Brazilian Biologic Registry: BiobadaBrasil implementation process and preliminary results

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ABSTRACT

Objectives: The present study aimed at describing the implementation process of a national registry in a developing country (Brazil) and at reporting the main preliminary results of the BiobadaBrasil registry. **Material and methods:** Through a PANLAR agreement, the Biobadaser protocol was used as a model for implementing the new registry in our country. During the first two years of this effort, the original protocol was adapted, translated, and presented to all Brazilian rheumatologists. For ten months, data of 1,037 patients (750 subjects treated with biological drugs and 287 control subjects) from 15 centers were collected. **Results:** Most patients had rheumatoid arthritis (RA) (n = 723). Infliximab was the most frequently used anti-TNF agent, and the total exposure to biologic drugs was 2,101 patient-years. The most common reason for interrupting drug use was lack or loss of efficacy (50%), while 30% withdrew from the treatment arm due to adverse events. Three cases of tuberculosis were observed in the biologic group, with an incidence higher than that of the general Brazilian population. Infections were observed in 23% of the biologic group, and the upper respiratory tract was the most commonly affected site. Only one case of tuberculoid leprosy was observed. No deaths or malignancies attributed to drug effects were observed as of February 2010. **Conclusions:** The implementation of the BiobadaBrasil registry was successful, and, although recent, the registry has provided important data.

Keywords: antirheumatic agents, Brazil, database.

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INTRODUCTION

New treatment modalities centered on biological therapies has undoubtedly improved outcomes for patients with severe rheumatoid arthritis (RA) and has definitively created new perspectives in the field of rheumatology.[1] In addition, these benefits have carried over to others diseases, such as ankylosing spondylitis (AS),[2] psoriatic arthritis (PsA),[3] juvenile idiopathic arthritis (JIA),[4] and systemic lupus erythematosus (SLE),[5] among others.

Since the introduction of anti-TNF agents and, later, other biological therapies, the safety of these agents compared to placebo has been demonstrated in clinical trials.[6] However, concerns about long-term safety, particularly serious infection and malignancy, as well as rare and unexpected adverse events, have not been adequately addressed by these trials.[7] Open-label extensions often do not accurately reflect patients in their daily routines, since they include only those who have been previously studied in randomized clinical trials. Moreover, national pharmacovigilance systems may not be accurate sources of information to address these uncertainties, as adverse events may be significantly underreported. This lack of information about long-term follow-up led to the creation of local registries that are able to collect data from a varied population of patients treated in daily practice. To date, most of the current registries are supported by national societies of rheumatology, mainly in European countries[8] and the United States.[9] Throughout the last decade, these registries have collected an impressive amount of data that have been shared worldwide.[8]

The European and American realities might be different from others countries, particularly a developing country like Brazil, which is as large as Western Europe and similar in size to the United States. Particular characteristics of the Brazil, such as the genetic diversity of the population,[10] unique socio-economic situations and certain endemic diseases, have prompted the establishment of a national registry of patients on biological therapies for rheumatologic diseases. The main propose of this registry was to develop a large, prospective epidemiological study for monitoring patients receiving these new drugs.

The aims of the present study were to describe the implementation process of a national registry in a developing country and to show the main preliminary results of BiobadaBrasil registry.

MATERIALS AND METHODS

In order to establish a new registry, the strengths and weaknesses of current registries had to be considered. In addition, the registry would have to encompass some unique characteristics of the country and its National Health System (NHS). For the Brazilian registry, the following were considered to be priorities:

a) To include an internal cohort control group of patients receiving traditional DMARDs (comparators).
b) To assure the quality of data regarding both accuracy and maintenance of a constant flow of information.
c) To enroll private clinics and public/academic centers, since both types of institution are part of the Brazilian NHS. In Brazil, biologic agents (i.e., anti-TNF agents) can be obtained from the public health system free of charge, and can be purchased from private insurance and securities companies for a fee.
d) To encourage the continuous voluntary participation of centers and rheumatologists.
e) To establish proper and independent funding without interference by sponsors.

As is true of other registries (BSBR,[11] CORRONA,[9] RABBIT,[12] ARTIS,[13] BIOBADASER,[14] DANBIO[15]), BiobadaBrasil was set up by a rheumatology society, the Brazilian Society of Rheumatology (SBR)[16] and aimed to include all licensed biologic agents for treatment of any rheumatic disease (regular and off-label indication) for an indefinite follow-up period. Through a PANLAR initiative (BIOBADAMERICA), the Spanish protocol (BIOBADASER)[17] was made available to the Brazilian Society of Rheumatology, and it was deemed capable of fulfilling the perceived needs of the country, since it properly addressed some of the priorities listed above. It included an internal cohort of patients taking non-biologic agents, which served as a control group. The control group included patients initiating treatment with a traditional DMARD and patients requiring an increased dose due to failure on at least one DMARD (switching or combining therapy strategies). Using these inclusion criteria, we aimed to minimize the problems of enrolling different populations when comparing disease severity. The difficulty of establishing a proper control group is an obstacle for any new registry, and it should always be taken into account during the analysis of results. Furthermore, the monitoring system of the Spanish registry had the advantage of monitoring online, via semi-annual phone calls and with annual on-site assessment (by a random sampling process).

In order to be attractive to academic and private centers and to guarantee the continued interest of the study participants, the following incentives were employed: scholarships, certificates of excellence, electronic medical records, access to an online shared knowledge system, VIP status at rheumatology events

and exclusive meetings with rheumatology experts. The registry is sponsored by the SBR and supported by joint grants from all pharmaceutical companies with currently licensed biologic agents in the country (equal shares). In terms of design, control, conduct, analysis and publication, independence of the registry was granted. Information regarding expenses and general data are provided regularly to all supporting companies; nevertheless, detailed reports of adverse events for each biologic agent are available only to the respective pharmaceutical company.

Five centers were chosen (phase I) to officially begin the registry (BiobadaBrasil) in January 2009. These five centers (four in public university hospitals, one in a private clinic) located 400-3000 km apart, assumed the responsibility of translation, cultural adaptation and standardization of procedures and reports. During this phase, 150 patients were entered into the registry. In April 2009, the project was presented and opened up to contributions from all SBR members (phase II). Data were collected from all participating centers, with as many as 30 patients enrolled without any pending monitoring issues as of February 2010. Ethics committee approval and written informed consent were mandatory for all participating centers.

STATISTICAL METHODS

The cumulative rate of discontinuation was calculated using actuarial methods, accounting for the time of observation from enrolment until the first withdrawal. The log-rank test was used to compare the survival curves of RA, AS, and other group. All analyses were performed using the Stata 9.1 program (StataCorp LP, College Station, TX, USA). Statistical significance was assumed for values of $P < 0.05$.

RESULTS

In addition to the 5 initial centers, 18 other centers (including one private clinic), located 80-4000 km apart (Figure 1), agreed to participate in the BiobadaBrasil registry. A total of 1,037 patients from these centers were registered as of February 2010. Another 18 centers are currently undergoing the approval process to join the registry. Since its presentation to Brazilian rheumatologists, the registry has steadily grown in number of patients and participating centers (Figure 1).

A total of 1,037 patients, defined as total group, were divided into two groups: one receiving treatment with biological agents (biologic; n = 750) and the other receiving treatment with DMARDs (control; n = 287). In both groups,

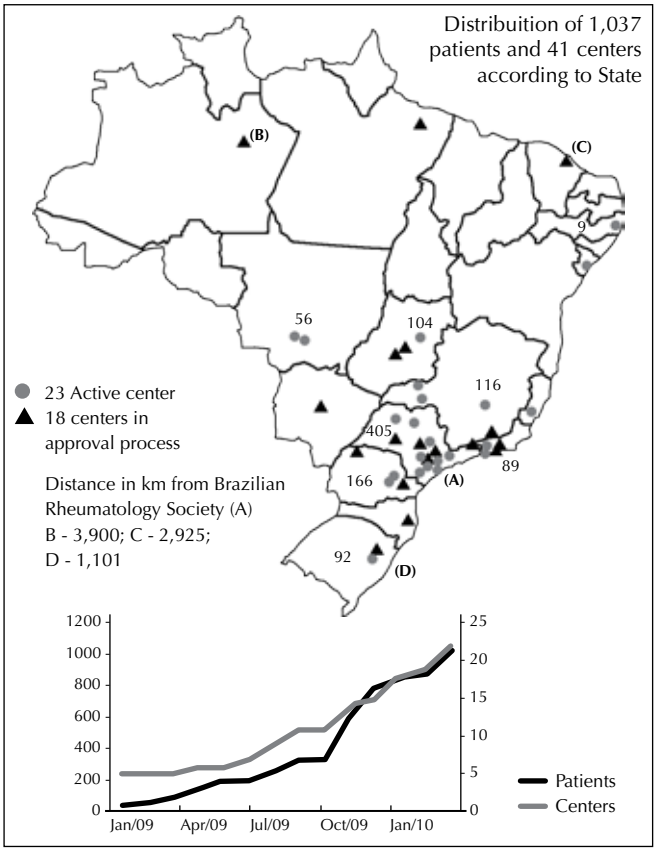

Figure 1
Inclusion of 1,037 patients between January 2009 and February 2010 (bottom left) and the distribution of the participating centers on Brazilian geographical map in the BiobadaBrasil registry.

the majority of patients were diagnosed with RA (69.7%; global); this prevalence of RA was greater in the control group (89.9%) compared to the biologic group (68.9%; $P < 0.001$, Table 1). Spondyloarthritis accounted for 21.2% of diagnoses (n = 220), AS was identified in 66% (n = 145), psoriatic arthritis in 27.3% (n = 60), Crohn's disease-related spondyloarthritis in 4% (n = 9) and undifferentiated spondyloarthritis in 2.7% (n = 6). Seventy-two percent of the patients were women and had a mean age of 47.3 ± 13.8 years. Mean exposure time to treatment was 2.09 ± 2.39 years, with 750 patients using biologic agents and 287 using only DMARDs. Most study subjects were recruited from public hospitals (85%), while 15% originated from the two private services. The characteristics of patients are summarized in Table 1.

Overall, infliximab was the TNF blocker most commonly used, followed by adalimumab and etanercept (Table 2). Biologic agents, such as abatacept, rituximab and tocilizumab, were not used in AS. Rituximab was also used in SLE (n = 6), overlap syndrome (n = 1), JIA (n = 1) and Sjögrens syndrome (n = 1).

Table 1
Clinical and demographic features of patients using biologic agents (Biologic) or DMARDs (controls) in the BiobadaBrasil registry

	Total	Biologic	Controls
Number of patients	1037	750	287
Number of treatments	1167	880	287
Age (years ± SD)	47.3 ± 13.8	46.2 ± 13.1	50.2 ±12.9
Female (%)	749 (72.2%)	517 (68.9%)	232 (80.9%)
Mean disease duration (years ± SD)	10.1 ± 8.2	10.8 ± 7.9	9.6 ± 8.6
Exposition time to treatment (years ± SD)	2.1 ± 2.4	1.8 ± 1.8	3.1 ± 7.5
% private patients	15%	----	----
Rheumatoid arthritis	723 (69.7%)	466 (62.1%)	257 (89.5%)
Ankylosing Spondylitis	145 (13.9%)	120 (16%)	25 (9.8%)
Others*	169 (16.4%)	164 (21.9%)	5 (0.7%)

* Psoriatic arthritis (60); Juvenile Idiopathic Arthritis (58); Psoriasis (11); Systemic Lupus Erythematosus (11); Crohn's disease-related spondyloarthritis (9); Undifferentiated spondyloarthritis (6); Still Disease (4); Vasculitis (3); Behçet (2); Uveitis (1); Relapsing polychondritis (1); Sjögren Syndrome (1); Overlap syndrome (1); SAPHO syndrome (1).

Table 2
Exposure to different biological treatments according to diagnosis in BiobadaBrasil registry

Biologic agents	Total n (%)	Rheumatoid Arthritis n (%)	Ankylosing Spondylitis n (%)	Others* n (%)
Infliximab	339 (39)	208 (37)	59 (45)	72 (40)
Adalimumab	243 (28)	174 (31)	28 (21)	41 (23)
Etanercept	183 (21)	83 (15)	44 (34)	56 (31)
Abatacept	48 (5)	47 (8)	0	1 (1)
Rituximab	44 (5)	34 (6)	0	10 (6)
Tocilizumab	23 (3)	23 (4)	0	0
Total	880 (100)	569 (100)	131 (100)	180 (100)

*Psoriatic arthritis (60); Juvenile Idiopathic Arthritis (58); Psoriasis (11); Systemic Lupus Erythematosus (11); Crohn's disease-related spondyloarthritis (9); Undifferentiated spondyloarthritis (6); Still Disease (4); Vasculitis (3); Behçet (2); Uveitis (1); Relapsing polychondritis (1); Sjögren Syndrome (1); Overlap syndrome (1); SAPHO syndrome (1).

The total exposure to TNF antagonists during the first four years of use was 2,101 patient-years for all patients (incidence rate = 7.9%), 1,306 patient-years for RA (incidence rate = 9.2%), 386 patient-years for AS (incidence rate = 4.9%) and 407 patient-years for the other groups (incidence rate = 6.6%). Patients with RA had longer exposures in terms of patient-years and had more commonly tried several different biologic treatments (Table 2).

Biologic therapy withdrawal (Table 3) was more frequently related to lack or loss of efficacy than to adverse effects in the whole study cohort (50% vs. 32%) and in RA patients (55% vs. 28%). Although the frequencies of loss or lack of efficacy and adverse events were different between the test and control groups, no statistical analyses were conducted due to the small size of the control group. For AS patients, similar frequencies for lack or loss of efficacy (50%) and for adverse events (50%) were observed, although the small sample size precluded definitive statistical analysis. Three deaths occurred, all in RA patients. Two of the deaths occurred in the biologic group, with one patient deceased due to H1N1 viral infection and the other due to giant extracranial carotid artery aneurysm. In the control group, one patient died due to acute myocardial infarction (Table 3).

With regard to adverse events, infections were the most frequent event seen in patients using biologic agents (n = 206, Table 4). The most common sites of infection were the upper respiratory tract (28.6%), urinary tract (27.6%), and skin and soft tissue infections (18.9%) (Table 4). The pattern of adverse events has been similar to that observed in other registries. Interestingly, to date, there has been one case of endemic tropical disease of tuberculoid leprosy reported, and three cases of active tuberculosis have been detected in the group using anti-TNF treatment. One of the cases was pulmonary and two were disseminated, but all three made a total recovery. During the period of observation, four cases of cancer were reported (breast and uterus).

Table 3
Causes for biological treatment withdrawal in BiobadaBrasil patients. (n = 196)

Causes for biological withdrawal	Global n (%)	Rheumatoid Arthritis n (%)	Ankylosing Spondylitis n (%)	Others* n (%)
a) Lack or loss of efficacy	98 (50)	78 (54)	8 (50)	12 (36)
b) Total adverse events	63 (32)	40 (28)	8 (50)	15(42)
- Serious	60 (30)	37 (25)	8 (50)	15(42)
c) Death	3 (2)	3 (2)	0	0
d) Other reasons#	32 (17)	24 (16)	0	8 (22)
Total	196 (100)	145 (100)	16 (100)	35 (100)

Treatment dropout, pregnancy, disease remission.

*Psoriatic arthritis (60); Juvenile Idiopathic Arthritis (58); Psoriasis (11); Systemic Lupus Erythematosus (11); Crohn's disease-related spondyloarthritis (9); Undifferentiated spondyloarthritis (6); Still Disease (4); Vasculitis (3); Behçet (2); Uveitis (1); Relapsing polychondritis (1); Sjögren Syndrome (1); Overlap syndrome (1); SAPHO syndrome (1).

Table 4
Serious and minor infections in patients using biological agents included in BiobadaBrasil registry (n = 206)

Infection	Total (n)	Percentage (%)
Upper respiratory tract infection	59	28.6
Urinary tract infection	57	27.6
Skin infection	39	18.9
Pneumonia	12	5.8
Herpes zoster	10	4.8
Bronchitis	6	2.9
Bacterial arthritis	4	1.9
Genital candidiasis	4	1.9
Pyelonephritis	4	1.9
Gastrointestinal infection	4	1.9
Pulmonary tuberculosis	3	1.4
Conjunctivitis	2	0.9
Stomatitis	2	0.9
Tuberculoid leprosy	1	0.4
Muscle abscess	1	0.4
Otitis	1	0.4
Prosthetic joint infection SME1	1	0.4
Sepsis	1	0.4
Total	206	100

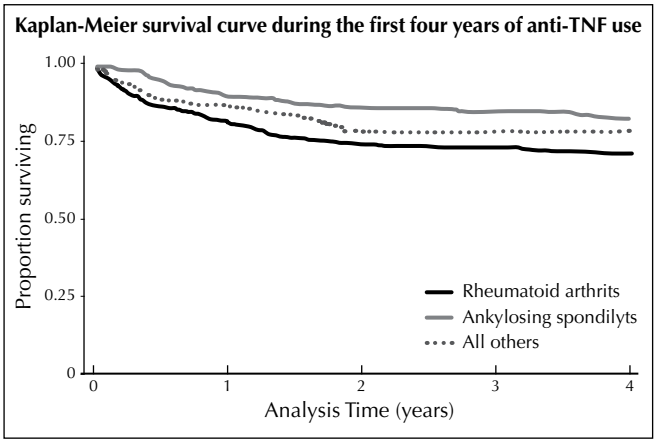

Figure 2
Survival curve of patients taking TNF antagonists for those with rheumatoid arthritis, ankylosing spondylitis and other diseases* during the first four years of use.

*Psoriatic arthritis (60); Juvenile Idiopathic Arthritis (58); Psoriasis (11); Systemic Lupus Erythematosus (11); Crohn's disease-related spondyloarthritis (9); Undifferentiated spondyloarthritis (6); Still Disease (4); Vasculitis (3); Behçet's disease (2); Uveitis (1); Relapsing polychondritis (1); Sjögren's Syndrome (1); Overlap syndrome (1); SAPHO syndrome (1).

Figure 2 represents the cumulative probability of drug survival for the three disease groups (RA, AS, and others), using drug discontinuation as the end point. Duration of use of TNF blockers in AS is significantly greater than in RA at 1, 2, 3 and 4 years (Figure 2), and the difference was greater with prolonged exposures ($P < 0.05$; log rank test).

DISCUSSION

In 1959, a group of Brazilian experts in the field of rheumatology sought to consolidate their efforts in order to solve a problem of communication and share experiences in a country with continental dimensions. As a result of this collaboration, the Brazilian Society of Rheumatology (SBR) was founded. Nowadays, SBR[16] has up to 1,250 members, all with rheumatology expertise certified by SBR through a rigorous exam that consists of written, oral and practical evaluations, as well as a critical curriculum analysis. Medicine in the modern era requires up-to-date scientific information and knowledge, and providing this information is one of the key aims of the SBR. New generation therapies against autoimmune diseases have given new insight into rheumatology. Since many countries have developed registries to collect self-reported data, the SBR decided to follow suit and connect to this innovative network of shared information. To achieve this, in December 2007, the SBR set out to implement a national registry using the experience and technology designed for one of the first European registries: the Spanish BIOBADASER.[17] There were important reasons for choosing BIOBADASER, namely, that it was already tested and in use, that it is written in a Latin language and that it was offered through an agreement with PANLAR as an extension of BIOBADAMERICA.

With a total area of 8,456,510 km^2, Brazil is divided into 26 federal states and one federal district,[18] and the main initial challenge was to create a project that could be accessible to all rheumatologists in every region. This task posed some obstacles because each state has unique genetic, racial and socio-cultural profiles, endemic diseases including tropical infections, unequal medication access, economic disparities and geographical challenges. The registry implementation was first discussed at great length, planned in detail, translated into Portuguese and then culturally adapted to guarantee good quality of information, decrease potential biases and attract Brazilian rheumatologists. Consequently, 23 active centers from 10 states during the first year are participating so far. Counting centers awaiting ethics committee approval, the total number of centers will reach 41 centers in 15 different states (Figure 1).

One of the major goals of this project is to ensure good data quality; to that end, all centers received a standard operating procedure manual and were continually monitored by a professional staff member. Each centre assumed the responsibility of monitoring each patient's medical chart once a year. The selection of these records was random and encompassed 20% of the total patients included at the registry.

BiobadaBrasil includes all patients undergoing biologic therapy and strict follow-up with complete data entered into the patient's chart. In Brazil, the SBR has published national guidelines for RA, AS and PsA[19,20] that are adhered to by most Brazilian rheumatologists. Nevertheless, there are some off-label indications for which each physician may prescribe medications at his or her own discretion. BiobadaBrasil does not interfere with the individual indications for biologic therapy, and each rheumatologist is responsible for making the decision to start or stop a medication.

These are preliminary data, and the registry is relatively small; therefore, it is very early to draw any specific conclusions. In addition, our internal control cohort is small, mainly due to the fact that in phase I of our project, the five centers included almost exclusively patients exposed to biologic therapy. Therefore, the control group cannot be compared to the biologic group in a statistically significant way. We believe that a cohort including a more robust group of patients using traditional DMARDs is essential to developing better data about safety of the biologics, and the goal is to have at least one control for each patient using biologic therapy. However, we found some unique and original results in the 1,037 patients included from January 2009 to February 2010. A very important observation was made when private practice patients were included. Remarkably, 15% of patients from our series came from only two private sources. There are no precise or official data about non-public assistance to obtain biologic therapy, but it is estimated that 15-20% of patients fall into the private practice realm. This observation reinforced the importance of private insurance and securities companies. In Brazil, patients have access to medications through judicial order, and the large number of patients from private practice sites may reflect the difficulty of public access to biologic agents.

It is important to point out that in Brazil, infliximab was the first biologic on the market (in 2000) and the first to be indicated for treatment of RA by the NHS (in 2002). Adalimumab and etanercept came on the market two years later and were approved by the NHS six years later for treatment of RA. By the end of 2009, however, the three anti-TNFs were approved for treatment of both AS and PsA. Rituximab, abatacept and tocilizumab were first available in Brazil in 2006, 2007 and 2009, respectively, for RA treatment but are still not available through the NHS. This availability could explain, at least in part, the higher frequency of infliximab use compared to other biologics, the longer drug exposure and the higher rate of switching drugs in RA compared to AS patients.

According to the mean time of exposure to biologic agents in our patients (1.8 ± 1.8 years), we observed discontinuation of drugs in 195/880 (22.2%), which is similar to the withdrawal rate observed in other registries.[8] Interestingly, 50% of drug withdrawals were due to lack or loss of efficacy, while only 30% were attributed to serious adverse events. In accordance to previous studies,[21,22] AS patients seem to have a lower rate of drug withdrawal due to lack or loss of efficacy than RA patients (6% and 12% respectively). In contrast, both RA and AS had similar frequencies of adverse events (7% and 6%, respectively). Issues related to drug access and governmental or judicial impediments were the other primary reason for biologic therapy interruptions. Furthermore, as observed in other registries, there was a longer mean survival for patients with AS when compared with RA in the biologics group.[21] This is explained in part by the younger age and fewer co-medications seen in patients with spondyloarthritis (SpA) compared to RA, because age and co-medications are associated with a greater number of adverse events.[23,24]

Infections are a major concern for patients using biologic therapies and must be a point of close attention in a registry. In accordance with the observations of Listing et al., we observed a higher frequency of infections in the group undergoing treatment with biologics.[25] However, while Listing reported an infection frequency of 15%, our cohort had a greater incidence of 23%. It is speculated that this higher rate of infection may be related to increased exposure to other immunosuppressants, comorbid conditions, use of corticosteroid and disease activity.[24] On the other hand, our data suggest that this is more likely to be a direct effect of anti-TNF agents and that all infections are more frequent in patients on biologics than those taking DMARDs. Additionally, lower respiratory tract infections, especially pneumonia, were the most common site of infection, which is agreement with observations from other registries.[8] Herpes zoster infection is another major concern in biologic patients, in the light of the fact that recent studies have published increased incidence in this subgroup of patients.[25,26] Hence, a recent systematic literature review[24] demonstrated lower rates of herpes zoster infection in RA patients treated with traditional DMARDs, such as methotrexate. This is supported by our study, in which ten biologics group patients

developed herpes zoster infection compared to no control subjects. Bacterial skin infections (erysipelas) and bone and joint infections were also higher in the biologics group. Unfortunately, there was one fatality in the biologic group, when a patient passed away from H1N1 viral pneumonia during the world pandemic in 2009. As discussed by other authors and our own group, we are aware that the potential underreporting of mild infections, especially in the control group, may be an important confounding variable and limitation of this type of registry.[25,27,28]

In view of the fact that tuberculosis (TB) remains an important public health problem in Brazil, this mycobacterial infection was persistently investigated in our cohort by performing PPD skin tests on each patient according to SBR and national guidelines and recommendations.[14,19,20] Brazil ranks 14th on a list of the 22 countries with the highest TB burden, and it accounts for 31% of all TB cases in the World Health Organization's (WHO's) Latin American region. Notwithstanding compulsory BCG vaccination in our country, it is still estimated an incidence of 25-49/100,000 cases of active TB.[29] Remarkably, despite the low frequency of three cases of non-fatal active tuberculosis in the group taking anti-TNF treatment, the incidence per 100,000 patients in our cohort was impressively higher than what was expected. There is some protection against TB provided by TNF,[30] and we are aware of the possibility of a higher incidence of mycobacterial infection in patients under TNF blockers. A Brazilian study showed a low prevalence of PPD reaction prior to infliximab use in RA, SA, and psoriatic arthritis patients, indicating that the test has limited value for diagnosis of tuberculosis infection in candidates to biological infliximab therapy.[31] In addition, a focus on tropical diseases is key for a South American registry. However, we observed only one case of tuberculoid leprosy, and no cases of histoplasmosis or other granulomatous diseases were reported. Although rare, acute reactions can be severe, being observed more commonly after the initial injections, both intravenous and subcutaneous.[32] To date, our registry has not observed any rare or unexpected adverse events, and could not compare the risk for malignancy between the biologic and control groups.

CONCLUSIONS

Although it is very early in its implementation, the BiobadaBrasil registry has collected important data that might be relevant to routine practice and academic studies. For a country with large geographical dimensions and a very heterogeneous cultural and socioeconomic makeup, proper data collection and event monitoring are needed to develop a uniform and cohesive body of information. We believe that the BiobadaBrasil registry will supply needed reference data on actual Brazilian rheumatology practices regarding indications for initiating or switching medications and safety profiles for these commonly used drugs. Certainly, longer observation periods will improve knowledge and clinical practices in the field of rheumatology. We concluded that the main aims of implementing a national registry were successfully reached.

Authors contributions

All authors were involved in drafting the manuscript, collecting data, or critically revising it for important intellectual content, and all authors approved the final version to be published. The data presented here were obtained from the centers participating in the BiobadaBrasil that included at least 30 patients until 31 January 2010.

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