ORIGINAL ARTICLE

# Profile of users of anticytokines offered by the health care system in the state of Paraná for the treatment of rheumatoid arthritis

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## ABSTRACT

**Introduction:** The Brazilian Unified Health Care System (SUS) offers treatment for patients with RA through federal funding (Ministry of Health) and state co-financing. The Clinical Protocol and Therapeutic Guidelines for the treatment of rheumatoid arthritis describe the therapeutic regimen for the disease, including the anticytokines adalimumab, etanercept or infliximab. **Objectives:** The aim of this study was to evaluate the profile of registered users of those anticytokines, biologics registered in the Information System of the Pharmaceutical Assistance Specialized Division, managed by the Paraná State Drug Center. **Methods:** A cross-sectional study regarding data from March 2010 was conducted. Based on dispensation data, information regarding the following variables were collected: age; gender; regional health care centers; International Classification of Diseases (ICD); and drug dispensed. In addition, the monthly cost with anticytokines for the SUS was calculated. **Results:** In the state of Paraná, 923 patients on anticytokines were identified, 40%, 44% and 16% of whom receiving adalimumab, etanercept and infliximab, respectively. This generated a monthly cost of R$3,403,195.59. Regarding the ICD, the distribution of patients was as follows: 55% had ICD M05.8; 27%, ICD M06.0; 9%, ICD M6.8; 8%, ICD M5.0; and 1% had other ICDs related to the disease. The regional health care centers of the state of Paraná with the largest number of patients on anticytokines were in the following municipalities: Ponta Grossa; Cornélio Procópio; Londrina; Cianorte; Maringá; Irati; and Campo Mourão. **Conclusion:** This study assessed the distribution and profile of users of anticytokines for the rheumatoid arthritis treatment covered by the SUS in the state of Paraná, in March 2010.

**Keywords:** rheumatoid arthritis, therapeutics, antirheumatic agents.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by symmetrical peripheral polyarthritis, which leads to articular deformity and destruction due to bone and cartilage erosion.[1–3] Its prevalence is approximately 1% of the world population.[4] In Brazil, a multicenter study has reported an RA prevalence of 0.2%–1%.[5]

Patients with RA have a two-fold increased mortality risk. When RA involves other organs, its morbidity and severity are higher, and life expectancy can be reduced by 5–10 years.[6] With disease progression, patients develop inability to perform their daily and professional activities. In addition, due to its chronic nature and the fact that RA affects individuals at a productive age, the disease has a high economic impact for the patient and the society.[3,7]

Treatments for RA are aimed at preventing or controlling joint lesions, preventing functional loss, reducing pain, and maximizing the patients' quality of life. The types of treatment vary according to the disease stage, and complete disease remission is rarely achieved.[1]

For controlling both pain and the inflammatory process, non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids are used. Once the diagnosis of RA is established, treatment with disease-modifying antirheumatic drugs (DMARDs) is recommended, reducing RA signs and symptoms, and slowing the disease radiological progression. Examples of DMARDs are: methotrexate (MTX), leflunomide (LFN), sulfasalazine (SFZ), and hydroxychloroquine (HCQ). Biological response modifiers are indicated for patients with persistently active disease despite treatment with NSAIDs and DMARDs. Some examples of biological response modifiers are tumor necrosis factor inhibitors (anti-TNF) and anticytokines, such as adalimumab (ADA), etanercept (ETA), and infliximab (INF).[1,8,9] According to the Methodological Guidelines for the Elaboration of Technical-Scientific Reports, the Brazilian Ministry of Health considers that those three anticytokines (ADA, ETA, and INF) have the same efficacy.[10] Thus, physicians should choose among those drugs.

Drugs for RA treatment are part of the list of the Pharmaceutical Assistance Specialized Division (CEAF) (Government Bulletin GM/MS #2,981/2009), former Exception Drug Dispensation Division (Government Bulletin GM/MS #2,577/2006). The Brazilian Unified Health Care System (SUS) offers treatment for patients with RA through federal funding (Ministry of Health) and state co-financing (Paraná State Secretariat of Health). The Paraná State Secretariat of Health, through the Paraná State Drug Center (CEMEPAR), is responsible for managing the Pharmaceutical Assistance in the state of Paraná.

CEMEPAR activities structured in the Pharmaceutical Assistance program comprise programming, acquisition forwarding, receiving, storing and distributing the CEAF list drugs to the Regional Health Care Centers of the Paraná State Secretariat of Health. The drugs are dispensed to patients residing in the state of Paraná by the Special Pharmacies of the 22 Regional Health Care Centers. To be registered in the program, the patient should meet the criteria established in the Clinical Protocol and Therapeutic Guidelines for RA.[10]

The following factors are extremely important for planning the acquisition of drugs and managing the Pharmaceutical Assistance program: control of the number of patients registered, variations in the doses prescribed by physicians, drug replacement and/or discontinuation, entrance of new patients, and exit of patients (discharge from the program, cure, abandonment

of the program, or death). Based on that demand, CEMEPAR, along with the Paraná State Information Technology Company (CELEPAR), has developed, since 2004, the information system called SESAFARM. SESAFARM was the base for the creation of the system currently used at national level by the Ministry of Health, the CEAF Information System (SISMEDEX), implanted at all Special Pharmacies. SISMEDEX has the following functionalities: (I) registration of the pharmacies and collaborators allowed to use the system; (II) data regarding drugs and ongoing Clinical Protocol and Therapeutic Guidelines; (III) registration of the user and the Exception Drug Request Form; (IV) registration of renovations and adequacies of the Exception Drug Request Form; (V) assessment and authorization of the process of drug request; (VI) registration of the dispensation of authorized drugs; (VII) registration and follow-up of the course of the process at the Regional Health Care Centers and/or CEMEPAR; (VIII) maintenance of the registration of the prescribing physicians and Referral Centers belonging to the program; (IX) storage; (X) automatic generation of the High Complexity Procedure Authorization; (XI) generation of reports and general consultations.

This study aimed at establishing the profile of the users of anticytokines for the treatment of RA registered in CEAF, based on dispensation data obtained from SISMEDEX, and at assessing the following variables: International Classification of Diseases (ICD); gender; age; Regional Health Care Centers; and drugs dispensed. In addition, the monthly cost to SUS for acquiring those drugs was also assessed. This study was not aimed at discussing the access to the RA diagnosis, but exclusively at assessing drug dispensation to patients diagnosed with RA and registered in the Pharmaceutical Assistance program.

## MATERIAL AND METHODS

This is a cross-sectional study comprising data collection from users registered in SISMEDEX in the state of Paraná in March 2010. Data were collected through search for pathology, based on the Clinical Protocol and Therapeutic Guidelines for RA. The assessment considered data from patients with the following ICDs:

M05.0 – Felty's syndrome;

M05.1 – Rheumatoid lung disease;

M05.2 – Rheumatoid vasculitis;

M05.3 – Rheumatoid arthritis with involvement of other organs or systems;

M05.8 – Other seropositive rheumatoid arthritis;

M06.0 – Seronegative rheumatoid arthritis;

M06.8 – Other specified rheumatoid arthritis.

Data on ICD, gender, age, Regional Health Care Centers, and drug dispensed were collected for all patients, who were kept anonymous. The number and percentage of patients related to each of those variables were calculated. Mean age and its standard deviation were calculated, and the number of patients in each age group (every five years) was tabulated.

To calculate the resources used every month for the RA treatments in the state of Paraná, only the costs of the drugs at their usual recommended doses in the Clinical Protocol and Therapeutic Guidelines, obtained in the SUS database (DATASUS) tables, were considered.[10]

## RESULTS

In the census carried out by the Brazilian Institute of Geography and Statistics (IBGE) in 2007, the Paraná state population was 10,511,862 inhabitants, distributed in 399 municipalities.[11] The number of users registered in SISMEDEX receiving treatment with anticytokines for RA in March 2010 was 923, of whom, 258 (28%) were men and 665 (72%), women. Their age ranged from 2–91 years (mean age, $50 \pm 13.8$ years). Over half of the individuals (54.9%) were 40–60 years old. The patients' age distribution is shown in Figure 1.

Regarding the ICD, the distribution was as follows: ICD M05.8, 55% of the individuals; ICD M06.0, 27%; ICD M06.8, 9%; ICD M05.0, 8%; and other ICDs (M05.1, M05.2, M05.3, and M06.8), 1% of the individuals. The 923 patients registered in SISMEDEX were being treated as follows: 403 (44%) with ETA; 372 (40%) with ADA; and 148 (16%) with IFX.

The distribution of patients with RA receiving anticytokines in the state of Paraná is shown in Table 1. The Regional Health Care Centers are presented in Figure 2.
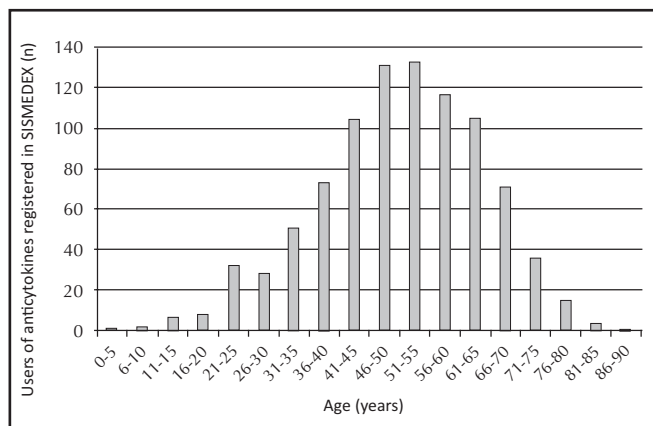
**Table 1**

Distribution of patients receiving anticytokines in the Regional Health Care Centers of the state of Paraná

| Regional Health Care Centers | n | % | Total of inhabitants | Individuals/millions of inhabitants |
|---|---|---|---|---|
| 01 – Paranaguá | 20 | 2.2 | 287,633 | 70 |
| 02 – Metropolitana | 319 | 34.6 | 3,385,145 | 94 |
| 03 – Ponta Grossa | 60 | 6.5 | 579,827 | 103 |
| 04 – Irati | 26 | 2.8 | 157,604 | 165 |
| 05 – Guarapuava | 10 | 1.1 | 457,361 | 22 |
| 06 – União da Vitória | 10 | 1.1 | 168,137 | 59 |
| 07 – Pato Branco | 4 | 0.4 | 244,406 | 16 |
| 08 – Francisco Beltrão | 11 | 1.2 | 313,370 | 35 |
| 09 – Foz do Iguaçu | 31 | 3.4 | 450,893 | 69 |
| 10 – Cascavel | 48 | 5.2 | 501,851 | 96 |
| 11 – Campo Mourão | 59 | 6.4 | 311,945 | 189 |
| 12 – Umuarama | 7 | 0.8 | 234,251 | 30 |
| 13 – Cianorte | 16 | 1.7 | 130,687 | 122 |
| 14 – Paranavaí | 18 | 2.0 | 254,256 | 71 |
| 15 – Maringá | 108 | 11.7 | 716,273 | 151 |
| 16 – Apucarana | 7 | 0.8 | 337,953 | 21 |
| 17 – Londrina | 98 | 10.6 | 846,428 | 116 |
| 18 – Cornélio Procópio | 26 | 2.8 | 243,178 | 107 |
| 19 – Jacarezinho | 6 | 0.7 | 271,897 | 22 |
| 20 – Toledo | 29 | 3.1 | 323,537 | 90 |
| 21 – Telêmaco Borba | 7 | 0.8 | 166,466 | 42 |
| 22 – Ivaiporã | 3 | 0.3 | 128,764 | 23 |
| Total | 923 | 100 | 10,511,862 | 88 |



**Figure 1**
Graphic representation of age as a function of the number of users of anticytokines registered in SISMEDEX.



more than 100 inhabitants/million
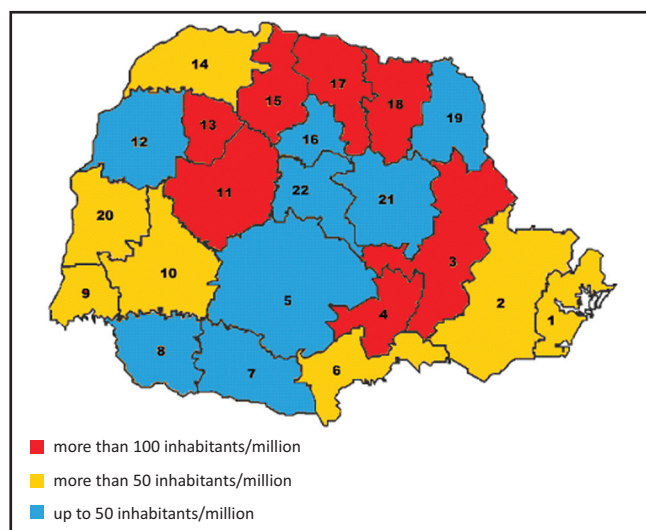more than 50 inhabitants/million
up to 50 inhabitants/million

**Figure 2**
Map of the Regional Health Care Centers of the state of Paraná.

Regarding the cost of the drugs, each ADA injection costs to SUS R$1,670.18. The total number of doses per year is 27 (monthly mean of 2.25 doses). Thus, the monthly cost per patient is R$3,757.90. Multiplying by the number of patients (372), the total monthly cost reaches R$1,397,940.66. Regarding ETA, the unit cost of the 25-mg dose is R$523.32, while the 50-mg dose costs R$1,046.65. Every month, 257 patients receive a mean of 8.7 doses/month of 25 mg (total of 104 doses/year/ patient), and 146 patients receive a mean of 4.3 doses/month of 50 mg (total of 52 doses/year/patient), generating a total monthly cost of R$1,827,788.13. Regarding IFX, its dose costs R$1,713.00, and each patient receives, on average, eight doses per year. Considering the number of users (148), the total monthly cost reaches R$177,466.80. The total monthly cost with anticytokines in the state of Paraná in March 2010 was R$3,403,195.59, of which, ADA accounted for 41%, ETA, for 54%, and IFX, for 5%.

## DISCUSSION

Despite the identification of more than 100 different types of cytokines and other factors involved in the pathogenesis of RA, TNF-α continues to play a significant role in joint erosive disease via osteoclast activation.[12–15] TNF-α inhibitors have shown clear benefits in randomized studies and controlled trials.[16] Rheumatoid arthritis can begin at any age, but its prevalence is from the fourth to the sixth decade.[1,4] In the present study, more than half of the individuals assessed belong to that age group, being in accordance with data in the literature.

Rheumatoid arthritis affects twice more women than men, and its incidence increases with age. Gender differences, however, are not so marked as age advances.[1,17,18] The users of anticytokines assessed in this study showed figures similar to those reported.

The cause of RA is unknown, but several arthritogenic agents can stimulate the immune response in genetically susceptible individuals.[18] In the state of Paraná, the Regional Health Care Centers of the following municipalities had the highest number of individuals undergoing treatment with anticytokines: Ponta Grossa; Cornélio Procópio; Londrina; Cianorte; Maringá; Irati; and Campo Mourão. It is worth noting that the present study assessed the profile of patients really undergoing treatment for RA, and not of those with difficulty in accessing either Regional Health Care Centers or physicians, or even difficulty in being diagnosed with RA, who are, thus, left without proper treatment. In addition, there are individuals who buy their medication with their own resources, being, thus, not computed in SISMEDEX.

The incidence of RA in Brazil is still underestimated. A study carried out in 2009[19] estimated that only half of the Brazilians with RA have their diagnosis established. The mean time between symptom onset and RA diagnosis was 1.8 year, which could have been due to difficulty in accessing the public health care system. Other barriers for the treatment of RA in Brazil include low number of rheumatologists, population's difficulty in accessing the medications, and delay in scheduling the medical consultations, which can vary between four and ten months in different regions of the country.[20]

In the Clinical Protocol and Therapeutic Guidelines for RA,[10] the three anticytokines are attributed the same efficacy. Some studies[21–23] have compared the efficacy and safety of those drugs with those of placebo, and not directly between them. In the meta-analysis carried out in 2010, Wiens et al.[24] reported that a difference in the efficacy and safety of those drugs might exist, and the prescribing physician should assess the risks and the benefits provided by each one.

Currently, the prospective epidemiological study BiobadaBrasil is ongoing.[25,26] In January 2011, that study included 1,785 patients distributed in 32 centers. BiodabaBrasil aims at reporting data of effectiveness and safety of anticytokines in the Brazilian population. The patients receive biologics or DMARDs (control group) for rheumatic diseases (69.7% of the patients have RA). So far, IFX has been reported as the most used drug (39% of the patients). In our study, a smaller number of IFX users was observed in the state of Paraná as compared with users of the other anticytokines. One factor accounting for that difference between the national data and those of the state of Paraná can be the choice of the anticytokines by the physicians. The anticytokine most frequently used in the state of Paraná in March 2010 was ADA.

The prescription and use of an anticytokine is an important decision, because it can generate a great impact on the patient's quality of life by reducing RA symptoms, and also a significant cost elevation for the health care system.[27] We assessed the cost of each medication for the SUS. However, to support the physician's choice between anticytokines, that information is not enough, because pharmacoeconomic studies in Brazil are scarce. An economic study has been recently conducted by Venson et al.[28] to assess the cost-effectiveness ratio of anticytokines for the RA treatment from the SUS perspective. Among the anticytokines, ADA and ETA showed the best cost-effectiveness ratio (R$511,633.00 and R$437,486.00, respectively) as compared with IFX (R$657,593.00). Infliximab showed higher incremental cost-effectiveness ratio (ICER) per

outcome unit, which was R$965,927.00, while for ADA and ETA, those values were R$628,124.00 and R$509,974.00, respectively. However, despite the differences in the incremental cost-effectiveness ratio between the anticytokines, it is worth noting that all three anticytokines should continue to be provided to the population, because each patient can respond differently to treatment.

In the context of RA treatment in the state of Paraná, this study established the profile of the users of anticytokines registered in CEMEPAR. In addition, the monthly cost with drugs for treating RA in that state could be assessed. Such values can be used for further economic evaluations, such as the cost-effectiveness ratio or even direct cost, from the SUS perspective, of the RA treatment in the state of Paraná.

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