health System (SUS) for treatments with higher individual costs, greater complexity, or those with increasing costs over time[9]. The drugs supplied by the CEAF are organized into three distinct groups according to the health care funding source; the federal government pays 87%, the states pay 12% and municipalities pay 1%[11].

Based on the lines of care present in the PCDTs, which aim at comprehensiveness and communication between the components of pharmaceutical care, users with diseases included in the CEAF can have access to medication in all its phases[9]. In 2020, this component met 101 clinical conditions recommended in 93 PCDTs, providing 172 different drugs in 321 presentations[12].

Especially with regard to access to bioDMARDs, CEAF is an arena of strong tensions in at least three areas: high health expenditures, pressure for the incorporation of new therapeutic alternatives by both user groups and pharmaceutical companies, and commercial competition among companies[13]. This stands to reason given the growth of the biosimilars market[14] and the demand for supplies from the Brazilian government[15].

Studies on the use of medications are an important tool to assist decision-making by managers in the field of pharmaceutical care. The SUS Outpatient Information System (SIA/SUS), which uses data from the Authorization for High Complexity/Cost Procedures (APAC), has not been mined for these studies and may contribute to the characterization of the system's users and identify gaps in care. Although information of pharmacoepidemiological interest may be lacking, this database is available to managers and professionals, and it is important to expand and discuss its possibilities for analysis. In this regard, the present study aimed to describe and analyze the characteristics of supply and factors associated with pharmacological treatment for RA in Brazil, focusing on bioDMARDs.

Methods

A cohort study was conducted in Brazil with the collection of retrospective, individualized and anonymized data from patients aged 16 years or older with a diagnosis of RA who received CEAF drugs from January to December 2019. This period was the last full year before the state decree of a 2020 public health crisis in Brazil due to the COVID-19 pandemic, which triggered different strategies in the supply of CEAF medicines.

Data from the APAC were used, referring to the dispensing of medications in the period between January and December 2019 for the 26 states of the federation and the federal district. The data were obtained from the SIA/SUS database and made available by the Department of Informatics of the SUS (DATASUS), by accessing the website https://datasus.saude.gov.br. The APAC system is used to control and pay for all CEAF medications. The APAC number is generated after the manager authorizes the medication to be dispensed to the user. The request for medication requires the presentation of various documents and tests provided for in the PCDT according to the clinical condition[11].

The treatment of RA, recommended in the 2019 PCDT, involved different pharmacological groups[16]:

• Synthetic disease-modifying drugs (csDMARDs): methotrexate (MTX), leflunomide, sulfasalazine, chloroquine diphosphate, hydroxychloroquine;

• Biological course-of-disease-modifying drugs (bioDMARDs): etanercept, adalinumab, certolizumab pegol, golimumab, infliximab, abatacept, tocilizumab, rituximab;

• Synthetic target-specific disease-modifying drugs (ADDMs): tofacitinib;

• Immunosuppressants: azathioprine, cyclophosphamide and cyclosporine;

• Glucocorticoids: prednisone and methylprednisolone;

• Nonsteroidal anti-inflammatory drugs (NSAIDs): ibuprofen and naproxen;

All ICD-10 codes present in the 2019 PCDT for RA were considered, namely, M05.0 Felty syndrome; M05.1 Rheumatoid lung disease; M05.2 Rheumatoid vasculitis; M05.3 Rheumatoid arthritis with involvement of other organs and systems; M05.8 Other seropositive rheumatoid arthritis; M06.0 Seronegative rheumatoid arthritis; and M06.8 Other specified rheumatoid arthritis. ICD-10 codes related to juvenile idiopathic arthritis[16] excluded those subjects from analysis.

The steps used to prepare the study database are shown in Figure 1.

Study variables

Three groups of variables were used to identify the factors associated with the dispensing of bioDMARDs for RA in the CEAF:

• Demographic and clinical characteristics of users: sex, age, weight, height, and body mass index (BMI) (calculated from user's weight divided by height squared)

• Provision of medication for RA: (i) biological medication (bioDMARD yes or no); (ii) main diagnosis (ICD-10) at the beginning of treatment; (iii) type of APAC (continuity or initial); (iv) number of dispensations per patient/year; (v) main procedure (drug dispensed); (vi) municipality that dispensed the medication at the beginning and end of the study period. From these variables, it was possible to generate the following variables: (vii) change in medication for rheumatoid arthritis (checked whether the medication at the beginning of treatment was different from the end); (viii) switch to a biological drug (if the drug at the beginning was from the csDMARDs group and passed or added a bioDMARD); (iv) maximum time of treatment (difference in months between the date of the last and first dispensing, indicating the maximum possible time of treatment in months, ranging from one to 12); (x) number of dispensations per month (calculated in relation to the maximum treatment time, expressing the effective treatment time in months); (xi) dropouts (patients who sought csDMARDs and/or bioDMARDs in only 20% of the total number of possible dispensations); and (xii) patient adherence to treatment (patients with at least 80% of the maximum possible dispensations, both for csDMARDs and for bioDMARDs). The definition of cutoff points for noncompliance and adherence was based on the indication of 80% in the literature[17]. Patients with the maximum number of dispensations for two months or less were excluded from the calculation of these variables because this would lead to erroneous results regarding noncompliance and adherence.

• Provision of RA care and municipality characterization: number of rheumatologists per 1,000 patients with RA (calculated by size of municipality where dispensing was performed and based on estimated RA patient population and number of rheumatologists)[18], municipality size (the municipalities for which the dispensation was registered were defined as small/up to 100,000 inhabitants, medium/100,000 to 500,000 inhabitants and large/more than 500,000 inhabitants), based on the estimated population for 2019[19].

Tofacitinib was categorized together with bioDMARDs because it is the second stage of RA treatment, according to the 2019 PCDT[16].

The prescription of CEAF medications can be made by any physician registered with the appropriate professional council of this class. In this study, only the presence of rheumatologists was analyzed, as this is the specialized medical field indicated for the care of patients with RA.

Data analysis

The analyses were performed using the SPSS V.22.0 program. Descriptive statistics were performed using means with confidence intervals (95%CI) for continuous variables and frequency distribution for categorical variables. These analyses were performed with the exposure factors in relation to the outcomes: bioDMARD (yes/no) and population size (small, medium and large). A descriptive analysis of the distribution of RA drugs according to diagnosis (by ICD), sex and municipality size was also performed.

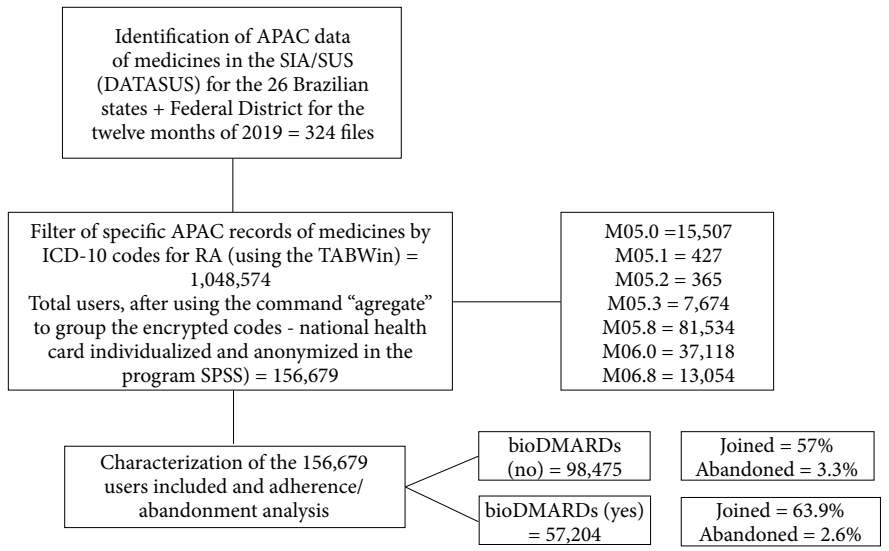

Figure 1. Steps used to prepare the study database, Brazil, 2019.

APAC = Authorization for High Complexity/Cost Procedures. SIA/SUS = SUS Outpatient Information System. Department of Informatics of the SUS (DATASUS). Tabwin = Tab for Windows. SPSS =Statistical Package for the Social Sciences. ICD-10 codes (The International Classification of Diseases): M05.0 Felty syndrome; M05.1 rheumatoid lung disease; M05.2 rheumatoid vasculitis; M05.3 rheumatoid arthritis with involvement of other organs and systems; M05.8 other seropositive rheumatoid arthritis; M06.0 Seronegative rheumatoid arthritis; and M06.8 Other specified rheumatoid arthritis. bioDMARDs = biologic disease-modifying drugs. RA= Rheumatoid arthritis.

Source: Authors.

Student's *t* test was applied to the mean difference of the continuous variables (e.g., weight, height, BMI, age, number of dispensations per maximum follow-up time, number of dispensations during the year and rheumatologists per 1,000 RA patients), taking bioDMARDs or not ($p<5\%$). The same verification between the continuous variables and the distribution by population size was performed using ANOVA ($p<5\%$).

The association between categorical exposure factors and bioDMARDs was assessed using Pearson's chi-square test. The odds ratios (crude OR) were calculated for the binary variables and univariate logistic regression ($p<5\%$) for the continuous variables.

Multiple logistic regression analysis (*stepwise backward*) was used to calculate the adjusted odds ratios (OR adj) at a significance level of 5%. The significant variables in the bivariate analysis were included in the logistic regression input ($p<5\%$), and only the significant variables ($p<5\%$) were included in the final model after the *stepwise* procedure. The proportion of total agreement of the model (*overall*) was calculated.

The study was exempted from ethical review by the Research Ethics Committee because it used secondary data from the public domain.

Results

The study included 155,679 individuals, of whom the majority (84.6%) were female, with a mean age of 57 years and a mean BMI of 27.4 kg/m² (mean of 26.8 for men and 27.5 for women). The most frequent ICD-10 codes were M05.8 "Other seropositive rheumatoid arthritis" (52.4%), followed by M06.0 "Seronegative rheumatoid arthritis" (23.8%).

Larger municipalities exhibited a greater number of changes in the regimens for RA and changes to biologicals when compared to medium and small municipalities. The number of rheumatologists showed a linear gradient according to population size (Table 1).

Information about medicines dispensed were registered in the SIA/SUS APAC by municipality, and the dispensing centers were listed on the

State Health Departments (SES) and the Federal District websites. There were differences among the locations, which influenced the analysis, primarily due to population size, especially in the state of Rio de Janeiro.

The dispensing of bioDMARDs was higher for individuals with a mean age of 55.8 years. Regarding the therapeutic approach according to the type of arthritis, 33 to 40% of the patients used bioDMARDs, except for diagnoses M05.1 (rheumatoid lung disease) and M05.2 (rheumatoid vasculitis), for which only 5% of patients received these medications. Adherence was higher for bioDMARDs, expressed both by the number of patients with at least 80% of the maximum possible dispensations (64%) and by the mean number of dispensations in the year (Table 2). The greater number of rheumatologists was also associated with greater dispensing, and thus prescription, of bioDMARDs.

The distribution of DMARDs for RA by ICD-10 is shown in Table 3. Among the synthetic immunosuppressants, azathioprine was the most frequently dispensed for ICD-10 M05.1 "Rheumatoid lung disease" (82.7%) and M05.2 "Rheumatoid vasculitis" (78.9%), while for the other diagnoses, this medication was dispensed to less than 0.3% of the patients. In the analysis that included all ICDs, leflunomide was the most frequently dispensed csDMARDs (25% of patients), followed by hydroxychloroquine (10% of patients) and methotrexate (8.9% of patients). The bioDMARDs most frequently dispensed were adalinumab and etanercept (9.6% and 5.6%, respectively). The municipalities with up to 100,000 inhabitants dispensed more csDMARDs than bioDMARDs when compared to the municipalities with the largest number of inhabitants. The greater use of bioDMARDs in medium and large municipalities compared to small municipalities was observed for all drugs in this group (Table 3).

Logistic regression indicated a statistically significant association (p<5%) between all the variables analyzed and the dispensing of bioDMARDs (Table 4). In addition, regarding the quality of the final model, the *overall* rating ratio was 60.4%. The chance of using bioDMARDs, according to the dispensing municipalities registered in the SIA/SUS APAC, was higher for males (ORaj 1.190; 95%CI: 1.151-1.230), for those more compliant (ORaj 1.156; 95%CI: 1.107-1.208) and where there were more rheumatologists per 1,000 RA patients (ORaj 1.037; 95%CI: 1.035-1.039). Age was inversely related to the use of bioDMARDs (ORaj 0.988; 95%CI: 0.987-0.989); that is, the older the patient was, the lower the chance of using bioDMARDs (Table 4).

Only the BMI variable exhibited loss of information (7%), with 1% of data referring to height and 6% data referring to weight.

Discussion

Approximately one-third (36.7%) of the 155,700 individuals from all Brazilian states and the federal district received bioDMARD as a treatment for RA in 2019. ICD 10 M5.8 (Other seropositive RA) was the most prevalent diagnosis. The most frequently dispensed csDMARDs was leflunomide, and the most frequently dispensed bioDMARD was adalinumab.

The higher proportion of women with RA, as well as the mean age, was consistent with findings in the literature[20-22]. In the present study, an inverse association was found between age and the dispensing of bioDMARDs, with an OR adj of 0.99 each year. PCDT[16] does not indicate a change in bioDMARD prescriptions with increasing age. The literature indicates that the aggressiveness of the disease in young and elderly patients is similar[23]. However, the elderly population is more subject to other comorbidities, requiring treatment with multiple drugs, which implies greater susceptibility to drug interactions and adverse events[24]. It is believed that these aspects may have influenced physicians' decisions regarding the lower bioDMARD prescription rate for older users.

The patients included in this study had a mean BMI of 27.4 kg/m², which is classified as overweight[25]. The literature indicates a higher prevalence of obesity in patients with RA than in the general population[26]. Overweight in RA is associated with worse quality of life, greater pain intensity, and higher treatment costs and is a risk factor for the development of other comorbidities[27]. As a result of the inflammatory characteristics of the disease, patients with RA have a greater loss of lean body mass concurrent with an increase in fat mass and central obesity, even without a significant increase in body weight[28]. However, Guimarães *et al.*[28], who also observed a predominance of women approximately 50 years of age, determined that the cutoff point to characterize obesity by BMI for the general population would be equal to 25 kg/m² in the population with arthritis[28]. Thus, on average, the population included in this study would be classified

Table 1. Data by population size, referring to the dispensing municipalities registered in the SIA/SUS APAC, demographic characteristics of users and provision of medication for rheumatoid arthritis RA by the Unified Health System in 2019, Brazil (N = 155,679).

Variables	Municipality size (in number of inhabitants)			p-value &	Total
	up to 100,000	100,000 to 500,000	+500,000		
Number of patients with RA	15,112	51,123	89,444	-	155,679
Demographic and clinical characteristics of users					
Women	83.3%	83.4%	85.4%	0.000	84.6%
Weight (kg) (mean; 95%CI)	72.0 (71.78-72.22)	71.9 (71.81-72.05)	71.0 (70.94-71.12)	0.000	71.4 (71.36-71.49)
Height (cm) (mean; 95%CI)	161.7 (161.60-161.88)	161.5 (161.45-161.61)	160.8 (160.72-160.83)	0.000	161.1 (160.07-161.16)
Body mass index (BMI) (average; 95%CI)	27.46 (27.37-27.54)	27.43 (27.38-27.47)	27.35 (27.32-27.39)	0.006	27.39 (27.36-27.41)
Age (years) (mean; 95%CI)	57.0 (56.80-57.21)	57.1 (56.97-57.20)	56.9 (56.78-56.96)	0.012	56.9 (56.89-58.02)
Provision of medication for RA					
Main diagnosis (ICD-10)*					
M05.0	5.6%	10.9%	10.2%	-	10.0%
M05.1	0.2%	0.3%	0.3%	-	0.3%
M05.2	0.2%	0.2%	0.2%	-	0.2%
M05.3	3.1%	4.8%	5.3%	-	4.9%
M05.8	53.3%	46.1%	55.8%	-	52.4%
M06.0	29.1%	26.7%	21.3%	-	23.8%
M06.8	8.5%	10.8%	6.9%	-	8.4%
Type of APAC**					
Continuity	65%	59.0%	65.6%	0.000	63.4%
Initial	34.5%	41.0%	34.4%	0.000	36.6%
Number of dispensations per patient/year					
Patient dropouts #1	3.3%	2.9%	3.1%	0.031	3.0%
Patient adherence #2	57.7%	63.5%	57.6%	0.000	59.6%
Period of treatment (months)	9.87	10.00	9.72	0.000	9.83
Number of dispensations per month (mean; 95%CI)	0.94 (0.93-0.95)	0.96 (0.96-0.97)	0.95 (0.94-0.95)	0.000	0.95 (0.95-0.95)
Switch to a biological drug	2.8%	2.8%	3.9%	0.000	3.4%
Change in medication for arthritis	11.0%	10.2%	14.1%	0.000	12.5%
Number of dispensations per year (mean; 95%CI)	8.52 (8.46-8.58)	8.89 (8.86-8.92)	8.36 (8.33-8.38)	0.000	8.55 (8.5-8.6)
Provision of RA care and municipality characterization					
Number of rheumatologists per 1,000 patients with RA (mean; 95%CI)	1.19 (1.14-1.25)	4.01 (3.96 - 4.05)	9.48 (9.45-9.51)	0.000	6.9 (6.85-6.91)

ICD-10 codes (The International Classification of Diseases)*: M05.0 Felty syndrome; M05.1 Rheumatoid lung disease; M05.2 Rheumatoid vasculitis; M05.3 Rheumatoid arthritis with involvement of other organs and systems; M05.8 Other seropositive rheumatoid arthritis; M06.0 Seronegative rheumatoid arthritis; and M06.8 Other specified rheumatoid arthritis, Type of APAC**: Authorization for High Complexity/Cost Procedures. #1 Patient dropouts: patients who sought csDMARDs and/or bioDMARDs in only 20% of the total number of possible dispensations. #2 Patient adherence to treatment (patients with at least 80% of the maximum possible dispensations, both for csDMARDs and for bioDMARDs). & p-valor da ANOVA to the continuous variables and Pearson's chi-square test to categorical variables.

Source: Authors.

as obese, a finding that deserves attention from health professionals caring for patients with RA.

Leflunomide was the csDMARDs most dispensed in the CEAF, but it would not be the first choice in the treatment of RA, according to the PCDT[16]. A study that compared the Brazilian recommendations for the treatment of RA with those of international institutions indicated the use of MTX as the the csDMARDs of first choice and then, if necessary, in combination with other

Table 2. Proportion and average of course-modifying biological drugs dispensing according to demographic characteristics of users and provision of medication for rheumatoid arthritis RA by the Unified Health System in 2019, Brazil.

Variables	Dispensing of bioDMARDs		p-value	Total
	No	Yes	&	
Number of patients with RA	98,475	57,204	-	155,679
Demographic characteristics of users				
Women	64.0%	36.0%	0.000	100%
Mens	59.1%	40.9%	0.000	100%
Weight (kg) (mean; 95%CI)	71.1 (71.05-71.22)	71.9 (71.81-72.04)	0.000	71.4 (71.36-71.49)
Heigt (cm) (mean; 95%CI)	160.8 (160.79-160.90)	161.6 (161.52-161.66)	0.000	161.1 (161.07-161.16)
Body mass index (BMI) (mean; 95%CI)	27.4 (27.33-27.39)	27.4 (27.40-27.48)	0.345	27.4 (27.36-27.41)
Age (years) (mean; 95%CI)	57.6 (57.56-57.72)	55.8 (55.66-55.88)	0.000	57.0 (56.89-57.02)
Provision of medication for RA				
Main diagnosis (ICD-10)*				
M05.0	60.1%	39.9%	-	100%
M05.1	94.8%	5.2%	-	100%
M05.2	95.9%	4.1%	-	100%
M05.3	61.2%	38.8%	-	100%
M05.8	62.1%	37.9%	-	100%
M06.0	66.6%	33.4%	-	100%
M06.8	64.1%	35.9%	-	100%
Type of APAC**				
Continuity	64.6%	61.3%	0.000	63.4%
Initial	35.4%	38.7%	0.000	36.6%
Number of dispensations per patient/year				
Patient dropouts [#1]	3.3%	2.6%	0.000	3.0%
Patient adherence [#2]	57.0%	63.9%	0.000	59.6%
Period of treatment (months)	8.0	8.0	0.000	8.0
Number of dispensations per month (mean; 95%CI)	0.94 (0.94-0.95)	0.97 (0.96-0.97)	0.000	0.95 (0.95-0.95)
Number of dispensations per year (mean; 95%CI)	8.35 (8.33-8.37)	8.89 (8.86-8.92)	0.000	8.55 (8.53-8.57)
Provision of RA care and municipality characterization				
Number of rheumatologists per 1,000 patients with RA (mean; 95%CI)	6.53 (6.5-6.57)	7.48 (7.43-7.52)	0.000	6.9 (6.85-6.91)

ICD-10 codes (The International Classification of Diseases)*: M05.0 Felty syndrome; M05.1 Rheumatoid lung disease; M05.2 Rheumatoid vasculitis; M05.3 Rheumatoid arthritis with involvement of other organs and systems; M05.8 Other seropositive rheumatoid arthritis; M06.0 Seronegative rheumatoid arthritis; and M06.8 Other specified rheumatoid arthritis. Type of APAC**: Authorization for High Complexity/Cost Procedures. [#1] Patient dropouts: patients who sought csDMARDs and/or bioDMARDs in only 20% of the total number of possible dispensations. [#2] Patient adherence to treatment (patients with at least 80% of the maximum possible dispensations, both for csDMARDs and for bioDMARDs). & p-valor Student's t test to continuous variables and Pearson's chi-square test to categorical variables.

Source: Authors.

the csDMARDs or bioDMARDs[29,30]. Considering that MTX is the drug of first choice in PCDT, the higher prevalence of leflunomide may be related to the possibility of obtaining MTX in the private network due to its availability and low cost. Another factor that may explain the lower dispensing of MTX compared to leflunomide would be the occurrence of commonly reported adverse reactions, leading to change or interruption of treatment with the first drug[30-32].

Table 3. High cost medicines for rheumatoid arthritis by the Unified Health System. Data by main diagnosis, sex and population size, referring to the dispensing municipalities registered in the SIA/SUS APAC medicines, in Brazil in 2019.

Medicines	ICD-10 codes* main diagnosis %							All ICD-10	Sex %		Population size %		
	M05.0	M05.1	M05.2	M05.3	M05.8	M06.0	M06.8		F	M	Up to 100.000	100.000-500.000	More than 500.000
Patients N (%)	15,507 (10.0)	427 (0.3)	365 (0.2)	7,674 (4.9)	81,534 (52.4)	37,118 (23.8)	13,054 (8.4)	155,679 (100.0)	131,643 (84.6)	24,036 (15.4)	15,112 (9.7)	51,123 (32.8)	89,444 (57.5)
Synthetic disease-modifying drugs- csDMARDs (% column)													
Leflunomide (20 mg)	35.3%	1.6%	1.6%	34.9%	36.8%	33.4%	32.7%	25.2%	35.6%	32.9%	33.1%	34.8%	35.8%
Hydroxychloroquine (400 mg)	14.1%	3.3%	0.5%	9.9%	10.2%	17.5%	14.8%	10.0%	13.1%	9.9%	22.3%	13.7%	10.4%
Methotrexate (2.5 mg and 25 mg/mL)	8.4%	0.5%	1.1%	14.6%	12.6%	12.2%	13.2%	8.9%	12.2%	12.0%	15.3%	11.4%	12.1%
Sualfasalazine (500 mg)	1.9%	0.2%	0.5%	1.5%	2.3%	3.2%	3.1%	1.8%	2.4%	3.2%	4.0%	2.2%	2.4%
Chloroquine (150 mg)	0.2%	0.0%	0.0%	0.1%	0.2%	0.3%	0.2%	0.1%	0.2%	0.2%	0.2%	0.2%	0.2%
Subtotal	60.0%	5.6%	3.8%	61.0%	62.0%	66.5%	64.0%	46.1%	63.5%	58.2%	75.0%	62.3%	60.8%
Immunosuppressants (% column)													
Azathioprine (50 mg)	0.1%	82.7%	78.9%	0.2%	0.1%	0.1%	0.0%	23.1%	0.4%	0.7%	0.3%	0.5%	0.5%
Cyclosporine (20, 25 and 100 mg)	0.0%	6.6%	13.2%	0.0%	0.0%	0.0%	0.0%	2.8%	0.1%	0.1%	0.0%	0.0%	0.1%
Subtotal	0.1%	89.2%	92.1%	0.2%	0.1%	0.1%	0.0%	26.0%	0.5%	0.8%	0.4%	0.5%	0.6%
Nonsteroidal anti-inflammatory drugs - NSAIDs (% column)													
Naproxen (250 and 500 mg)	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%
Subtotal	0.1%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.0%	0.0%	0.0%
Biological course-of-disease-modifying drugs - bioDMARDs (% column)													
Adalinumab (40 mg)	16.3%	0.9%	0.8%	14.3%	11.7%	11.8%	11.6%	9.6%	11.7%	15.4%	8.5%	12.5%	12.7%
Etanercept (25 and 50 mg)	8.4%	0.2%	0.0%	8.2%	7.7%	6.8%	7.6%	5.6%	7.2%	9.4%	5.6%	7.3%	8.0%
Golimumab (50 mg)	4.0%	0.0%	0.3%	3.4%	3.1%	2.8%	2.8%	2.3%	3.0%	3.3%	2.1%	3.2%	3.2%
Tocilizumab (20 mg/mL)	2.7%	0.5%	0.3%	2.3%	3.2%	2.1%	3.4%	2.1%	2.9%	2.2%	1.4%	2.7%	3.1%
Certolizumab Pegol (200 mg)	2.5%	0.0%	0.3%	2.6%	3.1%	3.0%	2.0%	1.9%	2.9%	2.6%	2.5%	2.9%	2.9%
Infliximab (10 mg/mL)	2.3%	0.5%	0.5%	1.9%	2.3%	2.2%	2.5%	1.8%	2.1%	3.4%	1.3%	2.9%	2.1%
Abatacept (250 mg and 125 mg/mL)	1.6%	0.7%	0.0%	2.6%	3.0%	1.6%	2.5%	1.7%	2.5%	1.9%	1.3%	2.5%	2.6%
Rituximab (10 mg/mL)	1.0%	1.2%	1.6%	1.8%	1.8%	1.3%	1.7%	1.5%	1.6%	1.2%	0.5%	1.3%	1.9%
Tofacitinib (5 mg)	1.2%	1.2%	0.3%	1.8%	2.1%	1.8%	1.9%	1.5%	2.0%	1.5%	1.4%	1.6%	2.1%
Subtotal	39.9%	5.2%	4.1%	38.8%	37.9%	33.4%	35.9%	27.9%	36.0%	40.9%	24.6%	37.1%	38.6%
Total	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%

ICD-10 codes* (The International Classification of Diseases): M05.0 Felty syndrome; M05.1 Rheumatoid lung disease; M05.2 Rheumatoid vasculitis; M05.3 Rheumatoid arthritis with involvement of other organs and systems; M05.8 Other seropositive rheumatoid arthritis; M06.0 Seronegative rheumatoid arthritis; and M06.8 Other specified rheumatoid arthritis.

Source: Authors.

Users with higher adherence (measured by regularity of dispensing) to RA treatment were those using bioDMARDs. In fact, because it corresponds to the second line of treatment for RA, it is possible that the majority of patients using bioDMARDs were refractory to regimens using only the csDMARDs[16] for several reasons, including lack of adherence. However, the user can seek CEAF only when he or she needs a bioDMARD. Thus, the search for access via CEAF and greater regularity in dispensing may still be related to greater dependence on SUS due to the high cost of bioDMARDs. The SIA-SUS does not provide data on the severity of the disease or previous medication use. To exemplify the magnitude of the values, the monthly cost per patient using

Table 4. Bivariate and multivariate analysis of the dispensing of biological drugs for the treatment of Rheumatoid Arthritis in Brazil, in 2019.

Variables	OR-bruto	CI	p-value	OR-aj	CI	p-value
Demographic characteristics of users						
Men	1.232	(1.198-1.267)	0.000	1.190	(1.151-1.230)	0.000
Weight (kg)*	1.004	(1.004-1.005)	0.000	1.002	(1.002-1.003)	0.000
Height (cm)*	1.010	(1.009-1.012)	0.000	1.003	(1.002-1.005)	0.000
Age (years)*	0.989	(0.988-0.990)	0.000	0.988	(0.987-0.989)	0.000
Provision of medication for Rheumatoid Arthritis						
Type of APAC Continuity	1.152	(1.128-1.177)	0.000	1.073	(1.046-1.100)	0.000
Number of dispensations per patient/year*	1.042	(1.039-1.045)	0.000	1.017	(1.009-1.025)	0.000
Period of treatment (months)*	1.035	(1.031-1.038)	0.000	1.021	(1.014-1.028)	0.000
Patient dropouts [#1] (Yes)	1.333	(1.305-1.362)	0.000	1.156	(1.107-1.208)	0.000
Patient adherence [#2] (Yes)	0.778	(0.731-0.828)	0.000	0.904	(0.837-0.976)	0.012
Number of dispensations per month (mean; 95%CI)*	1.075	(1.057-1.093)	0.000	1.052	(1.020-1.084)	0.001
Change in medication for arthritis (Yes)	1.260	(1.224-1.302)	0.000	1.133	(1.097-1.170)	0.000
Provision of RA care and municipality characterization						
Number of rheumatologists per 1,000 patients with RA*	1.033	(1.031-1.035)	0.000	1.037	(1.035-1.039)	0.000

*Continuous variables added in the model: Weight kg (Mean = 71.43, 95%CI = 71.43-71.43, Min/Max = 48.0/150); Height cm (Mean = 161.12, 95%CI = 161.12-161.12, Min/Max = 98.0/233.0); Age years (Mean = 56.95, 95%CI = 56.95-56.95, Min/Max = 16/99); Number of dispensations per patient/year (Mean = 8.55, 95%CI = 8.55-8.555, Min/Max = 1/24); Period of treatment (months) (Mean = 9.83, 95%CI = 9.83-9.83, Min/Max = 1/12); Number of dispensations per month (Mean = 0.95, 95%CI = 0.95-0.95, Min/Max = 0.08/24); Rheumatologists per 100,000 patients with RA (Mean = 6.88, 95%CI = 6.88-6.88, Min/Max = 0/43.5). Type of APAC**: Authorization for High Complexity/Cost Procedures. [#1] Patient dropouts: patients who sought csDMARDs and/or bioDMARDs in only 20% of the total number of possible dispensations. [#2] Patient adherence to treatment (patients with at least 80% of the maximum possible dispensations, both for csDMARDs and for bioDMARDs).

Source: Authors.

adalimumab was R$ 1,319.36 [33], according to the prices obtained by the MS for centralized purchases resulting from a bidding process with volume-dependent pricing with the pharmaceutical industry. The monthly cost of treatment with the same medication at the private pharmacy was between R$ 8,710.49 and R$ 10,888.11[34].

Larger municipalities had a higher concentration of rheumatologists, a greater number of registered users of bioDMARD and a greater number of changes in the therapeutic regimen for RA. The concentration of rheumatologists in the capitals and in the largest Brazilian municipalities[35] creates less access to care for individuals with RA who live outside the city centers.

Santos[36] emphasizes regular follow-up with a physician as essential for RA patients to control their disease and be able to receive medication by CEAF. In this service, in addition to the prescription and report of the request, evaluation and authorization of medications, laboratory and imaging tests are required periodically to analyze the effectiveness and safety of the the csDMARDs used[16]. The rheumatologist is the specialist most indicated for the follow-up of patients with RA[16], and the results of the present study showed that the availability of this professional was associated with the prescription profile in Brazilian municipalities.

In addition, demographic data for 2020 revealed an increase in the population of physicians in Brazil in the period 1920 to 2020 due to the greater supply of undergraduate and specialization courses[37]. However, the unequal distribution of professionals in the country remains, with a shortage of physicians, especially in sparsely populated and suburban areas. The physician/inhabitant ratio in the capitals is approximately four times higher when compared to the interior of the country. The 46 cities with large popula-

tions (more than 500,000 inhabitants) have 6.3 times more physicians than small cities (up to 100,000 inhabitants)[37].

In 2018, 62.7% of physicians had at least one specialist title, and rheumatology accounted for 0.6% of physicians in the country[38]. The capitals, together with the five largest municipalities of each FU, had 75.8% of the country's rheumatologists, of whom 49.9% provided care in the SUS. The distribution of these professionals was higher in places with higher Gross Domestic Product (GDP), Municipal Human Development Index (HDI-M) and number of medical residency students[35]. Although an ideal number has not been described in the literature, the Royal College of Physicians in the United Kingdom estimated the ideal ratio of one rheumatologist (40 hours per week) for every 86,000 inhabitants[39]. The supply of rheumatologists in the SUS was below this value in all states, and Rio de Janeiro has the highest ratio, with one rheumatologist for every 156,000 inhabitants[35].

The small municipalities dispensed the least bioDMARD. The large municipalities dispensed the most the csDMARDs, with the exception of leflunomide, and had a higher proportion of medication changes for RA when compared to medium-sized municipalities. Two hypotheses can be inferred for this result: lower bioDMARD prescription due to insufficient specialized service network or lower availability of bioDMARD bio in the municipality.

Regional asymmetries can compromise equal access to health services. Small municipalities may have higher relative expenses and larger budgets compared to larger municipalities due to the absorption of losses resulting from economies of scale. Municipalities with up to 5,000 inhabitants have high per capita health expenditures, which may be due to high medical wages, higher proportional expenditures on single purchase of care services and purchase of supplies, with medicines being the majority of these supplies[40].

BioDMARDs, belonging to Group 1A of the CEAF, are acquired by the MS, but the responsibility for programming, storage, distribution and dispensing lies with the SES and the DF[11]. All bioDMARDs, with the exception of tofacitinib, are injectable drugs that require refrigerated storage[16]. Thus, the availability of these drugs requires appropriate transportation and storage conditions, in addition to services that provide parenteral administration when necessary. The existing evidence[41,42] points to infrastructure problems at the dispensing sites. However, it is reasonable to assume that medium and large municipalities find it easier to dispense these medications because they have more resources and health services.

Another aspect is that bioDMARDs are an important object of judicialization, and some authors argue that this process drives their incorporation into RENAME, sometimes not sufficiently supported by scientific evidence[43,44].

The evolution of RA and, consequently, decisions regarding the therapeutic approach are associated with different clinical and behavioral factors[16]. However, this study was restricted to the possibilities offered by the database used. Thus, it was not possible to evaluate clinical aspects that could enrich the analyses, such as BMI, because the database used does not contain this information. Although the presence of comorbidities may influence the response to treatment, this information was not emphasized to guide the choice of therapeutic approach for arthritis in the PCDT in force at the time. There were indications only for monitoring and eventual treatment, and therefore, they would not have relevant influence for this analysis on the use of DMARD bio. Another limitation of this study was the use of an administrative measure to investigate adherence to treatment, which is consistent with the international literature[45,46]. Some authors argue that this measure would better express the concept of persistence and not that of treatment compliance because the latter is a more complex phenomenon that encompasses not only the supply of medications but also the user's behavior in carrying out health professionals' recommendations[42]. Further, the database used does not identify the reason why the prescribed medication was not dispensed, nor does it record the medical specialty related to each prescription.

All analyses performed at the municipal level, such as the size and density of rheumatologists, were based on the classification of the municipality as a drug dispenser in the SIA/SUS APAC. However, discrepancies were identified in the identification of dispensing centers, i.e., municipalities that dispense drugs in the CEAF, but the registration of dispensing in the state was performed in another municipality. For example, on the website of the Rio de Janeiro State Department of Health, there are 27 CEAF dispensing locations[47], but registration with the APAC occurred only in the capital. It is noteworthy that this discrepancy is also a limitation of other studies that use this database, in addition to causing difficulty in decision-making by managers. This

aspect deserves to be analyzed in future studies, as well as the impact of the lack of registration of clinical data for the longitudinal follow-up of patients by the CEAF services and the better use of the available data.

As strengths, it is worth mentioning that the study had a national scope, in which aspects were investigated at the municipality level regarding the management of CEAF and, finally, at the individual level. Although it is a secondary database, the reliability of the data is probably high, since the main objective of the SIA/SUS APAC medicines is to collect information that subsidizes payment for the services provided[48].

Conclusion

BioDMARDs were dispensed to approximately one-third of patients treated for RA in Brazil, and there was greater adherence of users to this therapeutic group when compared to the csDMARDs. A higher frequency of dispensing was associated with a higher percentage of rheumatologists. Despite the statistically significant association with the demographic variables, the odds ratio was not very high.

Monitoring the supply of medicines is a key instrument for evaluating the quality and performance of a care program. Because it has high added value, the monitoring of DMARD bio in the national territory can help managers evaluate the functioning of the CEAF and identify points of improvement in the supply of medicines, in addition to implementing policies that favor better monitoring of patients, which will result in a reduction in comorbidities, increase in quality of life and decrease in medication and legalization costs.

The prescriptive pattern according to age, as well as adherence to treatment, are findings that deserve more detail in future studies regarding their rationality, with a view to effectiveness and safety. The divergence of dispensing centers between the SIA/SUS APAC medicines and the websites of the state health departments should also be better explored, as this hinders analyses from the perspective of regionalization.

Collaborations

ALB Oliveira collaborated in the design of this study, collected the data, analyzed the data and wrote the text. VL Luiza assisted in the study design, analysis of the results and in the writing and revision of the final text. EC Lima assisted in the study design, analysis of the results and in the writing and revision of the final text. M Campos collaborated in the study design, data analysis and writing of the final text.

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